THE INJECTABLE CONTRACEPTIVE: USER, SOCIAL AND PHARMACOLOGICAL PERSPECTIVES

by

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Submitted in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in the Department of

Experimental and Clinical Pharmacology

Nelson R Mandela School of Medicine,

University of Natal, Durban

2003

DECLARATION

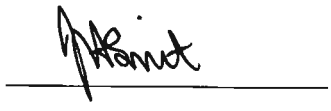
This study represents original work by the author and has not been submitted to any other university. Where use was made of the work of others it has been duly acknowledged.

Professor Julia Botha from the Department of Experimental and Clinical Pharmacology of the Nelson R Mandela School of Medicine, University of Natal, South Africa, Dr Lynn McFadyen from the Modelling and Simulation Group, Clinical Sciences, Pfizer Global Research and Development, United Kingdom, and Professor Eleanor Preston-Whyte from the Centre for HIV AIDS Networking, University of Natal, supervised the thesis.

Some of the statistical planning and analysis in this thesis were conducted in conjunction with the Biostatistics Unit of the South African Medical Research Council, Durban, South Africa, and with Development Research Africa, Durban, South Africa.

The medroxyprogesterone acetate assay was performed by Immunometrics Ltd., London, United Kingdom.

While many people in a variety of ways have contributed to the conceptualization and production of this thesis, responsibility for the arguments made is entirely mine.



Jennifer Ann Bodley Smit

July, 2003

ACKNOWLEDGEMENTS

Many people have contributed to whatever insights this thesis may contain.

Primary among these people is my close friend and colleague, Lynn McFadyen. Lynn has been a supportive, caring, incisive and inspirational supervisor. She has contributed substantially to my intellectual growth, elements of which are reflected in this thesis.

Special thanks are also due to another friend and supervisor, Julia Botha, who has provided expert guidance and unstinting support and encouragement in the writing of this thesis.

Both Lynn and Julia have provided a shining example of intellectual excellence, integrity and thoroughness; both were hard taskmasters.

I would also like to thank Eleanor Preston-Whyte, who has over many years shaped my understanding of the social and contextual environment of reproductive health in South Africa. This has contributed substantially to the development of aspects of this thesis.

Especial gratitude and acknowledgement is due to Mary Alexander, my great friend. Mary has supported me in many ways, spiritually and practically. She voluntarily took on the onerous task of proof reading this long document.

Thanks to the Hlabisa community leaders, health managers and providers, and the Durban local health authority staff for their enthusiasm and assistance.

I am also extremely grateful to the fieldworkers who trudged tirelessly up and down the Hills of Hlabisa, and to the women of Hlabisa and the Durban family planning clinics who so willingly participated in this study.

I wish to express my appreciation to Saulat Sufi of Immunometrics Ltd. for performing the medroxyprogesterone acetate assays and for his expert advice on the assay procedure.

I also wish acknowledge the Southern African Medical Research Council's HIV Prevention and Vaccine Research Unit and the Biostatistics Unit for their mentorship and support. In particular I wish to thank Khangelani Zuma for his assistance with statistical analyses and his expert tutoring; and Salo Pillay for capturing the data so meticulously.

I am indebted to my colleagues at the Reproductive Health Research Unit who have enthusiastically supported me and given me the space and courage to complete this thesis. My particular thanks go to my colleague, Mags Beksinska, who shares my passion for the field of contraception and has been an invaluable source of information and advice. Discussions with her have contributed substantially to my thinking about the field.

Thanks are also due to the staff of the Department of Experimental and Clinical Pharmacology who have assisted in every way. It has been a pleasure to undertake this work in a supportive and caring environment.

My gratitude and acknowledgement is also due to the Wellcome Trust for financial support. My particular thanks go to Wendy Ewart.

My deepest thanks go to my two daughters, Alexia and Olivia. They have endured my abstraction and the long hours stolen from them, with great patience and tender support. My two young women are a great source of inspiration to me.

Finally thanks to my many other friends and colleagues who have supported me both intellectually and through caring for me and my daughters.

CONTENTS

ABSTRACT

Despite its widespread use, little research has been undertaken on the use of progestogen-only injectable contraceptives by South African women. This thesis is comprised of two sections. Section 1 provides the first comprehensive description of injectable contraceptive use among rural South African women. It includes an analysis of the contraceptive method mix, prevalence of injectable contraceptive use, discontinuation patterns and reported side effects. A comparison of depot medroxyprogesterone acetate (DMPA) versus norethisterone oenanthate (NET-EN) focuses on utilization patterns and costs. The second section gives an account of the pharmacokinetics of DMPA including the first ever population analysis.

A cross-sectional, community-based household survey was undertaken in the Hlabisa sub-district of KwaZulu-Natal, South Africa. Interviews were held during 1998 and 1999, with 848 randomly selected women (aged 15-49years) and with 14 focus groups. There was a heavy reliance on injectable contraceptives which were used by 74% of women practising contraception. By contrast, the condom was the current method of only 4%. The injectable method was the most commonly used method among teenagers. However, in most cases, contraceptive use appeared to commence only after the first pregnancy. Slightly more NET-EN (54%) than DMPA (46%) was used, with younger women more likely to use NET-EN than DMPA ($p=0.0001$). No significant differences in self-reported side effects were found between current users of the two injectables. Health workers played an important role in women's decisions to use the injectable, and in product selection, with NET-EN being recommended for younger women on the basis of concerns about method reversibility. While some women used injectables for long periods of time,

discontinuation rates at two years were high, most commonly due to menstrual disturbances. Many side effects were reported by users of both DMPA and NET-EN, with amenorrhoea the most common, experienced by 63% of current injectable users. Heavy bleeding was most commonly reported by previous users (38%). Vaginal wetness was also common, mentioned by 18% and 29% of current and previous users respectively.

Utilisation patterns of the two injectable products (DMPA and NET-EN) were analysed by means of a Pareto analysis of injectables issued from four South African provincial pharmaceutical depots over three financial years (1997/8, 1998/9 and 1999/2000). Injectables accounted for a substantial share of total state expenditure on drugs. While more DMPA than NET-EN was issued, NET-EN distribution from two depots increased over the period of analysis, even though DMPA was the cheaper option.

The pharmacokinetic analysis was undertaken amongst DMPA users routinely attending family planning services in three Durban clinics in 1996. Medroxyprogesterone acetate levels at the end of the dosing interval were analysed for 94 women. In addition a population pharmacokinetic analysis of 291serum levels from 111 DMPA users was undertaken. This involved the use of Non Linear Mixed Effect Modelling (NONMEM) to fit the data and determine the pharmacokinetic parameters, apparent clearance (CL/F) and apparent volume of distribution (V/F), and to estimate the influence of covariates on CL/F and V/F (where F is the bioavailability). The final model estimates for CL/F and V/F were 1080 (95% confidence interval: 994, 1166) litres/day and 86200 litres (95% confidence interval: 68246, 104154) respectively. No significant relationships were found between the covariates tested and CL/F and V/F. Concerns raised in the literature about

the influence of weight or ethnicity on the pharmacokinetics of DMPA were shown to be unfounded.

In the context of South Africa's HIV epidemic, the heavy reliance on injectable contraceptives, which offer no protection against HIV, should be addressed by expanding the contraceptive method mix to include barrier methods such as the female condom. Health providers are influential in contraceptive decision-making and should be encouraged and supported to redress the dependence on the injectable method alone, taking into account the need of many for dual protection against HIV and unwanted pregnancy. Provider counselling should also focus on adherence to dosing regimens, improving continuation rates, and should provide appropriate advice for women complaining about vaginal wetness with injectable use. Promotion of one injectable product over another to younger women is not appropriate. Since DMPA is the cheaper product, provider training about the rational use of injectable contraceptives should include cost considerations.

PUBLICATIONS ARISING FROM THE THESIS

Published

Smit, J., McFadyen, L., Harrison, A., Zuma, K. 2002, 'Where is the condom? Contraceptive Practice in a Rural District in South Africa', *African Journal of Reproductive Health*, 6(2),71-78.

Smit, J., Gray, A., McFadyen, L. Zuma, K. 2001 'Counting the costs: Comparing depot medroxyprogesterone acetate and norethisterone oenanthate utilisation patterns in South Africa', *BMC Health Services Research,* 1(4). http://www.biomedcentral.com/1472-6963/1/4.

Smit, J., McFadyen, L., Zuma, K., Preston-Whyte, E. 2002, 'Vaginal wetness: an underestimated problem experienced by progestogen injectable contraceptive users in South Africa', *Social Science and Medicine*, 55, 1511-1522.

Accepted

Smit, J.A., Botha, J., McFadyen, M.L., Beksinska, M., 'Medroxyprogesterone acetate serum levels in new and repeat users of depot medroxyprogesterone acetate at the end of the dosing interval', *Contraception*, accepted (4 September, 2003).

In Preparation

'Population pharmacokinetics of medroxyprogesterone acetate using non linear mixed effects modeling', to be submitted to the European Journal of Clinical Pharmacology.

Cochrane Systematic Review. Title Registered with the Cochrane Collaboration Fertility Regulation Group: 'Progestagen-only injectable contraceptive depot medroxyprogesterone acetate versus norethisterone oenanthate for contraception'.

Where is the Condom? Contraceptive Practice in a Rural District of South Africa

Jennifer Smit[2], *Lynn McFadyen*[3], *Abigail Harrison*[1,4] *and Khangelani Zuma*[5]

ABSTRACT
Interviews were conducted with 848 African women aged 15-49 years in a rural area of South Africa to determine the extent to which condoms are used, reasons for contraceptive method choice and unmet contraceptive need. Injectable contraceptives were being used by 22.1% of respondents, who considered them to be convenient, safe, effective, and/or a method that could be used secretly. The decision to use this method was often made on the recommendation of a health worker Eleven women said they were using the male condom, seven of whom were using it because it provides protection against pregnancy and sexually transmitted infections. Many (70.3%) women were not using any form of contraception. Counselling about contraceptive options should take into account the need for dual protection, and strategies for increasing condom use should be promoted. *(Afr J Reprod Health* 2002; 6(2): 71-78)

RESUME
Ou est le preservatif? lusage du contraceptif dans un district rural de I'Afrique du Sud. Nous avons eu des entretiens avec 848 femmes africaines igees de 15-49 ans dans une region rurale de I'Afrique du Sud pour determiner l'ampleur de l'usage des preservatifs, la raison pour le choix de la methode contraceptive et le besoin de contraceptif qui n'a pas ete satisfait 22,1% des repondantes utilisaient des contraceptifs injectables qu'elles consideraient comme etant convenables, saufs, efficaces et/ou comme une methode qu'on pouvait utiliser en cachette. C'etait sur la recommendation d'une assistante sociale que la decision d'employer cette methode a ete souvent prise. Onze femmes ont declare qu'elles utilisaient le preservatif pour hommes; 7 d'entre elles l'utilisaient parce qu'il sect de protection contre la grossesse et les infections sexuellement transmissibles. Beaucoup de femmes (70,3%) n'utilisaient point de contraception. It faut que les conseils sur les options contraceptives tiennent compte de la necessite pour la double protection; il faut egalement promouvoir les strategies pour l'augmentation de l'usage du preservatif *(Rev Afr Sante Reprod* 2002; 6[2]:71-78)

Key Words: *Contraception, condoms, dual protection, South Africa*

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Introduction

Use of barrier methods of contraception in South Africa is reported to be very low. The *1998* South Africa Demographic and Health Survey (SADHS)[1] found current male condom use to be 1.9% amongst all women interviewed in the age range *15* to *49* years, and *2.3%* amongst women sexually active in the four weeks prior to being interviewed. Male condom use was reported to be only 0.6% amongst all non-urban women interviewed.[1] The SADHS report did not include information about female condom use. A national introductory strategy of the female condom to some South African public sector health facilities commenced in *1998*.[2] However, the female condom is not yet available at all facilities. On the other hand, the progestagen only injectable hormonal contraceptives are widely used by South African women.[1,3-8]

According to the SADHS,[1] injectable contraceptives were currently used by *27.3%* of all women aged *15-49* years and by *30.1%* of women sexually active in the four weeks prior to being interviewed. The injectable contraceptive is particularly popular amongst younger users and women living in rural areas.[1] While studies undertaken in South Africa have examined contraceptive prevalence, contraceptive method mix, and reasons for method switching or discontinuation,[1-10] an extensive literature search revealed no published studies that describe reasons for method choice amongst South African users. With the exception of one qualitative study amongst *40* adolescents in the Northern Province of South Africa,[11] published studies that explore reasons for non-use of contraception amongst potential South African users were not found. In this one study, the main barriers to contraceptive use among adolescents were the experience or fear of side effects and harassment by clinic nurses, who regard them to be too young to be sexually active.[11]

With one in four women attending antenatal clinics found to be infected with HIV in *2000*,[12] one would expect to see a move away from injectables as the main method of contraception to the use of condoms, which provides dual protection against sexually transmitted infections (STIs) including HIV and unwanted pregnancy. HIV prevalence as high as *37.4%* was reported among *20-24* year-old pregnant women in a study undertaken in rural KwaZulu-Natal.[13] Teenage pregnancy rates are also high, with *35.1%* of teenage girls reported to have been pregnant by age *19*,[1] and the need for effective contraceptive methods remains. However, the low use of barrier contraceptive methods is disquieting and the development of an understanding of what guides decisions about contraceptive use is urgently required. Against this background, this paper describes contraceptive use patterns and the extent to which condoms are used in a rural area of KwaZulu-Natal in South Africa. Reasons for contraceptive method choice and unmet contraceptive needs are analysed. Based on this analysis, and taking into account the need for dual protection against unwanted pregnancy and HIV infection, appropriate contraceptive options are proposed and strategies for increasing condom use identified.

Methods

Setting and Sample

Contraceptive patterns of use were determined by means of a community-based cross-sectional survey undertaken in a rural sub-district comprising *13* wards (*isigodi*) in northern KwaZulu-Natal, South Africa. Commencing from a randomly selected starting point, every second household in each *isigodi* was chosen until *40%* of the estimated *2088* households in each *isigodi* had been visited. Verbal and written explanations of the study were given to each woman selected, and *848* women aged *15-49* years were interviewed. Prior to commencing the survey, workshops and meetings were held to introduce the study to local traditional leaders, community health workers and health service providers. Approval to conduct the study was granted by the Ethics Committee of the University of Durban-Westville.

Data Collection and Analysis

Data were collected by means of an extensive structured interview, which included questions on demographic characteristics, reasons for selection of contraceptive methods, problems and side effects experienced with current and previous contraceptive methods, and reasons for not using contraception. Since the focus of the study was on contraceptive use and method choice, questions about HIV/AIDS were not included. The study did not explicitly explore concurrent use of more than one method (dual method use) or consistency of condom use.

Interviews were conducted in Zulu between September and December 1998. They were conducted during the day from Monday to Friday, but where a selected woman was not at home a repeat visit was made in the evening or on Saturday. Data were coded, double entered and analysed using *Epi-Info* Version 6.43 (Centre for Disease Control, Atlanta) and the *Statistical Analysis System (SAS)* Version 6.12.

Results

Description of the Study Population

In total, 848 African women, whose home language was Zulu, were interviewed. Selected demographic characteristics of respondents are shown in Table 1. Their mean age was 26.3 years (SD 7.7) and almost two thirds had an education level of Grade 8 or above. Only 8.6% were employed (formally or informally) and 23.9% were students or scholars. Most of the women (61.6%) were in a stable relationship, but few were married (17.1%). Whilst nearly all respondents (97.2%) were resident in the area, many of their partners (67.6%) were not, and 74.1% of these migrant partners did not return home for a month or longer. In a few cases (n = 14) partners returned only once a year, usually for the Christmas holidays. Many respondents (58.8%) were first pregnant in their teens and 41.3% of those under 20 years at the time of the survey were or had been pregnant at least once.

Current Contraceptive Practice

Less than one third (29.7%) of all women (N = 848) reported use of a contraceptive method at the time of the survey.

Only 1.3% of respondents reported the male condom as their current method and none was using the female condom. As expected, the most commonly used methods were the long-acting progestagen only injectable contraceptives, depot medroxyprogesterone acetate and norethisterone oenanthate, used by 22.1% of all the women. Current use of natural family planning methods such as the calendar or rhythm method or the basal body temperature method was not reported.

Of those using a method (n = 252), 94.4% were using a modern method (injectable or oral hormonal contraceptive, male condom, intrauterine contraceptive device, tubal ligation), 3.2% a traditional method and 2.4% other methods not registered with the Medicines Control Council for contraceptive use (Table 2). In contrast to the widespread use of the injectable method (74.2% of women practising contraception), the condom was used by only 4.4% of current users. In the age range 15-24 years, 73.0% of those using a method (n = 111) were using the injectable, whilst only four women (3.6%) were using the condom (Table 3). Amongst students and scholars, 18.4% were using the injectable and only 1.0% used the condom (Table 4).

Reasons for Method Choice

In response to an open-ended question about reasons for choosing the injectable method, the most common reason given by 35.0% of respondents was that it was convenient. The method was considered to be convenient since it only has to be used every two or three months, or because one does not have to remember to take it everyday as with the oral contraceptive. Nearly one quarter of the injectable users (23.0%) chose this method because it is effective, often making statements such as its always in my blood" or "it stays in the blood a long time". The third most common reason given for using the injectable is that it was recommended by the clinic health personnel (19.7%). Some respondents (4.9%) simply stated that the method "suited them", and others expressed a dislike for oral contraceptives because of side effects experienced (4.4%). A few respondents chose the method because it could be used without their partner's knowledge (2.7%).

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a24.8% of the 848 women interviewed reported that they were sexually inactive (n = 136), pregnant (n = 39) or infertile (self of partner), menopausal, or had a hysterectomy (n = 36).

Table 1 Selected Characteristics of Respondents (N = 848)

Characteristic	Percentage
Age (years)	
≤19	21.0
20-24	27.3
25-29	22.3
≥30	29.4
Mean (SD)	26.3(7.7)
Education level grade 8 or above	*65.2*
Employment status	
Employed	8.6
Housewife/pensioner	12.7
Students/scholars	23.9
Unemployed	54.8
Average household income of SAR1000 or less per month	*92.1*
Marital status	
Married (by civil, religious, traditional or customary ceremony)	17.1
Stable relationship	61.6
Single with casual relationships	7.8
No relationship	13.6
Number of living children mean (SD)	*2.3 (1.8)*
Age after first pregnancy (years)	
Mean (SD)	*19.2 (3.1)*
Proportion first pregnant <16 years	8.0
Proportion first pregnant <20 years	58.8
Proportion <20 years who were or had been pregnant	41.3
Proportion resident in the area	97.2
Proportion with migrant partners (of those married or in a stable relationship)	67.6

Note: Figures in italics are not percentages

Similar responses were given when injectable users were prompted to respond to each of a list of 10 possible reasons for choosing the injectable method. Almost all (96.3%) the 187 injectable users indicated that they chose this method for convenience, as they only had to return to the clinic every two or three months. Others said it was effective (47.6%), it was recommended at the clinic (37.4%), few problems or side effects were experienced (27.3%), it caused amenorrhoea (23.0%), it was recommended by friends or relatives (21.5%), and it was a method that could be hidden from partners (20.9%). Although not reported in response to the open-ended question, 52.9% agreed that they chose the injectable method because they felt that it was a safe way to prevent pregnancy.

A quarter (25.8%) women were using a method other than the injectable, and the most common reason for method choice given by 43.3% in response to an open-ended question was related to injectable side effects. Although almost half of the women giving this response had used the injectable method before, only 55.6% of these previous injectable users gave this as their reason for current method choice. A few were using a method on the recommendation of their partner (n = 4), relatives or friends (n = 1), or the health provider (n= 2). Six of the women giving this response were using the oral contraceptive and one was using the withdrawal method. Of note is that seven women were using the condom and three were using thigh sex, because these methods were considered to provide protection against both pregnancy and sexually transmitted diseases. The remaining condom users indicated that they did not like the side effects of oral contraceptives or that their partner was often away and a regular method was not needed.

Table 2 *Current Contraceptive Practice (n = 252)*

Current method	Number of users	%
Modern Methods		
Injectable contraceptive	187	74.2
Oral contraceptive	38	15.1
Male condom	11	4.4
Intrauterine device (IUD)	1	0.4
Tubal ligation	1	0.4
Total	238	94.4
Traditional methods		
Thigh sex *(ukusoma)*	3	1.2
Rope	2	0.8
Snail's shell	2	0.8
Withdrawal	1	0.4
Total	8	3.2
Other methods		
Quinine	3	1.2
Essence of life	2	0.8
Flagyl	1	0.4
Total	6	2.4

Table 3 **Current Contraceptive Practice according to Age Group (n = 252)**

Age group (years)	Current users n (%)	Current method used: Injectable	Oral n (%)	Condom n (%)	Other n (%)
15-24	111 (44.0)	81(73.0)	20 (18.0)	4(3.6)	6(5.4)
25-34	114 (45.2)	87(76.3)	16 (14.0)	16(5.3)	5(4.4)
35-49*	27 (10.7)	19(70.3)	2 (7.4)	1(3.7)	5(18.5)

**Only one woman over 44 years was using a method (the injectable)*

Table 4 **Contraceptive Practice of Scholars and Students (n = 201)**

Current method	Scholars (n)	Students (N)	Total [n (%)]
No method*	139	13	152 (75.6)
Injectable contraceptive	30	7	37 (18.4)
Oral contraceptive	5	1	6(3.0)
Male condom	2	0	2(1.0)
Other methods	4	0	4(2.0)

**Of these, 56 were not sexually active and 8 were pregnant.*

Reasons for not Using a Method

Of the 848 women interviewed 70.3% were not using a contraceptive method. Reasons for not using a method are broadly grouped as follows :

1. Most women (66.8%) indicated that they did not need to practise contraception. These women reported that they had never been sexually active (11.1%), were not sexually active (11.8%), had sex infrequently (11.1%), were pregnant (6.6%), were wanting to conceive or waiting until after the birth of their first baby (11.0%), were breastfeeding (9.1%), were menopausal, had had a hysterectomy, or their husbands were infertile (6.1%). Women who had sex infrequently and those who were' breastfeeding (20.2%) believed that they did not need to practise contraception, yet they were at risk of an unplanned pregnancy. Also potentially at risk of an unplanned pregnancy were those who reported that they were menopausal or had infertile husbands, as they may not have had these conditions clinically confirmed.

2. Disapproval of contraception was given as a reason for non-use by 13.3%. Disapproval was based on partners' views, personal views or the views of others, or on religious or cultural grounds.

3. Reasons related to the method itself such as side effects, health concerns and inconvenience were given by 14.6% of the respondents, with over three quarters of reasons in this category related to side effects. Close to 90% of these women had used a contraceptive method previously, most commonly the injectable method, suggesting that many had given reasons based on experience.

4. Reasons related to the provision of contraceptive services were given by only 2.4% and included lack of knowledge about contraceptives, long distances from the health facility, and that the respondent was too shy to go to the clinic.

5. Other reasons were given by 7.3% of the women. For instance, some respondents were awaiting parental permission to use contraception while others said that they didn't have a reason.

In all, less than two thirds (61.2%) of those not using a method were not sexually active, were pregnant or wanting to get pregnant, or had had a hysterectomy. This suggests an unmet need for more appropriate contraceptive methods or services than those available amongst nearly 40% of women not practising contraception.

Discussion

The pattern of low condom use and high injectable contraceptive use reported in this study is consistent with findings from the SADHS. Given the high prevalence of HIV in rural areas of KwaZulu-Natal, the low use of condoms for contraception requires attention. Only 11 women reported the male condom as their current method and none was using the female condom. The practice of thigh sex, which may offer some degree of protection against HIV and pregnancy, is also low with only three women reporting that they use this method. Since teenage pregnancy rate is also high, the need for effective but appropriate contraceptive methods is clearly evident.

Understanding why women choose a particular contraceptive method and recognising that many women do not need or wish to use a contraceptive method and why, are essential to the provision of effective advice about HIV preventive measures. Findings from this study assist in the development of pragmatic guidelines for counselling women about appropriate contraceptive options.

Understanding Method Choice

Health workers play an important role in women's decisions to use injectable contraceptives. In this study, many injectable users indicated that they chose the method because it was recommended at the clinic. Only two women using other contraceptive methods gave this as a reason for method choice. This suggests that there are missed opportunities for counselling potential condom uses about barrier method use to minimise the dual risk of pregnancy and HIV infection. Other reasons of note for choice of the injectable were that it was a convenient and effective method that could be used secretly. The low use of condoms may be explained by their failure to meet these criteria to the extent that the injectable does. The need by some for secrecy particularly precludes the use of the condom, which requires the cooperation of the partner. Where contraceptive efficacy is the criterion for method choice, women at risk of HIV infection should be counselled to use condoms in addition to their hormonal method.

An important observation from this study is that at least 10 respondents had embraced the concept of dual protection -the simultaneous prevention of pregnancy and STIs -indicating that they were using the male condom or thigh sex because it provided protection against pregnancy and STIs. This finding is encouraging as it may indicate that educational messages aimed at dual protection against unwanted pregnancy and HIV/STIs are reaching even remote rural areas of the country, or that women are recognising the need for dual protection.

'More than one reason was given by some respondents

Understanding why Women are not Currently Practising Contraception

Over two thirds of the women interviewed were not using a contraceptive method. Many had never been sexually active or were sexually inactive at the time, and these women were not at risk of unwanted pregnancy or infection. However, nearly 40% of non-users were estimated to be at risk of an unplanned pregnancy and even more, including those who were pregnant or wanting to conceive, were at risk of contracting HIV

Many of the women had migrant partners who were absent for long periods of time and a reason put forward for not practising contraception was infrequent sexual intercourse. These women's contraceptive needs are intermittent and often unpredictable. Provided that the partner is willing the condom (male or female) would be an appropriate contraceptive option for them, particularly as a dual protection method, since several studies have shown that migrants are at greater risk of being infected with HIV and other STIs.[14]

The much promoted message "use condoms to prevent HIV" is clearly inappropriate and unhelpful for women trying to conceive. These women, who are at risk of being infected, should be counselled about risk reduction strategies such as having unprotected sexual intercourse only at the fertile period of the cycle.

The "use a condom" message, which generally refers to male condoms, is also inappropriate for women whose partners refuse to use male condoms. For these women who want to prevent pregnancy the injectable remains a rational choice. The female condom was not widely available in South Africa at the time of this survey, however, the national female condom introductory strategy launched just prior to the survey is being expanded to more public sector health facilities.[15] This will make this female controlled method more widely available. However, it should be noted that two female condom acceptability studies undertaken in South Africa have reported a mixed reaction to the acceptability of the female condom.[2,16] Behavioural interventions designed to develop negotiation and decision-making skills for women and to promote gender equality and respect by men for women's reproductive rights are urgently needed. The promotion of mutual monogamy and other low risk sexual behaviours is also important Where women attempt to negotiate condom use and fail, awareness of emergency contraception to prevent pregnancy is important.

Women who do not need contraceptive protection; for example, those who are pregnant, should be encouraged to use protective measures against HIV infection should they be at risk. Breastfeeding women may derive a level of protection against pregnancy, but this is not an effective contraceptive method and it does not provide protection against HIV/STIs. If the mother is HIV positive breastfeeding also carries the increased risk of transmission of HIV to the child. Individualised counselling on the appropriateness of breastfeeding is thus extremely important.

Since this study did not explicitly explore whether condoms were used concurrently with other methods of contraception, it is possible that the number of women practicing dual protection could have been higher.

Recommendations

Dual protection against unwanted pregnancy and HIV/STIs is an appropriate strategy for many women in the context of South Africa's HIV epidemic, and should be integrated into counselling about contraceptive options. Strategies to increase use of male and female condoms should be promoted. First, for women wishing to delay or prevent pregnancy, counselling and decision-making about appropriate contraceptive methods should take into account the dual risk of pregnancy and infection with HIV/STIs. Second, appropriate counselling about reducing the risk of HIV/STIs for women wanting to conceive or those not wishing or needing to practise contraception is also required. Third, health workers clearly play an important role in decision-making about contraception and may be happier to promote condom use over the injectable method if they are reassured about efficacy. Promoting the use of emergency contraceptive pills as a back-up for condom use may result in increased likelihood of condom promotion. Fourth, more attention should be paid to promoting female condom, which provides dual protection and is under the control of women. Microbicides, which protect against HIV/STIs and pregnancy are being developed and may in the future be an important option for women. The search for microbicides that are not spermicidal is also underway. These research efforts should be vigorously supported. Finally, effective sexuality education programmes are urgently required especially for young women who are particularly vulnerable to unplanned pregnancies and HIV/STIs.

Acknowledgements

This research was supported by a grant from the Wellcome Trust (Grant Number **050543/Z/97/C**). We are grateful for the assistance of our fieldworkers and data capturers and to the women who willingly participated in the study.

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Research article

Counting the costs: Comparing depot medroxyprogesterone acetate and norethisterone oenanthate utilisation patterns in South Africa

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Published: 4 June 2001

BMC Health Services Research 2001, 1:4

Received: 16 March 2001
Accepted: 4 June 2001

This article is available from: http://www.biomedcentral.com/1472-6963/1/4

Abstract

Background: In South Africa, where health care resources are limited, it is important to ensure that drugs provision and use is rational. The Essential Drug List includes depot medroxyprogesterone acetate (DMPA) and norethisterone oenanthate (NET-EN) as injectable progestagen-only contraceptives (IPCs), and both products are extensively used.

Objectives and Methods: Utilisation patterns of the injectable contraceptive products DMPA and NET-EN are compared in the context of current knowledge of the safety and efficacy of these agents. Utilisation patterns were analysed by means of a Pareto (ABC) analysis of IPCs issued from 4 South African provincial pharmaceutical depots over 3 financial years. A case study from rural KwaZulu-Natal, South Africa, is used to examine utilisation patterns and self-reported side effects experienced by 187 women using IPCs.

Results: IPCs accounted for a substantial share of total state expenditure on drugs. While more DMPA than NET-EN was issued, NET-EN distribution from 2 depots increased over the 3-year period. Since DMPA was cheaper, if all NET-EN clients in the 1999/2000 financial year (annualised) had used DMPA, the 4 depots could have saved 4.95 million South African Rands on product acquisition costs alone. The KZN case study showed slightly more NET-EN (54%) than DMPA (46%) use; no significant differences in self-reported side effects; and that younger women were more likely to use NET-EN than DMPA ($p = 0.0001$).

Conclusions: Providing IPCs on the basis of age is not appropriate or cost effective. Rational use of these products should include consideration of the cost of prescribing one over another.

Introduction

Affordability of drugs by developing countries is currently a topic of heated debate. In South Africa, where financial resources for health care are limited, and where

health care costs are expected to soar as the HIV epidemic escalates, it becomes increasingly important to ensure that all drugs are rationally provided and used. The injectable progestagen-only contraceptives (IPCs) depot medroxyprogesterone acetate (DMPA) and norethisterone oenanthate (NET-EN) are by far the most widely utilised contraceptives in South Africa, especially amongst younger users and women living in rural areas [1]. Both drugs are on the South African Essential Drug List [2] and are available free of charge at public sector primary health care facilities. Although not extensively documented, it is claimed that there has been a shift away from the predominant use of DMPA, which is given every 12 weeks, to NET-EN, given every 8 weeks, especially amongst younger, nulliparous women [3, 4]. Combined injectable contraceptives (CICs), which contain a combination of oestrogen and progestagen, are not registered for use in South Africa.

The World Health Organisation's general criteria - safety, affordability, necessity and efficacy - for inclusion on the Model List of Essential Drugs (EDL) [5] provide a useful basis upon which to make decisions about drug selection and rational use. Taking into account published findings on efficacy, reversibility, side effects and safety, this paper analyses IPC supply patterns and costs from four pharmaceutical depots, and describes a case study of IPC utilisation patterns and side effects in a rural subdistrict of KwaZulu-Natal, South Africa. Based on these analyses, appropriate recommendations for the rational use of IPCs are made.

What the literature tells us

Published clinical trials and reviews on efficacy, side effects, reversibility and safety of DMPA and NET-EN were sought by means of computerized and hand searches. Copies of relevant publications and citations from these publications were obtained and reviewed. Relevant international and South African policy documents were also reviewed. This extensive search revealed that: DMPA is better researched than NET-EN, few studies directly compare DMPA and NET-EN, few clinical trials have been undertaken in Southern Africa, few clinical studies have been undertaken amongst young users, and most published studies, upon which review after review are based, were undertaken in the 1970s and early 1980s. Methodological differences in subject recruitment, exclusion criteria, frequency and nature of procedures for follow-up, types of observations made, method of recording, methods of analysis and large intersite variability in some studies, make it difficult to evaluate the published data. Trussel et al. provide a useful account of difficulties in analysing and comparing contraceptive efficacy trials [6]. Nevertheless, to the extent that this is possible, a comparative synopsis of the efficacy, side effects, delay in return to fertility and safety of DMPA and NET-EN is provided in this section. It is not the purpose of this paper to provide a detailed review, but merely to highlight relevant findings. The authors can be contacted for a more extensive bibliography.

Both IPCs are demonstrably highly effective. There are minor differences in published efficacy rates of both drugs depending on the study, timing of the first injection, the population, body weight, dosage regimen and provider training. An illustration of the high efficacy of these two products is provided by a World Health Organisation (WHO) comparative trial [7]. According to this study the efficacy of DMPA given every 90 days and NET-EN given every 60 days are comparable, with a cumulative 2-year pregnancy rate of 0.4 per 100 woman-years. In an evaluation of 5 large controlled multicentre studies, Kaunitz [8] reported that there were only 24 pregnancies among 7 849 women using DMPA for 122 496 patient-months. Trussel et al. [6] provide "summary estimates of contraceptive failure" and give the lowest expected, and typical percentage, of accidental pregnancies in the United States, during the first year of use, as 0.3 for DMPA and 0.4 for NET-EN (unspecified dose interval).

There is little direct comparative data on the reversibility of DMPA and NET-EN. While return to fertility is reported by some reviewers to be more rapid with NET-EN [9, 10], more recently, Bigrigg et al. [11] in examining early data, suggest that there is no delay in return to fertility with DMPA use, if one considers the methodological bias of early studies, which did not take in to account the date of the last DMPA injection. They state further that "if there is a delay it is not statistically significant and is less than 30 days". Kaunitz gives the shortest reported time before fertility is returned with DMPA, as 4 months after the last injection i.e. 4 weeks after the due date of the next injection [8] and, according to Hatcher et al. return to fertility is delayed by DMPA for about 4 months longer on average, compared with the combined oral contraceptive method, intrauterine contraceptive device, and condoms [12].

The poor side effect profile of progestagen-only injectables is extensively documented. The most frequently reported side effects, and those most likely to result in discontinuation, are menstrual disturbances such as amenorrhoea, irregular bleeding and heavy bleeding [3, 13]. Menstrual irregularities are reported to occur more often with DMPA than with NET-EN use. For instance, the WHO clinical trial undertaken in 1983 compared menstrual disturbances resulting from DMPA given at 90-day intervals, with NET-EN given every 60 days and with NET-EN given every 60 days for 6 months and then

every 84 days [7]. Significantly less amenorrhoea was reported by NET-EN users (on both dosage regimens), than by DMPA users. Amenorrhoea was also found to result in significantly higher discontinuation rates with DMPA users than with NET-EN. During the first six months of use, both dosage regimens of NET-EN were reported to result in more defined cyclic patterns and fewer prolonged bleeding and spotting episodes than DMPA, but similar discontinuation rates were found with the two products. However, in a study undertaken in Egypt, despite the more frequent occurrence of menstrual irregularities with DMPA, better one-year continuation rates were found with DMPA than with NET-EN [14]. Weight gain is also a commonly reported side effect and in comparing DMPA and NET-EN, the findings on weight gain appear to be similar. A multinational WHO comparative clinical trial found no statistical difference in weight gain between NET-EN and DMPA (both administered at 12 week intervals) after a year of use - the weight gain with NET-EN was reported as 1.5 kg and with DMPA was 2.0 kg [15]. Headache was the most common non-menstrual side effect reported in this comparative trial and was more frequently reported by DMPA users than NET-EN users, however, it is important to note that in this study, NET-EN was administered every 12 weeks.

IPCs are considered to be relatively safe contraceptive methods [16, 17] and recent studies indicate that there is little reason to be concerned about either DMPA or NET-EN causing an increased risk of breast cancer [18]. However, the possible effect of DMPA on bone density, particularly in adolescents and long-term users is cause for concern [19]. Little is published on the possible effect of NET-EN on bone density. Findings from prospective studies in progress are awaited.

The World Health Organization's *Medical Eligibility Criteria for Contraceptive Use* classifies DMPA and NET-EN together, and makes no differentiation between the two in regard to their side effects or contraindications [20]. The only restriction this document makes about age, for IPC use, is that "For women under 16 years of age, there are theoretical concerns regarding hypo-oestrogenic effects...." p.54. The WHO states further that there is no need to restrict use of progestagen-only contraceptive methods for nulliparous women. The Primary Health Care Essential Drugs List for South Africa provides no guidelines with respect to the circumstances under which DMPA rather than NET-EN should be prescribed (or vice versa) [2].

Methods

Supply patterns and costs

Consumption figures of IPC stock issued from provincial pharmaceutical depots were requested from the Deputy Director, Procurement of the South African National Department of Health. Data for DMPA and NET-EN were made available for the KwaZulu-Natal (KZN), Guateng and Free State Provincial Pharmaceutical depots and for the Port Elizabeth depot, which serves the western part of the Eastern Cape Province. These four provinces (of nine South African provinces) represent over 50% of the total South African population. Gauteng has a mostly urban population and KZN and Eastern Cape are more rural. The following data were analysed for financial years 1997/8, 1998/9, and for 1/04/99 to 7/12/99 of the 1999/2000 financial year:

• Position number on Pareto (ABC) analyses for DMPA and NET-EN. An ABC analysis is a method which ranks drugs according to their annual usage (unit cost times annual consumption). Class A items are the 10 to 20 % which account for 75 to 80% of the funds spent. Class B items have an intermediate contribution to total expenditure, whereas Class C items (the majority of items) account for a small percentage of funds spent. ABC analyses are used to identify priority cost drivers for intervention [21].

• Number of units of each item issued in the same time period per depot.

• Total cost of each item per time period per depot (at constant 1999 prices).

• Current and previous tender prices for DMPA and NET-EN. Note exchange rate: 1 British Pound ≈ 11 South African Rands.

Case study: use patterns and side effects

Prevalence of IPC use was determined by means of a community-based cross-sectional survey undertaken in a rural sub-district in northern KZN, South Africa. Commencing from a randomly selected starting point, every second household was chosen until 40% of households in the sub-district had been visited. In this way, 849 households of an estimated 2088 were selected and, one woman from each household, in the age range 15 to 49, was randomly selected for interview. Verbal and written explanations of the study were provided to each woman selected (in Zulu and/or English) and consent to participate in the study was requested. In all, 848 women were interviewed and no-one refused to participate. Prior to commencing the survey, workshops and meetings were held to introduce the study to local traditional leaders, community health workers, and health service pro-

viders. Ethical clearance for the study was provided by the Ethics Committee of the University of Durban-Westville.

Each woman selected was asked if she was currently using an IPC and those who were, were asked whether they were using DMPA or NET-EN. Data were collected by means of an extensive structured interview, including questions on demographic characteristics, reasons for method selection, and problems and side effects experienced. Interviews were conducted in Zulu, between September and December 1998. They were conducted during the day from Mondays to Fridays, but where a selected woman was not home, a revisit was made in the evening or on a Saturday. Data were coded, double entered and analysed using Epi-Info Version 6.43 and the SAS Version 6.12.

Table 1: Acquisition costs of injectable contraceptive products: 1997/8, 1998/9, 1999/2000

Product	Cost per vial (SAR*)		
	1997/8	1998/9	1999/2000
DMPA			
Innovator product (Pharmacia Upjohn)	2.17	4.56	4.78
Generic product (Aspen Pharmacare)	– #	2.07	4.29
NET-EN			
Innovator product (Schering)	4.10	4.28	4.78

*Exchange rate: 1 British Pound ≈ 11 South African Rands (SAR) # Tender not awarded

Table 2: Pareto analysis of injectable contraceptive products: 1997/8, 1998/9, 1999/2000

Pharmaceutical Depot	Rank		
	1997/8	1998/9	1999/2000
GAUTENG			
DMPA	3	4	4
NET-EN	2	3	2
KWAZULU-NATAL			
DMPA	4	6	4
NET-EN	19	19	19
FREE SATE			
DMPA	2	3	5
NET-EN	5	5	6
PORT ELIZABETH			
DMPA	3	6	3
NET-EN	4	4	4

Results

Supply patterns and costs

Cost of injectable contraceptive products

DMPA products issued at primary health care outlets in the three financial years analysed were obtained from the original patent holder (Pharmacia-Upjohn) and a generic manufacturer (Aspen Pharmacare). NET-EN was available only from the innovator (Schering). Table 1 shows that the acquisition cost of a vial of both DMPA and NET-EN products increased every year, and that the cost of both DMPA products rose particularly steeply. In the 1999/2000 financial year, the generic product, was almost the same price as the innovator product. Their costs were exactly the same in the 1999/2000 fiscal year.

Since DMPA is given less frequently than NET-EN, cost per couple years of protection (CYP) provides a more accurate cost comparison of DMPA and NET-EN. Based on the 1999/2000 state tender prices for the DMPA and NET-EN innovator products, the cost per couple year was SAR28.68 for NET-EN (6 vials per year) and SAR19.12 for DMPA (4 vials per year). If the calculation were based on the DMPA generic product price, use of DMPA would be even cheaper (SAR17.16). It should be noted that the cost of syringes, needles and swabs, personnel costs and client transport and time were not included in the calculations. These costs can be considerable and are obviously higher for NET-EN because it is administered more frequently.

Analysis of annual expenditure on DMPA and NET-EN

In all 4 depots, both IPCs consumed an important share of total drug expenditure (table 2). A Pareto analysis shows that both DMPA and NET-EN appeared in the top 10 in each year (based on actual volumes multiplied by constant 1999 prices), with the exception of NET-EN in KZN where it was 19^{th} in 1997/8, 1998/9 and 1999/2000. More was spent on NET-EN than DMPA in Gauteng in all 3 years, but less in the other 3 depots. Only in 1998/9 in the Port Elizabeth area was more spent on NET-EN than DMPA. Total annualised expenditure on both products in the 4 depots in 1999/2000 was projected to be SAR28.77 million.

Ratio of NET-EN:DMPA issued

The ratios of NET-EN:DMPA issued from the 4 depots were calculated based on CYP rather than on number of vials issued. As shown in Figure 1, DMPA was increasingly used in Port Elizabeth where the ratio of NET-EN:DMPA decreased from 0.64 in 1997/8 to 0.57 in 1999/2000. In Free State the market share was more or less stable (0.42, 0.44, 0.40). A similar picture emerged in KZN (0.22, 0.23, 0.25), with some increase in NET-EN use. However, in Gauteng, while DMPA was still used most, NET-EN use was clearly increasing (0.67, 0.73, 0.81).

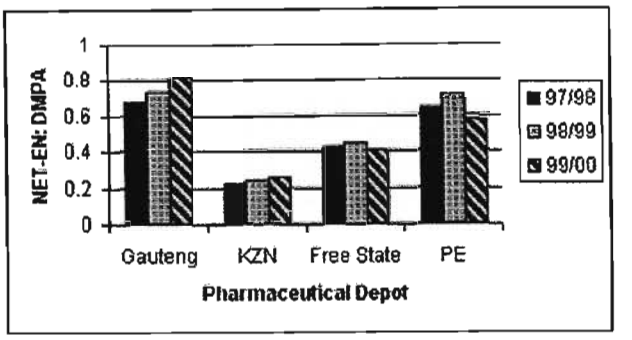

Figure 1
Ratio of NET-EN:DMPA issued from the four pharmaceutical depots in 1997/8, 1998/9, 1999/2000

Counting the cost of injectable contraceptive product choice

If all NET-EN clients in the 1999/2000 financial year (annualised) had been given DMPA instead, the 4 depots together might have saved SAR4.95 million. Conversely, if NET-EN had been issued to all DMPA clients, then the estimated additional cost in the same year for the 4 depots would have been SAR9.35 million. Savings and additional costs would be increased if other costs (surgical supplies, personnel costs, client transport etc.) were included. The savings are calculated on the annualised total CYP for innovator versions of both DMPA and NET-EN. If the price of the cheaper generic preparation of DMPA had been used in the calculation, the savings would have been greater.

To illustrate the potential savings or additional costs further, in KZN, a 9.0% saving on the expected 1999/2000 annual IPC drug bill might have been effected if only DMPA had been supplied. On the other hand, if only NET-EN had been available, the additional load would have been 36.5%. In Gauteng, the savings or additional costs could have been 18.3% and 22.6% respectively.

Case study: use patterns and side effects

Injectable contraceptive prevalence and cost

All respondents (848) were African, Zulu-speaking women in the age range 15-49 years. Of these, 187 (22.1%) were using an injectable contraceptive method, either the innovator product of DMPA or NET-EN. Forty-six per cent (86) of the IPC users were using DMPA and 54% (101) were using NET-EN. The mean age of DMPA users was 29.6 years (median 29, range 18-49) and that of NET-EN users was 23.2 (median 23; range 17-37). Younger women were thus more likely to use NET-EN than DMPA ($p = 0.0001$). The age distribution of DMPA and NET-EN users is shown in Figure 2. The mean length of use was 2.2 years (range 0.1 to 11).

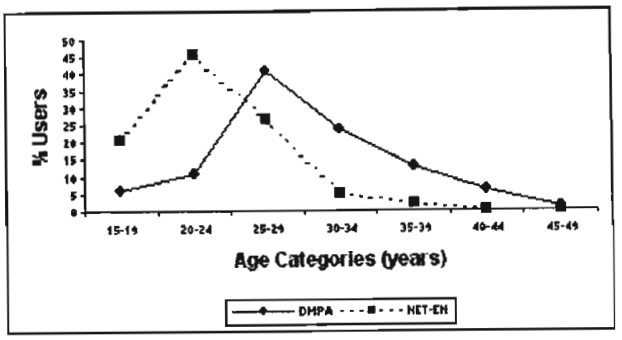

Figure 2
Age distribution of DMPA and NET-EN users

The ratio of NET-EN:DMPA users in this rural sub-district was 1.2 to 1. Based on 1999/2000 product costs, by supplying only DMPA, a saving of 21.3% on the annual drug bill for IPCs could have been achieved by the local health facility. On the other hand, if only NET-EN had been supplied, the annual IPC cost would have increased by 18.1%. These figures are based on product costs alone.

Reasons for product choice

Current users were asked, by means of an open-ended question, why they preferred the injectable product they were using, and the following findings are of note:

- Many DMPA users (42.4%) indicated that they preferred this product because it was "stronger". On the other hand, NET-EN was favoured by 36.0% of those using it as it was regarded as "weaker" or "lighter".

- Concern about delayed return to fertility with DMPA was expressed by 5.0% of NET-EN users and 14.0% indicated that they chose NET-EN because it did not delay return to fertility.

- The idea that the NET-EN is for younger women or teenagers and DMPA for older women was expressed by 14.6% of the IPC users. This preference is clearly reflected in the age distribution of DMPA & NET-EN users depicted in Figure 2.

- Recommendation by health worker was given as one of the most common reasons for product choice (21.1%).

- Relatively few women (6.5%) mentioned that concern about side effects influenced choice of either product.

Side effects with injectable contraceptives

IPC users were asked to indicate what side effects, if any, they were experiencing with DMPA or NET-EN by responding to a list of 22 possible side effects. Consistent with the international literature, many women reported menstrual irregularities such as amenorrhoea, spotting, heavy periods or irregular periods (table 3). Other side effects commonly reported were vaginal wetness and weight gain. The side effect profile for DMPA or NET-EN users was similar with no significant differences found between users of the two products in terms of their experience of side effects.

Discussion

In highlighting key issues in financing family planning services in Sub-Saharan Africa, Janowitz et al. make the following statement "Given limited resources, the universal provision of methods based on demand and without regard to cost will restrict the number of individuals whose need for family planning services can be met" p. 64 [22]. The balancing of needs and resources becomes even more challenging when attempting to meet reproductive health needs more broadly. For instance, in developing countries like South Africa many drugs, such as antiretrovirals for the management of HIV, are not available through the public sector. Careful analysis of current expenditure on drugs is thus required so that resources are allocated to meet changing therapeutic needs.

Findings presented in this paper show that IPCs account for a substantial share of the total state expenditure on drugs in South Africa. Of the two IPCs available on the EDL, DMPA is a cheaper option than NET-EN, even if only considering acquisition costs. Analysis of supply patterns from the 4 pharmaceutical depots shows that if all NET-EN clients had been given DMPA, between 9.0% and 18.3% of the expected annual drug bill for IPCs could have been saved per depot. Rational use of drugs cannot however be based on cost alone and clinical criteria, such as efficacy, safety, and acceptability of side effects, must also be considered. The context within which contraception is provided should also be taken into account. An extensive review of the literature on IPCs shows little difference between NET-EN and DMPA in terms of efficacy, safety, reversibility and side effect profile. However, a systematic comparative review has not been published and little clinical data on African women are available. NET-EN appears to have a slightly better side effect profile and a slightly shorter delay in return to fertility. DMPA is marginally more effective and is more convenient as users only have to return to the clinic every 12 weeks rather than after 8 weeks, as is the case for NET-EN users. As noted earlier, no differentiation in regard to side effects or contraindications of the two products is made by the WHO in terms of its medical eligibility criteria for contraceptive use [20].

Findings from the KZN case study show that slightly more NET-EN was used than DMPA. No significant dif-

ferences were found in self-reported experience of side effects. What does emerge clearly is that NET-EN is viewed as the product of choice for young women and DMPA for older women. This is reflected in reasons given for product preference by clients, and in the age distribution of DMPA and NET-EN users. Further, health workers appear to play an important role in decision-making about which IPC product is provided. That different products are considered to be more appropriate for different age groups may be linked to the perception that DMPA is "stronger" while NET-EN is "weaker", and may well be related to concerns about delay in return to fertility after IPC use, particularly with DMPA. This is consistent with results from a study undertaken in the Northern Province of South Africa where providers were found to recommend NET-EN for younger women based on their perception that DMPA use may result in permanent infertility, whilst NET-EN was considered ".... less strong and 'usually reversible' " p. 13 [4].

Age as a criterion for prescribing one or other IPC product is not supported by the literature, and some policy documents and publications specifically debunk the notion that IPCs should be restricted according to age. For instance, Lande recommends that:

"Providers may need to reassure clients and the public that injectables do not cause infertility but to note that women should expect a wait of some months after stopping injectables to become pregnant. Service policies based on a fear of infertility - in particular, age and parity restrictions - can be dropped p.7 [23].

Table 3: Side effects most frequently reported by DMPA and NET-EN users

Side Effect	DMPA (%) (n = 84)	NET-EN (%) (n = 95)	P Value*
Menstrual irregularities			
Amenorrhoea #	67.5	58.9	0.240
Spotting	9.5	12.6	0.510
Heavy periods	8.3	7.4	0.792
Irregular periods	3.6	10.5	0.074
Longer periods	2.4	4.2	0.497
Dysmenorrhoea	1.2	1.1	0.930
Vaginal wetness	22.6	14.7	0.175
Weight gain	14.3	8.4	0.214
Loss of libido	10.7	8.4	0.601
Dizziness	10.7	6.3	0.289
Headache	10.7	4.2	0.094
Nausea	9.5	3.2	0.077
Vaginal discharge	8.3	3.2	0.132
Vaginal discharge with odour	7.1	3.2	0.223

Includes thirty breastfeeding women. Although amenorrhoea was reported as a side effect of IPC use, it could have been lactational amenorrhoea
* Chi-square (1 degree of freedom, significance tested at the 5% level)

The second draft of the South African Department of Health's Draft *National Framework & Guidelines for Contraceptive Services* explicitly states that:

"Young clients should not be prevented from using either DMPA or NET-EN because of their age." p.64 [24].

If one were to embrace the WHO promoted Essential Drugs concept [5] the decision about which IPC to supply should be made on cost since DMPA and NET-EN have comparable efficacy and safety profiles. Based on the cost analysis presented in this paper, DMPA should be the product selected. However, reducing contraceptive options flies in the face of progressive reproductive health policies which promote expansion of contraceptive choice. For instance, the WHO "is giving priority to improving access to high-quality care in family planning through a variety of strategies" p.2, and lists one of these strategies as "promoting the widest availability of different contraceptive methods so that people may select what is most appropriate to their needs and circumstances" p.2 [20]. The Programme of Action adopted at the International Conference on Population and Development held in Cairo in 1994 recommended that family planning programmes should "Recognize that appropriate methods for couples and individuals vary according to their age, parity, family-size preference and other factors, and ensure that women and men have information and access to the widest possible range of safe and effective family-planning methods in order to enable them to exercise free and informed choice" p.39/132 [25]. The Population Council's new approach to contraceptive introduction in developing countries involves an assessment of the context of contraceptive use in that country, on the basis of which "recommendations for upgrading contraceptive services - which could include introducing new methods, improving the utilisation of existing ones, and/or removing one or more from the method mix". p.1 [26].

The injectable contraceptive method is an important option in South Africa, since many women choose this method because its use does not require partner knowledge or consent [27]. The review of the literature shows that menstrual irregularities are reported to occur more often with DMPA than with NET-EN use. In cases where side effects such as amenorrhoea are particularly problematic with DMPA, NET-EN may be a good alternative. By providing NET-EN explicitly as a second-line option, the range of contraceptive products would be restricted, but not reduced.

Conclusions and Recommendations

Providing IPCs on the basis of age is not appropriate or cost effective. Training of health workers and counselling of clients to correct this misconception is clearly required. Where clients require immediate return to fertility upon discontinuing contraception, neither IPC preparation is ideal. Since DMPA is a cheaper option than NET-EN, health worker training about the rational use of injectable contraceptives should include consideration of the cost implications of prescribing one product over another. DMPA should be considered as the first option, but where DMPA is not well tolerated, NET-EN should be available as a second option. It is also recommended that a comparative systematic review of DMPA and NET-EN be undertaken. Based on the outcome of this review, consideration may be given to conducting a comparative clinical trial of NET-EN and DMPA when used by African women.

Consideration should be given to encouraging the registration of the combined injectable contraceptive in South Africa, which has a better side effect profile than the IPCs [28]. This would be an expensive option thus combined injectable contraceptives should only be provided where side effects with the IPCs are intolerable. A better contraceptive option, especially for young people, might however be the male or female condom with back up of emergency contraceptive pills to provide dual protection against unwanted pregnancy and HIV and other sexually transmitted infections.

List of Abbreviations

CYP couple years of protection

DMPA depot medroxyprogesterone acetate

EDL essential drugs list

KZN KwaZulu-Natal

IPCs injectable progestagen-only contraceptives

NET-EN norethisterone oenanthate

SAR South African Rand

WHO World Health Organisation

Acknowledgements

This study was supported by the Wellcome Trust (Grant Number 050522/Z/97/Z). We thank Mr J van den Berg (Deputy Director: Procurement, National Department of Health) and Mr A Odendaal (Systems Manager, Coordinating Committee for Medical Procurement) for providing access to the data from the pharmaceutical depots and for the initial Pareto analysis.

Competing Interests

Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this paper?

A travel grant was awarded to the main author of this paper in March 1997 by the manufacturer of the generic depot medroxyprogesterone acetate product - one of the drugs mentioned in this manuscript.

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper? No.

Do you have any other financial competing interests? No.

Are there any non-financial competing interests you would like to declare in relation to this paper? No.

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Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/content/backmatter/1472-6963-1-4-b1.pdf

PERGAMON

Social Science & Medicine 55 (2002) 1511–1522

SOCIAL SCIENCE & MEDICINE

www.elsevier.com/locate/socscimed

Vaginal wetness: an underestimated problem experienced by progestogen injectable contraceptive users in South Africa

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Abstract

This paper reports on the common experience of vaginal wetness amongst South African users of progestogen-only injectable contraceptives. The observations emerged in the course of a community-based cross-sectional household survey undertaken in a rural district of KwaZulu-Natal in South Africa. The purpose of the survey was to elicit self-reporting on side effects of injectable contraceptive methods. Eight hundred and forty-eight women aged 15–49 were interviewed and 22.1% reported current use of an injectable contraceptive method, either depot medroxyprogesterone acetate (Depo-Provera®) or norethisterone oenanthate (Nur-Isterate®). Other modern methods used were oral hormonal contraceptives (4.5%), male condoms (1.3%), the intrauterine device (0.1%), and tubal ligation (0.1%). Vaginal wetness was reported by 18.4% of users and was one of the most common side effects, second only to amenorrhoea (62.5%). It was also what 17.5% of the women liked least about using this method. According to almost half the respondents, men regard women who use the injectable contraceptive as "wet", "cold" and/or "tasteless". These survey findings were supported by participants of 14 focus group interviews held in the sub-district. Since some South African men may prefer dry sex the perception that the injectable contraceptive increases vaginal wetness may be problematic for women who use it. Whilst vaginal wetness can only be classified as a subjective side effect at this stage, further investigations are needed as many South African women opt to use this method.

Keywords: Progestogen injectable contraceptives; Side effects; Vaginal wetness; South Africa

Introduction

Women who use injectable contraceptives struggle with the many side effects associated with their use. Yet, despite these side effects, long acting progestogen injectable contraceptives are by far the most popular method of contraception in South Africa, and have been for many years (Smit & Venter, 1993; Chimere-Dan, 1996; Beksinska, Rees, Nkonyane, & McIntyre, 1998). Depot medroxyprogesterone acetate was first introduced in South Africa in the late 1960s (Kaufman, 1997), and in the early 1990s accounted for between 66% and 80% of contraceptive use (Reproductive Health Task Force, 1994). In rural areas of South Africa injectables have become almost exclusively the method of choice of both user and provider. The two injectable contraceptives available in South Africa are progestogen-only preparations, depot medroxyprogesterone acetate (Depo-Provera® and Petogen®) and norethisterone oenanthate (Nur-Isterate®). The combined injectable contraceptive, containing a combination of oestrogen and progestogen

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[1] Supported by the Wellcome Trust.

0277-9536/02/$ - see front matter
PII: S0277-9536(01)00284-2

is not yet available in South Africa and all reference to injectable contraceptives in this paper is confined to progestogen-only products.

Side effects reported by South African women are, on the whole, consistent with those reported elsewhere in the world (Fraser & Weisberg, 1981; Paul, Skegg, & Williams, 1997), with amenorrhoea and other menstrual disturbances the most common (Beksinska et al., 1998). In addition, however, women refer frequently to the side effect described or translated from the vernacular as "vaginal wetness", and no reports of this side effect can be found in the published medical literature. However, four published references have been found which report vaginal discharge as a side effect. One quotes vaginal discharge as a rare symptom of depot medroxyprogesterone acetate (Tyler, 1970). Another reports vaginal discharge as a temporary, short-lived complaint, associated with the use of depot medroxyprogesterone acetate (Zartman, 1967), while the third refers to it as a major side effect (Schwallie, 1976). El-Mahgoub and Karim (1972) report vaginal discharge as a minor side effect of norethisterone oenanthate. Vaginal discharge was also reported as a side effect among injectable contraceptive users at a family planning clinic in KwaZulu-Natal, South Africa (Smit, Goga, & Khan, 1989a; Smit, Mahabeer, & Naranbhai, 1989b). The product brochure of Petogen®, the locally manufactured depot medroxyprogesterone acetate (DMPA) product, lists vaginal discharge under "other side effects" (Intramed, 1993). No such side effect is listed in the product brochures of Nur-Isterate® and Depo-Provera® (Schering (Pty.) Ltd., 1992; Pharmacia and Upjohn (Pty.) Ltd., 1993). It is not clear whether the early reports of vaginal discharge, and the vaginal wetness reported in the present study, are analogous. Whether either of these effects is in reality a consequence of injectable contraceptive use is also unclear, and if so the mechanisms by which they occur are not understood.

This paper reports on a study undertaken in a rural community of KwaZulu-Natal. The purpose of the study was to establish the prevalence of long acting injectable hormonal contraceptive use, to elicit self-reporting of associated side effects from injectable users, and to obtain the views of users, non-users and community groups about side effects and problems experienced with injectable contraceptive use. It was in respect to the reported side effects that interesting insights surfaced with regard to notions of "wetness" and perceptions of the link between injectable hormonal contraceptives and vaginal wetness. Since studies have shown that men and women in many parts of Central and Southern Africa have a preference for dry sex (Brown, Ayowa, & Brown, 1993a; Brown, Brown, & Ayowa, 1993b; Civic & Wilson, 1996; Morar & Abdool Karim, 1998; Beksinska, Rees, Kleinschmidt, & McIntyre, 1999; Brown & Brown, 2000), the perception that the injectable contraceptive increases vaginal wetness may be problematic for South African women who choose to use it. This paper documents reports of, and perceptions about "vaginal wetness" with the injectable contraceptive method.

Subjects and methods

Study design

Both quantitative and qualitative data were collected by means of a cross-sectional, community-based household survey and also from focus group interviews with community groups.

Research site

The study was undertaken in a rural sub-district in the province of KwaZulu-Natal, South Africa. The population in this sub-district is estimated at about 20 000. Contraceptive methods are provided by the only health facility in the area, a district hospital which houses a family planning clinic. Prior to commencing the survey, workshops and meetings were held to introduce the study to local leaders, community health workers, and health service providers. Ethical clearance for the study was provided by the Ethics Committee of the University of Durban-Westville.

Sampling

In order to test for significant differences in the prevalence of side effects between users of depot medroxyprogesterone acetate and norethisterone oenanthate, it was determined that at least 40% of the estimated 2088 households should be visited. The sub-district comprises 13 local areas, known as *isigodi*. Commencing from a randomly selected starting point, every second household in each *isigodi* was chosen until 40% of households in each *isigodi* had been visited. Among women in the age range 15–49 years, one woman was randomly selected to be interviewed from each household visited. Verbal and written explanations were given (in Zulu and/or English) and no one refused to participate. In all, 848 women were interviewed.

Community groups active in the study area were identified by key informants living in the area. Focus groups interviews (thematic guided discussions) were held with 14 groups identified in this way, to draw out contextual information and to provide insight, depth and perspective to the quantitative cross-sectional data. It is important to note that both women and men were focus group participants. Six groups were comprised of women only, two of men only, and six of women and

men. The composition of the groups is provided in Table 1.

Data collection

An extensive structured interview schedule was administered during home visits. The interview schedule was designed in consultation with health providers, other researchers and interviewers. A thorough review of instruments used in studies with similar methodologies, including the 1998 South African Demographic and Health Survey instrument (Department of Health of South Africa, 1999) was also undertaken. Included in the interview schedule were questions on household demographic characteristics; respondents' contraceptive history; user experiences such as reasons for selection of the injectable contraceptive, and problems and side effects experienced with this method; knowledge, perceptions and opinions about injectable contraceptives; relevant medical history; and plans about future contraceptive use.

After much consultation, the approach of partial translation of key phrases was adopted to ensure that nuances of meanings were not lost in the translation process. An extensive participative workshop was held to identify key phrases for translation. Senior researchers, the fieldwork manager and fieldworkers were involved in this process. Key phrases identified for translation were printed on the interview schedule in English and Zulu. For instance, the English and Zulu translation of all side effects listed, including increased vaginal wetness and vaginal discharge, appeared one below the other in all cases. The instrument was subjected to face validation (Katzenellenbogen, Joubert, & AbdoolKarim, 1997) by a group of Pharmacology master's students, and a skilled English/Zulu translator, and was piloted in a neighbouring sub-district.

Since almost all the respondents were expected to be Zulu speakers, interviewers whose first language was Zulu, but who were also fluent in English, were employed. They were all women, recruited from the study site, and were integrally involved in the development and translation of the interview schedule. Interviewers were intensively trained to standardize verbal translation of the complete instrument during interviewing. All the interviews were conducted in Zulu and the quality of interviewing was assessed on a daily basis. The interviews took place between September and December 1998 and were largely conducted during the day from Monday to Friday, but where a selected woman was not home, a revisit was made in the evening or on Saturday.

A semi-structured aide memoire was designed for the focus group interviews. Six themes, identified from responses to the individual household interviews, were included for discussion. The experience of vaginal wetness was included in the schedule as the fourth theme. The other five themes were: general views and opinions on contraception; general views about injectable contraceptive use; side effects associated with injectable contraceptives; the use of the injectable contraceptive in the context of high HIV prevalence; and the views of community leaders and elders on the use of contraceptives. The focus groups were held from February to April 1999 and were facilitated by a moderator and a recorder. The interviewers from the survey were trained to facilitate the group discussions and the fieldwork manager, a man, was the moderator for the groups which included men. Discussions were conducted in Zulu, tape recorded, transcribed and translated into English. Some basic demographic

Table 1
Composition of focus groups

Type of group	Number of women (age range in years)	Number of men (age range in years)
Sewing group	6 (34–59)	—
Gardening group	5 (26–35)	—
Community health workers	5 (34–47)	—
Nurses attached to the district hospital	8 (25–55)	—
Traditional healers	6 (35–60)	4 (48–74)
Church ministers	2 (47–48)	4 (37–75)
Taxi drivers	—	8 (24–48)
High school teachers	5 (23–37)	3 (26–28)
Primary school teachers	4 (23–33)	3 (26–33)
Parents	7 (30–60)	—
Members of a school governing board	3 (44–59)	3 (29–57)
Grade 12 secondary school girls	8 (17–24)	—
Grade 11 and 12 secondary school boys	—	8 (18–23)
Grade 11 and 12 secondary school girls and boys	4 (17–18)	4 (21–24)
Number of women aged 15–49 (reproductive age)	50	—
Total	63	37

information was collected from each participant of each focus group at the end of the group discussion.

Analyses

Household interview schedules were coded and double entered using Epi-Info Version 6.43 (Centres for Disease Control and Prevention, Atlanta). The Statistical Analysis System (SAS) Version 6.12 (SAS Institute, Cary NC) was used for statistical analyses. Statistical methods employed were univariate statistics. Differences in quantitative variables were assessed using Student's *t*-test. Tests of significance for categorical variables were based on the Chi-squared test or Fisher's exact test as appropriate. All *p*-values were based on a two-sided test. A *p*-value of less than or equal to 0.05 was considered to be statistically significant.

Focus group interviews were coded and analysed thematically using the pre-identified themes and others that emerged.

Results

Profile of respondents

All respondents ($n = 848$) who participated in the community-based survey were African, Zulu-speaking women. One hundred and eighty-seven women (22.1%) were using the injectable contraceptive method at the time of the survey, and it is this sub-sample which forms the main focus of this paper. The majority of the injectable users (75.3%) had an education level of Grade 8 (8 years of schooling) or above and 61.0% were unemployed. Their mean age was 26.1 years (median 25; range 17–49). On average, they had 1.9 living children and the maximum number of living children was seven. The mean age at first pregnancy was reported to be 19.2 years. The youngest age at first pregnancy was 12 and the oldest was 30, with 7.2% first pregnant when they were under 16 years and 60.2% when they were under 20. The average age at first contraceptive use was 22.1 years with an age range of 16–42 years.

Table 2 shows that injectable contraceptive users had attained a higher education level than non-injectable users ($p = 0.001$), more were in a stable relationship ($p < 0.001$) and were unemployed ($p = 0.025$), and they were more likely, on average, to have fewer children ($p = 0.005$). In other respects, the demographic characteristics of injectable contraceptive users were similar to those not using this method.

The total number of women participating in the focus group discussions was 63 and there were 37 male participants (Table 1). The age range of the women was 17–60 years and that of the men was 18–75 years. The age range and gender of the participants of each focus group are provided in Table 1.

Contraceptive use

Less than a third (29.7%) of all respondents ($n = 848$) interviewed at household level reported use of a contraceptive method at the time of the survey. Of these, 187 (22.1%) were using an injectable method, either Depo-Provera® (DMPA) or Nur-Isterate® (NET-EN), making the progestogen injectables by far the most popular contraceptive method. Other modern methods used were: oral hormonal contraceptives (4.5%); male condoms (1.3%); the intrauterine device (0.1%); and tubal ligation (0.1%). Traditional methods such as withdrawal and thigh sex were reportedly used by 0.9%, and medications not registered for contraceptive use (e.g. quinine) were being used for contraceptive purposes by 0.7% of respondents. Twelve (24.0%) of the women participating in the focus group discussions, who were of reproductive age (15–49), were using the injectable method.

Injectable contraceptive use

Forty-six per cent (86) of the women on injectables were using Depo-Provera® and 54% (101) were using Nur-Isterate®. The mean length of use was 2.2 years (range 0.1–11), with 41.2% (77) using injectable contraceptives for 1 year or less, 23.5% (44) using them for more than a year, but less than 2 years, and 10.2% (19) using them for 5 years or more.

Almost all injectable users (96.3%) chose the method for convenience, as they only had to return to the clinic every two months for NET-EN or every three months for DMPA. Respondents could provide more than one reason, and other reasons given were that: it was perceived to be safe (52.9%); it was effective (47.6%); it was recommended at the clinic (37.4%); few problems or side effects were experienced (27.3%); it caused amenorrhoea (23.0%); it was recommended by friends or relatives (21.5%); and it was a method that could be hidden from her partner (20.9%). Whilst many side effects were reported, as described in the next section, the majority of the injectable users (86.0%) were satisfied with the method, 6.5% were dissatisfied and 7.5% were unsure how they felt. Those who expressed dissatisfaction, only 12 women, indicated that their dissatisfaction was related to menstrual problems (61.5%) and/or to what they referred to as vaginal wetness (38.5%). A description of vaginal wetness is given in the next section. Almost all (98.4%) indicated that they would continue to use this method.

Participants of the focus group discussions corroborated the above survey findings, being of the opinion that the injectable contraceptive was the most popular

Table 2
Selected demographic characteristics of respondents according to injectable contraceptive user status (injectable users: $n = 187$; non-users $n = 661$)

Characteristic	Women using injectable contraceptives	Women not using injectable contraceptives	p-value
Age (years)			
Mean (SD)	26.1 (5.9)	26.4 (8.1)	0.636
Range	17–49	15–48	
Education level grade 8 or above (%)	75.3	62.3	0.001
Unemployed (%)	61.0	52.8	0.025
Average household income of SAR1000 per month or less (%)	91.6	92.3	0.775
Marital status			
Married[a]	13.4	18.2	0.125
Stable relationship	77.5	57.0	<0.001
Mean number of living children	1.9	2.4	0.005
Maximum number of living children	7	10	
Age at first pregnancy (years)			
Mean (SD)	19.2 (2.9)	19.2 (3.2)	0.777
Range	12–30	12–40	
Age at first contraceptive use (years)			
Mean (SD)	22.1 (4.9)	21.6 (4.9)	0.081
Range	16–42	14–41	

[a]By civil, religious, traditional or customary ceremony.

method in the area. The main reasons given for its popularity were:

- it is convenient, especially in that one does not forget to take it, as was thought to be the case with oral contraceptives,
- it is effective,
- it can be hidden from one's partner and others.

It was felt that whilst women experience many problems with the injectable method, they will continue to use it. The following statements illustrate these views:

> It is [used] because one forgets to take the pill. And with the injection, you forget nothing, because you might already have many children or maybe you have a small baby, and you do not want to get another one, so using injection is good although it has got problems. It stays a long time in the blood. It is also effective (female primary school teacher).

> ...there are lot of side effects associated with the use of the injection, but it still comes number one. [This is] because you will find that some of their husbands or partners do not like their women to use methods of contraception, and the injection will only be known by her—whereas there is no hiding place for the pill, the husbands find them within no time (nurse).

> They do not want to fall pregnant, they tolerate all kinds of side effects for only one thing which is prevention of pregnancy (high school girl from group of girls and boys).

Side effects

Injectable users interviewed in the household survey were asked to indicate what side effects, if any, they were experiencing with the injectable contraceptive method. They were first asked to respond to an open-ended question about their experience of side effects, and were subsequently prompted to respond to a list of 22 possible side effects. This list was compiled after a comprehensive review of the published and unpublished literature and after consultation with family planning health care providers. Both English and Zulu versions of each side effect appeared on the interview schedule. In responding to this list, the majority of women (88.4%) reported that they experienced at least one side effect and 7% reported 5 or more side effects. The side effects most commonly reported were amenorrhoea (62.5%), vaginal wetness (18.4%), weight gain (11.2%) and spotting (11.2%) (Table 3). The side effect profile for DMPA and NET-EN users was similar (Table 3). No significant differences were found between DMPA users and NET-EN users in terms of their experience of side effects. Findings from the unprompted version of the question on side effects were consistent with the prompted responses, but frequencies of reporting were lower. All those who spontaneously reported vaginal wetness as a side effect, also reported vaginal wetness when prompted. Again, amenorrhoea and vaginal

Table 3
Side effects reported by DMPA and NET-EN users

Side effect[a]	DMPA (%) ($n = 84$)	NET-EN (%) ($n = 95$)	Total % ($n = 179$)
Amenorrhoea[b]	67.5	58.9	62.5
Vaginal wetness	22.6	14.7	18.4
Weight gain	14.3	8.4	11.2
Spotting[c]	9.5	12.6	11.2
Loss of libido	10.7	8.4	9.5
Dizziness	10.7	6.3	8.4
Heavy periods	8.3	7.4	7.8
Irregular periods	3.6	10.5	7.3
Headache	10.7	4.2	7.3
Nausea	9.5	3.2	6.1
Vaginal discharge	8.3	3.2	5.6
Vaginal discharge with odour	7.1	3.2	5.0
Longer periods	2.4	4.2	3.4

[a] Side effects reported by five or less respondents are not listed. These side effects were: hair falls out, depression, painful periods, breast tenderness, sweating, bloating of abdomen, bloating of breasts, delayed return to fertility, vaginal dryness.

[b] Amenorrhoea is the absence of menstrual periods (Hatcher, Rinehart, Blackburn, Geller, & Shelton, 1997). The number of women reporting amenorrhoea as a side effect of the injectable contraceptive includes thirty breast feeding women. The amenorrhoea could have been lactational amenorrhoea.

[c] Spotting refers to light vaginal bleeding that occurs at a time other than during a menstrual period (Hatcher et al., 1997).

moistness were the most frequently experienced side effects, reported by 45.3% and 8.4%, respectively.

In response to an unprompted question in the household survey, none of the women using contraceptive methods other than the injectable reported any of the side effects most frequently experienced by injectable users. However, in the focus groups discussions, reference was made to vaginal wetness being a problem with use of oral hormonal contraceptives only once in each of three groups. In each of these cases, the participants linking vaginal wetness to oral contraceptives were men.

Vaginal wetness was the second most common side effect reported by survey respondents (see Table 3), and was reported separately from vaginal discharge. Vaginal wetness, vaginal discharge, and vaginal discharge with unpleasant odour were listed 15th, 16th and 17th, respectively, on the list of side effects provided. Whilst the nature of the difference in the experience of vaginal wetness and vaginal discharge was not explicitly explored in the survey, different Zulu phrases were used in referring to vaginal wetness and vaginal discharge. The distinction was identified in the development and translation of the interview schedule prior to commencing the survey and has been corroborated with Zulu/English translators subsequently (Gwamanda, Z., Kubeka, M., Ngcamu, R., 1998; Dlamini, W., Msweli, D., 2000, personal communication). The approximate English translations of Zulu concepts or commonly used phrases (in brackets) were:

- Increased vaginal moisture or wetness (*Ukubamanzi*)
- Vaginal discharge (*Ukuphuma koketshezi ebulilini bowesimame*)
- Vaginal discharge with unpleasant odour/smell (*Ukuphuma koketshezi olunephunga elibi*).

Vaginal wetness was less likely to be reported as a side effect by those who stated that they had used the injectable contraceptive for a longer period of time ($p = 0.005$), with the mean length of use of 1.21 years for those who reported vaginal wetness and a mean length of use for those who did not report it of 2.33 years. Less frequently reported side effects, given only in response to the prompted question about side effects, were vaginal discharge (5.6%) and malodorous vaginal discharge (5.0%).

Amenorrhoea (24.6%), heavy periods (18.6%) wetness (17.5%) and weight gain (13.7%) were the most frequent responses given when the respondents were asked what they liked least about using the injectable contraceptive. Similar dislikes were expressed by DMPA and NET-EN users (Table 4). However, 24.0% of the respondents indicated that there was nothing they disliked about using this method. All the respondents who least liked amenorrhoea, 59.4% of those who least liked wetness, 30.3% of those who least liked heavy periods and 28.0% of those who least liked weight gain, indicated that they were experiencing these side effects. This may indicate that the amenorrhoea and wetness are less tolerable side effects than heavy bleeding and weight gain. On the other hand, it is worth noting that many women worry about the potential for experiencing wetness, heavy bleeding and weight gain when using

Table 4
Main reasons given by DMPA and NET-EN users for not liking the injectable contraceptive

	DMPA users % ($n = 84$)	NET-EN users % ($n = 99$)	Total % ($n = 183$)
Amenorrhoea	25.0	24.2	24.6
Heavy bleeding	21.4	16.2	18.6
Vaginal wetness	21.4	14.2	17.5
Weight gain	13.1	14.1	13.7

Table 5
Relevant Zulu phrases transcribed from focus group interviews with English translation

Zulu	English
Ukubamanzi	Wetness
Ukubamanzi ngaphansi nomakwesitho sowesifazane sangasese	Vaginal wetness
Amanzi anukayo	Water with odour
Okuphumayo	Discharge
Okuphumayo okunukayo/okunephunga	Discharge with unpleasant odour
Yabanda	Coldness
Ntukuntuku noma phakathi nendawo	Luke warm
Kazwakali	Tastelessness
Akasenawo umdlandla wokuya ocansini	Loss of sexual appetite

the injectable, even if they were not experiencing these side effects.

During focus group interviews, the most commonly mentioned side effects of injectable contraceptives were: vaginal wetness (14 groups), delayed return to fertility (13 groups), heavy bleeding (12 groups), weight gain (12 groups) and amenorrhoea (10 groups). The side effects regarded as the worst were vaginal wetness (9 groups), heavy bleeding (7 groups) and amenorrhoea (1 group).

The problem of vaginal wetness with injectable contraceptive use was raised repeatedly in every focus group interview, and was raised spontaneously in the first instance. It came up repeatedly in the discussions with the group of high school teachers (women and men), with the group of high school girls, with the traditional healers (women and men), with the gardening group (women), and with the members of the school governing board (women and men). As noted previously, the worry about the potential for experiencing vaginal wetness exists even among those not using this method. Some comments about the experience of vaginal wetness follow,[2] with the English translations of relevant Zulu phrases used by focus group participants provided in Table 5:

> I heard that if you use injectables you become wet and experience lots of problems but we have no alternative..... (high school girl in the girls only group).

People using the injection used to complain about vaginal wetness. They say their partners do not enjoy sex with them and state that it all becomes a big dam. This vaginal wetness is associated with coldness and you eventually loose sex appetite (woman from sewing group).

Depo makes you wet. You feel that you are wet and become ashamed or sorry when sleeping with your husband (community health worker).

They say a lot of things like the injection makes one to be always wet and sometimes that their male partners complain that women who are using injection do not taste good..... (nurse). The group of nurses all agreed that women report experiencing vaginal wetness with injectable contraceptive use.

.....truly speaking our children are finished by this injection, they are big in sizes, they are wet. There is another problem from the male side, I once overhead them talking saying that it is much better to have sex with an old lady because she is not wet, teenagers are just swimming pools (woman traditional healer).

.....injection makes them gain weight, not that they are fat, the body is just full of water, and when having sex with such a person she is just a pool of

[2] All quotes have been translated from Zulu. Responses, which are the outcome of probing, are identified as such.

water, you do not feel anything (male church minister).

The nature of vaginal wetness

Several participants (mainly women) in the focus group discussions described vaginal wetness associated with injectable use. Some of their comments, in addition to those made above, were:

> .....they become wet, this is continous slow flowing of water, that makes them to be always wet (female traditional healer).

> You feel wet always when you have sex with your partner. Sometimes you feel that wetness even if you are alone and not having sex (woman from gardening group).

> You can feel it [the wetness from injectable use] even when you are alone but it is worse when you are making love (woman from parent group).

> They [women] say they become wet when on injection, it causes wetness, and this water just oozes, other women sometimes always wear a pad to block it from going down the legs (female member of the school governing board). This same respondent, when prompted, stated that it was supposed to have an unpleasant odour.

> There is great difference [between wetness of sexual arousal and wetness of injectable], you know how far she will be wet when you have touched her (male primary school teacher).

> Yes we do feel that we are wet and we do not only feel it when doing sex even if you are just sitting you can feel it and it comes as a discharge with unpleasant smell, and .....this wetness is not a thing that is psychological to men it does happen to us (2 female high school teachers in response to the question Does the female feel that she is wet or it is something said by men?)

> Wetness is worse [the worst side effect with the injectable] because these girls always wear pads to stop water from oozing down (high school girl from group of girls and boys).

> ...as soon as the woman gets injection, she becomes wet, it makes the body to be full of water. It is a water with some kind of odour (female primary school teacher in response to what kind of water is it?).

> ...sometimes this wetness comes out as an unpleasant discharge making you not confident of yourself in public (woman from sewing group).

Partners and injectable contraceptive use

Sixty-one women (32.6%) surveyed reported that their partners did not know that they were using this contraceptive method and 4 (2.1%) did not know if their partners knew. However, 121 women (65.1%, $n = 186$) believed that men are not well disposed towards women using the injectable method of contraception, and, in explaining why they felt this way, the problem of vaginal wetness really came to the fore. Table 6 shows that reasons related to vaginal moistness, causing "coldness" and making women "tasteless" amount to nearly half (46.3%) of the reasons given.

Focus group participants, men and women, made frequent reference to the problems of "wetness" "coldness" and "tastelessness" with injectable contraceptive use. Coldness was used in the context of the female partner being perceived to be sexually unresponsive or losing her sexual appetite, and tastelessness as the female partner being sexually unappetizing or undesirable. Examples of comments made are:

> They [men] also say we become cold, wet and the vagina opens, as it opens you are tasteless (high school girl in the girls only group).

> Wetness, bleeding, becoming fat, tasteless, coldness which is caused by moistness in the vagina (high school boy in the boys only group in response to the question What don't you like about injectables?).

Table 6
Reasons, given by 121 injectable users, for why men do not favour this contraceptive method

Reason	Respondents (%) ($n = 121$)
Reasons related to vaginal wetness/coldness/tastelessness	46.3
Men want more children	34.7
Women who use it misbehave	9.1
Causes sterility	3.4
Harmful to health	2.5
Causes vaginal discharge	0.8
Other	3.4

.....a lot of men know that once she is wet she is using the pill or injection, so these days secret is out. Men can sense that the woman is using contraceptive method (traditional healers).

They also say you become tasteless and cold (woman high school teacher, in response to the question What do men think about women using the injection?).

Users say that the injection makes the girl or the woman to become tasteless, they are cold because of the moistness of the vagina, they are so wet, they are bleeding for a long time, and that they are always wet (high school girl from group of girls and boys).

To tell you the honest truth my son, there are women out there who are luke warm and there are women out there who are ice cold and full of water, the reason for that is one they are using injection. So I have got muti that I can give them as a drying agent to this water (male traditional healer).

They say we are wet (one woman), they say we become tasteless (another woman) they say we are cold (a third woman) (parent group in response to the question What do men think about women using the injection?).

Much concern was expressed that women who use the injectable contraceptive are, or are perceived to be, promiscuous—because they are freed from the worry of pregnancy and/or they are "wet".

Men commented as follows:

.....if the women begin at an early age to use these things [injection], when she has sexual intercourse with her man, she becomes wet. Sometimes, you can even think that she has been with the other man (male primary school teacher).

This wetness is the main problem and since it is associated with lack of desire for sex, then when the women prove not to worry much about sex then the man adds these two things up, which is wetness and no desire for sex and come up with an answer which is that the woman has been with another man. Then the fight breaks out (male primary school teacher).

The injection causes women to be wet and you as a man do not enjoy sex with such a woman to the extent that if it is your girlfriend and not a wife, you can be sure that she is from another man, she has been with someone else (male member of the school governing board).

Women made the following comments:

They say we are always wet, and also that we are having many boyfriends and misbehave (woman from gardening group, in response to the question What do men think about women using the injection?).

To me wetness is the worst because the partner fights thinking that you have been sleeping with other men (woman high school teacher).

They do not tell them [their husbands that they are using the injection], but it happens sometimes that the secret gets out, when the partner will be asking as to why are you so wet, and it will only be then that the woman will tell him that it is because she is using the injection that is why she is wet and not that she has been with someone, sexually (female nurse).

.....it [the injection] gets them into trouble, once she is wet the man would say she is having an affair (female member of the school governing board).

Discussion

Among injectable contraceptive users, vaginal wetness, often linked to "coldness" and "tastelessness", was a recurrent theme and was the second most commonly reported side effect for DMPA and NET-EN. Vaginal wetness was more frequently reported by DMPA users (22.6%) than by NET-EN users (14.7%), but, as previously noted, this difference was not statistically significant. Wetness was significantly less likely to be reported as a side effect by those who stated that they had used the injectable contraceptive for a longer period of time.

Early studies and the Petogen® product brochure describe vaginal discharge as a side effect, whereas respondents in the survey differentiate between vaginal wetness and vaginal discharge, both of which are reported as side effects. Respondents in the survey were not asked to describe vaginal wetness, however, reproductive health workers suggest that it is of a watery consistency (N. Ntuli, 1999, personal communication) and discussions in the focus groups also describe it as a watery substance which occurs in excessive quantities. Female participants in a study described by Brown et al. (1993a) distinguish between three types of vaginal secretions—(i) secretions which occur in small amounts at certain stages of the menstrual cycle and during sexual arousal; (ii) excessive secretions described as "too much water", resulting in a "wet vagina"; and (iii) unusual discharges resulting from infections. The second type of secretion described by Brown et al. is consistent with the KZN focus group respondents' description of the vaginal moistness they associate with injectable contraceptive use. A study is being developed to discover more information about the nature and possible etiology of vaginal wetness, how it may differ from the vaginal discharge reported by

respondents, and whether it is a consequence of a vaginal infection or a relatively transient problem that resolves for most women on continued use.

Since vaginal wetness also comes up as the third most frequently mentioned reason for what the survey respondents liked least about using the injectable contraceptive, and was identified as the worst side effect in the majority of focus group discussions, it can be assumed that vaginal wetness is a side effect that is not well accepted in the study area, and may result in method discontinuation. Many comments made in focus group interviews convey the negative way in which vaginal wetness is regarded and the negative impact it may have on the enjoyment of sexual intercourse and on relationships. It is noteworthy that some survey respondents who did not report it as a side effect (40.6%) were clearly concerned about the possibility of experiencing it, as they listed this as a reason for least liking the injection.

Previous studies have shown that men and women in many parts of Central and Southern Africa have a preference for "dry sex",[3,4] (Brown et al., 1993a, b, 2000; Civic & Wilson, 1996; Morar & Abdool Karim, 1998; Beksinska et al., 1999). For instance, in a study undertaken in Zaire (now the Democratic Republic of Congo), Brown et al. (1993b) found that "Both men and women expressed a definite preference for dryness and tightness, saying that when a woman's vagina is moist or large, neither she nor her partner experience full sexual pleasure" p. 97. Further, Beksinska et al. (1999) found that 60% of men and 46% of women surveyed in Orange Farm, South Africa expressed a preference for dry sex. One of the main reasons for practising dry sex given by both men and women respondents was that it shows that the woman is not promiscuous. Another reason given, but only by women, was "for partner satisfaction" (Beksinska et al., 1999). Where dry sex practices are preferred women resort to potentially harmful measures to dry, tighten and warm their vaginas (Baleta, 1998; Beksinska et al., 1999).

Increased vaginal wetness associated with the most popular contraceptive method used in South Africa, is consequently a problem which must be regarded seriously. According to respondents in our study, some men regard women who use the injectable contraceptive as "wet", "cold" and "tasteless". Almost half the injectable contraceptive users surveyed, who believed that men do not favour the injectable contraceptive, used one or more of these words to describe why men do not like the method. Women also stated that the reason men dislike the injectable was because women who use it misbehave. Injectable users are clearly concerned about the response of their male partners to vaginal wetness thought to be produced by injectable use. Likewise, in focus group discussions, women using the injectable method were frequently described as wet, cold and/or tasteless and were sometimes perceived as being unfaithful or promiscuous. This notion can only serve to deepen the disempowerment experienced by many South African rural women.

A limitation of this study is that it draws upon the experiences and views of African women and men from a deep rural area of KwaZulu-Natal. It is, therefore, not possible to directly extrapolate the findings to residents of urban areas or even of rural areas in other provinces in South Africa. Nevertheless, findings from this study indicate that increased vaginal wetness is regarded as a problem experienced by injectable contraceptive users, and it needs to be addressed.

At this stage we do not have an explanation for this problem which is widely reported by women in our study as well as by family planning service providers. It is possible that, even if women from western countries have experienced vaginal wetness with injectable use, it may not have been reported or documented, since in these countries, increased vaginal moistness may not be regarded as a problem. One would in fact expect the anti-oestrogenic properties of progestogen to result in vaginal dryness, which is a documented, though rarely reported side effect (Guillebaud, 1993; Nelson, 1996). One possible explanation for the reported wetness is that the women who report this problem have sexually transmitted infections (STI's). However, the nature of the wetness does not, for the most part, appear to fit the description of an infection. It is important though to note that the prevalence of sexually transmitted infections in South Africa is very high (Baleta, 1998; Abdool Karim & Abdool Karim, 1999). Abdool Karim et al. (1999) reported that on any given day, approximately one in every four of the women between the age of 15 and 49 years from a rural area of KwaZulu-Natal was infected with at least one STI. The prevalence of STI's amongst injectable contraceptive users should, therefore, be investigated. Another possible explanation is that vaginal wetness, attributed to progestogen injectable contraceptive use, is a perception that has grown and spread over time, possibly fueled by men's concerns about loss of control of their partner's fidelity and fertility if she uses the injectable contraceptive. This too warrants further investigation.

In summary, this study has found that vaginal wetness is a commonly reported side effect of the widely used progestogen-only injectable contraceptive. This side effect appears to be particularly disturbing in terms of

[3]The practice of dry sex is defined as the drying, tightening, and sometimes warming of the vagina for sexual intercourse (Brown et al., 1993a; Dallabetta et al., 1995; Beksinska et al., 1999).

[4]Only some of these studies were conducted exclusively amongst commercial sex workers and the practice of dry sex is not restricted to commercial sex workers.

the way in which men view women who use it. Yet, despite this undesirable effect, women continue to use the injectable method, mainly because they find it a convenient and effective method which can be hidden from their partners. Whilst vaginal wetness can only be classified as a subjective side effect at this stage, further investigations are needed. It is also an issue that must be addressed by health workers responsible for counselling women who use this method of contraceptive.

Acknowledgements

This research was supported by a grant from the Wellcome Trust (Grant Number 050543/Z/97/Z). We would like to thank the Wellcome Trust, the University of Durban-Westville and the Medical Research Council for their support. We are grateful for the assistance of our fieldworkers and data capturers, and to the women and men who so willingly participated in this study.

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Serum Medroxyprogesterone acetate levels in new and repeat users of depot medroxyprogesterone acetate at the end of the dosing interval

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Keywords: Depot medroxyprogesterone acetate; progestagen-only injectable contraception; medroxyprogesterone acetate serum concentrations; South Africa

Running head: Serum medroxyprogesterone acetate trough concentrations

Abstract

In the absence of published data on serum medroxyprogesterone acetate (MPA) levels in South African users, this study examines such levels in new and repeat users of depot medroxyprogesterone acetate at the end of the dosing interval. The study was undertaken at three family planning clinics in Durban, South Africa. Serum MPA levels were measured in 94 Black African, Indian and White women returning between 11 and 14 weeks after their last injection. The median (range) serum MPA level was 0.88(<0.04-1.77) ng/mL and wide interindividual variability was observed. Levels in all but one woman were higher than 0.1 ng/mL, the level at which ovulation is reported to resume. MPA levels were not found to vary according to weight, BMI or ethnicity. Although there was a slight tendency towards higher MPA levels with longer duration of use (r=0.13), the wide interindividual variability precluded the possibility of determining whether this was a real trend. A prospective study, using standardized assay techniques and following individual women, is required to further clarify this issue.

Introduction

Early published studies have determined serum or plasma concentrations of medroxyprogesterone acetate (MPA) after intramuscular injection of 150 mg of depot medroxyprogesterone acetate (DMPA) [1-9]. These studies used a variety of different assay techniques and, in all but three [2,4,9], MPA levels were reported after only one dose. In addition, the sample sizes were small and none of the populations studied were African. Following injection of DMPA, blood concentrations of MPA are reported to peak within 3 weeks [3,6,9], after which they remain somewhat constant in the range of

1.0-1.5 ng/mL for the 2 to 3 months post injection [3]. Levels then decrease gradually to 0.2 ng/mL by the sixth month and eventually to undetectable levels of less than 0.02 ng/mL by up to nine months [3,10].

DMPA has been shown to be effective as a contraceptive for at least 90 days [3,5-7,9,10] and ovulation is reported to resume when MPA blood concentrations decline to less than 0.1 ng/mL [3,10]. Three studies have reported specifically on serum or plasma MPA levels at the end of the dosing interval after injection of 150 mg DMPA intramuscularly in women who had at least one previous DMPA injection. In the first study of two women, the MPA levels 12 weeks after injection were reported to be approximately 0.5 ng/mL in a woman who had had one previous injection, and 1.0 ng/mL in a woman who had received her 20^{th} injection [9]. The second study of 11 women, who had received between 6 and 18 injections, found a mean (SD) MPA level of 0.6 (±0.1) ng/mL 84 days after the last injection [2]. In the third study, amongst Thai women who had received only one injection (n=10) 90 days earlier, plasma MPA levels ranged between <0.10 ng/mL and 1.28 ng/mL, with a mean of 0.61 ng/mL. In those who had received 8 consecutive doses (n=11) the range was 0.12 ng/mL to 2.56 ng/mL, with a mean of 0.90 ng/mL. The difference between the group receiving multiple injections and the group receiving only one injection was not statistically significant [4].

The injectable progestagen-only contraceptives DMPA and norethisterone oenanthate (NET-EN) are the most widely used contraceptives in South Africa, especially amongst Black African women, and account for almost half of all contraceptive use (48%) [11-

13]. Injectables which contain a combination of oestrogen and progestagen are not registered for use in South Africa. Whilst use of NET-EN is increasing, especially amongst younger women [12], DMPA is still the most commonly used injectable [13]. Despite its extensive use there are no published data on serum MPA levels in South African users. This paper examines serum MPA levels amongst new and repeat South African DMPA users at the end of the dosing interval.

Materials and Methods

The study was approved by the ethics committees of the Nelson R Mandela School of Medicine of the University of Natal, and the University of Durban-Westville, Durban South Africa. Permission to conduct the study was obtained from the Durban local health authority.

Trough serum MPA levels were measured in 97 DMPA users attending three Durban family planning clinics between October 1996 and January 1997. The DMPA product supplied at these clinics was Depo-Provera® (Pharmacia & Upjohn (Pty.) Ltd., Johannesburg, Gauteng Province). Ninety-four of the women returned between 11 and 14 weeks of receiving their last dose. The remaining three returned more than 14 weeks after their last injection and were classified as "defaulters" in keeping with clinic policy. The dosage regimen for DMPA at the clinics is 150 mg every 12 weeks.

Blood samples were obtained immediately before administration of the next dose of DMPA. After being allowed to clot, they were centrifuged and the serum obtained was

stored at -70°C. The MPA assay was performed by Immunometrics Ltd., London, United Kingdom, using materials and methods developed for the World Health Organization (WHO) Special Programme of Research in Human Reproduction [14]. These standardized materials have been extensively used for over 15 years in international clinical trials sponsored by the WHO, pharmaceutical companies and non-governmental organizations. The assay methodology is a first generation radioimmunoassay (RIA) involving an ether extraction step (standards and samples); incubation with antibody and a tritium labelled MPA; a charcoal separation of free and antibody bound analyte. All samples are measured in duplicate. Standards were prepared by weighing pure material prepared for WHO. The concentration of stock solutions were checked using UV absorption before the standards were further diluted in human serum. The potency of these serum standards was further cross checked by RIA against reference standards previously prepared for WHO and external quality control samples. In four separate recovery sample vials per assay, after adding tritiated MPA to plasma and an ether extraction step, an aliquot was taken for recovery measurement and results were corrected for losses. Four replicates of each of three quality control (QC) samples (target concentrations 0.12, 0.29, 0.77 ng/mL) were included in each assay batch. QCs were in two groups, one set of duplicates at the front of the assay, the remaining duplicates at the end. Assay runs were accepted if the mean values of all three QC pools were within the acceptance limits (±15% of the target value) or if five out of the six QC results were within limits.

The antibody was tested for cross-reaction with MPA (100%), 17α-hydroxy-6α-methylprogesterone (0.02%), 6-dehydromedroxyprogesterone acetate (9.5%), 6β-hydroxy-medroxyprogesterone acetate (64.6%), 20α-dihydroprogesterone (none detected), 20β-dihydroprogesterone (none detected) and 17α-hydroxyprogesterone (none detected). Results were statistically indistinguishable (using a paired t-test) when samples from 35 patients were assayed with and without chromatography [LH-20 column, using toluene:methanol 85:15] (means: 1.48 ng/mL and 1.49 ng/mL respectively; ranges: 0.17-5.02 ng/mL and 0.15-4.87 ng/mL respectively).

The lower limit of detection was 0.04 ng/mL. This was estimated by using an immunoassay data processing program which calculated precision profiles in the range of 0.02 ng/mL to 3.13 ng/mL. No drift was observed in any assays performed for this study. The percentage coefficient of variation (CV) observed in the 11 assay runs carried out for this study were 8.8%, 6.9% and 6.5% for QCs with mean values 0.12, 0.30, and 0.76 ng/mL respectively. Any sample whose duplicates showed poor replication (more than three times the expected SD at that dose) was re-analysed. Results below the bottom standard were reported as <0.04 ng/mL. Samples found to contain doses higher than the top point of the standard curve were diluted (1:2, 1:4 and 1:8 times) in zero standard serum and re-analysed. Samples from subjects who had not received MPA exhibited unmeasurable levels of MPA in most cases; in about 20% of plasma samples, low (<0.08 ng/mL) apparent MPA levels (plasma blanks) were found.

Body weight, height and blood pressure were recorded and body mass index (BMI) was calculated. Participants were interviewed to obtain relevant demographic and medical details. Data were analysed using Microsoft® Excel 2002.

Results

Demographic data and serum MPA levels of the 94 women returning between 11 and 14 weeks after their last dose are presented in Table 1. On recruitment into the study, 12% of these had had one dose of DMPA, 7% two doses, 5% three doses and the remainder had been using DMPA for a year or more. Sixty-four were Black Africans, 24 were of Indian descent, and six were White. The MPA level of one woman was below the minimum level of detection (0.04 ng/mL). Where this value was included in determining a mean value, the level was set at half the limit of quantitation (0.02 ng/mL).

Serum MPA levels in relation to the time after the last injection are presented in Figure 1. Levels of those who returned up to a week early, or up to two weeks late, were similar to those returning exactly 84 days after their previous dose. The large interindividual variability is well illustrated by the wide range of levels, particularly in the large group who returned at 84 days. MPA levels in these 55 women ranged between <0.04 ng/mL and 1.53 ng/mL (median: 0.90 ng/mL; mean [SD]: 0.86[0.31] ng/mL). The MPA levels of the three defaulters who returned 109, 112 and 168 days after their last dose were 0.77 ng/mL, 0.74 ng/mL and 0.29 ng/mL respectively.

Figure 1 also shows that the trough MPA levels of Africans and Caucasians were similar. In the group returning at 84 days, the median (range) MPA levels were 0.90 (0.10-1.40) ng/mL and 0.90 (<0.04-1.53) ng/mL for Africans (n=41) and Caucasians (n=14) respectively. Although widely varied within each ethnic group, BMIs were similar between groups with a median (range) BMI of 25.8 (17.4-39.4) for African women (n==51) and 23.6 (15.4-33.8) for Caucasians (n=29). The MPA levels of subjects with a BMI less than 25 were similar to those of subjects with a BMI of 25 or more (Table 2).

There was a slight trend (Pearson's Product Moment=0.13) towards higher MPA levels at the end of the dosing interval with longer duration of use (Figure 2). However, wide interindividual variability was evident irrespective of length of use.

Discussion

Wide interindividual variability in serum MPA levels has been noted before [5,15,16]. Our findings, based on a much larger sample size than those of previous studies, also clearly show the wide interindividual variability in MPA levels in DMPA users on return for their next dose. MPA levels were found to be in a similar range to levels reported in previous studies [2,4,9].

Most studies have found MPA levels at the end of the three month dosing period to be above the level at which ovulation is reported to resume (0.1 ng/mL) [1-4,6]. In our study, with the exception of one undetectable level (<0.04 ng/mL), all MPA levels between 11 and 14 weeks after the dose were above this level, although the level for one

woman was found to be 0.104 ng/mL. Even the MPA levels of three defaulters, two who returned 4 weeks late and one 12 weeks late, were still above 0.1 ng/mL. In four of five women studied, Fotherby et al. reported undetectable levels by day 55, 64, 87 and 87 post injection respectively (minimum detectable level >0.1 ng/mL) [5] and, in a study by Koetsawang et al., two of 21 women had levels of less than 0.1 ng/mL at the end of the dosing period [4]. It should be noted, however, that the assay used in these two earlier studies was less sensitive (0.1 ng/mL) than that of our study where the lower limit of quantitation was 0.04 ng/mL. In addition, assays used in early studies varied. More recently, recognizing the difficulty in interpreting results from different studies, the World Health Organisation's Task Force on the Long Acting Systemic Agents for Fertility Regulation has produced standardized protocols and matched reagents for radioimmunoassay of synthetic progestagens [14]. These procedures were used in our study assays and should be used in future studies to improve standardization and between-center comparability of assay results.

The possible influence of weight, BMI and ethnicity on MPA levels has been studied by other investigators [6,7,16,17,18]. One study comparing the rate of uptake and metabolism of DMPA in obese and thin women showed no difference in MPA serum levels between the two groups [17]. However, Garza-Flores et al. reported a tendency for DMPA to be absorbed more rapidly in thin than in obese women [18]. Bassol et al. reported a longer delay in resumption of ovulation in Mexican than in Thai women, which they considered to be in keeping with the longer disappearance of MPA from the serum of the Mexican women [7]. In another study undertaken amongst Indian and

Swedish women [6], luteal activity was found to return later in the Swedish women, but no difference was found between the two populations in time taken for plasma MPA to become undetectable. In our study of Black African, Indian and White South Africans, MPA levels at the end of the dosing interval were not found to vary according to weight, BMI or ethnicity. Overall, few studies have investigated the population differences in DMPA users and the methodologies of some of the published studies is unclear, once again suggesting a need for more rigorous investigation.

The possibility of MPA levels increasing with successive injections has also been investigated, although not by many. For instance, the study undertaken in Thailand by Koetsawang et al. reported a higher mean plasma level at the end of the dosing period for those receiving multiple injections than that of those receiving a single dose [4], although the difference was not significant. Fraser and Weisberg [15] in reviewing these findings, suggested that no significant difference was found because of the wide interindividual variation within each group and recommended further investigation. In an early review of Depo-Provera® studies, Schwallie presented data (Depo-Provera Protocol 9A) which showed no accumulation of MPA when comparing median serum levels after the first and fifth injection period [19]. Our South African study showed a slight tendency towards increased MPA levels at the end of the dosing interval with longer duration of use. However, the wide interindividual variability precluded the possibility of determining whether or not this was a real trend. In addition, our study, like that of Koetsawang et al. was cross-sectional. A prospective study, which follows DMPA use in the same women over time would be required to determine if accumulation actually occurs.

Acknowledgements

Financial support for this study was provided by the Wellcome Trust, London, UK (Grant Number 050543/Z/97/C) and the University of Durban-Westville, Durban, South Africa. We thank the Durban local health authority staff for their assistance, and the family planning clients who participated so willingly. We also wish to express our appreciation to Immunometrics Ltd., in particular to Saulat Sufi, for performing the MPA assays. In addition, Saulat Sufi and Walter Deppe are thanked for their expert advice on the assay procedure.

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Table 1. Demographic data and MPA levels

	Age (years) n=94	Weight (kg) n=94	BMI n=80*	MPA level (ng/mL) n=94
Mean	28	62	25.4	0.88
Median	27	61	24.3	0.88
Range	17-42	38-106	15.4-39.4	<0.04-1.77

*The heights of 14 women were not recorded

Table 2. MPA levels of women of different BMIs

	MPA level (ng/mL)			
	n	Mean	Median	Range
BMI < 25	43	0.85	0.85	<0.04-1.58
BMI ≥ 25	37	0.88	0.88	0.31-1.45

Desirable BMI range is 19-24 [17]

Figure 1. MPA levels in relation to dosing interval by ethnic group

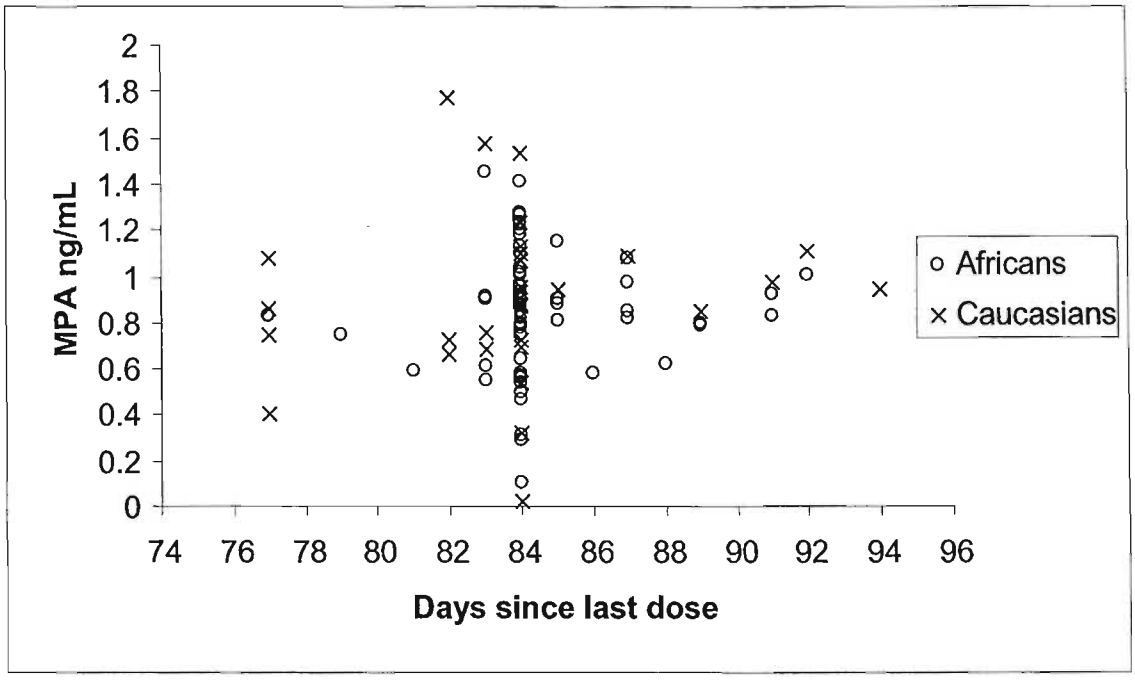
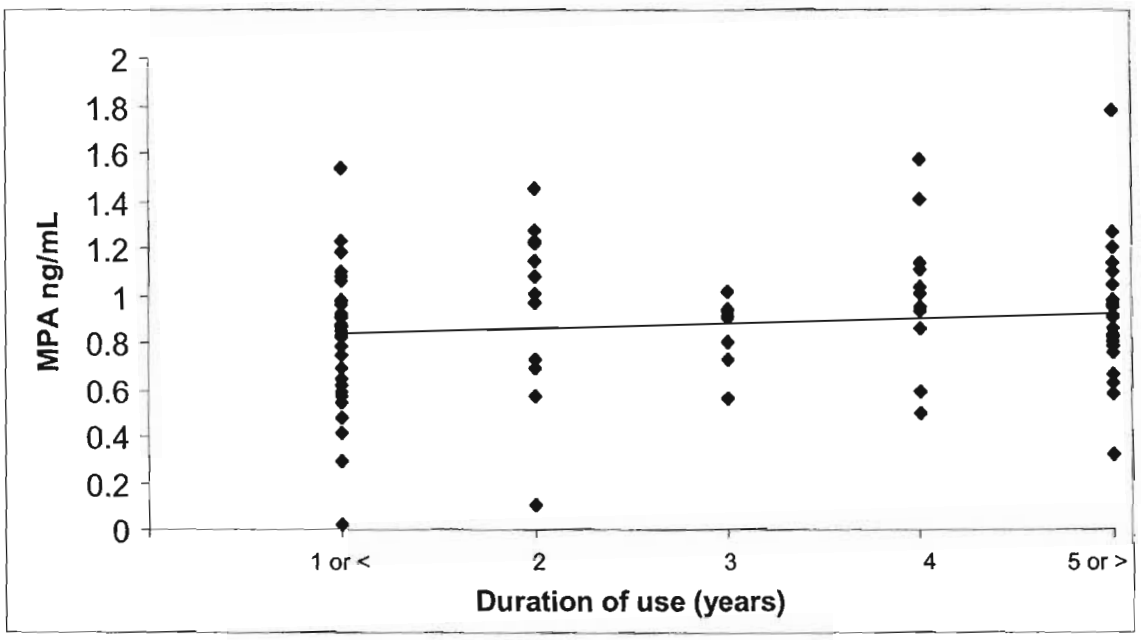


Figure 2. MPA levels in relation to duration of use (n=93)



LIST OF PRESENTATIONS ARISING FROM THE THESIS

1. Smit J, Botha J, McFadyen ML.

Population pharmacokinetics of medroxyprogesterone acetate using non linear mixed effects modeling.

Poster presentation at the Population Approach Group: Australia, New Zealand & South Africa (PAGANZA) 2002 Workshop, Cape Town, 20-22 November 2002.

2. Gray AL, Smit JA, McFadyen ML.

Counting the costs: Should depot medroxyprogesterone acetate and norethisterone oenanthate both be on the EDL?

Poster presentation at the 15th Annual Conference of the SA Association of Hospital and Institutional Pharmacists, Knysna, March 2001.

3. Smit J, Gray A, McFadyen ML.

Cost implications of injectable contraceptive utilisation patterns in South Africa.

- Podium presentation at the Colloquium of the Africa Centre for Population Studies and Reproductive Health, Hlabisa, 21 June 2000; and at the 6th Reproductive Health Priorities Conference, Cape Town, 15-18 August 2000;
- Poster presentation at the VII World Conference on Clinical Pharmacology and Therapeutics of IUPHAR, and the 4th Congress of the European Association for Clinical Pharmacology and Therapeutics. Florence, Italy. 15-20 July, 2000.

4. Smit J, Gray A, McFadyen ML, Zuma K.

A community-based survey of injectable contraceptive utilisation in rural South Africa: Patterns of use and experience of side effects.

Poster presentation at the VII World Conference on Clinical Pharmacology and Therapeutics of IUPHAR, and the 4th Congress of the European Association for Clinical Pharmacology and Therapeutics. Florence, Italy. 15-20 July, 2000.

5. Smit JA, McFadyen ML, Harrison A, Zuma K.

An analysis of contraceptive use patterns in a rural district of KwaZulu-Natal: Are dual protection needs being met?

Poster presentation at the joint meeting of the South African Pharmacology Society and the Neuroscience Society, Durban, 20-23 September 2000.

6. Smit JA, McFadyen ML, Zuma K.

Self-reported side effects with progestogen-only injectable contraceptive use.

Poster presentation at the 2nd International Conference on Pharmaceutical and Pharmacological Sciences. Cape Town, 3-6 October 1999.

7. Smit JA, McFadyen ML, and Zuma K.

Vaginal wetness and progestogen-only injectable contraceptive use vaginal wetness and progestogen-only injectable contraceptive use.

Podium presentation at the 5th Reproductive Health Priorities Conference, Drakensburg, 17-20 August, 1999.

List of Abbreviations and Acronyms

AUC	Area under the curve
BMI	Body mass index
C	Clearance
CI	Confidence interval
CL/F	Apparent clearance
CIC	Combined injectable contraceptive
CYP	Couple-years of protection
D1	Duration of input
DMPA	Depot medroxyprogesterone acetate
DV	Measured concentration
EDL	Essential drugs list
FDA	Food and Drug Administration
F	Bioavailability
FO	First-order estimation method in NONMEM
FOCE	First-order conditional estimation method in NONMEM
FSH	Follicle stimulating hormone
GAM	Generalised additive models
HIV	Human immunodeficiency virus
HSRC	Human Sciences Research Council
ICMR	Indian Council of Medical Research
i/m	Intramuscular
IIV	Interindividual variability
IOV	Inter-occasion variability
IPC	Injectable progestogen-only contraceptive
IPRE	Individual predictions
IRR	Incidence rate ratio
IUD	Intrauterine device
IWRES	Individual weighted residuals
KA	Absorption rate constant
KAPB	Knowledge, attitude, behaviour and practice
kg	Kilogram
KZN	KwaZulu-Natal
L	Litre
LH	Lutenizing hormone

mg	Milligram
ml or mL	Milliltre
mol	Mole
MPA	Medroxyprogesterone acetate medroxyprogesterone acetate
N or n	Number; sample size
NET-EN	Norethisterone oenanthate
ng	Nanogram
NONMEM	Non Linear Mixed Effect Modelling
OC	Oral contraceptive
OFV	Objective function value
ΔOFV	Difference in objective function value
OR	Odds ratio
PD	Pharmacodynamic
PK	Pharmacokinetic
pg	Picogram
POC	Progestogen-only contraceptives
PRED	Predicted
QC	Quality control
RSE	Relative standard error
SADHS	South Africa Demographic and Health Survey
SD	Standard deviation
STIs	Sexually transmitted infections
$t_{½}$	Half-life
TAD	Time after dose
UK	United Kingdom
UL	Units per litre
USA	United States of America
V	Volume of distribution
V/F	Apparent volume of distribution
WHO	World Health Organization
WRES	Weighted residuals
ZAR	South African Rands
η (eta)	Variance of interindividual random effects
ϵ (EPS)	Variance of the residual error,
π	Inter-occasion random effects

INTRODUCTION

BACKGROUND AND NEED FOR THE STUDY

Access to safe and effective contraception is an essential prerequisite to the promotion of reproductive health (United Nations Population and Development, 1994; United Nations 1995; World Health Organization, 1996a; 1996b; 2000; 2002). In South Africa, the long acting injectable progestogen-only contraceptives are by far the dominant method used (Roberts and Ripp, 1984; Smit and Venter 1993; Reproductive Health Task Force *et al*, 1994; Chimere-Dan, 1996; Progress in Human Reproduction, 1996; Westaway *et al*, 1996a; Westaway *et al*, 1996b; Bailie *et al* 1997; Beksinska *et al*, 1998; Beksinska *et al*, 2001a; Smit *et al*, 2001; Department of Health *et al,* 2002). In a study undertaken in 1994, injectables were reported to account for between 60% and 95% of contraceptive methods used (Reproductive Health Task Force *et al*, 1994). More recently, the 1998 South Africa Demographic and Health Survey (SADHS) reported that 57% of all the women (aged 15-49 years) interviewed had used the injectable method at some time. Of the women who were sexually active in the four weeks prior to being interviewed and using a modern contraceptive method, 49% reported that they had been using an injectable progestogen-only contraceptive (IPC) (Department of Health *et al,* 2002).

Injectables are more extensively used in rural areas of South Africa (Reproductive Health Task Force *et al*, 1994; Department of Health *et al,* 2002), and are used for longer periods of time than anywhere else in the world (Bailie *et al*, 1997). The injectable contraceptive is also widely used by young South African women (Lucas, 1992; Chimere-Dan, 1993; Department of Health *et al*, 2002). Furthermore, in South Africa, the injectable is used far

more extensively by African[1] and coloured women than by Asian, or white women (Chimere-Dan, 1993; Bailie *et al*, 1997; Kaufman, 1997; Molefe and Mthembu, 1997; Ramsaran *et al*, 1997; Department of Health *et al*, 2002). The Reproductive Health Task Force *et al* (1994) reported that 70 to 80% of black family planning clients were using injectable contraceptives compared with 10% of white clients. A study (Morrison, 1995, p.9) undertaken in Durban, South Africa, pointed to the extensive use of injectable contraceptives by young women and stated further that there is "extreme racial and economic stratification of users of the injection".

Unlike many countries in the world, where only one IPC product is available, in South Africa both progestogen-only injectable contraceptives, depot medroxyprogesterone acetate (Depo-Provera® and Petogen®) and norethisterone oenanthate (Nur-Isterate®), are available. The combined injectable contraceptive, containing both oestrogen and progestogen, is not yet available. Both depot medroxyprogesterone acetate (DMPA) and norethisterone oenanthate (NET-EN) are extensively used in the public sector in South Africa, both are on the South African Essential Drug List (National Department of Health, 1998) and both are available free of charge at public sector primary health care facilities. However, few studies have been undertaken which directly compare DMPA and NET-EN in terms of utilization patterns, side effects, reversibility, and discontinuation. Affordability of drugs by developing countries is currently a topic of heated debate, especially with regard to access to HIV (human immunodeficiency virus)

[1] **Racial Classification.** The Health Systems Trust approach to race classification is used in this thesis, namely African, Asian (or Indian), coloured and white. "The categories reflect the system of racial classification under apartheid. The use of these classifications is necessary in order to indicate the challenges and progress made in achieving goals of equity. The terms African, Asian, coloured and white are used except when referring to Africans, Asians and coloureds collectively, in which case the term Black is used." (Health Systems Trust, 1997, p. 16)

related drugs. In South Africa financial resources for health care are limited. At the same time, health care costs are soaring as the HIV epidemic bites and anti-retroviral treatment through the public sector becomes inevitable. It thus becomes increasingly important to ensure that all drugs are rationally provided and used. Taking into account published findings on efficacy, reversibility, side effects and safety, a cost analysis of the provision of IPCs is essential if appropriate policies for the rational use of IPCs are to be developed. Yet no analyses of this nature have been published.

The efficacy of the progestogen-only injectable contraceptives is extremely high (Garza-Flores *et al*, 1992; Garza-Flores *et al*, 1994; Kaunitz, 1994; Kaunitz and Rosenfield, 1994; Lande, 1995; Díaz, 2001; Kaunitz, 2002). An illustration of the high efficacies of these two products is provided by a World Health Organization (1983) comparative trial. According to this study, the efficacy of DMPA given every 90 days and NET-EN given every 60 days are comparable, with a cumulative 2-year pregnancy rate of 0.4 per 100 woman-years. Trussell *et al* (1990) provide "summary estimates of contraceptive failure" and give the lowest expected, and typical percentage, of accidental pregnancies in the United States, during the first year of use, as 0.3 for DMPA and 0.4 for NET-EN (unspecified dose interval). Progestogen-only injectables are also considered to be relatively safe with regard to the risk of serious adverse events (Fraser, 1986a; Garza-Flores *et al*, 1992; Kaunitz, 1994; Kaunitz and Rosenfield, 1994; Lande, 1995; Cayley, 1998; Díaz, 2001), although there are concerns about the reduction of bone density in long-term users of DMPA (Cayley, 1998; Bigrigg *et al*, 1999; Díaz, 2001). The relatively poor side effect profile of IPCs is extensively documented in the international literature (World Health Organization, 1978; Fraser and Weisberg, 1981, Fraser 1982; World Health Organization, 1983; Fraser,

1986b; Lande, 1995; Polaneczky *et al*, 1996; Paul *et al*, 1997; Bigrigg *et al*, 1999; Kaunitz, 2000). However, there is little published literature about the experience of side effects with injectables in South Africa, although side effects are frequently mentioned by users and are well-known amongst health workers (Smit *et al*, 1989a; Smit *et al*, 1989b; Smit and Venter, 1993; Beksinska *et al*, 2001b). As in other parts of the world, side effects are considered to be a major reason for discontinuing the method amongst South African users (Beksinska *et al*, 1998).

Whilst pharmacokinetic studies of IPCs have been undertaken internationally, pharmacokinetic studies of these drugs, when used by South African women, are entirely lacking. It is widely recognised that a high priority should be placed on understanding the pharmacokinetic variability of drugs (Whiting *et al*, 1986) and the assessment of pharmacokinetic parameters of contraceptives is considered to be critically important in assessing efficacy and side-effects (Sang, 1994). Given their extensive use, the lack of pharmacokinetic data for IPCs in South African women is a serious omission, as international studies suggest that regional and population differences, and intraindividual and interindividual variation exist in the pharmacokinetics of steroidal contraceptives (Fotherby *et al*, 1980b; Sang, 1994; Garza-Flores *et al* 1994).

Importantly, a pharmacokinetic study undertaken amongst Thai and Mexican women found that medroxyprogesterone acetate disappeared more rapidly from the blood and that return of ovulation was more rapid in the Thai than in the Mexican women participating in the study (Garza-Flores *et al*, 1994). These authors postulated that the pharmacokinetic differences between the Thai and Mexican women could be explained by ethnic differences

in fat distribution and the behaviour of fat cells in steroid storage. The implications of this study for South African women are important, as it is possible, given the morphology of African women, that DMPA may remain in the body for longer periods of time than expected. Garza-Flores *et al* (1992) recommended that each country or region collect its own pharmacological data for fertility regulation agents, pointing to the need for pharmacokinetic studies to be undertaken amongst African users of the injectable. Further, an extensive literature search reveals that no population[2] pharmacokinetic studies of injectable hormonal contraceptives have been published and Sang (1994) highlights the need to undertake population pharmacokinetic studies in order to assess regional or population differences. He questions the clinical significance of comparisons made between regions or populations where a population approach has not been adopted and stresses the importance of collecting data in the population actually using the contraceptives. A population approach can be successfully used to estimate population pharmacokinetic data from sparse clinical data (Whiting and Kelman, 1985).

Despite its proven efficacy and its widespread use, the injectable contraceptive has been an extremely controversial method. The pharmaco-politics surrounding this form of contraception has long been under debate in South Africa and elsewhere. An important theme in this debate has been the coercive imposition of long-acting injectable contraceptives (Weisberg, 1992; Chimere-Dan, 1993; Moskovitch and Jennings, 1996; Kaufman, 1997), particularly amongst black women, in the apartheid era (Gready, 1996). Whilst in post-apartheid South Africa the context of the debate has

[2] Population Pharmacokinetics: Defined as ".. the estimation of population-typical (e.g. mean) and population-variability (e.g. standard deviation) values for each pharmacokinetic parameter" (Sang, 1994, p. 233).

changed, the concerns remain similar. Moreover the issues of women's rights in reproductive health, and more specifically freedom of contraceptive choice, informed consent, quality of care and safety of contraceptive method have come more sharply into focus: "The basis for action in family planning, as stated in the Programme of Action of the United Nations International Conference on Population and Development, must be to enable couples and individuals to decide freely and responsibly the number and spacing of their children, to have information and means to do so, to ensure informed choices and to make available a full range of safe and effective methods" (World Health Organization, 1996a, p.1). South Africa's National Health Policy, based on the primary health care approach to the delivery of health care, emphasises reproductive health and contraceptive choice as a priority. An important component of the South African National Drug Policy is its emphasis on the promotion of the rational use of drugs (Department of Health, 1996). The White Paper on Health states that " Women and men will be provided with services which will enable them to achieve optimal reproductive and sexual health" (Department of Health, 1997, p.98). These progressive policy developments have important implications for the use and provision of the widely used injectable hormonal contraceptive method in South Africa.

Considering the wide-spread use of IPCs in South Africa, the controversy about its use and the need to promote informed and rational use of this method of contraception, research which examines the extent of use, the demographic characteristics of users, reasons for choice, side effect profile and the relative advantages and disadvantages of brands is essential. Research of this nature becomes particularly important in a setting like

South Africa where HIV prevalence, fertility rates and teenage pregnancy rates are high as illustrated below.

There has been a dramatic increase in HIV infection in South Africa, with sero-prevalence among antenatal clients of public sector health clinics increasing from less than 1% in 1990 to almost 25% in 2001. KwaZulu-Natal is particularly hard-hit with a prevalence of 34% amongst women attending antenatal clinics (Department of Health, 2002). Of great concern are the HIV rates in young pregnant women amongst whom the prevalence was found to be 15% in 2001 (Department of Health, 2002). Pregnant women in their late twenties were found to have the highest infection rate (31%) with a rate of 28% found for those aged 20 to 24 years (Department of Health, 2002). A recent national population-based survey of South African men, women and children, irrespective of whether or not they were sexually active, estimates the HIV prevalence to be 11%, with 15% in the 15-49 year age group found to be HIV positive. Prevalence amongst women in the age group 25-29 years was the highest at 32% (Shisana and Leickness, 2002). HIV infection is reported to be more prevalent among women than men, women are infected at a younger age than men, (Health Systems Trust, 2000; Shisana and Leickness, 2002) and Africans are disproportionately infected compared to other race groups (Shisana and Leickness, 2002.

Although contraceptive prevalence is relatively high in South Africa (Department of Health *et al* (2002), so is teenage pregnancy, especially amongst rural South African women (Makiwane, 1998). The 1998 SADHS reports that by the age of 19 years, 35% of teenagers would be pregnant (Department of Health *et al*, 2002). Further, many teenage mothers are

unmarried (Makiwane, 1998; Garenne *et al* 2000). The rate of unplanned pregnancies is also high, as indicated by a recent survey of women attending primary health care facilities in South Africa in 1999/2000, where 65% of those ever pregnant indicated that they had been pregnant (at least once) when they were not ready to have a baby. Fourteen of the 89 health facilities surveyed in this study were those which served the Hlabisa district, including the Hlabisa Hospital, and the rate of unplanned pregnancies reported by clients attending these clinics was higher than in the other areas (78%) surveyed (Smit *et al*, 2001). The SADHS also found high rates of unplanned or mistimed pregnancies (Department of Health *et al*, 2002).

Given the high HIV prevalence, especially amongst young women, the low use of barrier contraceptive methods is disquieting. The 1998 SADHS (Department of Health *et al*, 2002) reported current condom use to be 2% amongst women sexually active in the 4 weeks prior to being interviewed. Condom use amongst sexually active women aged 15-24 years was 4%. By contrast, this survey found that the most widely used contraceptive method was the injection, which was currently used by 27% of all women aged 15-49 and by 30% of women sexually active in the 4 weeks prior to being interviewed. It is particularly popular amongst younger users, being used by 51% of 15-19 year old women who were sexually active in the 4 weeks prior to interview. Unlike the barrier methods, injectables do not offer protection against HIV and sexually transmitted infections (STIs). Moreover, there are questions about whether injectable hormonal contraceptives may increase the risk of contracting HIV and other STIs (Daly *et al*, 1994; Marx *et al*, 1996; Mostad *et al*, 1997; Stephenson, 1998). Whether a relationship exists between progestogens and HIV

transmission warrants further investigation (Family Health International, 1996) as the evidence currently available is conflicting (Ntozi and Kirunga, 1998; Stephenson, 1998).

The more recent Nelson Mandela/Human Sciences Research Council survey conducted in 2002 found higher levels of condom use amongst men and women in the 15-24 year age range (57% and 46% respectively at last sexual intercourse) (Shisana and Leickness, 2002). This survey did not collect data on hormonal contraceptive use. While condom use may be increasing amongst younger South Africans, it is likely that some young people use two methods for dual protection: condoms for HIV/STI prevention, and the injectable for the most effective method of pregnancy prevention. For instance, Morroni *et al* (2003) found that dual method use was more common amongst primary health facility clients than condoms used alone. An integrated strategy which addresses contraceptive needs and the simultaneous need to prevent HIV and STIs is advocated (Ntozi and Kirunga, 1998, Mantell *et al*, 2003; Morroni *et al*, 2003). In order to do this, a sound understanding of injectable use in South Africa is urgently required.

Little research focusing exclusively on injectable hormonal contraceptives has been undertaken in South Africa. Few studies have drawn comparisons between the two injectable products available (Depo-Provera® and Nur-Isterate®). Even fewer studies examine a number of interlinked aspects on utilization and pharmacokinetics of injectable contraceptives. Moreover, research which has been undertaken has been largely clinic-based, amongst current users of the injectable contraceptive. The clinic-based orientation of the scant research that has been undertaken has meant that the voices of those who have discontinued injectable use, and those who have never opted to use it, have seldom been

heard. In-depth studies of this nature have also not been undertaken in rural areas where the injectable method is extensively used, and where HIV rates are at their highest.

FOCUS OF THE THESIS

This thesis investigates and analyses factors which impact on utilisation of long acting injectable hormonal contraceptives in South Africa. Findings from this comprehensive research programme will feed into and inform, on a scientific basis, contemporary policy formulation about appropriate provision and use of injectable contraceptives. This is particularly necessary in the context of soaring HIV prevalence, which is driving a move towards the promotion of barrier methods of contraception and dual method use (Department of Health, 2001). As detailed below, the thesis provides primary data collected at household and health facility level in a deep rural area of KwaZulu-Natal, South Africa, and at family planning clinics in the Durban Metropolitan area. It also comprehensively and critically reviews, analyses and synthesizes data from secondary sources in order to understand, interpret and validate primary data. Guidelines for injectable contraceptive use within a progressive reproductive health policy are developed and priority research needs are identified.

a) The primary research comprises one of the largest community-based surveys ever undertaken in a deep rural area of South Africa. The geographical focus of this study is the Hlabisa District of KwaZulu-Natal, and the study is designed to provide primary data about:
   - the prevalence of long acting progestogen-only injectable contraceptive use
   - injectable contraceptive product mix (Depo-Provera® and Nur-Isterate®)

- contraceptive method mix
- characteristics of the injectable contraceptive user
- reasons for choosing to use injectable hormonal contraceptives
- side effects experienced by current and previous users of injectable hormonal contraceptives
- discontinuation rates and reasons for discontinuation of the injectable method
- perceptions of users and nonusers, and community groups about side effects and reversibility of injectable contraceptives.

b) Findings from a population pharmacokinetic study of DMPA undertaken at family planning clinics in Durban, South Africa are reported.

c) This thesis also examines data drawn from secondary sources as follows:
   - primary data obtained from the community-based survey are compared with the contraceptive use patterns reported in the 1998 South Africa Demographic and Health Survey
   - a comprehensive review of the literature on injectable contraceptive use in South Africa, Africa, and other parts of the world, including a review of randomised clinical trials, pharmacokinetic and pharmacodynamic studies and other clinical studies of the injectable contraceptive is undertaken.

d) A cost analysis of DMPA versus NET-EN use in South Africa is undertaken.

e) Guidelines for the rational provision, choice of contraceptive method and use of injectable contraceptives are developed and priority areas for further research are identified.

AIM AND RESEARCH QUESTIONS

The aim of this thesis is to develop a picture of long acting progestogen-only injectable contraceptive use among South African women, with a view to informing contemporary policy formulation for appropriate contraceptive service provision.

This is not a thesis which seeks to test one or two hypotheses. It is more inductive in orientation and involves:

- The scoping of injectable contraceptive use in rural South Africa and the identification of possible statistical associations and their statistical analysis.
- A comparative analysis of DMPA versus NET-EN focusing particularly on utilization patterns, side effects, discontinuation patterns and costs.
- A pharmacokinetic analysis of depot medroxyprogesterone.

To do this, the following research questions are posed:

1. What is the prevalence of injectable contraceptive use amongst rural women in KwaZulu-Natal, South Africa?
2. What are the demographic characteristics of the injectable contraceptive user?
3. What other contraceptive methods are used by women in rural KwaZulu-Natal?
4. What side effects are experienced by users of the two progestogen-only injectable contraceptive products?
5. What are the discontinuation patterns of injectable contraceptive use?
6. What are the costs of providing one injectable contraceptive brand compared to the other?
7. What are the pharmacokinetics of depot medroxyprogesterone acetate?

8. What are appropriate recommendations for rational use of injectable contraceptives?
9. What aspects of injectable contraceptive use should be investigated further?

FORMAT OF THE THESIS

The issues addressed in this thesis are numerous, complex and often interrelated. To facilitate reading and application of the findings and recommendations to practice, the thesis is divided into two main sections as follows:

Section 1: A detailed description and analysis of injectable contraceptive use including: a detailed literature review; the methodology used in the community-based survey undertaken in the Hlabisa district of KwaZulu-Natal; survey data and analysis; a discussion section.

Section 2: The Pharmacokinetics of depot medroxyprogesterone acetate including: a detailed review of the literature; the methods used in collecting and analyzing the data obtained from family planning clinics in the Durban Metropolitan area; a description of the data and application of the population approach to determine pharmacokinetic parameters of depot medroxyprogesterone acetate; a discussion section.

These two sections are preceded by an overall introduction chapter and copies of the four publications emanating from the thesis findings. In the concluding chapter of the thesis recommendations for rational provision of injectable contraceptives and priority areas for further research are presented.

CONTRIBUTION TO THE FIELD

A main contribution of this study to the field is to provide the first comprehensive description and analysis of injectable contraceptive use in a deep rural area in South Africa. It serves to address the paucity of rigorous community-based research on injectable hormonal contraceptives and to establish user experiences amongst rural women. The clinic-based orientation of the few existing South African studies on injectable contraceptives has meant that little is known about reasons for discontinuation of the injectable, or about why some women do not access contraceptive services. This study addresses this knowledge gap and in this respect makes a unique and original contribution.

The inferences drawn from this study are wide in scope and have important policy implications with respect to the provision of injectable contraceptives, not only in rural KwaZulu-Natal, but also in the rest of South Africa and elsewhere in Africa. The guidelines for provision and rational use of injectable contraceptives developed in this thesis are considered a major contribution to the effective formulation of reproductive health policy. Whilst others (Lucas, 1992; Chimere-Dan, 1993; Chimere-Dan 1996; Kaufman 1997) have provided analyses of "reproductive control", family planning and contraceptive use in South Africa more broadly, this is the first comprehensive study which focuses specifically on the injectable contraceptive.

The study has, based on empirical findings, identified a number of unique outcomes and correlations which suggest an agenda for further research. Identifying these associations is considered a major contribution. Particularly important in this regard are side effects,

not documented in the literature, reported by South African injectable users. The relationship between age of user and injectable contraceptive product used is also highlighted.

An in-depth review of studies reporting on utilization patterns, efficacy, reversibility, side effects and discontinuation patterns experienced by users of both progestogen-only contraceptive methods since the method was first introduced in South Africa in the late 1960s is provided. An attempt is made to interpret the meaning of this information in relation to the experience of South African women. Little analysis of this kind has been undertaken amongst African women. Further, many of the studies were undertaken in the late 1970's and early 1980's. Current practice tends therefore to be based on studies undertaken over two decades ago. A critical examination of the design of these studies is long overdue and is another important contribution of this thesis. Data drawn from secondary sources are utilized and synthesized into a set of reviews which have value in their own right. More specifically, contributions in this regard include a review of contraceptive use patterns reported in the 1998 South Africa Demographic and Health Survey and a review of studies which examine injectable method reversibility, side effects and discontinuation patterns of injectable users.

Another unique contribution is the first ever population pharmacokinetic study of DMPA which includes an exhaustive review of relevant pharmacokinetic literature.

SECTION 1

INJECTABLE CONTRACEPTIVE USE IN RURAL SOUTH AFRICA

LIST OF TABLES: SECTION 1

LIST OF FIGURES: SECTION 1

CHAPTER 1.1 LITERATURE REVIEW AND OBJECTIVES

In this chapter a detailed review of studies relevant to the use of long acting progestogen-only hormonal contraceptive injectables in South Africa is undertaken. Published surveys, clinical trials, and reviews, focusing particularly on utilisation patterns, efficacy, reversibility, side effects and discontinuation patterns of medroxyprogesterone acetate (DMPA) and norethisterone oenanthate (NET-EN), were sought by means of computerized and hand searches. Copies of relevant publications and citations from these publications were obtained and reviewed. International and South African policy documents were also reviewed. As there appears to be a shift away from the predominant use of DMPA, to NET-EN, in South Africa, (Wood, Maepa and Jewkes, 1997RM473; Beksinska, 1998; Beksinska *et al*, 2001a) studies which specifically compared DMPA and NET-EN were particularly sought. A review of the pharmacokinetic literature is not included here as a detailed review of the pharmacokinetics of DMPA is provided in Section 2, Chapter 2.1.

This extensive literature search reveals that few clinical trials have been undertaken in Southern Africa, few studies have been undertaken amongst younger users, DMPA is better researched than NET-EN and most published studies, upon which review after review are based, were undertaken in the 1970s and early 1980s. Few systematic reviews of studies have been undertaken and studies directly comparing DMPA and NET-EN preparations are rare. Methodological limitations and differences in study population, sample size, subject recruitment, exclusion criteria, frequency and nature of procedures for follow-up, types of observations made, doses and dosing regimens of injectable progestogen-only contraceptives (IPC), provider counselling, definitions of side effects,

methods of recording, reliability of self-reported data, methods of analysis, criteria for determining efficacy or discontinuation rates, and large inter-site variability in some studies, make it difficult to evaluate and compare the published data. Trussell *et al* (1990) provide a useful account of difficulties in analysing and comparing contraceptive efficacy trials. A critical review of the literature on injectable progestogen contraceptives published since the late 1950s, including a comparison of DMPA and NET-EN, is provided in this chapter.

1.1.1 INJECTABLE CONTRACEPTIVE UTILISATION PATTERNS

The first injectable progestin was developed in 1953 and NET-EN was the first injectable contraceptive, developed in 1957 (Lande, 1995). MPA was first synthesized in the late 1950s (Babcock *et al*, 1958) and the first clinical trials of DMPA were conducted in 1963 (Weisberg, 1992). Johns Hopkins' Population Program's Population Report (Lande, 1995) provides a comprehensive international review of injectable contraceptive use up to the mid-1990s (Lande, 1995). According to this report, DMPA was available in more countries in the world than NET-EN. In general, injectable contraceptives were not a commonly used method except in South Africa, Indonesia, Thailand and New Zealand (Lande, 1995). The report, published in 1995, estimates that 12 million couples in developing countries used injectable contraceptives, and Bigrigg *et al* (1999) reported that Depo Provera® has been used by more than 30 million women in the world since its introduction in 1963.

Although it has been widely available in the developing world since its introduction, DMPA was only approved for contraceptive use in the United States of America (USA) in 1992 (Weisberg, 1992). Since the USA Food and Drug Administration's (FDA) approval of DMPA for contraceptive use, and the granting of a general license for DMPA

in the United Kingdom (UK) in 1995 (Cayley 1998), use of DMPA has increased in countries in the developed world (Moore *et al*, 1995; Bigrigg *et al*,1999; Margulies and Miller, 2001). For instance, Bigrigg *et al* (1999) report that the number of women in the UK using Depo-Provera® increased from 40000 in 1993 to 270000 in 1996. There also appears to be increasing popularity of injectable contraceptives among adolescents (American Health Consultants, 1994; Davis, 1996; Chotnopparatpattara and Taneepanichskul, 2000; Margulies and Miller, 2001).

The Population Report (Lande, 1995) indicated that the ratio of DMPA to NET-EN shipments by the United Nation's Population Fund was 3:1, and stated further that donor agencies reported increasing orders for both progestogen-only injectable products in the 1990s. Use of injectable contraceptives by married women of reproductive age, based on survey findings from 1984 to 1994, as published in the Population Report (Lande, 1995) were found to vary widely from country to country. For instance, the percentage of contraceptive users using injectables in India (1992-1993) was reported to be 0%, and in Burundi (1987) to be 100%. Figures for South Africa (1987-1989) were reported to be 41%, the third highest usage rate of the 55 countries listed. The report does not differentiate between DMPA and NET-EN use and figures providing this level of detail do not appear to be readily available in a comprehensive form.

A more recent account of worldwide contraceptive use amongst women married or in informal unions reports that injectable contraceptives were used by 4% of women in less developed countries and by 4% of women in Sub-Saharan Africa (Population Reference Bureau, 2002). This data sheet claimed to provide the most recent statistics on contraceptive use globally, reporting on 138 countries in the developed and developing

world. It should be noted that data on injectable use were not available for all countries included in the data sheet. The data are based on reproductive health surveys from 1990 onward, and injectable use amongst all women married or in informal unions in South Africa was reported to be higher (23%) than in any other country. The next highest rate of use was in Indonesia (21%), followed by Malawi and Thailand (16% each) and Peru (15%). Use in the UK, New Zealand and the USA was reported to be quite low (2%, 2% and 1% respectively).

According to Bongaarts and Johansson (2002) the contraceptive method mix is highly variable across regions and countries, with sterilization more prevalent in Asia and Latin America, and oral contraceptive (OC) and traditional method use more common in Africa. They comment that in some countries a single method accounts for more than half of all use. The predominance of one method is ascribed to the emphasis placed on that method by providers, with little method choice offered to users (Bongaarts and Johansson, 2002).

As reported in the introductory chapter of this thesis, the widespread use of the injectable method among Black South African women was the focus of much criticism in the 1970s and 1980s. Nevertheless, post-apartheid, with a progressive national contraceptive policy in place (Department of Health, 2001), the method is still the most widely used contraceptive -- being used, according to the South Africa Demographic and Health Survey (SADHS), by 27% of all women aged 15-49 and by 30% of sexually active women[3] (Department of Health *et al*, 2002). As Bongaarts and Johansson (2002) found for certain countries in the

[3] The SADHS defines "sexually active" as those who were sexually active in the four weeks preceding the interview (Department of Health *et al*, 2002).

developing world, South African contraceptive use reflects a heavy reliance on one method, the injectable method, used by 54% of current contraceptive users in 1998 (Department of Health *et al*, 2002).

Although the contraceptive prevalence found in the SADHS was higher in urban than non-urban areas, injectable use was higher in non-urban areas (33% versus 28% amongst sexually active women). Of the non-urban women using a modern method of contraception, 62% were using the injectable (Department of Health *et al*, 2002). Contraceptive prevalence in KwaZulu-Natal (KZN) was lower (58%) than the overall contraceptive prevalence (62%), and injectable contraceptives were used by 26% of sexually active women -- lower than all but one other province (23% in Gauteng) (Department of Health *et al*, 2002). Just under half (46%) of KZN women practicing contraception were using the injectable method. The SADHS does not provide statistics for urban and non-urban areas within provinces. The injectable method was particularly popular amongst younger South African users, used by 51% of 15-19 year old sexually active women (Department of Health *et al*, 2002). This means that 80% of these young women who were using a modern method of contraception, were using the injectable.

The SADHS does not break down injectable use according to whether DMPA or NET-EN was being used. Findings from other studies show that NET-EN is particularly popular amongst younger, nulliparous South African women (Wood *et al*, 1997; Beksinska *et al*, 1998; Beksinska *et al*, 2001a). However no studies have specifically explored the reasons for this pattern of use. Comparative data of this kind is not readily available in other

countries of the world, perhaps because of the availability of only one injectable product in most countries.

After the injectable contraceptive, the next most commonly used methods were the oral contraceptive and female sterilization, used by 13.2% and 12% of sexually active women respectively (SADHS). The intrauterine device (IUD), male condom and male sterilization were each used by 2% of sexually active women (Department of Health *et al*, 2002). The SADHS also reports that condom use at last sexual act was 8%.

The injectable contraceptives currently available in South Africa are the progestogen-only preparations, depot medroxyprogesterone acetate (DMPA), registered as Depo-Provera® and the generic equivalent, Petogen®, and norethisterone oenanthate (NET-EN) registered as Nur-Isterate®. DMPA was first used in South Africa in the late 1960s (Karstadt, 1970; Ferguson, 1974), and NET-EN became available in 1978 (Sapire, 1979). The product formulation, brand name, manufacturer and dosing schedule of each of these products is provided in Table 1.1.1. The same progestogen-only formulations are widely available across the world. According to Lande in a report published in 1995, DMPA was registered in over 100 countries and NET-EN in over 60 countries worldwide. Combined injectable contraceptives (CICs), which contain a combination of oestrogen and progestogen, are not yet registered for use in South Africa, but are widely available in other parts of the world, especially China and Latin America (Lande, 1995).

Table 1.1.1 Formulation, brand name, and dosing schedule of injectable contraceptives available in South Africa

Formulation	Brand Name	Manufacturer	Dosing Schedule
Progestogen-only: DMPA 150mg depot medroxyprogesterone acetate	Depo-Provera	Pharmacia & Upjohn	(a) Every 3 months (b) Every 12 weeks
Progestogen-only: DMPA 150mg depot medroxyprogesterone acetate	Petogen	Intramed	(a) Every 3 months (b) Every 12 weeks
Progestogen-only: NET-EN 200mg norethisterone oenanthate	Nur-Isterate	Schering	(a) Every 8 weeks for 24 weeks, then every 12 weeks thereafter (b) Every 8 weeks

(a) According to the approved package insert (Pharmacia and Upjohn, 1993; Intramed, 1993; Schering, 1992)
(b) According to the South African Medicines Formulary (Gibbon, 2000)
Note: according to Lande (1995), the 2-month schedule for NET-EN is recommended by the World Health Organization

1.1.2 MECHANISM OF ACTION AND EFFICACY OF INJECTABLE PROGESTOGEN CONTRACEPTIVES

1.1.2.1 Mechanism of Action

The main mode of action of DMPA is the inhibition of ovulation by suppression of the release of pituitary gonadotrophins, resulting in the abolition of the mid-cycle surge of lutenizing hormone (LH) and follicle stimulating hormone (FSH) (Mishell *et al*, 1968; Mishell *et al*, 1972; Kirton and Cornette, 1974; Schwallie, 1974; Jeppsson and Johansson, 1976; Garza-Flores *et al*, 1992; Mishell, 1996; Clark *et al*, 2001). Other mechanisms of action include alteration of cervical mucus secretion; thinning of the endometrium thus secreting insufficient glycogen to support the entry of a blastocyte into the endometrial cavity (Mishell 1968; Mishell, 1996); alteration of the normal contractile pattern of the reproductive tract (Kirton and Cornette, 1974) and inhibition of capacitation of spermatozoa and reduced sperm motility (Theron and Grobler, 1998). DMPA does not have oestrogenic, anti-oestrogenic or androgenic effects (Theron and Grobler, 1998). A more detailed account of the pharmacology and pharmacokinetics of DMPA is provided in Section 2.

The contraceptive mechanism of NET-EN is more complex than that of DMPA (Fraser and Weisberg, 1981; Theron and Grobler, 1998), inhibiting fertility through a mixed mechanism (Benagiano and Primiero, 1983a). Initially, the effect is the same as DMPA:- inhibition of ovulation, thickening of cervical mucus, prevention of implantation and possibly alteration of tubal function (El-Mahgoub *et al*, 1972; Fraser and Weisberg, 1981; Benagiano and Primiero, 1983a; Theron and Grobler, 1998). After 60 days, ovulation is not always inhibited and the main action is reported to be on the cervix (Fraser and Weisberg, 1981; Benagiano and Primiero, 1983a; Theron and Grobler, 1998).

Little is known about the molecular mechanisms of action of DMPA and NET-EN, but work in progress by a team of researchers in the Department of Biochemistry at the University of Stellenbosch, led by Dr Janet Hapgood, suggests that the two substances have different molecular modes of action (J Hapgood, pers. comm., January 2001).

1.1.2.2 Efficacy

The progestogen-only injectable contraceptives are demonstrably extremely effective (Mishell *et al*, 1968; Tyler, 1970; Garza-Flores *et al*, 1992; Kaunitz, 1992; Garza-Flores *et al*, 1994; Kaunitz, 1994; Kaunitz and Rosenfield, 1994; Lande, 1995; Bigrigg, 1999). Many clinical trials have investigated the efficacy of these preparations, but most were conducted some time ago, in the 1970s and early 1980s. Efficacy findings are discussed below and a summary of relevant studies is presented in Table 1.1.2.

DMPA Studies

One of the first efficacy studies undertaken on DMPA (150mg given every 3 months) found no pregnancies, even amongst women who reported from one to four weeks late for

their next injection (Mishell *et al*, 1968). This study was conducted amongst 100 Caucasian women and lasted for one year. Another early collaborative study of 3857 women receiving 150mg of DMPA every three months was conducted between 1965 and 1971. It set the two year cumulative pregnancy rate for DMPA, calculated by the life table technique, at 0.53 per 100 women after two years (Schwallie and Azenzo, 1973). The DMPA efficacy findings (pregnancy rate=0.4 at 15 months) in Chinnatamby's (1971) study were comparable with the efficacy reported in the World Health Organization (WHO) (1983) trial (Table 1.1.2). A recent study, which retrospectively examined contraceptive failures amongst DMPA users, reported to the Insurance Division of the Planned Parenthood Federation of America Inc. from 1994 to 1998, found a crude rate of pregnancy of 0.42 per 1000 women using DMPA in each year (Borgatta *et al*, 2002). Overall, in the studies summarized in Table 1.1.2, the failure rates for DMPA were similar.

NET-EN Studies

Banerjee *et al* (1984) conducted a large clinical trial (N=2388) on NET-EN, used by Indian women from 16 Human Reproductive Research Centres located in different parts of India, with two dosing schedules (two monthly, and two monthly for six months then three monthly). They reported failure rates at six months of 1.2 per 100 users for the two monthly group, and 0.7 per 100 users from the second dosage regimen[4] These authors suggested that the unexpectedly high method failure rates in the first six months of use, compared with findings from previous studies, could be due to the lower average body weight of Indian women compared to women from western countries. However, failure rates reported in a field study in six family planning clinics in Bangladesh (Rahman *et al*,

[4] Note: during the first six months the dosage schedule was the same for the two groups.

1985) were lower than the Indian study (Banerjee *et al*, 1984). In this study, Rahman *et al* (1985) found a cumulative pregnancy rate at 18 months of 0.4 for NET-EN given every 8 weeks for six months and then every 12 weeks. In a study of Mexican women taking NET-EN on a two monthly dosage regimen, the efficacy at 18 months was reported to be 0.3 (Meade *et al*, 1984). The NET-EN efficacy findings from the studies summarized in this chapter are less consistent, even within dosage regimens, than the DMPA efficacy findings.

Comparative Studies

One of the earliest multi-national clinical trials compared the efficacy of DMPA (150mg) and NET-EN (200mg), with both preparations given every twelve weeks (World Health Organization, 1977). This study was to have lasted for two years, but was terminated after about one year as the NET-EN pregnancy rate exceeded the allowed maximum. The cumulative pregnancy rate at one year was found to be 0.7 for DMPA and 3.6 for Net-EN. It should be noted that 75% of all conceptions with NET-EN were estimated to have occurred during the first injection period, that 54% of all pregnancies occurred in only two of the ten centres (Bangkok and Chandigarh), and that efficacy was found to decrease with decreased body weight, as the mean admission body weight of NET-EN users who became pregnant was significantly lower (World Health Organization, 1977). El-Mahgoub and Karim (1972), in a study of Egyptian women (1968-1971), found no pregnancies with NET-EN given every 84 days, even though, in some instances, delays between injections of 95 days were reported. Zanartu and Navarro (1968) in a study in Chile, and Chinnatamby (1971) in a study in Ceylon (now Sri Lanka), reported a pregnancy rate of 2.3 per 100 woman-years for NET-EN given every twelve weeks, which is lower than the pregnancy rate recorded in the World Health Organization (1977)

trial. A later WHO multi-national clinical trial (World Health Organization, 1983) of 1587 women given DMPA every 90 days, 789 women given NET-EN every 60 days, and 796 women given NET-EN every 60 days for 6 months and then every 84 days, found the cumulative life-table accidental pregnancy rates after two years to be 0.4, 0.4 and 1.4 per 100 women respectively.

Reviews

Several reviews of studies on progestogen-only injectable efficacy have been published and the pregnancy rates are reported as follows:

- DMPA 150mg given every 12 weeks/3 months: 0 to 1.2 pregnancies per 100 women (Fraser and Weisberg, 1981; Fraser, 1982; Fraser and Holck, 1983); 0.5 per 100 woman-years in the largest trials (Fraser and Weisberg, 1981; Fraser, 1982); not exceeding 0.5 per 100 woman-years at one year Benagiano and Primiero, 1983a); life table failure rate: less than 1.0 per 100 woman-years (Hickey and Fraser, 1995); first-year failure rate in the United States of 0.3% (Lande, 1995); in-use failure rate of 0.0 to 0.7 per 100 woman-years (Kaunitz, 1992; Bigrigg *et al*, 1999; Kaunitz, 2000); in taking the mean of all available studies at the time, a 'typical' failure rate of 0.3% (Trussell and Kost, 1987).
- In an evaluation of five large controlled multi-centre studies, Kaunitz (1992) reported that there were only 24 pregnancies among 7849 women using Depo-Provera for 122496 patient-months.
- Weight and concurrent medication does not affect DMPA efficacy, presumably because of high circulating levels of MPA (Kaunitz, 2000).
- Contraceptive failure of DMPA with perfect or typical use is <0.3% per year which is comparable with the failure rate of surgical sterilization (Kaunitz,2002)

- NET-EN given every 8 weeks or 60 days: less than one pregnancy per 100 woman-years at 18 months (World Health Organization 1982); 0.6 per 100 woman-years (Benagiano and Primiero, 1983b).
- NET-EN given 10 weeks after the first injection, and then every 12 weeks; or given every 60 days or 8 weeks for six months and then every 12 weeks: 0.7 per 100 woman-years (Benagiano and Primiero, 1983b); less than 1 per 100 woman-years at 12 months and 1.6 at 18 months (World Health Organization 1982).
- NET-EN given every 12 weeks/90 days: 3.6 per 100 woman-years (World Health Organization, 1982); 1.5 to 5.2 per 100 woman-years (Benagiano and Primiero, 1983b)
- NET-EN (unspecified regimen): 1.0 to 1.5 per 100 woman-years (Fraser, 1982); 0.5 to 1.5 (Bigrigg *et al*, 1999).
- Trussell *et al* (1990) provide "summary estimates of contraceptive failure" and give the lowest expected, and typical percentage, of accidental pregnancies in the United States, during the first year of use, as 0.3 for DMPA and 0.4 for NET-EN (unspecified dose interval).

Bigrigg *et al* (1999, p.71) state that Depo Provera is "... the most effective reversible contraceptive available", with a user failure rate approaching the method failure rate. The efficacy of DMPA and NET-EN given every 8 weeks is comparable, however, since women on the NET-EN regimen have to return to the clinic every eight weeks (versus every 12 weeks with DMPA) for their next injection, the in-use failure rate for NET-EN may be higher.

Conclusion

Whilst there are minor differences in published efficacy rates, depending on the study, timing of the first injection, the population, body weight, dosage regimen and provider training, the efficacy rate of both the IPCs is very high. The efficacy of 150mg DMPA given every 90 days and 200mg NET-EN given every 60 days are comparable. Because women using NET-EN have to return for their next dose earlier than DMPA users, the in-use failure rate for NET-EN may be higher.

Table 1.1.2 Summary of findings on efficacy from relevant studies

Study	Notes	Measure	DMPA 150mg*	NET-EN 200mg#		
				Regimen 1	Regimen 2	Regimen 3
			Pregnancy rate per 100 woman-years			
1. Zanartu & Navarro, 1968 (NET-EN only, fertile ♀, Chile, N=130)		Pregnancy rate (average observation per patient for 17.6 months)	N/A	N/A		N=130 2.3
2. Chinnatamby, 1971 (Comparative study, Ceylon - now Sri Lanka, N=1035)	Most NET-EN users who became pregnant, did so in the 1st course of therapy	Pregnancy rate at 15 months	N=515 0.4	N/A	N/A	N=520 2.3
3. El-Mahgoub & Karim, 1972 ("birth control clinic", NET-EN only, Egypt (1968-1971), proven fertility, non-breastfeeding, no hormonal contraceptive history, N=171)	In some instances, delays between injections of 95 days occurred	Pregnancy rate	N/A	N/A	N/A	N=171 0.0
4. Schwallie & Azenzo, 1973† (Multi-centre, collaborative study, 1965-1971, 54 investigators, DMPA only, healthy women, 54.7% were white, demonstrated fertility, N=3857)		Pregnancy rate: at 12 months at 24 months	N=3857 0.31 0.53	N/A	N/A	N/A

* Given every 12 weeks or every 90 days

\# Regimen 1: Given every 60 days; Regimen 2: Given every 60 days or 8 weeks for six months and then every 12 weeks; Regimen 3: Given every 12 weeks.

Table 1.1.2 Continued

Study (WHO=World Health Organization)	Notes	Measure	DMPA 150mg*	NET-EN 200mg#		
				Regimen 1	Regimen 2	Regimen 3
			Pregnancy rate per 100 woman-years			
5. WHO, 1977† (Randomised 10-centre comparative trial, healthy non-breastfeeding ♀ of demonstrated fertility, N=1678) Participating Centres: Alexandria, Bahia-Salvador, Bangkok, Bombay, Chandigarh, Ibadan, Ljubljana, Manila, Utrecht, Lima	Study was to have lasted for 2 yrs, but was terminated after ± 1 yr as NET-EN pregnancy rate exceeded the allowed maximum No pregnancies in Ibadan & Utrecht 54% of pregnancies for NET-EN observed in Bangkok & Chandigarh 75% of all conceptions with NET-EN estimated to have occurred during first injection period Mean admission body wt. of NET-EN users who became pregnant significantly lower	Cumulative 12-month gross pregnancy rate per 100 woman-years *statistically significant*	N=846 0.7 ± 0.4	N/A	N/A	N=832 3.6 ± 0.7
6. WHO, 1983† (2 year multi-national comparative randomized trial, 13 centres, healthy non-breastfeeding ♀ N=3172) Participating Centres: Alexandria, Bangkok, Ibadan, Karachi, Lusaka, Manila, Mexico City, Salvador, Santiago, Ljubljana, Luxembourg, Milan, Utrecht		Cumulative 12-month pregnancy rate per 100 woman-years *not statistic. significant* Cumulative 2-year pregnancy rate/100 woman-years *not statistic. significant*	N=1587 0.1± 0.1 0.4 ± 0.3	N=789 0.4± 0.2 0.4 ± 0.2	N=796 0.6± 0.3 1.4 ± 0.6	N/A

* Given every 12 weeks or every 90 days

Regimen 1: Given every 60 days; Regimen 2: Given every 60 days or 8 weeks for six months and then every 12 weeks; Regimen 3: Given every 12 weeks

† Additional information about the study design obtained from Kaunitz (1992).

Table 1.1.2 Continued

Study	Notes	Measure	DMPA 150mg*	NET-EN 200mg#		
				Regimen 1	Regimen 2	Regimen 3
			Pregnancy rate per 100 woman-years			
7. Banerjee *et al* 1984 (comparative clinical trial of two dosage regimens of NET-EN, Indian ♀, 16 Human Reproductive Research Centres, N=2388)	Speculated that the unexpectedly high failure rates may be a result of lower body weights of Indian women		N/A	N=1181	N=1207	N/A
		Method failure rates: at 6 months *not statistic. significant*		1.2	0.7	
		Life-table reconstructed & day 1 set where dosage schedule was changed (i.e. after the 4th injection) *(statistic. Significant diff. found*				
		at 12 months		0.0	1.1	
		at 18 months		0.2	2.1	
		at 24 months		0.2	6.0	
8. Rahman *et al*, 1985 (field study in 6 clinics, NET-EN only, Bangladesh, N=913)						
Cumulative pregnancy rate at 18months					0.4	

* Given every 12 weeks or every 90 days

\# Regimen 1: Given every 60 days; Regimen 2: Given every 60 days or 8 weeks for six months and then every 12 weeks; Regimen 3: Given every 12 weeks.

1.1.3 RETURN TO FERTILITY

DMPA Studies

Delay in return to fertility has been more extensively documented for DMPA than for NET-EN. A very early study (n=752), conducted from 1965 to 1968 (44months), only one pregnancy occurred (Seymour *et al*,1970). Tyler (1970), in studying the time to returned ovulation in 30 women who had used DMPA, reported that a third of these women ovulated within six months of the last injection and almost all ovulated within a year. McDaniel and Pardethaisong (1973) studied the return to fertility of 135 Thai women who discontinued DMPA to become pregnant, and reported a life-table return to fertility rate of 82% after 14 months. Discontinuation was taken at 15 weeks after the last injection. Even if women lost to follow-up were included in the analysis, the return to fertility rate would have been 71.3% (McDaniel and Pardethaisong, 1973). These authors concluded that "the monthly probabilities of conception among IUD users were equal to, or lower than, those of DMPA users within 4 months of discontinuation" p.511. In a later study of 796 Thai women, Pardethaisong *et al* (1980) reported a median delay before conception after discontinuing DMPA of 5.5 months plus the duration of effect of the last injection, and 4.5 months after discontinuing the IUD. The proportions who did not conceive within one year and two years of discontinuation of these two methods were similar. Prolonged use of DMPA did not appear to increase the delay, and return to fertility among never pregnant and ever pregnant ex-users was similar (Pardethaisong *et al* 1980).

Schwallie and Azenzo (1973) found the mean time to return to normal cyclic menses in 245 women using DMPA was 5.8 months with a range of 1-28 months. A range of 3 to 31.5 months and an average of 12 months from last injection to conception are reported

for 285 women who became pregnant after discontinuing the method. However the authors warn that the number of months to conception may be biased upward as it was not known if the subjects, on discontinuing the method, actually tried to conceive immediately. Schwallie and Azenzo (1973) also found no difference in time to return to fertility between short and long term users of DMPA. Pardethaisong *et al* (1980), in referring to Schwallie and Azenzo's (1973) findings and McDaniel and Pardethaisong's (1973) findings, noted that these earlier studies used different study designs, had smaller sample sizes with women of differing ages and that observations were made for shorter time periods. Nevertheless, the findings from these three studies were fairly consistent. In an updated analysis of the data from the 796 Thai women (Pardethaisong *et al*, 1980), Pardethaisong (1984) concluded that the return of fertility with DMPA is only about a month longer (after the date of the last scheduled injection) than after removal of the IUD.

NET-EN Studies

In 81 Egyptian women who had received at least ten doses of NET-EN injections at a dosing interval of 84 days, El-Mahgoub and Karim (1972) found that a normal menstrual pattern had been established within 2-4 months. Only seven women in the follow-up study wished to conceive, and four of these became pregnant within 5 to 14 months. Fotherby *et al* (1984) found that 14 of 40 women who stopped using NET-EN were pregnant within 12 weeks of discontinuing the method and 21 women within 6 months and suggested that NET-EN does not impair fertility. The Indian Council of Medical Research (ICMR) (Banerjee *et al*, 1986) reported a median time for conception of 7.8 months for 69 NET-EN users who had discontinued use because they planned to get pregnant. The dosage regimen of NET-EN used by the women participating in this study is not mentioned. The ICMR also found that the return to fertility was slower in 51

subjects who had discontinued NET-EN because of amenorrhoea. Only 51% of these women conceived within 12 months, compared with 73% of those who discontinued injectable use as they were planning a pregnancy. A difference in the median time for conception of 4 months longer in NET-EN users who had discontinued the method, compared with former copper IUD users, was reported. The authors of this study concluded that NET-EN does not adversely affect the return of fertility (Banerjee *et al*, 1986).

Comparative Studies

Few studies have been undertaken which directly compare DMPA and NET-EN in terms of return to fertility. However, in a comparative pilot study carried out by the WHO to determine the pharmacokinetic and pharmacodynamic properties of DMPA and NET-EN it was found that ovarian function returns more quickly after discontinuation of NET-EN than after DMPA discontinuation (Fotherby *et al*, 1980b). Garza-Flores *et al* (1985) in a comparative study of 24 women who discontinued DMPA and NET-EN, found that the mean time to return to ovulation occurred significantly earlier with NET-EN than with DMPA – 2.6 months and 5.5 months respectively "... overall data was interpreted as demonstrating a clear-cut difference between the two long-acting progestogens in terms of ovulation suppression" p.31. These authors also conclude that neither DMPA nor NET-EN permanently or irreversibly affect ovarian function (Garza-Flores *et al*, 1985).

Reviews

Several reviews of the reversibility of progestogen-only injectables have been undertaken. Fraser (1986a, p. 40) stated that "the conception rate curve following DMPA use parallels the normal conception rate curve but is shifted 3-5 months to the right". The reviews

show no evidence that the injectables cause permanent infertility (Fraser, 1982; Fraser and Weisberg, 1982; Fraser and Holck, 1983; World Health Organization, 1982; Kaunitz, 1992; Kaunitz, 1994; Fraser, 1986a; Lande, 1995). Nor is it felt that any of the injectables should not be given to adolescent and nulliparous women (Fraser, 1982; Fraser and Holck, 1983; Kaunitz, 1992; Lande, 1995) and no difference in time to return to fertility has been found when comparing long-term and short-term users (Fraser, 1982; Fraser and Holck, 1983; Kaunitz, 1992; Lande, 1995).

In a more recent review, Bigrigg *et al* (1999), in examining early data, suggest that there is no delay in return to fertility with DMPA use if one considers the methodological bias of early studies, which did not take in to account the date of the last DMPA injection. They state further that "if there is a delay it is not statistically significant and is less than 30 days. According to Hatcher *et al* (1997) return to fertility is delayed by DMPA for about 4 months longer on average compared with the combined OC method, IUD, and condoms. It is reported that the pregnancy rates for users of DMPA, the IUD and OCs are the same two years after discontinuation of the method (Lande, 1995).

A South African textbook (Theron and Grobler, 1991; revised edition, 1998), recommended in the early 1990s by the National Department of Health for training of pharmacists and pharmacy students, gives the average time to pregnancy following administration of the last injection of DMPA as 9 months and of NET-EN as 7-8 months The average time to pregnancy reported by these authors for no method is 5 months. The South African Medicines Formulary (Gibbon, 2000, p.215) gives a delay of 'usually 9 months' for DMPA and 'generally' 6 months for NET-EN and the draft National Contraception Service Delivery Guidelines (Department of Health, 2001) records an

average delay of 6-9 months without referring to a particular product. According to the World Health Organization medical eligibility criteria for contraceptive use, the median delay in return to fertility is ten months from the date of the last injection for DMPA and six months for NET-EN (World Health Organization, 2000).

The approved package insert for the NET-EN product (Nur-Isterate®) registered for use in South Africa states that "Following discontinuation, normal ability to conceive usually returns 7-8 months after the last injection" (Schering, 1992). The Depo-Provera® package insert states that "Restoration of normal menstrual cycling may take from 5 to 28 months after the last injection..." (Pharmacia and Upjohn, 1993). There is no reference to reversibility or return to fertility in the Petogen® package insert (Intramed, 1993).

Conclusion

The delay in return to fertility with progestogen-only injectables appears to be only a few months longer than with oral contraceptives, IUDs and condoms, regardless of length of use. The methodological bias of early studies which did not take into account the date of the last DMPA injection should be noted. Further, earlier studies also tended to have smaller sample sizes with women of differing ages, and in some cases observations were made for short time periods. The search of the literature on return to fertility revealed no publication of primary data after 1986. The existing evidence thus seems to be based entirely on these early studies. Published studies also used different study designs. While there is little direct comparative data on the delay in return to fertility between DMPA and NET-EN users, it seems that NET-EN is likely to result in a slightly shorter delay, but there appears to be little long term difference.

1.1.4 SIDE EFFECTS

The poor side effect profile of progestogen-only injectables is extensively documented in the international literature. It is clear that IPCs result in numerous side effects, with many women experiencing a number of side effects concurrently. For instance, in the study of 3857 women undertaken by Schwallie and Assenzo (1973), side effects were reported by 36% of the DMPA users, giving an average of five side effects per woman. Many clinical studies investigate one or other of these products and some directly compare the side effects associated with their use. The injectable contraceptive has also been extensively reviewed. It is beyond the scope of this thesis to review data on every possible side effect. Rather, this sub-section focuses on side effects most frequently reported or most likely to result in discontinuation, particularly in regard to South African women. Studies which compare the side effects experienced with DMPA and NET-EN were of particular interest. To avoid repetition, a selection of only the most pertinent studies and reviews are described below. A summary of studies which compare common side effects experienced by DMPA and NET-EN users is also provided in Table 1.1.3. It is of note that little is documented about side effects experienced by South African injectable users and no publications could be found which provide a detailed description of the experience of side effects amongst South African users.

1.1.4.1 Menstrual Disturbances

The most frequently reported side effects experienced, and those most likely to result in discontinuation, are menstrual disturbances (Zanartu and Navarro, 1968; Seymour *et al*, 1970; Tyler, 1970; Chinnatamby, 1971; El-Mahgoub and Karim, 1972; Schwallie and Assenzo, 1973; World Health Organization, 1977; World Health Organization, 1978; Sapire, 1979; Fraser and Weisberg, 1981, Fraser 1982; Benagiano and Primiero, 1983b;

Fraser, 1983; Howard *et al*, 1985; Belsey *et al*, 1986; Fraser, 1986b; Salem *et al*, 1988; Kaunitz, 1992; Olive and Schlaff, 1992; Datey *et al*,1995; Belsey and World Health Organization Task Force, 1988; Hadisaputra and Affandi, 1990; Keller, 1995; Lande 1995; Polaneczky *et al*, 1996; Paul *et al*, 1997; Beksinska *et al*, 1998; Bigrigg *et al*, 1999; Chotnopparatpattara and Taneepanichskul, 2000; Danli *et al*, 2000; Kaunitz, 2000; Beksinska *et al*, 2001a).

Findings from earlier studies have been criticized, with clinical evaluations referred to by Olive and Schlaff (1992) as "crude and inadequate" because, for instance, of the lack of uniformity in definitions. From the mid-eighties methodological advances led to a more standardized approach and more sophisticated analytical procedures (Olive and Schlaff, 1992). In contrast to the prolific amount of published information worldwide, and despite the widespread use of the injectable contraceptive in South Africa, little data on side effects experienced by South African injectable users are published. One very early South African study was undertaken which compared two dosage regimens of DMPA (150mg every three months and 450 mg every 6 months) (Rall *et al*, 1977). This was a large study (n=19875) undertaken from 1970 to 1975 and few side effects were reported. However, the authors point out that a large number of participants were lost to follow-up and it was not known what proportion of these dropped out for personal reasons.

Bleeding disturbances frequently reported are amenorrhoea, irregular bleeding, spotting between periods, unpredictable bleeding patterns, heavy bleeding, prolonged menses (Kaunitz, 1992; Kaunitz, 2000; International Planned Parenthood Federation, 2002). Some side effects (e.g. amenorrhoea) predominate in the early months of use, but with increased duration of use, amenorrhoea becomes very common (Kaunitz, 1992; Kaunitz, 2002). The

effects of the IPCs on the menstrual cycle result in what has been referred to as "menstrual chaos" (Fraser, 1986b; Datey *et al*, 1995). Tyler (1970, p.3), in referring to bleeding problems associated with DMPA, states that "These occurrences are so numerous as to be considered an inherent part of the method."

DMPA Studies

Data from menstrual diary records of 314 women using DMPA were analysed by Belsey and the World Health Organization Task Force (1988) and showed that DMPA users had unpredictable menstrual patterns. What is predictable however is that the proportion of woman experiencing excessive bleeding decreases over time (Schwallie and Azenzo, 1973). In the study by Belsey and the World Health Organization Task Force, (1988), the rate of amenorrhoea rose from 8% in the first injection interval to 45% in the fourth. By contrast, prolonged bleeding decreased from 29% in the first injectable interval to 10% in the fourth. Further, a marked inter-regional variation in bleeding patterns was noted. For instance, by the fourth dosing interval amenorrhoea was reported by 25% of respondents from Europe compared with 72% of those from North Africa (Belsey *et al*, 1988). In a study among 108 Thai adolescents (under 19 years) amenorrhoea increased from 7% in the first injection cycle to 58% by the fourth. In the same time-frame, irregular bleeding decreased from 94% to 42% Chotnopparatpattara and Taneepanichskul, 2000). The main side effects reported in a multi-centre clinical trial of DMPA use among 1994 Chinese women who were followed up for a total of 20294 months were spotting, bleeding, prolonged bleeding and amenorrhoea (Danli *et al*, 2000). Sixty Thai women between 36 and 45 years were followed for a year and most commonly reported irregular bleeding with DMPA use (Taneepanichskul, 2000).

NET-EN Studies

In a trial conducted from 1968 to 1971 amongst 171 NET-EN users in Egypt, El-Mahgoub and Karim (1972) found that a high proportion (46-71%) of women using NET-EN had disturbed menstrual cycles. Menstrual irregularities (prolonged bleeding, spotting or amenorrhoea) were the most commonly reported side effects reported in a London-based clinical trial of NET-EN undertaken among 707 women, from 1974 to 1981 (total women months=9024) (Howard *et al*, 1985). In an analysis of clinical trials carried out by the Indian Council of Medical Research from 1981 to 1987, Datey *et al*, (1995) determined that NET-EN use (2 monthly and 3 monthly dosage regimen) resulted in disturbances in bleeding pattern in the majority of users (80% during the first year of use). The proportion of women experiencing bleeding disturbances did not improve with prolonged use. Very heavy or prolonged bleeding was uncommon with infrequent bleeding more commonly observed (Datey *et al*, 1995).

Comparative Studies

Menstrual irregularities are reported to occur more often with DMPA than with NET-EN use (World Health Organization, 1978; Fotherby *et al*, 1980b; Howard *et al*, 1985; Salem *et al* 1988). A World Health Organization (1978) multi-national comparative clinical evaluation of the two injectables found that 71% of DMPA users and 47% of NET-EN users did not experience even one normal cycle over four injection intervals. It is important to note that in these studies both NET-EN and DMPA injections were administered every twelve weeks. During the first six months of use, NET-EN was reported to result in more defined cyclic patterns and fewer prolonged bleeding and spotting episodes than DMPA (World Health Organization, 1983). These results were obtained for both NET-EN dosage

regimens in the WHO multi-national comparative study in which NET-EN was given every 60 days to one group of women and every 60 days for 6 months and then every 84 days to another group of women. On the other hand, Swenson *et al* (1980) reported that NET-EN, given 10 weeks after the first injection and then every twelve weeks, resulted in more irregular bleeding than DMPA (given every 12 weeks). They found that less than 15% of both DMPA and NET-EN users reported having regular cycles by the fourth injection.

The Multi-national WHO comparative clinical trial (World Health Organization, 1978) found that amenorrhoea occurred significantly more often with DMPA than with NET-EN, with 35% of DMPA users and 9% of NET-EN users experiencing total amenorrhoea at the end of one year. They found further that the number of women who experienced total amenorrhoea increased significantly over time for both drugs, and that the difference in the proportion of women experiencing amenorrhoea with use of the two drugs increased over time (World Health Organization, 1978). It is important to note that NET-EN was administered every 12 weeks in this study. This same trial also found that heavier women, who used DMPA, were more likely to experience total amenorrhoea than lighter women, with amenorrhoea occurring in 17% of women under 47kg, in 19% of women 48 to 61kg and in 25% of women over 62kg (World Health Organization, 1978). The relationship between weight and amenorrhoea was not found among women using NET-EN on a 12 week dosing schedule. That efficacy was found to decrease with body weight of NET-EN users (World Health Organization, 1977) has already been mentioned in sub-section 1.1.2.2 above. A later clinical trial undertaken by the World Health Organization (1983) comparing DMPA given at 90-day intervals with NET-EN given every 60 days to one group of women and with NET-EN given every 60 days for 6 months and then every 84 days to

another group of women, reported significantly less amenorrhoea with both groups of NET-EN users than with the DMPA users. Findings from a study undertaken by Swenson *et al* (1980) in Bangladesh, concurred with the finding of greater experience of amenorrhoea amongst DMPA users than NET-EN users.

The World Health Organization (1978) reported that DMPA caused significantly more spotting than NET-EN (given every 12 weeks). The later World Health Organization (1983) findings are consistent and significantly longer episodes of bleeding and spotting were found to occur with DMPA than with either of the NET-EN regimens used. The experience of spotting is reported to diminish over time (World Health Organization, 1978), especially for DMPA and the NET-EN 60 day regimen (World Health Organization, 1983).

Chinnatamby (1971) reported that leucorrhoea is experienced more by NET-EN users than DMPA users, bearing in mind though that the number reporting this side effect at all was small.

Reviews

Comprehensive reviews highlight the extensive menstrual disturbance that occurs with injectable use (Rosenfield, 1974; Gray, 1979; Fraser and Weisberg, 1981; Benagiano and Primiero, 1983b; Lande 1995; Bigrigg *et al*, 1999). Kaunitz (2002) encapsulates the evidence well, noting that injectables alter menstrual bleeding patterns, particularly during the first three to six months of use when spotting and prolonged bleeding are common. Spotting and prolonged bleeding diminish over time, but the incidence of amenorrhoea increases. By a year after discontinuation of DMPA, regular menstrual cycles are said to be resumed in three quarters of users (Kaunitz, 2002). Heavy bleeding is not a common side

effect of IPCs, with reported incidences of 1-2% (Fraser, 1983). Menstrual irregularities are reported to occur more often with DMPA than with NET-EN use (Fraser, 1982; Fraser, 1986b).

Amenorrhoea has been found to be more frequent in obese women than in underweight women (Fraser and Weisberg, 1981; Benagiano and Primerio, 1983b). Lande (1995) suggests that bleeding patterns with IPC use may differ with ethnicity. For instance he reports that Southeast Asian women using DMPA reported more days of spotting and bleeding than those in the Caribbean, Europe, South East Asia, or North America, and amenorrhoea was reported more often by North African women than by European women.

Conclusion

Bleeding disturbances with IPC use are the norm. Amenorrhoea is the most prevalent menstrual irregularity, especially with DMPA, and incidence increases with duration of use (Table 1.1.3). The weight of evidence suggests that menstrual irregularities are reported to occur more often with DMPA than with NET-EN use. Some studies raise the possibility that factors such as body weight and ethnicity may influence the frequency of bleeding disturbances.

1.1.4.2 Weight Gain

Weight gain is also a commonly reported side effect amongst progestogen-only injectable users (Schwallie and Assenzo, 1973; Guillebaud, 1993; Lande 1995; Paul *et al*, 1997; Bigrigg *et al*, 1999). Many studies have examined the association between weight gain and IPC use. For instance, Westhoff (1996) systematically reviewed five cross-sectional

studies comparing weights in women receiving DMPA with non-hormonal contraceptives users. Whilst all studies showed higher weights amongst the DMPA users, Westhoff suggests that the findings are not conclusive as the studies did not consider the differences in weight of study participants when contraception was started, and that several confounders – age, parity, smoking – were not taken into account by the investigators. Westhoff (1996) also reviewed a number of longitudinal studies and opined that, since these studies did not include a control group, the observed changes in weight could not be attributed to DMPA use. Indeed the author of one of the studies she reviewed, who found a small mean weight gain of 3kg with 5-8 injections (n=76), reported that this finding had "little statistical validity" (Fraser and Dennerstein, 1994, p.555). Westhoff (1996, p.404) concluded that "Weight gain is not inevitable during DMPA use, although some of the other data suggest that DMPA or MPA use may be associated with increased appetite".

Taneepanichskul *et al* (1998), in a study designed to limit some confounders through subject selection and matching techniques, found no difference in the mean weight of 50 DMPA users at 120 months of use and 50 women using an IUD over the same period. These authors, like Westhoff, suggested that the conflicting findings of studies reporting on weight changes with DMPA use results from differing study designs and the lack of control for confounding factors such as age, parity, smoking, income, nutrition, lifestyle and duration of contraceptive use. However, more recently, Espey *et al* (2002) studied weight gain in Navajo DMPA users (n=172) and non-users (n=134). After controlling for age, parity and initial weight, they found that DMPA use is associated ($p<0.001$) with weight gain in this population and that weight gain increased with duration of use. These authors also point to possible metabolic differences between racial and ethnic groups as this study demonstrated greater weight gain with injectable use than that reported in studies of non-

Navajo DMPA users. Bahamondes *et al* (2001) also concluded that weight increases in DMPA users were significantly higher compared with IUD users. This finding was based on a five year retrospective record review of 103 DMPA users and an equal number of IUD users.

As already highlighted above, there is concern that weight gain increases with increased duration of use of IPCs. Schwallie and Azenzo (1973) found that weight, in DMPA users, increased over time, and Westhoff (1996) reported the weight gain in this study as 10kg over five years. Bigrigg *et al's* (1999) review of DMPA suggests that studies have shown (unreferenced) that there is an increase in weight gain over time with DMPA, reporting that the mean weight increase after a year was 2kg, but after 5.5 years of use it was 9kg. Benagiano and Primiero (1983b, p.48) make similar inferences about weight gain and NET-EN use, saying that there is "...a direct correlation between total dose over time and gain in body weight".

In comparing DMPA and NET-EN, the findings on weight gain appear to be similar (Table 1.1.3), although comparative studies are few and far between. The Multi-national WHO comparative clinical trial (World Health Organization, 1978) found no statistical difference in weight gain between NET-EN and DMPA, after a year of use. The weight gain with NET-EN was reported as 1.5kg and with DMPA was 2.0kg. Chinnatamby (1971) reported that changes in weight changes are more frequent amongst DMPA than NET-EN users, but found that weight change was not given as a reason for discontinuing the method. Salem *et al* (1988) reported no statistically significant increase in mean weight gain between DMPA and NET-EN users.

Conclusion

Few studies on the association between weight gain and IPC use have dealt adequately with confounders including age, weight at the beginning of the study, nutritional habits, ethnicity and level of physical activity. Findings on weight gain and IPC use are inconclusive, although findings from more recent studies seem to indicate that there may be an association. There appears to be little evidence of differences in weight gain between users of DMPA and NET-EN.

1.1.4.3 Vaginal Discharge

A side effect of IPCs occasionally reported in early published studies is vaginal discharge. It is described here, as anecdotal reports suggest that it is a problem amongst South Africa injectable users. Four early publications reported vaginal discharge as a side effect. It has been described as a rare symptom of DMPA (Tyler, 1970), as a temporary, short-lived complaint, associated with the use of DMPA (Zartman, 1967), and as a major side effect of DMPA (Schwallie, 1976). El-Mahgoub and Karim (1972) reported vaginal discharge as a minor side effect of NET-EN. Only recently, in South Africa, has this side effect been reported again -- by injectable users at a family planning clinic in Soweto, South Africa. In this study, 20% reported vaginal discharge as a side effect experienced with IPC use (Beksinska *et al*, 2001b). There was no difference between DMPA users and NET-En users in the reporting of this side effect. Described as a watery discharge, it was more often experienced in the first few months of use and was given as a reason for discontinuation by 4% of those discontinuing the method. It was also reported to be disliked by men (Beksinska *et al*, 2001b). The product brochure of Petogen®, the South African generic depot medroxyprogesterone acetate (DMPA) product, lists vaginal discharge under "other side effects" (Intramed, 1993). No such side effect is listed in the product brochures of Nur-

Isterate® and Depo-Provera® (Schering, 1992; Pharmacia and Upjohn, 1993). Finally, Nelson (1996) provides a list of DMPA side effects from a committee meeting of the United States Food and Drug Administration. Vaginal discharge was one of the side effects listed.

Conclusion

Although reference to vaginal discharge as a side effect of IPCs is sparse, it has been documented, particularly in early studies. While no association between IPCs and vaginal discharge has been published (Wright, 2003), it can be classified as a subjective side effect.

1.1.4.4 Other Side Effects

Headache was the most common non-menstrual side effect reported in the World Health Organization (1978) study and was said to be more frequently reported by DMPA users than NET-EN users (reported by 11% and 7% respectively). Similar results were reported by Salem *et al* (1988), who also found that the incidence of headache increased with prolonged use for both products. In the study published by Chinnatamby (1971) "headaches and giddiness" were more frequently reported by NET-EN (12%) than by DMPA users (10%). Numerous other side effects are less commonly reported such as mood changes (e.g. depression), weight loss, abdominal bloating and discomfort, nervousness, fatigue, backache, loss of libido, nausea, diarrhoea, chills, acne, breast discomfort and galactorrhoea (Fraser and Weisberg, 1981; Bigrigg *et al*, 1999).

Table 1.1.3 Summary of findings on side effects from comparative studies

Study (WHO=World Health Organization)	Measure	Notes	DMPA 150mg*	NET-EN 200mg#		
				Regimen 1	Regimen 2	Regimen 3
1. WHO, 1978 (Randomised 10-Centre comparative trial, healthy non-breastfeeding women of demonstrated fertility, N=1678) Participating Centres: Alexandria, Bahia-Salvador, Bangkok, Bombay, Chandigarh, Ibadan, Ljubljana, Manila, Utrecht, Lima			N=846	N/A	N/A	N=832
	No normal cycles Over 4 injection intervals	Significant difference, incidence ↑ with time	70.6%			47%
	Total **amenorrhoea** after one year	Significantly more frequent with DMPA; ♀ on DMPA with higher body wts. significantly ↑ amen.	35%			8.6%
	Spotting	Significant difference				
	Frequency/duration of bleeding episodes	Minor differences				
	Headache	Most important non-menstrual side effect (statistically significant)	10.7%			6.9%
	Average **weight gain** after one year	Slight ↑ in both groups (not statistic. significant)	2.0kg			1.5kg
2. Swenson *et al* 1980 (randomized, single blind control study, one clinic, all ♀ had at least one child, Bangladesh, N=239)		More ♀ received DMPA as supplies of NET-EN ran out.	133	N/A	106	N/A
	No regular cycles at 3rd follow-up visit (4th injection)	Less than 15% from both groups	4 of 26		4 of 28	
	Amenorrhoea					
	at 3rd follow-up visit (4th injection)	Significantly higher for DMPA	14 of 26		10 of 28	
	at 4th follow-up visit (5th injection)	Significantly higher for DMPA	12 of 14		7 of 14	
	Irregular bleeding at 4th follow-up visit (5th injection	Significantly higher for NET-EN	2 of 14		6 of 14	

* Given every 12 weeks or every 90 days

\# Regimen 1: Given every 56/60 days; Regimen 2: Given 10 weeks after the first injection, and then every 12 weeks (study 2 above) or given every 60 days for six months and then every 12 weeks; Regimen 3: Given every 12 weeks.

Table 1.1.3 Continued

Study (WHO=World Health Organization)	Measure	Notes	DMPA 150mg*	NET-EN 200mg#		
				Regimen 1	Regimen 2	Regimen 3
3. WHO, 1983† (2 year multi-national comparative randomized trial, 13 centres, healthy non-breastfeeding ♀ N=3172)			N=1587	N=789	N=796	N/A
	Amenorrhoea > 90days at 6-12 months	Significant difference between DMPA & both NET-EN regimens	54.1%	27.4%	30.9%	
Participating Centres: Alexandria, Bangkok, Ibadan, Karachi, Lusaka, Manila, Mexico City, Salvador, Santiago, Ljubljana, Luxembourg, Milan, Utrecht	at 18-24 months	Significant difference between the two NET-EN regimens	61.9%	33.5%	28.7%	
	Bleeding &/or spotting at 0-6 months	Both NET-EN regimens significantly different from DMPA	10.5%	4.1%	4.4%	
	at 7-12 months	No statistical difference	4.6%	2.4%	3.3%	
	at 19-24 months	NET-EN Regimen 2 statistically different from DMPA	1.9%	0.9%	3.5%	
4. Salem *et al*, 1988 (randomized comparative field trial, Egypt, N=400)			N=200	N=200	N/A	N/A
	Amenorrhoea incidence at 12 months	Most common complaint	55.1%	42.5%		
	Incidence of irregular bleeding at 12 months		9.4%	16.9%		
	Incidence of heavy bleeding at 12 months		0.0%	2.1%		
	Weight gain	Not statistic. significant	73.8%	72.3%		

* Given every 12 weeks or every 90 days

\# Regimen 1: Given every 56/60 days; Regimen 2: Given 10 weeks after the first injection, and then every 12 weeks (study 2 above) or given every 60 days for six months and then every 12 weeks; Regimen 3: Given every 12 weeks

† Additional information about the study design obtained from Kaunitz (1992).

1.1.5 DISCONTINUATION PATTERNS

The literature abounds with findings from studies on discontinuation patterns and reasons for discontinuation of the IPCs. However, only one South African study could be found which provides any detail on discontinuation patterns amongst South African injectable users (Beksinska *et al*, 2001a). As described earlier in this chapter, bleeding disturbances are the most commonly reported reasons for discontinuation. Some studies directly compare discontinuation rates of DMPA and NET-EN and these are described in this sub-section. Where pertinent, studies on discontinuation of one or other injectable product are also described. Findings from relevant studies are summarized in Table 1.1.4 below.

1.1.5.1 Overall Discontinuation of DMPA and NET-EN

As can be seen in Table 1.1.4, no statistical difference was found for the 12-month gross cumulative discontinuation rate for the two products for bleeding irregularities in the World Health Organization 1983 clinical trial, with continuation rates slightly better for NET-EN than for DMPA. Salem *et al* (1988) show better continuation rates at one year with DMPA than with NET-EN. In a study of NET-EN use, given every 8 weeks for the first 6 months and every 12 weeks thereafter, in 6 clinics in Bangladesh, amongst 913 women (Rahman *et al*, 1985), the overall cumulative discontinuation rate at 12 months was 37.3 per 100 women, less than that found for the same NET-EN dosage regimen in the World Health Organization (1983) trial which documented a discontinuation rate of 50.3 per 100 women.

Discontinuation rates of 41% at one year, reported by Schwallie and Azenzo (1973) for DMPA were similar to the NET-EN discontinuation rates reported by Rahman *et al* (1985), lower than the discontinuation rate of 50.4 per 100 women reported in the World

Health Organization (1983) trial, and higher than those (31.2 per 100 women) reported by Salem *et al* (1988). In a comparative trial of NET-EN and DMPA conducted in Ceylon (now Sri Lanka), Chinnatamby, (1971) found a much higher continuation rate, with only 15% discontinuation at end of 15 months. Although both DMPA and NET-EN were studied, discontinuation rates were not broken down according to the product used. The continuation rate for injectables was reported to be much higher than for other methods used in Ceylon at the time (Chinnatamby, 1971). Similarly, El-Mahgoub and Karim (1972) report a lower crude drop-out rate for Egyptian women using NET-EN, than for women from the same health facility who were using oral contraceptives or IUDs.

Fraser's (1982) review of published trials reports that 50-80% of women would continue to use DMPA after a year, which was better than the continuation rate for users of oral contraceptives and comparable to that of IUD users. Westfall *et al* (1996) report low continuation rates (23% at one year) amongst injectable users (n=5178) compared with rates cited for other contraceptives such as the oral contraceptives, IUD and implant. However in a study undertaken in New Zealand amongst 2469 OC users, 2072 IUD users and 1721 DMPA users, discontinuation rates at two years were similar across methods used (42%, 44%, 48%, respectively) (Colli *et al*, 1999). In one of few studies undertaken among African women, Sekadde-Kigondu *et al* (1996) found discontinuation rates highest among OC users (80%), lowest among IUD users (20%) and 39% for DMPA users.

In a prospective study of South African IPC users (n=189; 52 using DMPA; 137 using NET-EN) at an urban Soweto family planning clinic, discontinuation rates of 28% and 41% were found after one and two years respectively (Beksinska *et al* 2001a). These rates do not include women who were lost to follow-up (35% after two years). The authors

report no difference in **continuation** rates between DMPA and NET-EN (21% versus 20%) users after two years.

Potter (1999) writes that "DMPA's apparently high discontinuation rates are artificially inflated" compared to condoms and OCs because of the application of different criteria in determining continuation among methods. She suggested that DMPA is required to meet a higher standard than other methods in regard to discontinuation, with women returning late for their next injectable often classified as discontinuers. Potter advocated the development of a more systematic definition of discontinuation for application to all contraceptive methods, taking into account rates of protection, adherence and discontinuation.

1.1.5.2 Side Effects Leading to Discontinuation of DMPA and NET-EN

As described earlier in this chapter, bleeding disturbances are the most commonly reported side effect for discontinuation of IPCs. Although there is little published data for South Africa users, bleeding disturbances, mainly amenorrhoea, are the most common as reported in a study on IPC use undertaken in a family planning clinic in Soweto (Beksinska *et al*, 2001a). In one study, undertaken in New Zealand, weight gain was given as the most common side effect leading to discontinuation, followed by heavy bleeding (Colli *et al*, 1999).

Bleeding Disturbances

Some studies report that DMPA users were more likely to discontinue use of the method due to amenorrhoea than NET-EN users. For instance, a statistically significant difference was found between DMPA and NET-EN given every 12 weeks, for the 12-month gross cumulative discontinuation rate for amenorrhoea (1.8 per 100 woman-years for NET-EN

and 11.5 for DMPA) (World Health Organization, 1977). The later World Health Organization (1983) clinical trial verified these results, finding the discontinuation rates for amenorrhoea at 12 months and at 24 months to be significantly greater with DMPA than with NET-EN given on a 60 day regimen and for NET-EN given for 60 days for six months and then every 84 days. By contrast, Salem *et al* (1988) found that, even though amenorrhoea was more commonly experienced by DMPA users than by NET-EN (given every 8 weeks) users, the rate of discontinuation for amenorrhoea amongst NET-EN users was higher than amongst the DMPA users. The findings on discontinuation due to amenorrhoea for NET-EN users from Banerjee *et al's* (1984) comparative study of different dosages of NET-EN (Table 1.1.4 below) were similar to the findings for NET-EN discontinuation reported in the World Health Organization (1983) study.

Salem *et al* (1988) found that the second most common reason for method discontinuation was "bleeding irregularities" with rates for DMPA found to be lower than for NET-EN (8.1 and 12.5 per 100 women respectively). The discontinuation rate for DMPA (Salem *et al*, 1988) was less than the rates found in the World Health Organization comparative trials (1977; 1983). Rhaman *et al* (1985) reported that the most common reasons for discontinuing NET-EN were bleeding disturbances with heavy and/or prolonged bleeding being the single most frequent reason with a discontinuation rate of 6.3 per 100 women. The discontinuation rate at 12 months for amenorrhoea was found to be somewhat less at 5.1 per 100 women (Rhaman *et al*, 1985), and this is also less than the findings from the World Health Organization (1983) study which found the discontinuation rate for amenorrhoea at 12 months, amongst NET-EN users on the same dosage regimen, to be 8.4 per 100 women (Table 1.1.4 below).

Benagiano and Primerio's (1983b) analysis of the 1978 World Health Organization study suggests that increased bleeding and amenorrhoea are more likely to lead to discontinuation of injectables than spotting, decreased flow and irregularity of menstrual cycles. These authors submit therefore that bleeding patterns produced by NET-EN may be more acceptable than those resulting from DMPA use. On the other hand, Datey, *et al* (1995), in an analysis of clinical trials carried out by the Indian Council of Medical Research from 1981 to 1987, found that women experiencing frequent or prolonged bleeding were more likely to discontinue contraceptive use than those having delayed bleeding episodes or oligomenorrhoea.

Other Side Effects Leading to Discontinuation

Other reasons for discontinuation commonly reported in the World Health Organization (1983) trial were abdominal distention and weight gain, once again more frequently given as reasons for discontinuation by DMPA users, but not statistically different. Salem *et al* (1988) reported that weight gain, which occurred in both DMPA and NET-EN users was welcomed by the Egyptian women who participated in the study, particularly those living in rural areas. Other side effects given as reasons for discontinuation amongst South Africa users in the study by Beksinska *et al* (2001a) were: weight change (increase and decrease), headache, vaginal discharge, skin problems, breast tenderness and dizziness.

1.1.5.3 Other Factors Influencing Discontinuation of DMPA and NET-EN

Dose of DMPA

In a WHO multi-centre Phase III comparative clinical trial of DMPA 100mg given every three months versus 150mg given every three months found that users of the higher dose (150mg) of DMPA were significantly more likely to discontinue use of the method than

those using the lower dose (100mg) preparation (World Health Organization, 1986). Of note is the comparison drawn by the authors of the publication of this study (World Health Organization, 1986) who observe that the discontinuation rate for amenorrhoea of 7.2% found with the 100mg group is similar to the rate for NET-EN users (6.8%) previously reported in a comparative trial of DMPA and NET-EN (World Health Organization, 1983).

Provider Influence and Attitudes towards Bleeding Irregularities

Meade *et al* (1984) conducted a phase IV prospective clinical study of NET-EN, given every two months, in rural Mexico in the late 1970s. They reported higher discontinuation rates with NET-EN (57.0 per 100 women) than reported in the WHO Phase III Clinical Trial (World Health Organization, 1983, 49.7 per 100 women), but point out that the Mexico study findings are similar to those reported for the Mexico City centre participating in the WHO study (53.1 per 100 women). These authors found further differences with the World Health Organization (1983) trial, in that discontinuation rates due to amenorrhoea were higher and those due to bleeding problems to be lower than the World Health Organization (1983) study. They suggested that these differences could be attributed to different attitudes toward bleeding irregularities; different counselling by health workers on provision of the method; or different drug effects amongst users of different ethnicity (Meade *et al*, 1984). They point to the marked inter-centre variation found in discontinuation rates which characterize phase III studies of IPCs. Paul *et al* (1997) also draw attention to the marked inter-centre variability in study continuation rates and suggest that cultural differences may be an important influence on continuation patterns. Rahman *et al* (1985) also commented on the inter-clinic variation in discontinuation patterns of NET-EN in their Bangladesh study and attribute this variability to differences in staff attitudes and counselling approaches.

More recently, a prospective study of 430 DMPA users was undertaken to determine factors influencing continuation rates (Hubacher *et al*, 2000). The continuation rate at one year was 51%. Consistent with the findings above, providers were found to have an important influence on continuation rates, with women counselled to return to the clinic if they experienced side effects 2.7 times more likely to continue with the method. Those told that amenorrhoea might occur with injectable use were more than 2.5 times more likely to continue. Other factors found to be influential were number of children, attitudes towards menstruation, lactating on admission and spousal input on method choice.

Study Population

Paul *et al* (1997) report on a national population-based retrospective study of 1864 women in New Zealand. They submit that most studies undertaken on DMPA use have been among clinic attenders or women recruited into clinical trials, including the studies conducted by the WHO, and are therefore less likely to be representative of DMPA users. In comparing DMPA continuation rates from their study with other studies, rates were found to be "as short or shorter". For instance, continuation rates at one year for first-time users was only 49% in the population-based New Zealand study, compared to 69% in the clinic-based Egypt study (Salem *et al* 1988).

1.1.5.4 Temporary Discontinuation

A handful of studies have followed injectable users after method discontinuation and have found that some discontinuers return to the method after having a "break" (Howard *et al*, 1985; Beksinska *et al*, 1998; Beksinska *et al*, 2001a). Potter *et al* (1997), reporting on a retrospective population based study of IPC users (n=510), found that about 20% of

discontinuations could be attributed to default, because return for a repeat injection occurred more than 16 weeks after the last dose. It was suggested that these women be regarded as "poorly compliant continuers" rather than discontinuers (Potter *et al*, 1997, p.310). This poor compliance behaviour was also reported to occur amongst IPC users in a Kenyan study (Sekadde-Kigondu *et al*, 1996). A reason given for taking a break was to allow menstruation to recommence before returning for the next injection (Beksinska *et al*, 2001a; Department of Health *et al*, 2002). Beksinska *et al* (2001a) reported further that some injectable users believed that they would not conceive as long as they were amenorrhoeic. Periods of temporary discontinuation, referred to as nonuse segments (Beksinska *et al*, 2001a), can lead to unintended pregnancy. Counselling about side effects and the need to adhere to the dosing regimen is advocated.

Conclusion

In general, discontinuation rates for IPCs were high. Study findings are conflicting and confusing and need to be interpreted cautiously. Discrepancies in overall discontinuation rates are found to be the rule rather than the exception. Cultural, religious and personal attitudes and provider influence are important determinants of individual response to menstrual disturbances (Fraser and Weisberg, 1981; Meade *et al*, 1984; Salem *et al*, 1988; Datey *et al*, 1995), and generalization of findings from discontinuation studies may not be appropriate. Poorly defined criteria for discontinuation and differences in study design and population also make comparison of discontinuation rates problematic. However, discontinuation based on experience of side effects, will not, with the possible exception of amenorrhoea, lead to greater improvement in continuation rates with one injectable product above another.

Table 1.1.4 Summary of findings on discontinuation patterns from relevant studies

Study (WHO=World Health Organization)	Notes	Measure	DMPA 150mg*	NET-EN 200mg#		
				Regimen 1	Regimen 2	Regimen 3
1. Chinnatamby, 1971 (comparative study, Ceylon - now Sri Lanka, N=1035)	Discontinuation rates were not broken down according to whether DMPA or NET-EN was used	**Discontinuation rate at 15 months**	N=515 ± 15%	N/A	N/A	N=520 ± 15%
2. Schwallie & Azenzo, 1973† (Multi-centre, collaborative study, 1965-1971, 54 investigators, DMPA only, healthy women, 55% white, demonstrated fertility, N=3857)		**Continuation rates:** at 12 months at 24 months at 36 months at 48 months	N=3857 59.4/100♀ 41.5/100♀ 30.2/100♀ 24.1/100♀			
3. WHO, 1977† (Randomised 10-centre comparative trial, healthy, non-breastfeeding women of demonstrated fertility, N=1678) Participating Centres: Alexandria, Bahia-Salvador, Bangkok, Bombay, Chandigarh, Ibadan, Ljubljana, Manila, Utrecht, Lima	Chandigarh had an atypically high discontinuation rate for menstrual abnormalities with both products which had a pronounced effect on the analysis of the pooled data	**Cumulative discontin. Rates at one year:** Amenorrhoea *difference significant* Bleeding problems *difference not significant* All medical reasons *difference significant* Non-medical reasons *difference not significant*	N=846 11.5/100♀ 9.3/100♀ 23.4/100♀ 7.7/100♀	N/A	N/A	N=832 1.8/100♀ 10.3/100♀ 16.9/100♀ 9.5/100♀

* Given every 12 weeks or every 90 days

Regimen 1: Given every 56/60 days; Regimen 2: Given every 60 days or 8 weeks for six months and then every 12 weeks; Regimen 3: Given every 12 weeks

† Additional information about the study design obtained from Kaunitz (1992).

Table 1.1.4 Continued

Study (WHO=World Health Organization)	**Notes**	**Measure**	**DMPA 150mg***	**NET-EN 200mg#**		
				Regimen 1	Regimen 2	Regimen 3
4. WHO, 1983† (2 year multi-national comparative randomized trial, 13 centres, healthy non-breastfeeding ♀ N=3172) Participating Centres: Alexandria, Bangkok, Ibadan, Karachi, Lusaka, Manila, Mexico City, Salvador, Santiago, Ljubljana, Luxembourg, Milan, Utrecht	Considerable variation found between centres		N=1587	N=789	N=796	N/A
		Total discontinuation rates:				
		at 1 year (*no significant difference*)	51.4/100♀	49.7/100♀	50.3/100♀	
		at 2 years (*no significant difference*)	73.5/100♀	70.7/100♀	72.4/100♀	
		Discontinuation rates due to:				
		Amenorrhoea				
		at one year (*significant difference*)	11.9/100♀	6.8/100♀	8.4/100♀	
		at two years (*significant difference*)	24.2/100♀	14.7/100♀	14.6/100♀	
		Bleeding problems				
		at 1 year (*no significant difference*)	15.0/100♀	13.6/100♀	13.7/100♀	
		at 2 years (*no significant difference*)	18.8/100♀	18.4/100♀	21.8/100♀	
		Weight at 2 years				
		(no significant difference between DMPA & NET-EN Regimen 1)	2.1/100♀	1.6/100♀	0.8/100♀	

* Given every 12 weeks or every 90 days

Regimen 1: Given every 56/60 days; Regimen 2: Given every 60 days or 8 weeks for six months and then every 12 weeks; Regimen 3: Given every 12 weeks

† Additional information about the study design obtained from Kaunitz (1992).

Table 1.1.4 Continued

Study	Notes	Measure	DMPA 150mg*	NET-EN 200mg#		
				Regimen 1	Regimen 2	Regimen 3
5. Banerjee *et al* 1984 (comparative clinical trial of two dosage regimens of NET-EN, Indian ♀, 16 Human Reproductive Research Centres, N=2388)				N=1181	N=1207	
	No statistical differences	**Total discontinuation rates:**				
		at 6 months		21.8/100♀	22.0/100♀	
		at 12 months		41.5/100♀	40.2/100♀	
		at 18 months		56.9/100♀	55.5/100♀	
		at 24 months		68.6/100♀	67.4/100♀	
	No statistical differences	**Discontinuation rates due to:**				
		Amenorrhoea				
		at 6 months		1.6/100♀	1.8/100♀	
		at 12 months		7.6/100♀	6.9/100♀	
		at 18 months		13.2/100♀	12.7/100♀	
		at 24 months		23.8/100♀	20.1/100♀	
	No statistical differences	Heavy & prolonged bleeding				
		at 6 months		3.5/100♀	3.2/100♀	
		at 12 months		7.5/100♀	6.5/100♀	
		at 18 months		11.1/100♀	10.6/100♀	
		at 24 months		15.6/100♀	13.5/100♀	
	No statistical differences	Irregular bleeding				
		at 6 months		2.5/100♀	4.0/100♀	
		at 12 months		7.8/100♀	7.5/100♀	
		at 18 months		10.6/100♀	11.8/100♀	
		at 24 months		12.1/100♀	16.4/100♀	

* Given every 12 weeks or every 90 days

Regimen 1: Given every 56/60 days; Regimen 2: Given every 60 days or 8 weeks for six months and then every 12 weeks; Regimen 3: Given every 12 weeks.

Table 1.1.4 Continued

Study	Notes (WHO=World Health Organization)	Measure	DMPA 150mg*	NET-EN 200mg#		
				Regimen 1	Regimen 2	Regimen 3
6. Meade *et al*, 1984 (prospective clinical field study, rural Mexico, N=5792)	Rates > WHO (1983, 49.7), but similar to the Mexico City participating centre of the WHO study (53.1 at 12 months)			N=5792		
		Total discontinuation rates:				
		at 12 months		57.0/100♀		
		at 18 months		69.0/100♀		
		Discontinuation rates due to:				
		Amenorrhoea		12.6/100♀		
		at 12 months		14.3/100♀		
		at 18 months				
		Bleeding problems				
		at 12 months		8.0/100♀		
		at 18 months		9.3/100♀		
7. Rahman *et al*, 1985 (field study in 6 clinics NET-EN only Bangladesh, N=913)	Overall discontinuation rate and reasons for discontin-uation varied markedly between clinics, in spite of similar participant age, parity, residence and history of contraceptive use.				N=913	
		Total cumulative discontin. rates:				
		at 6 months			26.3/100♀	
		at 12 months			37.3/100♀	
		at 18 months			42.9/100♀	
		Discontinuation due to:				
		Heavy and/or prolonged bleeding				
		at 6 months			4.3/100♀	
		at 12 months			6.3/100♀	
		at 18 months			6.7/100♀	
		Irregular bleeding or spotting				
		at 6 months			2.8/100♀	
		at 12 months			3.9/100♀	
		at 18 months			5.2/100♀	
		Amenorrhoea				
		at 6 months			2.8/100♀	
		at 12 months			5.1/100♀	
		at 18 months			6.4/100♀	

* Given every 12 weeks or every 90 days

Regimen 1: Given every 56/60 days; Regimen 2: Given every 60 days or 8 weeks for six months and then every 12 weeks; Regimen 3: Given every 12 weeks.

Table 1.1.4 Continued

Study	Notes	Measure	DMPA 150mg*	NET-EN 200mg#		
				Regimen 1	Regimen 2	Regimen 3
8. Salem *et al*, 1988 (randomized comparative study, Egypt, N=400)	DMPA users had better one-year continuation rates More commonly experienced by DMPA users, but higher discontinuation with NET-EN	**Continuation rates at one year** **Cumulative discontin. rates due to:** Amenorrhoea Bleeding problems	N=200 68.8/100♀ 10.6/100♀ 8.1/100♀	N=200 57.1/100♀ 13.0/100♀ 12.5/100♀		
9. Beksinska *et al*, 2001a (prospective cohort study, South Africa, urban clinic recruits, n=189)	No difference in continuation rates for DMPA and NET-EN	**Continuation rates:** at one year at two years	N=52 42% 21%	N=137 41% 20%		

* Given every 12 weeks or every 90 days

Regimen 1: Given every 56/60 days; Regimen 2: Given every 60 days or 8 weeks for six months and then every 12 weeks; Regimen 3: Given every 12 weeks.

1.1.6 CURRENT SAFETY CONCERNS

A comprehensive description of the safety of progestogen-only injectable contraceptives is beyond the scope of this thesis. However, for the sake of completeness, the most important safety concerns are briefly described in this sub-section.

Progestogen-only injectables are considered to be relatively safe contraceptive methods (Fraser, 1986a; Garza-Flores *et al*, 1992; Kaunitz, 1994; Kaunitz and Rosenfield, 1994; Lande, 1995; Cayley, 1998). Little is published comparing the safety of DMPA and NET-EN. Current safety concerns about progestogen-only injectables use are the reduction of bone mineral density, particularly in young and or long-term progestogen injectable users (Cayley, 1998, Watts, 1998), and increased risk of HIV acquisition (Stephenson, 1998; Kiddugavu, 2003). A concern largely laid to rest, but about which has been the focus of some South African researchers, is the relationship between IPC use and breast cancer (Bailie *et al*, 1997; Shapiro *et al*, 2000).

1.1.6.1 Bone Mineral Density and IPCs

Considerable attention is currently focused on the possible suppression of oestrogen in long term DMPA users and resultant concerns about the reduction of bone mineral density (Cundy *et al* 1991; Weisberg, 1992; Cayley, 1998; Bigrigg *et al*, 1999; Weisberg, 1999) particularly in young users (American Health Consultants, 1998; Watts, 1998), and long-term users (Watts, 1998). These concerns are particularly pertinent in South Africa where the injectables are used for longer periods of time than anywhere else in the world (Bailie, 1997, Shapiro, 2000) and where they are used widely by young women (Department of Health *et al*, 2002). Findings from many studies are inconclusive and have been criticized for their small sample size and failure to control for confounding factors

(Weisberg, 1992; Lande, 1995; Cayley *et al*, 1998; Bigrigg *et al*, 1999). Findings from prospective studies in progress are awaited (Bigrigg *et al*, 1999; Weisberg, 1999). Some of these studies, on DMPA and NET-EN, are being undertaken in South Africa (M Beksinska, Director, Reproductive Health Research Unit, pers. comm., June 2003). Attention has largely focused on DMPA. However, Cundy *et al* (1996), point out that progestins possessing androgenic properties, like norethisterone, have beneficial effects on bone density, in that they ameliorate the effects of oestrogen deficiency induced by Gonadotrophin-releasing hormone analogs in young women. The WHO comments that there are theoretical concerns regarding the hypo-oestrogenic effects of IPCs, particularly of DMPA, when used by women under 18 years of age and over 45 years (World Health Organization, 2000). Concern was also expressed about whether women over 45 years regain bone mass after discontinuation of DMPA. The WHO does not however advise that NET-EN rather than DMPA should be used by women under 18 years or over 45 years and DMPA and NET-EN are assigned the same medical eligibility category (2), where the advantages of using a method are considered to outweigh the theoretical risks (World Health Organization, 2000).

Of note from the published data on DMPA and bone density are the following:

- Cundy *et al* (1991) compared cross-sectional lumbar and femoral neck bone densities in long-term DMPA users with pre- and post-menopausal women (n=30 in each group). They found the bone density values for DMPA users between those of the pre- and post-menopausal groups and concluded that DMPA may adversely affect bone density.
- Cundy *et al* (1994) undertook a comparative study (n=54) of long-term DMPA users who discontinued use during the course of the study, and were followed-up for two

years, women who were currently using DMPA, and women who had never used DMPA. The authors suggest that, even after long-term use of DMPA, bone loss may be almost completely reversible.

- Cromer *et al* (1996), in study amongst 15 adolescents, suggested that DMPA may decrease bone density, at least temporarily.
- Taneepanichskul *et al* (1997), in a study of bone density in long-term use of DMPA by 50 Thai women, suggested that long-term use of DMPA should not adversely affect bone density, even if oestrogen levels are suppressed.
- Watts (1998) reported that DMPA is associated with a significant reduction in bone density and that the risk for long-term users and users who have not reached peak bone mass may be highest.
- Orr-Walker *et al* (1998) in a cross-sectional study of bone density in 34 post-menopausal former users of DMPA, concluded that fracture risk in post-menopausal women who used DMPA are minimal as the residual effects of DMPA on post-menopausal bone density are small. These authors point out that fracture rates in pre-menopausal women are low, thus current DMPA users are not at great risk of fractures due to decrease in bone density.
- Tang *et al* (2000), who undertook a longitudinal cohort study on 59 Chinese women using DMPA, concluded that DMPA could be used long-term without worrying about linear bone loss leading to early osteoporosis.
- Wanichsetakul *et al* (2002) found that DMPA use results in decreased bone mineral density only at the lumbar spine and that it was safe for long-term contraceptive use.

Conclusion

Findings from prospective studies currently undertaken should provide conclusive evidence about the effect of injectables on bone mineral density. Findings from the South African studies amongst young users and long-term users will be of note. Existing evidence is inconclusive, but suggests that effects on bone mineral density do occur at some bone sites.

1.1.6.2 Risk of HIV Acquisition and IPCs

Ever since Marx *et al* (1996) found an increase in simian immunodeficiency virus infection in SIV-exposed monkeys, there has been concern about the effect of hormonal contraceptives on HIV acquisition (Marx *et al*, 1996; Mostad *et al*, 1997; Stephenson, 1998; Kiddugavu, *et al*, 2003). Mechanisms by which HIV risk could, theoretically, be increased include: Thinning of the vaginal epithelium, increasing cervical ectopy, increasing HIV shedding in the genital tract, increasing vaginal pH, direct influence on HIV virulence, changes in menstrual bleeding patterns and immunological changes (Stephenson, 1998; le Riche *et al*, 2002; Kiddugavu *et al*, 2003). Whether a relationship exists between progestogens and HIV transmission warrants further investigation (Family Health International, 1996) as the evidence currently available is conflicting (Ntozi and Kirunga, 1998; Stephenson, 1998; Kiddugavu *et al*, 2003).

A systematic review of epidemiological evidence on hormonal contraception and risk of HIV transmission was undertaken by Stephenson in 1998. This comprehensive review revealed the poor quality of studies undertaken and highlighted the considerable methodological problems which need to be overcome in designing a study to adequately answer this research question. These include the timing between contraceptive use and HIV

infection, confounding of sexual behaviour on method choice, what an appropriate control group might be and difficulties in precisely measuring the level of exposure to HIV. She concluded that the relationship between hormonal contraceptives and HIV transmission is uncertain and recommended that hormonal contraceptives should continue to be provided.

The most recent data published on the association between hormonal contraception use and HIV acquisition originated from a study undertaken in a rural community-based cohort in the Rakai District of Uganda (n=5117). This is the first prospective study undertaken to investigate if there is an association between hormonal contraceptives and HIV acquisition. After adjustment for behavioural confounding, use of injectable hormonal contraception was not associated with HIV acquisition with an adjusted IRR of 0.84 (95%Confidence Interval: 0.41-1.72) (Kiddugavu *et al*, 2003). The authors of the study do not indicate whether the injectable product used by respondents of this study was DMPA or NET-EN or a mix of these. Results of other studies on IPC use and risk of HIV are expected in 2003 (Best, 2001).

Conclusion

While the association between IPCs and HIV acquisition is questionable, we do know that IPCs offer no protection against STI and HIV infection. In cases where risk of HIV infection is high, counselling on the need to use a method for dual protection against infection and unwanted pregnancy is essential. This could take the form of a barrier method (male or female condom), or the use of two methods (dual method used) one of which should be a barrier method, the other could be a hormonal injectable method.

1.1.6.3 Breast Cancer and IPCs

A possible relationship between IPCs and breast cancer has long been a cause of concern. The main bases for this concern were the results of toxicology experiments which found that DMPA caused benign and malignant mammary tumours in beagle dogs (Senanayake, 1991; Thomas, 1992). These findings were the reason for the delay in the licensing of DMPA for contraceptive use in the United States (Duncan and Kirton, 1992; Kaunitz, 1996; Bailie *et al*, 1997; Shapiro *et al*, 2000). DMPA was only finally licensed for contraceptive use in 1992 after studies undertaken by Paul *et al* (1989) and the World Health Organization (1991) showed no increase in the risk of breast cancer among women who had started DMPA use more than 5 years previously or those who had used DMPA for a long time. A pooled analysis of the World Health Organization (1991) study and the New Zealand (Paul *et al*, 1989) study confirmed these findings. However, Paul *et al* (1989) reported increased relative risks in women under age 35 years, and in those who had used DMPA for at least two years before age 25 years. The World Health Organization (1991) study raised similar concerns about an increased risk within the first 4 years of exposure, particularly in women younger than 35 years (Skegg *et al*, 1995).

Little research appears to have been undertaken on the risk of breast cancer amongst NET-EN users. Lande (1995) in an extensive review of IPCs discusses the risk of breast cancer in relation to DMPA use, but makes no reference to the risk of breast cancer for NET-EN users. Fraser (1982, p.75) in his review of long acting injectable hormonal contraceptives suggested that there was no good clinical evidence to support the concern about neoplasias and DMPA …" or any of the other injectable contraceptives". Fraser and Weisberg (1981) document that NET-EN was also part of the tumour controversy related to IPCs, but report that the studies undertaken on rats were discounted as the rat,

like the beagle, is an inappropriate test model. The Toxicology Review Panel of the World Health Organization (1982) concluded, from a review of animal studies, that both DMPA and NET-EN were safe for human use.

A recent study described by Bailie *et al* (1997) and Shapiro *et al* (2000) was undertaken amongst users of both DMPA and NET-EN. The published findings from these latter studies do not differentiate between DMPA and NET-EN users, but Shapiro *et al* (2000) state: "...that IPCs, principally DMPA, do not increase the overall risk of breast cancer" p. 400. It can be assumed therefore that these findings also apply to NET-EN users, but it would be useful if the findings from this study were disaggregated by product. Of note about this study also, is that it was undertaken amongst African and Coloured women in Cape Town, South Africa, and is thus one of the few studies that provides local data about IPC use. The study reports the relative risk of breast cancer with IPC use to be 0.9 (95% confidence interval: 0.7, 1.2) and found that age category, recency of use and length of use are not consistently associated with risk of breast cancer (Shapiro *et al*, 2000).

Conclusion

The review of the literature, especially the more recent studies (Bailie *et al*,1997; Shapiro *et al* 2000) is reassuring and there seems little reason to be concerned about either DMPA or NET-EN causing an increased risk of breast cancer.

1.1.7 OBJECTIVES

The objectives of Section 1 are to:

- Determine the prevalence of injectable contraceptive use amongst rural women in KwaZulu-Natal, South Africa.

- Investigate the contraceptive method mix among women in rural KwaZulu-Natal.
- Determine the side effects and discontinuation patterns among injectable contraceptive users.
- Undertake a comparative analysis of DMPA versus NET-EN focusing particularly on utilization patterns, side effects, discontinuation patterns and costs.
- Make appropriate recommendations for rational use of injectable contraceptives.
- Identify aspects of injectable contraceptive use for further investigation.

CHAPTER 1.2: METHODOLOGY

1.2.1 STUDY AREA

This study was undertaken in the Hlabisa sub-district, a deep rural area and one of four sub-districts of the Hlabisa magisterial district. This site was selected as it was fairly easily accessible, yet preserved its rural nature because of the intervening game reserve; was relatively safe from crime and political unrest; and had strong community support for research activities. In addition, the establishment of an international research Centre in the Mpukunyoni sub-district provided scientific and financial support to local research studies.

Hlabisa is situated in the northern part of the province of KwaZulu-Natal (KZN), about 300km north-east of Durban on the Indian Ocean coast of South Africa. A map showing the location of the district in South Africa and the four sub-districts is provided in Appendix 1.2.1. Hlabisa is approximately 50 x 70km in aerial extent and according to the 1996 Census had a population of 198179 (Curtis *et al*, 2002), who are largely Zulu-speaking. A major national road, the N2 runs through the eastern half of the district, linking the major port and commercial towns of Durban, Richards Bay and Empangeni to Swaziland and Mozambique. There are large sugar farms and eucalyptus plantations along the N2. The district is home to a relatively poor populace who rely largely on income from subsistence farming, migrant labour, pension remittances and casual labour.

Key reproductive health issues are HIV, sexually transmitted infections, poor pregnancy outcome and high fertility. Just before the survey commenced, the incidence of HIV in women, aged 15 to 30 years, attending antenatal clinics in Hlabisa, was reported to be 12% in 1997 (Abdool Karim, 1997). The prevalence of HIV amongst women attending antenatal clinics in the district was reported to have increased from 4% in 1992 to 22% in

1997 and it was estimated that a quarter of women in Hlabisa in the age range 15 to 49 years, were infected with at least one STI on any given day (Wilkinson *et al*, 1999). Wilkinson and Sach (1999) placed the infant mortality rate in the Hlabisa District at 53 per 1000 total births. Whist the fertility rate for the Hlabisa district was not known, the fertility rate for KZN Province was reported to be 4.3 in 1991 (Erasmus, 1994) and 3.3 in 1998 (Department of Health *et al*, 2002). A teenage birth rate for KZN of 15.3 was reported in 1994 (Erasmus, 1994) and 16.7%of KZN teenagers interviewed in the 1998 SADHS had been pregnant (Department of Health *et al*, 2002).

The Hlabisa sub-district, where the survey was conducted, is separated from the rest of the district and the main transport routes by the Hluhluwe and Umfolozi Game Reserves. It lies to the north of the game reserves and is characterised by hilly undulating terrain and savannah like vegetation. Giraffe, zebras, impala, buffalo, warthog, rhino and elephant are commonly encountered on the way to Hlabisa sub-district. It has a sub-tropical climate, with summer rainfall and average summer temperatures of 28 to 30 degrees centigrade and winter temperatures between 16 and 25 degrees. Only 7% of households had piped water in 1996 and 25% had access to public taps (Curtis *et al*, 2002). Most households obtained water from rivers and dams (Curtis *et al*, 2002). Only 3% of households had flush toilet systems with the majority (66%) having access to pit latrines, and 29% having no sanitation system (Curtis *et al*, 2002). Typical rural homesteads (*kraals)* are sparsely scattered across the sub-district. Some modern style houses are also to be found, usually close to the Hlabisa village. The further one moves from the village, the more scattered the homesteads become. Most homes are electrified, on a card system basis, and most roads are gravel or dirt.

The Hlabisa sub-district is governed by a traditional tribal authority system, typical of rural areas of KZN, and a chief, Inkosi M. Hlabisa was the local traditional leader. At the time of the survey, it was estimated, from aerial photographs to be comprised of 2088 homesteads, with an estimated population of 20000 people. A detailed mapping exercise undertaken subsequent to this study places the population at 2316 homesteads, a population of 16124, and an average number of people per household of 7 (F Tanser, GIS Specialist, Africa Centre for Population Studies and Reproductive Health, pers. comm., September 1998). Figures from the 1996 Census released after the survey was conducted placed the population of the sub-district at 21425 with an average household size for the whole district of 7.5 (Curtis *et al*, 2002). Most households comprise extended families.

The sub-district was further divided into 13 *isigodi* or wards, each of which was governed by an *induna* (headman), responsible for the allocation of tribal land and the maintenance of a local census of those living within the *isigodi.* The thirteen *isigodi* were: Qunwane, Madondo, Khalokazi, Emajikeni, Mabundeni, Hlambanyathi, Matshamnyama, Macekeni, Mabhokweni, Makopini, Empembeni, Amabhokisi, and Stezi. The boundaries of the *isigodi* can rarely be delineated by the *induna* or people living within the *isigodi.* A Council of *Izinduna* is chaired by the Chief of Hlabisa, and he serves on the KZN Council of Traditional Leaders (Abdool Karim, 1996).

At the time of the study, the only health facility in the area was a 400-bed district hospital, the Hlabisa Hospital, situated close to the Hlabisa village in the Lutheran Mission area. Services provided by the hospital included medicine, basic surgery, obstetrics and paediatrics (Abdool Karim, 1996). In addition, 3 primary care mobile clinics serviced the area. Community health workers provide a health service to those

who do not have access to the mobile clinics or the hospital. The location of the hospital can be seen on the map provided in Appendix 1.2.1. There were eight primary schools and four secondary schools.

1.2.2 STUDY DESIGN

Over the period September 1998 to April 1999, data were collected by means of a cross-sectional community-based survey at household level and focus group interviews, drawing upon both quantitative and qualitative techniques. The focus group interviews (thematic guided discussions) were conducted to draw out contextual information and to provide insight, depth and perspective to the quantitative cross-sectional data. Records of contraceptive use at the local family planning clinic at the Hlabisa Hospital were also analysed. Triangulation, also known as the "inter-technique" approach, is used to ensure the validity of findings, by corroborating data with other data collected in a different way from another source (Jick, 1979; Bernard, 1994). In the Hlabisa study, this was done by combining a quantitative technique, the cross-sectional community-based household survey; a qualitative technique, the focus group interviews; and the analysis of health services records.

1.2.3 SAMPLING

1.2.3.1 Household Survey

A large enough total sample size had to be determined in order to be able to make statistical inferences about side effects experienced by the sub-sample of women who were current users of the injectable contraceptives. For example it was important to be able to test for significant differences between users of the two injectables, Depo-Provera® and Nur-Isterate®. It was also considered necessary to have a large enough total

sample size to be able to test for significant differences in the prevalence of injectable use and/or experience of side effects between sub-samples of those surveyed. In consultation with a statistician and using the formula cited by Fleiss (1981, p.45) which includes the continuity correction, it was determined that 107 women should be selected in each injectable product user group (i.e. DMPA users and NET-EN users) to show a significant difference (at the 0.05 level) in respect to the main side effects documented in the literature (assuming at least 20% difference between the two groups) with 80% power. In this way it was predicted that approximately 200 injectable contraceptive users should be interviewed. The remaining women interviewed would either have discontinued use or never have used this method. The minimum sample size required, allowing for a 5% sampling error and a 5% refusal rate, and using an estimated ratio of 3 non-users to one user of the injectable contraceptive (Abdool Karim, 1997), was determined to be 835 women. Thus it was determined that 40% of the estimated 2088 households should be visited. Further, in order to ensure an even spread of households across the sub-district, the sample was stratified by *isigodi*, selectively including a fixed sampling fraction in each *isigodi*. **A total of 848 women were interviewed.**

Household Selection

A baseline mapping exercise of the Hlabisa sub-district had taken place prior to the survey. A starting point for the household interviews was selected in each *isigodi* by blind random placement of a pencil mark on the *isigodi* map. Commencing from this selected point, the fieldworkers radiated out in different directions, each in a straight line. An interview was conducted at every second household until 40% of households in each isigodi had been visited. If no one was home or if a woman refused to be interviewed, the nearest neighbouring household was visited.

Selection within a Household

Among women in the age range 15 to 49, one woman was randomly selected to be interviewed from each household visited. Only one woman was interviewed from each household to avoid within household correlation. The random selection was achieved by ascertaining the number of women resident in the household between the ages of 15 and 49. The age of each woman was recorded and a ribbon of a different colour was assigned to each woman of the household. One of these ribbons was then randomly selected and the woman to whom that coloured ribbon was assigned was interviewed. When arriving at the selected household, the interviewer was asked to comply with the following procedure:

- Knock on the door.
- Introduce yourself - show the letter of introduction.
- Explain the study - give the person who answered the door the study information sheet.
- Ask how many women between the ages of 15 and 49 live in the household.
- Record the number and ages of the women living in the household on the sheet provided for this purpose. No names should be recorded.
- If there is more than one woman, assign a different coloured ribbon to each woman, by entering the colour next to the age of the woman on the sheet referred to above.
- Select **one** of these women in the following way:
  - if there is only one woman, she is the person who should be asked for her consent to be interviewed
  - if there are two or more women, draw one of the ribbons out of the box. The woman whose age corresponds with that ribbon colour should be interviewed

- if that woman is present, she is the person who should be asked for consent to be interviewed
- if that selected woman is not in, ask when she is likely to be home. Ask if it would be in order to come back and talk to her at that time. Come back at the appointed time, introduce yourself, explain the study and ask for consent to interview her
- if she is not going to be back at any time in the next six days, re-select another ribbon and go through the selection process again amongst the remaining women of that household.

- If the person selected to be interviewed does not give consent, go to the house next door and go through the selection process again.

1.2.3.2 Focus Group Interviews

Community groups active in the study area were identified by key informants living in the area. At least one group of each type was selected for interview. Where two or more groups of the same type had been identified, a group was selected by convenience sampling, according to availability of the group and availability of a venue to hold a discussion. **Focus group interviews were held with fourteen groups in all.** The size and composition of each group and the characteristics of individuals within these groups are provided in Chapter 1.5, Table 1.5.3.

1.2.3.3 Analysis of Family Planning Clinic Records

An analysis of the records of contraceptive methods supplied by the family planning clinic of the Hlabisa Hospital was undertaken for the period July 1998 to July 1999.

1.2.4 COMMUNITY ENTRY AND ETHICAL SAFEGAURDS

1.2.4.1 Community Entry and Community Consultation

Extensive consultation was undertaken prior to designing the research instruments and collecting the data. The study was first introduced to community leaders in the Hlabisa district as part of the research programme of the Africa Centre for Population Studies and Reproductive Health. More specifically, the study was introduced to the Chief of the Hlabisa district along with other studies, also being undertaken in this sub-district area. The Medical Superintendent, Chief Matron, Community Matron, Medical Officer in charge of training and other nursing staff of the Hlabisa Hospital were informed about the study. Under the auspices of the Chief Matron, a workshop was conducted for Hlabisa Hospital family planning nursing staff. The objectives of the workshop were to inform family planning nursing staff about the study, and to seek assistance in designing the data collection instruments.

Workshops and meetings were also held with the *indunas* of each *isigodi*, with community health workers from the sub-district, with traditional healers and with other researchers working in the study area. Across-the-board support and encouragement were provided for the study. In addition, much helpful advice and information were proffered about study design. This phase of the study took place over the period February 1998 to September 1998. Feedback about the study has been provided to the Hlabisa community in the form of scientific colloquia and *imbizos* through the Africa Centre for Population Studies and Reproductive Health. A final community meeting to report on findings will be held once results have been finalized.

1.2.4.2 Informed Consent

Care was taken to obtain informed consent from individuals requested to participate in the study. Interviewers were intensively trained in the ethics of informed consent and were exhorted not to place pressure on anyone who was, or appeared to be, reluctant to participate in the study. It was made clear to potential respondents that they did not have to participate if they did not wish to, and that they could withdraw from the interview at any time. A patient information sheet was designed to acquaint potential respondents of the household survey with the institutional affiliations of the researchers, the objectives of the study, the methodology to be employed and the potential benefits of the study. A similar information form was developed for focus group participants. The information sheets were made available in English and Zulu (Appendix 1.2.2) and were given to all study participants. The information was also provided verbally. Each fieldworker also carried a personal letter of introduction with her.

1.2.4.3 Confidentiality

Individual Household Interviews

Since women who use the injectable contraceptive may do so secretly, great care was taken to ensure that confidentiality was maintained. Fieldworkers were intensively trained about the right of study participants to confidentiality. Particular care had to be taken since the fieldworkers were drawn from the study area. Since women were to be interviewed regardless of whether or not they were injectable contraceptive users, the mere fact that they were being interviewed did not identify them as users of the injectable contraceptive method.

Of note are these excerpts from the fieldworker training notes:

"Many respondents will not want other people to know if they are using the injectable contraceptive. It is very important to ask the questions in a place where other people can't hear the answers."

"The answers you are given must be kept strictly confidential. In other words, you must not tell anyone else what the respondent has told you and you must not show the answers to the questions to anyone else."

Respondents were assured of the confidentiality of their responses in both the patient information sheet and the interviewer letter of introduction.

Focus Group Interviews

Whilst confidentiality is less easy to control in the group discussions, members were assured that care would be taken to maintain individual confidentiality. Group facilitators also requested that members of a group should respect the right to confidentiality of other members of the group. Since the discussion was to be captured by means of a tape recorder, permission to record the interview was obtained prior to commencing the discussion.

Family Planning Clinic Records

Names of women appearing on the records of the family planning clinic at the Hlabisa Hospital were not recorded.

1.2.4.4 Approval to Conduct the Study

The study was approved by the ethics committees of the University of Durban-Westville (Ethics approval Number 97296B) and the Nelson R Mandela School of Medicine of the University of Natal (Ethics clearance number H150/00).

1.2.5 DATA COLLECTION

1.2.5.1 Data Collection Instruments and Procedures

Individual Household Interviews

An extensive structured interview schedule was designed in consultation with health providers and other researchers and after a thorough literature review of instruments used in studies with similar methodologies, including the 1998 South African Demographic and Health Survey instrument (Department of Health *et al*, 2002). Many questions are common to users, previous users and those who had never used the method, but some questions were designed specifically for only one or two of these categories. For simplicity of administering and analysing, the questions relevant to each sub-category were assembled in separate interview schedules. The three schedules were colour coded to allow easy recognition by the interviewers: the interview schedule for current users was printed on yellow paper, blue was used for previous injectable users and white interview schedules were printed for those who had never used the method. This gross visual recognition technique was very successful and the schedules soon became known as the "yellows", "blues" and "whites". Copies of the interview schedule, broken down according to the type of injectable contraceptive user to whom it would be administered, can be found in Appendix 1.2.3. As can be seen, the most extensive schedule was developed for current users of the injectable contraceptive.

Questions on demographic characteristics, contraceptive history, plans about future use, knowledge, perceptions and opinions of injectable contraceptives, men's views and friend's views were asked of all user categories. Extensive questions on brand of injectable being used or previously used, side effects, length of use, reasons for choice of method, secrecy of use and source of method, were included for current and previous users. Questions on medical history relevant to injectable contraceptive use, e.g. breastfeeding status and concomitant use of enzyme inducing drugs, were included for those currently using the injectable. Contraceptive methods currently used by those not using the injectable were directed towards the non-user and previous user categories. Questions exploring reasons for discontinuing use were included for previous users. The interview schedule was comprised of dichotomous questions, lists of options to be ticked, and open-ended questions.

The interview schedule was developed in English, but the interviews were to be conducted in Zulu since almost all the respondents were expected to be Zulu speakers. Considerable research and consultation were undertaken to determine the best method of administering an interview schedule in a language other than that in which it was developed. Current practice favoured the approach of partial translation of key phrases rather than complete translation of the whole instrument. In using this approach, nuances of meanings are less likely to be lost in the translation process and one is not forced to find a translation for a word that doesn't exist or that may be taboo (Katzenellenbogen *et al*, 1997). The use of this type of approach to translation is supported by the views of African participants (from Botswana, Kenya and Ghana) of the London School of Health and Tropical Hygiene's 1998 Short Course on Reproductive Health Research. They indicated that, if respondents understand English in addition to their home language,

questions on sensitive issues such as sexual practice, are better asked in English, since translating some questions may require the use of words which are taboo in the home language (M L McFadyen, course participant, pers. comm., August, 1998).

Thus, a partial translation approach was adopted for this study. An extensive participative workshop was held to identify key phrases for translation. Senior researchers, the fieldwork manager and fieldworkers were involved in this process. Zulu was the first language of the fieldworkers and they were also all fluent in English. Phrases identified for translation were printed on the interview schedule in English and Zulu. For instance, the English and Zulu translation of all side effects listed appeared one below the other in all cases. The interviews were all conducted in Zulu. A description of the fieldworker training process for translation is provided in the section on training below.

Various techniques were employed to ensure that the instrument was valid and reliable. The face validity of the household interview schedule was checked to determine whether or not, on the face of it, the questions make sense (Bernard, 1994, Katzenellenbogen *et al*, 1997), by conducting a validation process with a group of pharmacology master's students from the University of Durban-Westville. The students were asked to read and critique the interview schedule in the advanced stages of its development. A seminar with the students was arranged for feedback and comment. A very useful discussion was held which helped to identify ambiguous questions and issues omitted. For instance, additional side effects associated with injectable use were identified and included.

A face validity check was also performed to ensure that the standardised translation agreed on was valid. This involved one of the interviewers conducting the interview with

a skilled English/Zulu translator and obtaining her view on the accuracy of the translation. The translator (Z Gwamanda) who participated in this process was a first language Zulu speaker from the Biostatistics Division of the Medical Research Council. She was of the opinion that the translation was accurate.

In designing the interview schedule, the 1998 South African Demographic and Health Survey (SADHS) instrument was consulted and some similar questions were included. In this way, criterion validity, which involves evaluating the results of this study's findings against a "gold-standard" can be assessed (Bernard, 1994, Katzenellenborgen *et al*, 1997).

The instrument was also designed to incorporate reliability measures, i.e. whether or not the same answer is provided when a question is repeated:

(a) Some questions were asked in different ways in different parts of the schedule. For instance:

- the answer to the question about the type of injectable contraceptive being used (question 16), should be consistent with the answer given to question 21, which asks how often the respondent returns to the clinic.
- respondent's age (question 2) can be cross-checked by adding age of first pregnancy (question 9) and age of first child (question 10).

(b) An important objective of this study was to obtain detailed information about the experience of side effects while using the injectable contraceptive. A question exploring side effects experienced by current users was asked first in open-ended form (question 25) followed by a closed question (question 26), where respondents had to indicate whether or not they had experienced any of 22 different pre-listed side effects. This was done to elicit the side effects uppermost in respondent's mind without prompting, whilst

ensuring that side effects were not forgotten, and also as a reliability check. Questions 41(d) and 41(e) (side effects experienced by past users) were handled in the same way. Findings from the unprompted version of the question on side effects were found to be consistent with the prompted responses, although, as expected, frequencies of reporting were lower.

Interviews were conducted by three young women hired from the Hlabisa community. These young women were of a similar age and all three had achieved their matriculation certificates. Researchers participating in research projects under the umbrella of the Africa Centre for Population Studies and Reproductive Health have made an undertaking to hire local people wherever possible and this policy was applied in hiring fieldworkers for this study. The hiring of local people proved to be advantageous as these three young women are familiar with the terrain and are well accepted by the community. Their advice and insight into appropriate ways of approaching community leaders and respondents were invaluable. A fourth, older and very experienced fieldworker, based in Durban also assisted with interviews. She has been involved in interviews on reproductive health issues for 10 years and is trained in anthropology and sociology. She was involved in the early training stages and was part of the interview team for the first two weeks, and from time to time thereafter. Her role was to conduct interviews (with older women where appropriate), but also to guide the newly trained fieldworkers and monitor the quality of their interviewing. After much discussion, it was decided that it would not be appropriate to have males to interview women. The fieldworkers were supervised by a male fieldwork manager who was continuously on site during the data collection phase of the study.

The household interviews, 848 in total, were conducted in September, October, November and December 1998. They were mainly held during the day from Monday to Friday, but where a selected woman was not at home during the day, a revisit was made in the evening or on Saturday. No one refused to participate in the study, although one interview was terminated before completion as the respondent did not wish to continue. No substitutions were made, as revisits were arranged where no one was in at the selected household or where the selected woman was not home. The univariate statistics for interview lengths are provided in Table 1.2.1 below:

Table 1.2.1 Interview length

	Mean (minutes)	**Median (minutes)**	**Mode (minutes)**	**Range (minutes)**
Injectable users	41	40	45	30-85
Previous IPC users	37	35	35	15-60
♀who had never used IPC	24	25	25	5-49

Focus Group Interviews

A semi-structured aide memoire was designed for the focus group interviews. Six themes, identified in the consultative phase of the study and from responses to the individual household interviews, were included for discussion. The themes included were: general views and opinions on contraception; opinions of the injectable contraceptive; side effects of the injectable contraceptive; the experience of vaginal wetness with injectable contraceptive use; the use of the injectable contraceptive in the context of high HIV prevalence and the views of community leaders and elders on the use of contraceptives. A copy of the semi-structured focus group interview schedule can be found in Appendix 1.2.3. A short questionnaire was also administered to each person participating in the group discussion to obtain demographic information so that the discussion group could be described. This questionnaire can also be found in (Appendix 1.2.3).

Each group was facilitated by two trained interviewers. The same four interviewers hired to undertake the household survey were hired to conduct the group discussions. In addition, the male fieldwork manager (see next section for a description of his role), was also part of the team, and conducted the interviews with male groups. The focus groups were comprised of men and/or women, therefore it was essential to include a male interviewer in the team. Discussions were conducted in community halls, schools or at the hospital. The interviews were conducted in Zulu and were recorded using an audio tape recorder. One facilitator conducted the interview while the other took notes by hand and ensured that the tape recorder was functioning throughout the interview. The second facilitator was also responsible for ensuring that the discussion stayed on the topic, that the discussion was not dominated by one individual and that reticent members of the group were drawn into the discussion.

Fourteen focus group interviews were conducted from February to April 1999. By the time these fourteen group interviews had been held, very little new information was gained from successive group interviews. Only one type of group could not be assembled, namely the *indunas*. There were never more than two of them available at any one time as they were very busy with the run-up to the country's national elections on the 2nd of June 1998. However, it was felt that sufficient information was obtained from the focus groups which were conducted, so attempts to organise this group were halted.

Family Planning Clinic Records

A data collection form (see Appendix 1.2.3) was developed to record contraceptive units issued per month at the family planning clinic of the Hlabisa Hospital. Data were collected by a senior researcher for the period July 1998 to June 1999.

1.2.5.2 Training and Fieldwork Management

Training

The training of fieldworkers was considered very important in obtaining quality data and much time and effort was accorded to this aspect of the study. As mentioned above, an initial workshop was held to identify key phrases for translation. This was the first in a process of participative workshops with the fieldwork manager, fieldworkers and researchers. The fieldworkers were provided with detailed information about the objectives of the study and were trained in general survey research methods. Good ethical practice and the rights of respondents regarding informed consent and confidentiality were emphasised. Issues about appropriate conduct, for instance introduction of themselves and the study were emphasised. Safety issues were also discussed and the fieldworkers were advised to withdraw immediately from potentially unsafe situations.

The importance of accurate translation and the need to accurately convey the meaning of each question was highlighted repeatedly. Intensive workshop sessions to standardise translation and fine tune interpretation of the household survey instrument were held in the first two weeks of September 1998. In this way a "gold standard" for translation and interpretation (method described by Montgomery and Harrison, 1998) was agreed on by the end of the workshops. This process was led by the fieldwork manager Sihle Ncgamu, whose home language was Zulu. He is an experienced social scientist and academic with considerable experience in education and survey research, and was completing his master's degree in education at the time the fieldwork was being undertaken.

Once the translation had been standardised, the fieldworkers were required to "role play" interviews, first with each other, then with friends or colleagues and finally with

strangers. The role play included the whole interviewing process: knocking on the potential respondent's door; introducing the study; selecting a respondent; asking for permission to interview; conducting the interview in Zulu; thanking the respondent and saying goodbye. These "role-play" sessions were monitored by the fieldwork manager. For the first week of interviewing, the fieldworkers worked in pairs, swapping partners to entrench consistency in interview technique and translation. Thereafter, interviews were conducted individually. Once fieldwork had commenced, on-going training was provided on a daily basis on site. Opportunities to train and clarify issues were provided at a briefing session at the beginning of each day of interviewing, at mid-day and at the end of the day.

Intensive training for conducting focus group discussions was provided in February 1999.

Fieldwork Management

In order to ensure quality of data a fieldwork manager, Sihle Ngcamu, was appointed. Sihle was also responsible for other aspects of the project, namely community liaison, translation tasks, fieldworker training, and organising and conducting focus group discussions. He was familiar with the customs and traditions of the people of northern KwaZulu-Natal, as he has lived, studied and worked in this area all his life. The study area is very remote and it was no easy task to implement and monitor the fieldwork. A local office was set up at the Hlabisa Hospital with the kind assistance of the Medical Superintendent. This office served as the administrative and training centre during the fieldwork phase. Sihle lived at the fieldsite and weekly visits were made to the fieldsite by the principal investigator of the study (the author of this thesis). Daily telephonic contact was maintained between the principal investigator and the fieldstaff.

The following quality control procedures were put in place:

- Interview schedules were numbered in advance and issued to fieldworkers on a daily basis.
- At the end of the day, completed questionnaires were submitted to Sihle and were checked overnight. Each checked questionnaire was signed off as checked.
- Interview schedules issued and returned were entered in a daily log sheet designed for this purpose.
- A map of the *isigodis* and a chart of the number of households to be visited in each *isigodi* were displayed on the office wall. Each day, the number of households visited in the isigodi was entered on the chart.
- Fieldwork commenced in the Mabundeni *isigodi* which was close to our field-site office, so that teething problems could be ironed out.
- Sihle informed the interviewers which households to visit according to the preplanned sampling strategy. He transported the fieldworkers to the selected households and ensured that the correct household was visited and that the interview was conducted.
- On-going training was provided at briefing sessions held at the administrative centre each morning. At these sessions Sihle discussed problems he may have noted from the previous day's interviews and clarified responses where necessary. The fieldworkers were also given opportunities to raise problems they were experiencing or to seek clarity about the interviewing process.
- Longer briefing sessions were held when the weekly site visit was made by the principal investigator. In the initial stages of interviewing, all completed questionnaires were also checked by the principal investigator. Problems were

addressed at these sessions. As the fieldwork progressed, spot checks of completed interview schedules were made by the principal investigator.

- One of the roles of the fourth fieldworker was to provide additional quality checks and to provide advice and support to the less experienced fieldworkers.
- The principal investigator provided support, in the form of training, advice and on-going consultation with the field staff during the focus group discussion phase.

Measures to ensure safety of the fieldworkers were also put in place. The fieldworkers always worked in the same general area and thus could easily access help from a colleague. Sihle transported them directly to the households to be interviewed and ensured that all was in order before he left. He knew at all times where the fieldworkers were and fetched them again at lunchtime, so they were never left alone for extended periods of time. They were also instructed to withdraw immediately from potentially unsafe situations. Fortunately, no such incidents occurred.

The diligence and competency of the fieldwork team, working in very rugged terrain, often having to walk up hill and down dale in inclement weather, are to be commended.

1.2.5.3 Validity and Reliability

As described above, various techniques were employed to ensure that the instruments were valid and reliable. These included face validity checks, evaluation of this study's findings with findings from the South African National Demographic and Health Survey (Department of Health *et al*, 2002) for criterion-related validity, checks for predicted validity, consistency checks between similar or related questions, asking the same question first as an open-ended question followed by a closed-ended question,

standardization of translation, hiring of interviewers with similar characteristics (age, gender, education level), intensive and continuous fieldworker training, close supervision and monitoring of fieldworkers by the fieldwork manager and a more senior interviewer, continuous quality control of completed interview schedules, intensive probing of important issues during interviewing and the use of triangulation or inter-technique approach.

1.2.6 PILOT STUDY

A pilot study to test the interview schedules for ambiguity, interpretation and appropriateness was conducted in an adjacent sub-district of Hlabisa. Eleven interviews were conducted. The pilot study occurred after the workshop processes set up to design and translate the questions, and after the face validation of the instrument had been undertaken. By the stage the pilot study was undertaken most problems had been solved. Only one minor correction was made and an extra coding option 'None/No Problems' was added to question 70.

1.2.7 DATA ANALYSIS

1.2.7.1 Individual Household Interviews

The responses to questions were painstakingly postcoded by two of the fieldworkers who conducted the interviews and by the fieldwork manager. Detailed uniform coding instructions were developed for this purpose. The coding of each and every questionnaire was checked by one of the coding team who had not coded that questionnaire. The coding of all the questionnaires was rechecked by the principal investigator with particular attention being paid to complicated questions or questions considered to be key to the objectives of the study.

A database was developed using Epi-Info Version 6.43 (Centers for Disease Control and Prevention, Atlanta, Y2K compliant). Data were captured and double entered by skilled data punchers of the Biostatistics Division of the Medical Research Council. Data were cleaned and the analysed using Epi-Info Version 6, the Statistical Analysis System (SAS) Version 6.12 (SAS Institute, Carry N.C.) and SPSS Version 9.0 (SPSS Corporation, USA). Data analysis was undertaken with the expert advice and assistance of Khangelani Zuma, a biostatistician of the Medical Research Council. Statistical methods employed were univariate statistics. Differences in quantitative variables were assessed using Student's t test. Significance tests for categorical variables were based on the Chi-squared test, Fisher's exact test or Cochran-Mantel-Haenszel statistics where appropriate. Multiple logistic regression analyses and survival analyses were also undertaken where appropriate. All p-values were based on a two-sided test. A p-value of less than or equal to 0.05 was considered to be statistically significant.

1.2.7.2 Focus Group Interviews

The focus group interviews were transcribed and translated from Zulu into English. The translation/transcription process was undertaken by one member of the data coding team and checked by another. Data from the focus group interviews were manually analysed in terms of identified themes (thematic analysis) and standard content analysis approaches. Where feasible and appropriate, descriptive statistics and frequency tables were generated. Demographic data from individual members of groups were captured and analysed using Epi-Info Version 6.43 (Centres for Disease Control and Prevention, Atlanta, Y2K compliant).

1.2.7.3 Family Planning Clinic Records

Annual consumption (units dispensed) was calculated for each method supplied. Couple-Years of Protection (CYP) for each method was estimated using standard tables (Centers for Disease Control and Prevention, 1998) and percentage contraceptive method mix was determined.

1.2.8 LIMITATIONS

- Caution should be exercised in generalising these findings too broadly as this study was conducted in a remote deep rural area. However, the area is not atypical of other deep rural areas of KwaZulu-Natal. Findings are not inconsistent with those of the 1998 South African Demographic and Health Survey as discussed in Chapter 1.6.
- Data obtained are self-reported by respondents and are therefore subjective.
- The instrument was conceptualised and designed in English and conducted in Zulu. Responses were analysed and reported on in English. Under these circumstances, it is difficult to ensure that intended meaning is not lost in translation. However, as described above, great lengths were taken to ensure maximum accuracy in translation.
- Limitations inherent to survey research, and knowledge, attitude, behaviour and practice (KABP) surveys apply (Katzenellenbogen *et al*, 1997). However, every attempt was made to overcome these inherent limitations.

CHAPTER 1.3 RESULTS (I). INJECTABLE CONTRACEPTIVE PREVALENCE, USER CHARACTERISTICS AND CONTRACEPTIVE METHOD MIX

In this chapter, an analysis of injectable contraceptive use, who uses the method and reasons for use, is undertaken. Other contraceptive methods used and reasons for not practising contraception are also explored. An in depth investigation of this kind has not previously been undertaken. However, it is extremely important to understand why injectable contraceptive use is so high, when the use of barrier methods, for dual protection against HIV and pregnancy, should be a primary consideration in decision-making regarding the choice of contraceptive method.

1.3.1 DESCRIPTION OF THE STUDY POPULATION

In total 848 African women, whose home language was Zulu, were interviewed. Selected demographic characteristics of respondents are shown in Table 1.3.1. Their mean age was 26.3 years (SD 7.7) and almost two thirds had an education level of Grade 8 or higher. Only 8.6% were employed (formally or informally) and 23.9% were students or scholars. Most of the women (61.6%) were in a single-stable relationship, and few were married (17.1%). Many (58.8%) were first pregnant in their teens and 41.3% of those under 20 years at the time of the survey were or had been pregnant at least once. Whilst nearly all respondents (97.2%) were resident in the area, many of their partners (67.6%) were not, and 74.1% of these migrant partners did not return home for a month or longer. A more detailed description of the respondent's demographic characteristics, by injectable user status, is provided later in this chapter.

Table 1.3.1 Selected characteristics of respondents (N=848)

CHARACTERISTIC	
Age (years)	
≤ 19	21.0%
20-24	27.3%
25-29	22.3%
≥30	29.4%
Mean (SD)	26.3 (7.7)
Education level grade 8 or above	65.2%
Employment status	
Employed	8.6%
Housewife/pensioner	12.7%
Students/scholars	23.9%
Unemployed	54.8%
Average household income of ZAR1000 or less per month	92.1%
Marital status	
Married (by civil, religious, traditional or customary ceremony)	17.1%
Single-stable relationship	61.6%
Single with casual relationships	7.8%
No relationship	13.6%
Number of living children: mean (SD)	2.3 (1.8)
Age at first pregnancy (years)	
Mean (SD)	19.2 (3.1)
Proportion first pregnant < 16 years	8.0%
Proportion first pregnant < 20 years	58.8%
Proportion < 20 years who were or had been pregnant	41.3%
Proportion resident in district	97.2%
Proportion with migrant partners	67.6%
Proportion of migrant partners who did not return home for a month or longer	74.1%

1.3.2 INJECTABLE PROGESTOGEN CONTRACEPTIVE PREVALENCE AND USER CHARACTERISTICS

A detailed analysis of the demographic patterns of injectable progestogen contraceptive (IPC) use is undertaken here, to provide some explanations for the popularity of this method in South Africa. This understanding should inform contraceptive policy for

service delivery which better suits the needs of South African women. Each of the three injectable user categories of the study are described, i.e. those women who were using the injectable contraceptive at the time of the survey; those who were not using it but had used it previously; and those who had never used it. These three sub-samples will be referred to as IPC users (injectable users), previous or discontinued users (those who had used IPCs previously but were not current users) and a never-used group (those who had never used IPCs).

1.3.2.1 IPC Prevalence

At the time of the survey, 187 (22.1%) of the 848 women interviewed were using an injectable contraceptive method, either Depo-Provera® or Nur-Isterate® (Table 1.3.2). Just over half the women had used an IPC at some time.

Table 1.3.2 Prevalence of IPC use

IPC Use Status of Respondents	N=848	%
Current IPC Users	187	22.1
Discontinued IPC Users (currently not using IPC's)	244	28.8
Total Ever-Used IPCs	431	50.8
Never-Used IPCs	417	49.2

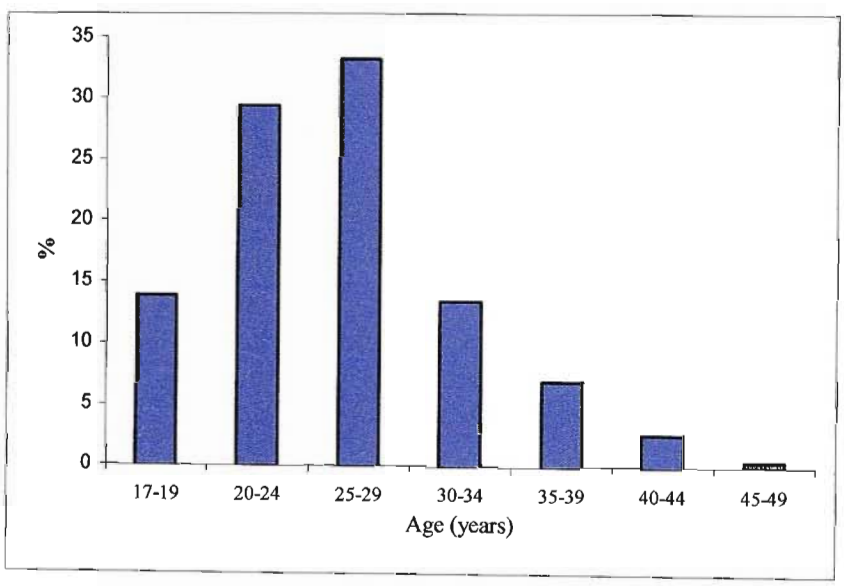
1.3.2.2 Demographic Characteristics of IPC Users

All the injectable contraceptive users interviewed in the Hlabisa sub-district were Zulu-speaking African women. The predominant religions practiced were Zionist (31.5%), Lutheran (19.6%) and Roman Catholic (17.9%). Similar proportions of Roman Catholics had ever used the injectable method (52% used DMPA; 51% used NET-EN). Key

demographic characteristics of IPC users are summarized in the second column of Table 1.3.3 (see sub-section 1.3.3.1 later in this chapter), which also provides comparative demographic data of discontinued users and the never-used group.

Only women in the age range 15 to 49 years were selected into the study. Injectable users' ages ranged from 17 to 49 years, with a mean age of 26.1 (median and mode = 25) years. Over three quarters (76.4%) were under 30 years of age, with 13.9% under 20 years (Figure 1.3.1). Of all the under 20 year-olds interviewed, 14.6% were IPC users and 23.9% of all respondents under 30 years were using an IPC. Injectables are thus widely used by young women. A more detailed analysis of the age of injectable users in comparison to discontinued users and the never-used group is provided later in this chapter.

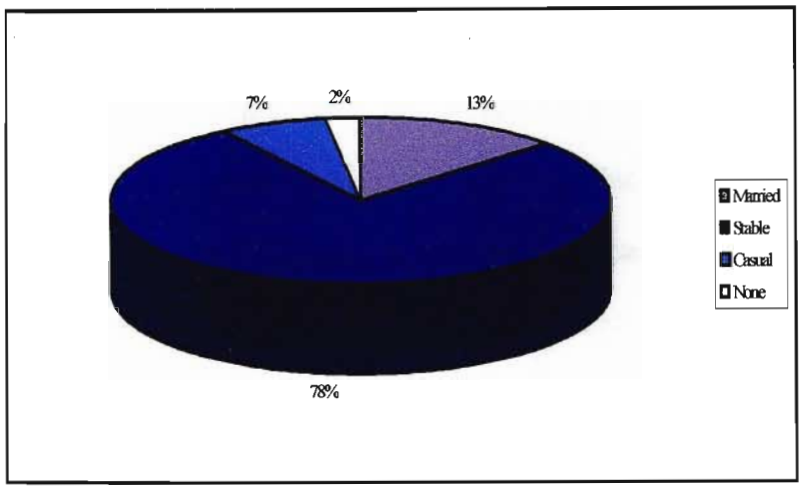
Figure 1.3.1 Age distribution of injectable contraceptive users



Most IPC users (77.5%) were in a single-stable relationship and only 13.4% were married by civil, religious, traditional or customary ceremony (Figure 1.3.2). Two women had

been divorced, and six had been widowed. Four women, who indicated that they were not in any type of relationship, yet were using the injectable contraceptive method, had all lost their partners within the few weeks preceding the interview. Two were recently widowed and the partners of two had recently left the relationship.

Figure 1.3.2 Marital status of injectable contraceptive users



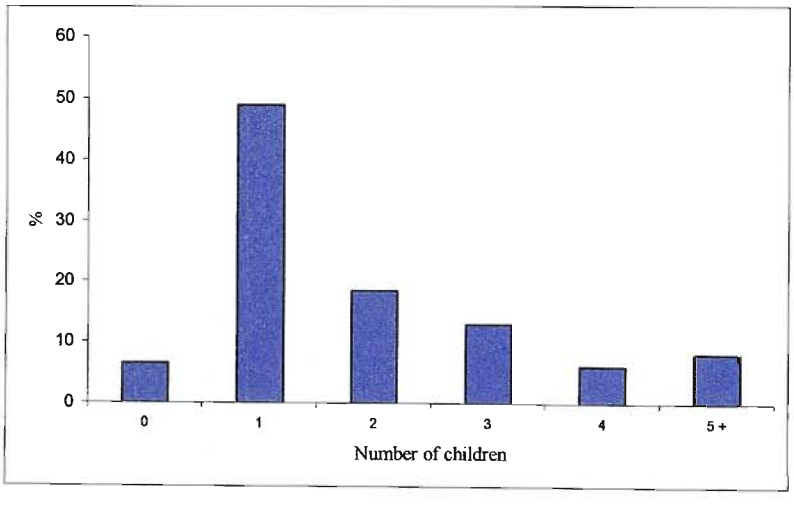
The average household size of IPC users was 8.5 people, with a median of 8, a mode of 7 and a range of 2 to 25 people. The average number of women (aged15 to 49 years) per household was 1.7 (median 2, mode 1, range 1-5).

IPC users were fairly well educated with 75.3% having attained an education level of Grade 8 (8 years of schooling) or higher. However, 70.6% were unemployed or housewives and 19.8% were scholars or students. Of those employed, in both the formal and informal sector, seven were professionals (teacher or nurse), five were working as semi-skilled workers (clinic assistant, cook or dressmaker), three were involved in sales work, and one was a domestic worker. Most IPC respondents (91.8%) had no personal income and 91.6% reported a household income of R1000 per month or less.

1.3.2.3 Reproductive and Contraceptive History of IPC Users

Table 1.3.4 (see sub-section 1.3.3.2 later in this chapter) provides a summary of the reproductive history and past contraceptive use of IPC users. Only six IPC users had never been pregnant, with 96.8% having been pregnant. The mean age at first pregnancy was reported to be 19.2 years. Of those ever pregnant, the youngest age at first pregnancy was 12 and the oldest was 30, with 7.2% first pregnant when they were under 16 years and 60.2% when they were under 20 years. Only 12 (including the six never pregnant) had no children and the maximum number of living children was seven. Of those who had children (n=175) the average number was 2 (median and mode =1). Nearly half the IPC users (48.7%) had one child (Figure 1.3.3). Twenty-eight women reported miscarriages, six of these had miscarried twice; only four women had had children who had died. Of the IPC users under 20 years at the time of the survey all but one, a 19 year old, had been pregnant.

Figure 1.3.3 Distribution of numbers of children of injectable contraceptive users



The average age at first contraceptive use was 22.3 years with an age range of 16 to 42 years. In most cases IPCs were the first method used. NET-EN was the first method used by 54.0% and DMPA by 36.4%. The oral contraceptive was the first method for 9.1% of the respondents and only one woman first used the male condom.

1.3.2.4 Residential Status

Most of the injectable users (98.4%) were, for the purposes of this study, classified as Hlabisa residents, since they slept at their home for at least 4 nights per week and for at least 50% of the time. In contrast, most of their partners did not reside with them, with 88.2% of women married or in a stable relationship reporting that their partners resided elsewhere (i.e. for four nights a week or more, and for more than 50% of the time), and 76.3% of the partners resided out of the Hlabisa sub-district. Hence, few couples were co-habiting. Thirty-two percent of married women's partners resided with them, compared with 8.3% of the women in stable relationships. Most partners returned to their partners once a month (31.5%) or 2 to 3 times a month (21.1%). Their locations when they were away were mainly Johannesburg (20.3%), Richards Bay/Empangeni/Nseleni/Ulundi (16.2%), Durban/Pietermaritzburg (10.8%), Mtubatuba/St Lucia (10.1%) and Nongoma/Buxedeni (7.4%), with 23.0% of partners residing elsewhere in the Hlabisa/Hlululwe area. Only one respondent's partner returned only once a year and he lived in Johannesburg when he was away. Eight respondents could not predict when their partners would return, and in all these cases the partners lived in the Hlabisa sub-district (six) or close by (Mtubatuba or Richard's Bay area).

1.3.3 COMPARISON OF INJECTABLE CONTRACEPTIVE USERS WITH DISCONTINUED USERS AND THOSE WHO HAD NEVER USED THE METHOD

1.3.3.1 Comparing Demographic Characteristics

The three user groups were similar in terms of age, average household income and household size (Table 1.3.3). While few women in all three categories were employed, more of those never having used the injectable were students or scholars and, predictably, more had never had a relationship. More IPC users were students or scholars than previous users ($p=0.025$). IPC users were better educated than the other user groups ($p=0.002$), with previous users the least well educated ($p=0.012$). Less than 20% of all respondents were married (by civil, religious, traditional or customary ceremony) with more in the discontinued user group being married. More IPC users were in a stable relationship (77.5%), and more were married or in a stable relationship (90.9%) (Table 1.3.3).

More IPC users had migrant partners than previous users, but in the case of IPC users, fewer partners were away for a month or more (Table 1.3.3).

Table 1.3.3 Comparative demographic characteristics according to IPC user status

Demographic Characteristic	Current Users N=187	Previous Users N=244	Never Used N=417
Age (years)			
Mean (SD)	26.1 (5.9)	28.6 (7.2)	25.1 (8.4)
Range	17-49	17-48	15-48
Education level grade 8 or above (%)	75.3	58.7	64.5
Employment status (%)			
Employed (formal or informal)	8.6	9.5	8.0
Housewife/pensioner	10.7	16.9	11.6
Students/scholars	19.7	11.9	32.9
Unemployed	61.0	61.7	47.4
Average household income of ZAR1000 per month or < (%)	91.6	92.4	92.2
Average household size	8.5	8.3	7.9
Range of household size	2-25	2-18	2-25
Marital status (%)			
Married*	13.4	19.7	17.3
Stable relationship	77.5	64.3	52.8
Single, casual relationships	7.0	6.6	8.9
No relationship	2.1**	9.4	8.4
Never had a relationship	-	-	12.7
Proportion with partners residing with respondent***	11.8	20.0	9.8
Proportion with migrant partners (i.e. living outside the district)***	76.3	59.0	69.2
Proportion of migrant partners who did not return home for a month or longer	61.1	81.0	79.9

* by civil, religious, traditional or customary ceremony
** partner recently died or left
*** of those married or in a stable relationship

A logistic regression analysis which explores associations between current use of IPCs and demographic variables is described later in this chapter (sub-section 1.3.3.3).

1.3.3.2 Comparing Reproductive and Contraceptive History

Pregnancy History

Forty percent of those who had never used the injectable method had never been pregnant. Of those who had never used IPCs and who had ever been sexually active, 31.3% had never been pregnant. By comparison, very few of the current IPC users and previous users had never been pregnant (3.2% and 4.1% respectively) (Table 1.3.4).

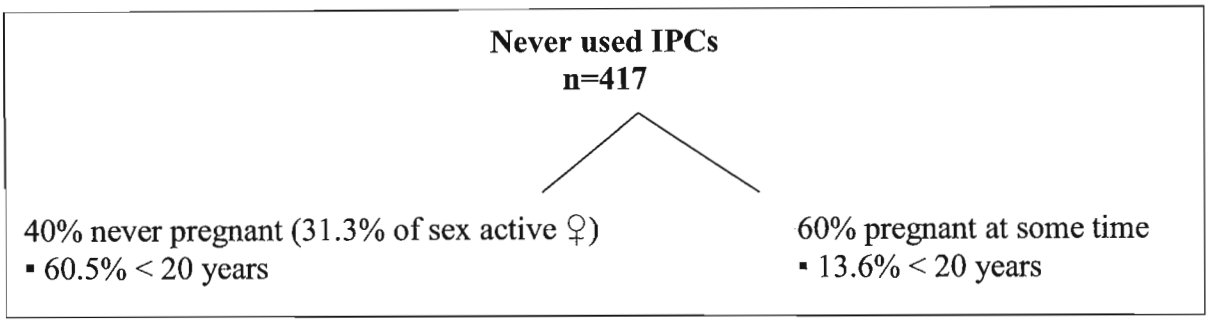
Table 1.3.4 Comparative reproductive history by IPC user status

Reproductive History	Current Users N=187	Previous Users N=244	Never Used N=417
Pregnancy history			
% never pregnant	3.2	4.1	40.0
% never pregnant (of those ever sexually active)	-	-	31.3
Number pregnant at time of interview	-	25	23
Number unsure if pregnant at time of interview	-	7	8
Age at first pregnancy (years)			
Mean (SD)	19.2 (2.8)	18.8 (2.7)	19.6 (3.3)
Range	12-30	12-31	13-31
% < 20 years who were or had been pregnant (p=0.000)	96.2	82.4	24.4
% first pregnant < 16 years (of those ever pregnant)	7.2	9.8	12.5
% first pregnant < 20 years (of those ever pregnant)	60.2	63.8	53.1
Parity			
Mean number of living children (total sample)	1.9	2.2	1.4
Mean number of living children (of those ever pregnant)	2.0	2.4	2.3
Maximum number of living children	7	10	10
% with one child (of total sample)	48.7	38.9	25.2
% with more than one child	44.9	54.1	29.7
Contraceptive history			
Ever used a contraceptive method (%)	100	100	18.2
Ever used a contraceptive method (% of those ever sexually active)	100	100	21.5
Age at first contraceptive use (years)			
Mean (SD)	22.3 (4.9)	22.0 (5.2)	20.1 (3.3)
Range	16-42	14-41	15-34
First contraceptive method used	n=187	n=244	n=74
IPC	90.4	94.3	-
OC	9.1	5.7	71.6
Male condom	0.5	0	2.7
Female condom	0	0	1.4
IUD	0	0	2.7
Tubal ligation	0	0	1.4
Thigh sex	0	0	10.8
Withdrawal	0	0	2.7
Rope*	0	0	1.4
Quinine	0	0	2.7
Essence of life	0	0	1.4
Other	-	-	1.4

* The rope is a traditional contraceptive method obtained from a faith healer or a traditional healer. According to a male traditional leader who participated in the group discussions, a few threads from a mule's tail are used to make a rope. The woman ties this rope around her waist to prevent pregnancy.

Most of those who were in the group that had never used IPCs and who had never been pregnant were under 20 years (60.5%). By contrast, few who had been pregnant were under 20 (13.6%) (Figure 1.3.4).

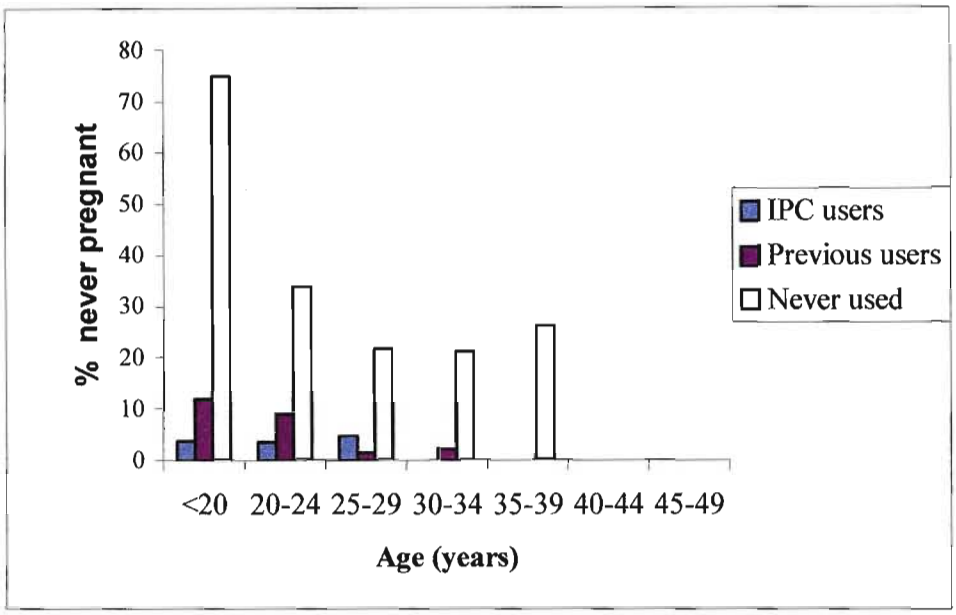
Figure 1.3.4 Pregnancy history of women who had never used IPCs



Just over two thirds (68.2%) of those who had never used an IPC and who had never been pregnant, had had a relationship at some time. Those who had never been pregnant and had never had a relationship (31.8%), were particularly young -- 84.9% were under 20 years and 58.5% were 15, 16 or 17 years old (9 were 15 years, 12 were 16 years and 10 were 17 years old).

Figure 1.3.5 shows that many of the non-users who were under 20 had never been pregnant (74.8%) in contrast to the very few under 20s in the IPC user group (3.8%) and the discontinued user group (11.8%) who had never been pregnant.

Figure 1.3.5 Percentage never pregnant, within age group, by IPC user status



Many of the IPC users and discontinued users were first pregnant before they turned 20 (60.2% and 63.4% respectively), compared to only 53.1% of the ever sexually active non-users (Table 1.3.4). Mean age at first pregnancy was similar for the 3 user categories (Table 1.3.4).

Relatively few respondents reported that they had ever had difficulty in conceiving:

- 0.5% of current IPC users
- 0.8% of previous IPC users
- 3.9% of those who had never used the injectable.

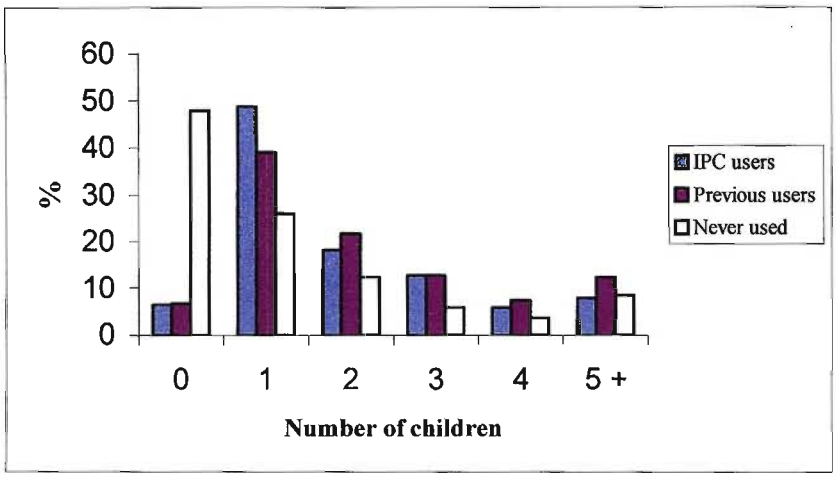
Slightly more women were unsure about whether or not they had a fertility problem:

- 1.2% of current IPC users
- 0.8% of previous IPC users
- 7.3% of those who had never used the injectable.

Parity

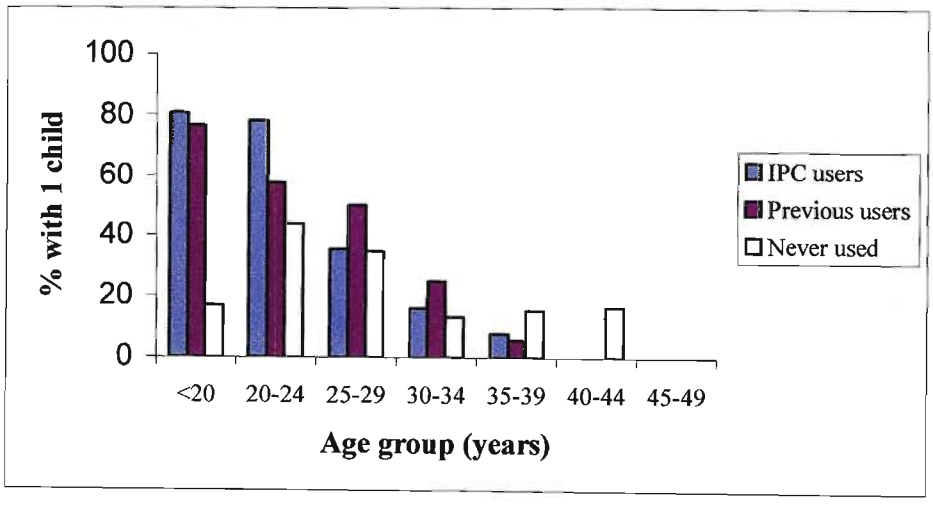
More IPC users had only one child than the other user categories (Table 1.3.4 and Figure 1.3.6), and many of those who had never used the injectable had no children.

Figure 1.3.6 Distribution of number of children by IPC user category



Whilst many current and discontinued IPC users in the under 20 year age group had only one child, fewer teenagers who had never used the injectable had one child (Figure 1.3.7). Bearing in mind however that many non-users, particularly those under 20 years, had never been pregnant (Figure 1.3.6).

Figure 1.3.7 Percentage with one child by age and IPC user category



Contraceptive History

Very few of those who had never used the injectable had ever used any method of contraception (18.2%) (Table 1.3.4). Excluding those who had never been sexually active, 21.5% of those who had never used an IPC had ever used any contraceptive method -- most often the oral hormonal contraceptive method which was the first method used by 71.6%. The oral contraceptive was the first method for far fewer current IPC users and discontinued IPC users (Table 1.3.4). A greater mix of first contraceptive methods is evident for those never having used the injectable method, including a wide range of traditional methods – thigh sex, withdrawal, rope (Table 1.3.4) and substances not registered with the Medicines Control Council as contraceptives (quinine, essence of life). Mean age at first contraceptive use was similar for the 3 user categories, and, particularly for users and discontinued users, was higher than mean age at first pregnancy (Table 1.3.4).

1.3.3.3 Characteristics Independently Associated with IPC Use

A logistic regression analysis model was developed, using Nagelkerke R^2, to explore associations between current use of IPCs and demographic and reproductive variables. A backward stepwise dropping approach was used. The dependent variable was "currently using IPC or not". The independent variables included in the model were: "age", "education", "employment status", "marital status", "ever pregnant" and "number of children" (Table 1.3.5). Nagelkerke R^2 was found to be 0.186 with 77.7% correctly classified.

The analysis showed that younger, more educated women in a married or stable relationship were more likely to be using an IPC (Table 1.3.5). Having ever been

pregnant was strongly associated with IPC use (OR=12, see Table 1.3.5). Whilst a non significant association was found between IPC use and employment status, or IPC use and number of children, removal of these variables from the model increased the variance and they thus played some role in the association.

Table 1.3.5 Characteristics independently associated with IPC use

	Odds Ratio	Confidence Interval (95%)	P Value
Age (years)			0.0288
15-24	1.50	0.74; 3.03	0.2569
25-34	2.08	1.15; 3.77	0.0157
35-49	1		
Education			
No school or primary	0.50	0.33; 0.77	0.0017
Secondary or higher	1		
Marital status			
Married or stable relationship	2.10	1.20; 3.69	0.0099
Casual or no relationship	1		
Ever pregnant			
Yes	12.23	3.40; 43.97	0.0001
No	1		
Employment status			0.3837
Employed	0.87	0.46; 1.65	0.6596
Student or scholar	1.39	0.83; 2.34	0.2162
Housewife	0.70	0.38; 1.29	0.2556
Unemployed	1		
Number of children			0.9552
No children	0.90	0.32; 2.55	0.8450
One child	0.94	0.61; 1.45	0.7801
More than one child	1		

1.3.4 CONTRACEPTIVE METHOD MIX

Contraceptive prevalence amongst survey respondents is described here and contraceptive methods used by respondents as well as reasons for method choice are presented. Reasons for not practising contraception are also explored. A manuscript describing the results of this analysis has been published in the peer reviewed journal *African Journal of Reproductive Health* ('Where is the condom? Contraceptive Practice in a Rural District in South Africa', 2002, 6(2), 71-78. For a copy of this manuscript, see page xvii of the thesis

in the section after the abstract). An analysis of the contraceptive method mix issued from the Hlabisa Hospital family planning clinic is also undertaken.

1.3.4.1 Current Contraceptive Practice

Less than a third (29.7%) of all women (N=848) reported use of a contraceptive method at the time of the survey. The most commonly used methods were the IPCs depot medroxyprogesterone acetate and norethisterone oenanthate, used by 22.1% of all the women. The oral contraceptive (OC) was used by 4.5% of the total sample and only 1.3% of respondents reported the male condom as their current method. No-one used the female condom. While 17.4 % of respondents under 20 years were using a contraceptive method, over a third (37.8%) of the teen respondents who had ever been pregnant were using a contraceptive method. Excluding the 211 respondents who were not sexually active, or were pregnant, infertile or menopausal, 28.6% were using IPCs, 5.9% were using the oral contraceptive and 1.7% were using the male condom.

Of those who reported using a method (n=252), 94.4% were using a modern method (injectable or oral hormonal contraceptive, male condom, intrauterine contraceptive device [IUD], tubal ligation), 3.2% a traditional method and 2.4% substances not registered with the Medicines Control Council for contraceptive use (Table 1.3.6). Current use of natural family planning methods such as the calendar or rhythm method or the basal body temperature method was not reported. In contrast to the wide spread use of the injectable method (74.2% of women practising contraception), the condom was used by only 4.4% of current users.

Table 1.3.6 Current contraceptive practice (n=252)

Current method	Number of users	%
Modern methods	**238**	**94.4**
Injectable contraceptive	187	74.2
Oral contraceptive	38	15.1
Male condom	11	4.4
IUD	1	0.4
Tubal ligation	1	0.4
Traditional methods	**8**	**3.2**
Thigh sex (ukusoma)	3	1.2
Rope	2	0.8
Snail's shell*	2	0.8
Withdrawal	1	0.4
Other methods	**6**	**2.4**
Quinine	3	1.2
Essence of life	2	0.8
Flagyl	1	0.4

* Use of a snail's shell is a traditional contraceptive practice which involves taking the cloth or pad used during menses, putting it in the shell of a snail, and digging a hole and burying it. Care has to be taken to prevent it from getting washed away when it rains as it is believed that if it gets washed away the woman following this practice won't be able to conceive (female parent, from focus group discussion)

In the age range 15-19 years, 83.9% of those using a method were using the injectable, whilst only one woman reported the male condom as her current contraceptive method (Table 1.3.7). More women in the 20-24 year age group were using the oral contraceptive compared to other age groups, but OC use was still much lower than IPC use in this age group. In the group of women who were 40 years or older, injectable use was very high (85.7%) and no OCs or condoms were used.

Table 1.3.7 Current contraceptive method by age

CURRENT METHOD	AGE GROUP (YEARS)					
	<20 n (%)	20-24 n (%)	25-29 n (%)	30-34 n (%)	35-39 n (%)	40-49 n (%)
Injectable contraceptive	26 (84)	55 (69)	62 (73)	25 (86)	13 (65)	6 (86)
Oral contraceptive	3 (10)	17 (21)	13 (15)	3 (10)	2 (10)	0 (0)
Male condom	1 (3)	3 (4)	5 (6)	1 (4)	1 (5)	0 (0)
Other methods	1 (3)	5 (6)	5 (6)	0 (0)	4 (20)	1 (14)
Total number	**31 (100)**	**80 (100)**	**85 (100)**	**29 (100)**	**20 (100)**	**7 (100)**

All but three teen respondents who had ever been pregnant and were using a contraceptive method were using the injectable method. The other methods used by teenagers ever pregnant were: oral contraceptives (n=2) and flagyl (1), which is not a contraceptive and should not be used as such. Amongst students and scholars, 18.4% were using the injectable and only 1.0% the male condom (Table 1.3.8).

Table 1.3.8 Contraceptive practice of scholars and students (n=201)

CURRENT METHOD	SCHOLARS n = 180 (%)	STUDENTS n = 21 (%)	TOTAL n =201 (%)
No method*	139 (77.2)	13 (61.9)	152 (75.6)
Injectable contraceptive	30 (16.7)	7 (33.3)	37 (18.4)
Oral contraceptive	5 (2.8)	1 (4.8)	6 (3.0)
Male condom	2 (1.1)	0 (0)	2 (1.0)
Other methods	4 (2.2)	0 (0)	4 (2.0)

* Of these, 56 were not sexually active, and 8 were pregnant

Not surprisingly, given the low use of any method other than the injectable, contraceptive practice was very low amongst the non IPC users and discontinued IPC users (Table 1.3.9). Condom use was low amongst women in these two user groups and some methods, such as quinine and Flagyl, with questionable contraceptive efficacy and safety were used.

Table 1.3.9 Current contraceptive use by IPC user status

Contraceptive use	Current Users	Previous Users	Never Used	Total
Current contraceptive use				
	n=187	**n=244**	**n=417**	**n=848**
% Currently using a contraceptive method (all women)	100	11.5	8.9	29.7
	n=187	**n=178**	**n=272**	**n=637**
% Currently using a contraceptive method (excluding: sexually inactive, pregnant, had hysterectomy, menopausal, infertile)	100	15.7	13.6	39.6
Current contraceptive method				
	n=187	**n=28**	**n=37**	**n=252**
IPC	187	-	-	187
OC	-	12	26	38
Male condom	-	7	4	11
Female condom	-	-	-	-
IUD	-	1	-	1
Tubal ligation	-	-	1	1
Thigh sex	-	1	2	3
Withdrawal	-	-	1	1
Rope	-	1	1	2
Quinine	-	2	1	3
Essence of life	-	1	1	2
Snail's shell	-	2	-	2
Flagyl	-	1	-	1

1.3.4.2 Reasons for Contraceptive Method Choice

In response to an open-ended question about reasons for choosing the injectable method, the most common reason, given by 35.0% of respondents, was that it was convenient. The method was considered to be convenient since it only has to be used every two or three months, or because one does not have to remember to take it every day as with the oral contraceptive. Nearly a quarter of the injectable users (23.0%) chose this method because it is effective, often making statements such as "its always in my blood" or "it stays in the blood a long time". The third most common reason given for using the injectable was that it was recommended by the clinic health personnel, with 19.7% giving this response. Some respondents (4.9%) simply stated that the method "suited them", others expressed a

dislike of oral contraceptives because of side effects experienced (4.4%). A few (2.7%) chose the method as it could be used without their partner's knowledge.

Similar responses were given when injectable users were prompted to respond to each of a list of 10 possible reasons for choosing the injectable method. Almost all (96.3%) the 187 injectable users indicated that they chose this method for convenience, as they only had to return to the clinic every two or three months. Other common responses were that: it was effective (47.6%); it was recommended at the clinic (37.4%); few problems or side effects were experienced (27.3%); it caused amenorrhoea (23.0%); it was recommended by friends or relatives (21.5%); and it was a method that could be hidden from partners (20.9%). Although not reported in response to the open-ended question, 52.9% said that they chose the method because they felt that it was a safe way to prevent pregnancy.

A quarter (25.8%) of the women who were practicing contraception were using a method other than the injectable, and the most common reason for method choice, given by 43.3% in response to an open-ended question, was related to injectable side effects. Although almost half of the women giving this response had used the injectable method before, only 55.6% of these previous injectable users gave this as their reason for current method choice. A few were using a method on the recommendation of their partner (n=4), relatives or friends (n=1), or the health provider (n=2). Six of the women giving this response were using the oral contraceptive and one was using the withdrawal method. Of note is that 7 women were using the condom and 3 were using thigh sex, because these methods were considered to provide protection against both pregnancy and sexually

transmitted diseases. The remaining condom users indicated that they did not like the side effects of oral contraceptives, or that their partner was often away and a regular method was not needed.

1.3.4.3 Reasons for Not Using a Method

Of the 848 women interviewed 70.3% were not using a contraceptive method. Reasons for not using a method are broadly grouped as follows:[5]

1. Most women (66.8%) indicated that they did not need to practise contraception. These women reported that they: had never been sexually active (11.1%); were not sexually active (11.8%); had sex infrequently (11.1%); were pregnant (6.6%); were wanting to conceive or waiting until after the birth of their first baby (11.0%); were breastfeeding (9.1%); were menopausal, had had a hysterectomy, or their husbands were infertile (6.1%). The 20.2% of women who had sex infrequently and those who were breastfeeding, believed that they did not need to practise contraception, yet they were at risk of an unplanned pregnancy. Also potentially at risk of an unplanned pregnancy were those who reported that they were menopausal or had infertile husbands, as they may not have had these conditions clinically confirmed.
2. Disapproval of contraception was given as a reason for non-use by 13.3%. Disapproval was based on partners' views, personal views or the views of others, or on religious or cultural grounds.

[5] More than one reason was given by some respondents.

3. Reasons related to the method itself such as side effects, health concerns and inconvenience were given by 14.6% of the respondents, with over three quarters of reasons in this category related to side effects. Close to 90% of these women had used a contraceptive method previously, most commonly the injectable method, suggesting that many had given reasons based on experience.
4. Reasons related to the provision of contraceptive services were given by only 2.4% and included: lack of knowledge about contraceptives; long distances from the health facility; and that the respondent was too shy to go to the clinic.
5. Other reasons were given by 7.3% of the women. For instance some respondents were awaiting parental permission to use contraception, while others said that they didn't have a reason.

In all 61.2% of those not using a method were not sexually active, were pregnant or wanting to get pregnant, or had had a hysterectomy. This suggests an unmet need, amongst nearly 40% of women not practising contraception, for more appropriate contraceptive methods or services than those available.

1.3.4.4 Method Mix according to Hlabisa Hospital Clinic Records

The ratio of oral to injectable contraceptives issued by the family planning clinic of the Hlabisa Hospital in the July 1998 to June 1999 period was similar to the ratio of ICP to OC amongst respondents surveyed within the same timeframe. According to the clinic records, there were 4.3 injectable users to 1 OC user (Table 1.3.10), compared with 4.9 injectable users to 1 OC user, according to the survey (Table 1.3.6).

No intrauterine contraceptive devices were issued and no records were kept of the number of condoms distributed. IPCs are clearly the most commonly used contraceptive method in the sub-district.

Table 1.3.10 Contraceptive methods issued from Hlabisa Hospital: July 98-June 99

Contraceptive Method	Units issued	Time period covered by unit issued	CYP
Injectable contraceptives			
DMPA	1401	3 months	350
NET-EN	2289	2 months	382
Total			732
Oral contraceptives			
Ovral	342	1 month	29
Nordette	615	1 month	51
Triphasil	963	1 month	80
Microval	141	1 month	12
TOTAL	2061		172
IUD	0		0
Condoms	No records kept		No records kept

1.3.5 MAIN FINDINGS

- Injectable contraceptives were much more widely used than other contraceptive methods (IPCs are used by 74% of women practicing contraception).
- Condom use was low (used by 4% of women practicing contraception).
- A few women were practicing dual protection, the simultaneous prevention of pregnancy and STIs.
- Amongst women under 20 years, 83.9% of those using a contraceptive method were using IPCs. Only one respondent reported the male condom as her current method.
- Younger, more educated women in married or stable relationships were significantly more likely to be using an IPC.
- Mean age at first contraceptive use was higher than the mean age at first pregnancy, particularly amongst those who had previously used an IPC.

- Having ever been pregnant was strongly associated with IPC use with almost all (97%) the IPC users having been pregnant at least once.
- Many IPC users had only one child, suggesting that IPC use commences after the first pregnancy.
- Health workers play an important role in women's decisions to use IPCs.
- There is an unmet need for more appropriate contraceptive methods and services amongst many of the sexually active women not practising contraception.
- The survey findings on contraceptive method mix are consistent with methods issued from the Hlabisa Hospital family planning clinic.

CHAPTER 1.4 RESULTS (II): INJECTABLE CONTRACEPTIVE PRODUCT MIX AND DISCONTINUATION PATTERNS

Findings on current users and discontinued users of DMPA and NET-EN are the focus of this chapter. The data presented here provide a comparative analysis of the usage of the two IPCs. This includes a cost analysis of the provision of DMPA or NET-EN based on utilization patterns of these two products in the Hlabisa District, and on distribution patterns from four pharmaceutical depots in South Africa. A manuscript based on this comparative analysis has been published in the peer reviewed journal *BMC Health Services Research* (2001, 1(4), http://www.biomedcentral.com/1472-6963/1/4), under the title 'Counting the costs: Comparing depot medroxyprogesterone acetate and norethisterone oenanthate utilisation patterns in South Africa'. A copy of this paper can be found on page xxv of this thesis immediately after the abstract. A comprehensive analysis of this kind has not previously been undertaken. In the final sub-section of this chapter the discontinuation patterns of the two IPCs are described.

1.4.1 DEMOGRAPHIC CHARACTERISTICS OF DMPA AND NET-EN USERS

1.4.1.1 Current DMPA and NET-EN Users

An analysis of the demographic profile of respondents using the injectable progestogen contraceptive (IPC) at the time of the survey shows that NET-EN users were significantly younger than DMPA users (p=0.0001). The mean age of DMPA users was 29.6 years and that of NET-EN users was 23.3 years (Table 1.4.1). Figure 1.4.1 below further illustrates the age discrepancy between users of the two injectable products. NET-EN users were also more likely to be students or scholars, and to be more highly educated (Table 1.4.1).

Table 1.4.1 Demographic characteristics of current DMPA and NET-EN users[6]

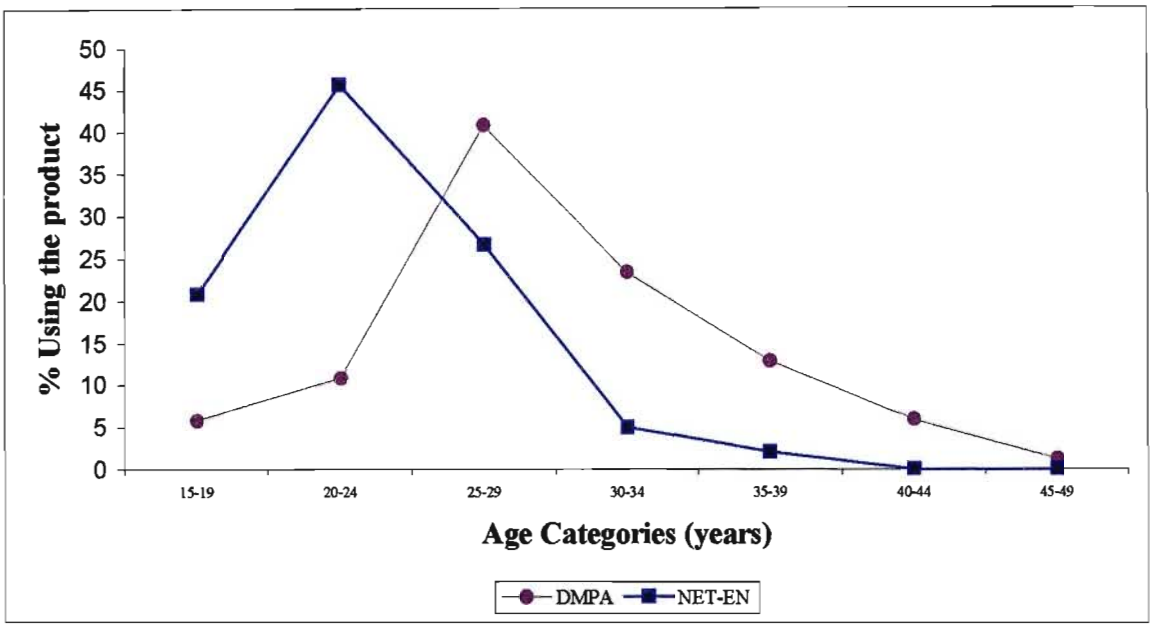
Characteristic	DMPA Users	NET-EN Users
Age (years)	**n=86**	**n=101**
Mean (SD)	29.6 (6.0)	23.2† (4.1)
TTest p=0.0001		
Median	29	23
Mode	28	22
Range	18-49	17-37
Education (%)	**n=85**	**n=101**
No formal education	4.7	0.0
Up to Grade 3	11.8	1.0
Grade 4 – Grade 7	30.6	5.0
Grade 8 – Grade 10	27.6	47.5
Grade 11– Grade 12	22.4	40.6
Tertiary	3.5	5.9
% Grade 8 and above	52.9	94.1†
Chi-Square: p=0.001		
Employment status (%)	**n=86**	**n=101**
Employed – formal sector	5.8	5.9
Employed – informal sector	4.7	1.0
Housewife/pensioner	19.8	3.0
Unemployed	64.0	58.4
Scholar (n=5;25)	5.8	24.8
Student (n=0;7)	0.0	6.9
*Chi-Square: p=0.001**		
Marital status (%)	**n=86**	**n=101**
Married	22.1	5.9
Stable relationship	69.8	84.2
Single – casual relationship	5.8	7.9
Single no relationship	2.3	2.0
Monthly personal income (%)	**n=85**	**n=98**
No income	89.4	93.9
R1-R500	3.5	1.0
R501-R1000	2.4	2.0
R1001-R2000	3.5	3.1
R2001-R3000	1.2	0.0

† Significant difference between DMPA and NET-EN users

* Significant difference between DMPA and NET-EN users based on sum of scholars & students

[6] Note: where the sample size is less than expected, the missing values were where responses were not recorded or were inappropriate, unless otherwise indicated.

Figure 1.4.1 Age distribution of current DMPA and NET-EN users (n=187)



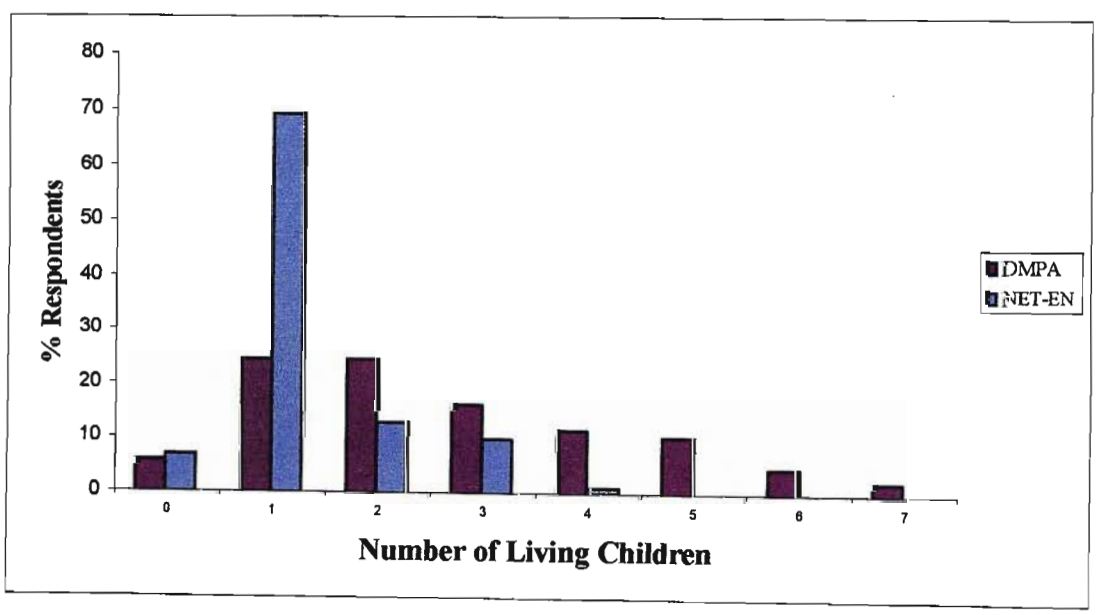
NET-EN users were more likely to have fewer children and to start using a contraceptive method at a younger age than DMPA users (Table 1.4.2). Many of both DMPA and NET-EN users had only one child, with more NET-EN (69.3%) users having only one child than DMPA users (24.4%), $p<0.001$) (Figure 1.4.2).

Table 1.4.2 Reproductive history of current DMPA and NET-EN users

	DMPA Users	NET-EN Users
% ever pregnant	**n=86**	**n=101**
Chi-Square p=0.527	97.7	96.0
Number never pregnant	2	4
Age first pregnant (years)	**n=84**	**n=97**
Mean (SD)	19.3 (3.0)	19.1 (2.7)
TTest p=0.7129		
Median (years)	19	19
Mode (years)	18	20
Range (years)	13-30	12-27
Age first used any method (years)	**n=86**	**n=101**
Mean (SD)	24.4 (5.7)	20.6† (3.1)
TTest p=0.0001		
Median	23	20
Mode	22	17
Range	16-42	16-30
Number of children	**n=84**	**n=97**
(excluding women never pregnant)		
Mean (SD)	2.7 (1.7)	1.3† (0.7)
TTest: p=0.0001		
Median	2	1
Mode	1	1
Range	0-7	0-4

† Significant difference between DMPA and NET-EN users

Figure 1.4.2 Proportion of number of children of current DMPA and NET-EN users



In order to determine the influence of multiple variables on product choice, a forward stepwise logistic regression analysis was performed. The variables selected for the model were age, education, employment status, age at which a contraceptive method was first used, number of living children and number of side effects experienced with the injectable product being used. Age and education were found to be independently associated with which injectable product was used, with younger, more educated women more likely to be using NET-EN[7] (Table 1.4.3).

Table 1.4.3 Factors independently associated with product choice

Variable	Odds Ratio	Wald Confidence Limits (95%)	P value
Age	1.24	1.14; 1.35	0.0001
Education			
Primary school or <	9.55	3.32; 26.95	0.0001
Secondary school or >	1		

1.4.1.2 Previous DMPA and NET-EN Users

Despite the differing times since discontinuation of the injectable, similar trends to current user characteristics are apparent, with considerably more previous NET-EN users found to be students or scholars and more highly educated than DMPA users. A summary of the main demographic characteristics of previous DMPA and NET-EN users is provided in Table 1.4.4. At the time of the survey, previous NET-EN users were younger and had fewer children than previous DMPA users. Tests of significance were not

[7] The Hosmer-and-Lemeshow Goodness-of-Fit Statistic = 2.7667 with 7 degrees of freedom (p=0.9057). This is not significant, indicating a good fit of the model to these data.

performed because of the differing times since discontinuation of the injectable among the respondents.

Table 1.4.4 Demographic characteristics of previous DMPA and NET-EN users

Characteristic (at the time of the survey)	**Previous DMPA Users n=138**	**Previous NET-EN Users n=96**	**Used Both Previously n=10**
Age (years)			
Mean	31.9	23.9	28.4
Range	17-48	17-39	24-37
% ever pregnant	97.1	87.5%	100%
Number never pregnant	4	12	0
Number of living children			
Mean	3.0	1.5	2.0
Range	0-10	0-6	1-4
Education grade 8 & > (%)	43.8	76.8	90.0
Married/stable relationship (%)	87.6	80.2	80.0
No personal income (%)	88.3	87.4	100.0
% scholars or students	5.8 (6 scholars, 2 students)	21.8 (20 scholars, 1 student)	0

* Ten respondents had previously used DMPA and NET-EN

1.4.2 UTILISATION PATTERNS AND REASONS FOR CHOICE

1.4.2.1 Product Mix

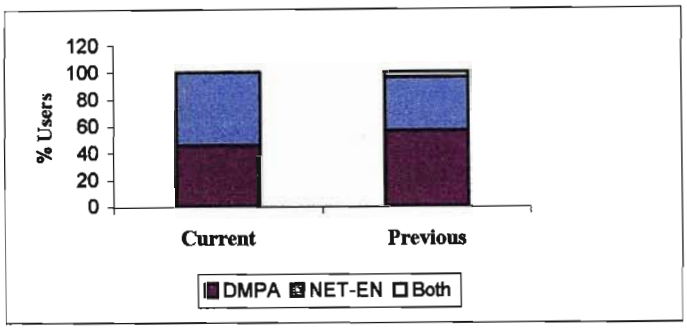
The injectable contraceptive method was extensively used in the Hlabisa sub-district, with 50.8% (n=431) of the respondents ever having used it and 22.1% using it at the time of the survey (Table 1.4.5). Both injectable contraceptive products were widely used with more current users found to be using NET-EN and more previous users having used DMPA (Table 1.4.5 and Figure 1.4.3).

Table 1.4.5 Injectable contraceptive product mix

	DMPA		NET-EN		DMPA & NET-EN[#]		TOTAL	
	N	%	N	%	N	%	N	%
Current Users	86	46.0	101	54.0	-	-	187	22.1
Discontinued Users[†]	138	56.6	96	39.3	10	4.1	244	28.8
Total Ever-Used	224	26.4	197	23.2	10	1.2	431	50.8
Never-Used	-	-	-	-	-	-	417	49.2

[#] Ten respondents had previously used DMPA & NET-EN
[†] Discontinued users were not using the injectable contraceptive method at the time of the survey

Figure 1.4.3 Injectable product mix: Current and previous DMPA and NET-EN users



Amongst the sub-sample of respondents not currently using the injectable, but who had previously used this contraceptive method, 10 had previously used both products (Table 1.4.5). Twenty-one current users had previously used an IPC. Fourteen current DMPA users had previously used NET-EN; one had previously used both products. Five NET-EN users had previously used DMPA and one had used both before. In this study, these 21 women are regarded as current users and do not form part of the sub-sample of previous users.

As described in the literature, both products have been available in South Africa for some time. Records indicate that both DMPA and NET-EN were available through the public sector as far back as 1994. There are however no records indicating which products were available prior to this (J van den Berg, Deputy Director: Medical Stores and Systems, National Department of Health, pers. comm., March 2001). A Gray remembers issuing both products from the South African Defence Force to state clinics in the late 1980s (A Gray, Department of Experimental and Clinical Pharmacology, Nelson R Mandela School of Medicine, pers. comm., March 2001).

1.4.2.2 Duration of Injectable Use

The mean length of use for current users of DMPA and NET-EN were very similar. For previous injectable users, the mean length of use of NET-EN was less than that of DMPA users, although the difference is not significant (Table 1.4.6).[8] As far as can be determined, both products could have been available at the Hlabisa Hospital for more than a decade preceding the study. According to the sister in charge of family planning at the hospital, both products were available at the hospital when she first started working there in 1980 (D Masondo, Sister-in-Charge, Hlabisa Hospital, pers. comm., August 2001). For both current and previous users, the range of length of use of DMPA was greater than for NET-EN. Table 1.4.6 shows that DMPA had been used for up to 11 years by current users and for up to 10 years by previous users. By contrast, current NET-EN users had only used the method for up to 6 years and all previous NET-EN users (excluding those who had used both products) had discontinued by 7 years of use.

[8] Note that, in the case of current users, the end of the use period had not yet been reached.

Previous DMPA users were more likely to continue the method beyond 5 years than were NET-EN users (p=0.001).

Table 1.4.6 Duration of use of current and previous DMPA and NET-EN Users

Duration of Use	**DMPA**	**NET-EN**
Current Users*	**N=86**	**N=101**
Mean (years) (SD) *TTest p=0.886*	2.3 (2.3)	2.2 (1.6)
Mode (years)	2	4[#]
Median (years)	1.4	2
Range (years)	0.1-11	0.1-6
% using for 1 year or less	45.3	37.6
% using for 2 years or less	69.8	60.4
% using for 5 years or more	14.0	6.9
Previous Users[+]	**N=137**	**N=95**
Mean (years) *TTest p=0.088*	2.1	1.7
Standard deviation	2.0	1.3
Mode (years)	2	2
Median (years)	1.4	1.1
Range (years)	0.2-10	0.2-7
% using for 1 year or less	48.9	49.5
% using for 2 years or less	67.9	77.9
% using for 5 years or more *Chi-Square: p=0.001*	9.5	3.2

* Since these are current users, the end of their use period had not yet been reached
[#] 21 respondents had used NET-EN for 4 years and 18 for 2 years, almost a bimodal distribution
[+] The 10 respondents who had used both products previously were excluded from the analysis

1.4.2.3 Reasons for Choosing the Injectable Method According to Product Used

Current Users – Responses to Open-Ended Question

In response to an open-ended question, the most common reason for choice of the injectable method by current DMPA users was that it was effective. This reason was given by 2.6 times more DMPA users than NET-EN users (Table 1.4.7). For current NET-EN users, the most common reasons given were: because one doesn't forget to take

it, as with the oral contraceptive (31%) and the method was recommended by the health worker (27%). By comparison, only 10.8% of current DMPA users gave "recommendation by the health worker" as a reason for selecting DMPA. A few NET-EN users indicated that it was a good method for young women, while no DMPA users gave this as a reason for choice.

Table 1.4.7 Reasons for <u>current</u> DMPA and NET-EN users choosing the injectable method

Reasons for Choice*	DMPA (%) (n=83)	NET-EN (%) (n=100)
Effective	33.7	13.0
Don't forget like pill	21.6	**31.0**
Recommended by health worker	10.8	27.0
Convenient	10.8	6.0
Easy to hide method from partner	2.4	3.0
Good method for young people	0.0	3.0
Other	24.1	18.0

* Some respondents gave two reasons (# of reasons =187, n=183)

Previous Users – Responses to Open-Ended Question

Women who had discontinued the injectable contraceptive method were asked why they had decided to use the method previously (Table 1.4.8). Responses to this open-ended question were unprompted. As with the current users, the most common reason for method choice was that it was effective, but in this sub-sample many more women gave this reason, particularly NET-EN users. Again forgetting to take the pill was a frequently given reason.

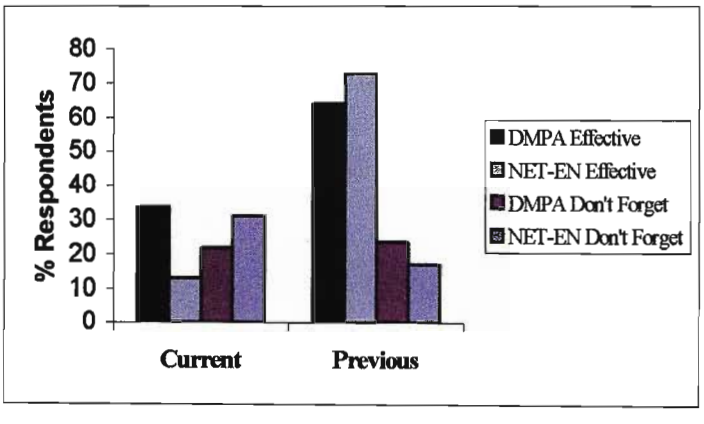
Table 1.4.8 Reasons for <u>previous</u> DMPA and NET-EN users choosing the injectable method

Reasons for Choice* #	DMPA (%) (n=134)	NET-EN (%) (n=92)
Effective	**64.2**	**72.8**
Don't forget like the pill	23.1	18.5
Recommended by health worker	7.5	1.1
Convenient	3.7	3.3
Easy to hide method	4.5	4.3
Good method for young people	0.0	0.0
Other	4.5	4.3

* Excludes the 10 respondents who had previously used both products
# Some respondents gave two reasons (# of reasons =233, n=226)

Figure 1.4.4 shows clearly the extent to which previous users of both DMPA and NET-EN chose the injectable method because of its effectiveness – evidently a lasting memory.

Figure 1.4.4 Main reasons for choosing the injectable method: <u>Current</u> and <u>previous</u> DMPA and NET-EN users



Current Users – Responses to Pre-constructed List of Possible Reasons

When asked to respond to a pre-constructed list[9] of possible reasons for choosing the injectable method, findings for current users were consistent with responses to the unprompted question, with respondents indicating that they chose the method because it was considered safe, effective, convenient and often recommended by the health provider (Table 1.4.9). Although more NET-EN users indicated that the health provider played a role in the decision about method use, the difference was not significant. A third of both product users also indicated that the privacy afforded by the injectable method was a factor in choosing the method. It is interesting to note that 32.8% of the current users reported that their partners did not know that they were using the injectable.

Table 1.4.9 Reasons given by <u>current</u> injectable users for choosing the injectable method

Reasons for Choice*	DMPA (%) n=86	NET-EN (%) n=101	Total % n=187	Chi-Square P Value
NET-EN convenient	-	97.0	51.9	-
DMPA convenient	95.3	-	44.4	-
Safe	51.2	54.5	52.9	0.653
Effective	52.3	43.6	47.6	0.232
Recommended at the clinic	32.6	41.6	37.4	0.204
Suits her, few problems or side effects	25.6	28.7	27.3	0.632
Causes amenorrhoea	17.4	27.7	23.0	0.096
Recommended by friends or relatives	21.2	21.8	21.5	0.920
Want to hide method from partner	20.9	20.8	20.9	0.982
Want to hide from friends & relatives	12.8	12.9	12.8	0.987

*Respondents were asked to respond in the affirmative or negative to each option listed in this table

[9] This list was administered to current users only.

A fair proportion of both DMPA and NET-EN users (17.4%; 27.7% respectively – Table 1.4.9) regarded amenorrhoea as a positive effect of IPCs, with more NET-EN reporting this, possibly because amenorrhoea is more favoured by younger (more modern) women. An analysis of the ages of the respondents who chose the injectable method because it causes amenorrhoea showed that younger women were more likely to give this reason than older women (p=0.0405). Further analysis showed that, in the case of NET-EN users, younger women were significantly likely to choose the injectable method because it caused amenorrhoea (p=0.0311), whilst amongst DMPA users, age did not influence whether or not the injectable method was chosen because it caused amenorrhoea (p=0.7349).

In response to a question on the source of advice about how the method was chosen[10], health providers were most commonly reported to have recommended IPC use for users of both products (Table 1.4.10).

Table 1.4.10 Who advised method use?

Source of advice	DMPA (%) (n=86)	NET-EN (%) (n=100)
Health worker	25.6	27.0
Partner	14.0	11.0
Relative	3.5	11.0
Friend	8.1	11.0
No-one	46.5	36.0
Other	2.3	4.0

[10] This question was asked in relation to current contraceptive use only and therefore did not apply to previous IPC users.

1.4.2.4 Reasons for Current Users' Choice of a Particular Injectable Product

Current users were asked, by means of an open-ended question, why they preferred the injectable product (DMPA or NET-EN) they were using, and their reasons for choice are provided in Table 1.4.11. The following findings are of note:

- Many DMPA users (42.4%) indicated that they preferred this product because it was "stronger", on the other hand, NET-EN was favoured by 36.0% of those using it as it was regarded as "weaker" or "lighter".
- Concern about delayed return to fertility with DMPA was expressed by 5.0% of NET-EN users and 14.0% indicated that they chose NET-EN because it did not delay return to fertility.
- The idea that NET-EN is for younger women or teenagers and DMPA for older women was expressed by 14.6% of the IPC users. This preference is clearly reflected in the age distribution of DMPA & NET-EN users depicted in Figure 1.4.1 earlier in this chapter.
- Recommendation by health workers was given as one of the most common reasons for product choice especially in the case of NET-EN users.
- Relatively few women (6.5%) mentioned that concern about side effects influenced choice of either product. This minor influence of side effects on product choice was reflected for both NET-EN and DMPA. Of interest is that a few women (n=7) were particularly concerned that NET-EN caused more bleeding. This concern was not expressly mentioned in relation to DMPA use.

Table 1.4.11 Reasons for current users selecting a particular injectable product

Reasons for Preference*	DMPA Users % (n=85)	NET-EN Users % (n=100)
Effectiveness/strength		
DMPA more effective, "stronger"	42.4	-
NET-EN "weaker", "lighter"	-	36.0
Fertility		
Easy to conceive after discontinuation	1.2	14.0
DMPA delays fertility/causes infertility	-	5.0
Age		
NET-EN is for young people	3.5	18.0
DMPA used by older women	-	6.0
Advice		
Recommended by nurse	16.5	25.0
Convenient	16.5	-
Side effects		
NET-EN causes **less** side effects	-	5.0
DMPA causes **less** side effects	2.4	-
NET-EN causes **more** side effects		
more bleeding	8.2	-
weight gain	1.2	-
DMPA causes **more** side effects		
weight gain	-	3.0
amenorrhoea	-	1.0
Other	9.4	8.0

*Some respondents gave two reasons (# reasons=207)

Efficacy was also given as the characteristic current users "liked most" about both products with this response given by 77.6% of DMPA users and 76.2% of NET-EN users. Other reasons given were: one doesn't forget to take it - like the pill (DMPA users: 4.7%; NET-EN users: 4.0%); it could be used secretly (DMPA users: 2.4%; NET-EN users: 4.0%); amenorrhoea (DMPA users: 3.5%; NET-EN users: 2.0%); convenience (DMPA users: 3.5%; NET-EN users: 2.0%).

1.4.3 DISCONTINUATION PATTERNS OF PREVIOUS INJECTABLE USERS

1.4.3.1 Discontinuation Rates

Survival analysis was used to calculate life table discontinuation rates and the average discontinuation rate was found to be 2.1 years for previous DMPA users and 1.7 years for

previous NET-EN users (Table 1.4.12).[11] As shown in the survival distribution curve below (Figure 1.4.5), all NET-EN users had discontinued use by 7 years, whilst some DMPA users continued to use the product for 10 years. Although DMPA was used for longer periods than NET-EN, the difference in average discontinuation rates was not significant. However, previous DMPA users were more likely to continue the method beyond 5 years than were NET-EN users (p=0.001).

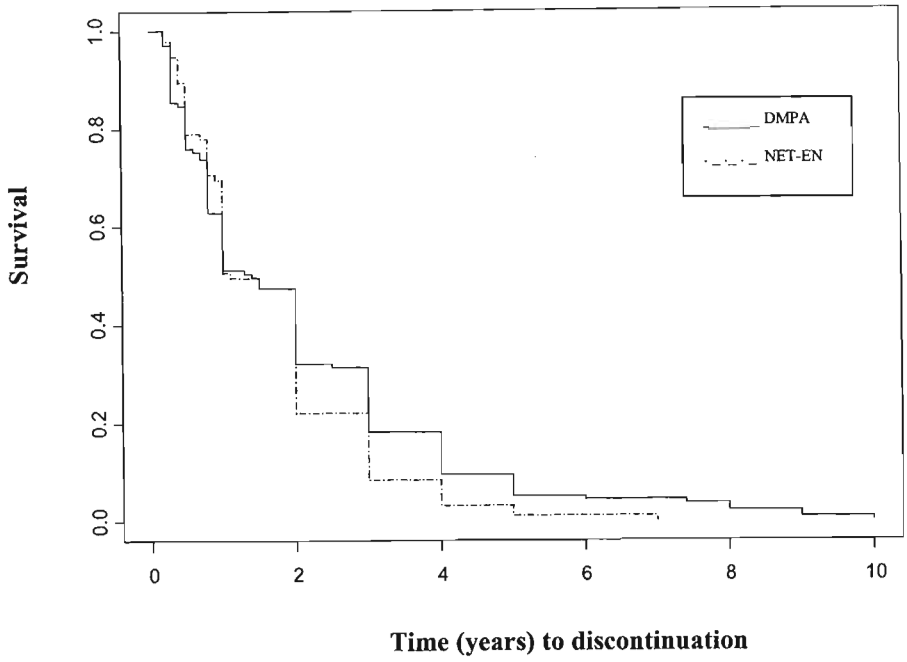
Table 1.4.12 Cumulative discontinuation rates and mean according to injectable product (DMPA and NET-EN) used by previous users

Discontinuation Rates	**DMPA**	**NET-EN**
	N=137	**N=95**
Cumulative Discontinuation Rates (per 100 women years of exposure)	**%**	**%**
at 6 months	24.1	21.1
at 2 years	67.9	77.9
at 3 years	81.8	91.6
at 4 years	90.5	96.8
at 5 years	94.9	98.9
at 6 years	95.6	98.9
at 7 years	95.6	100.0
at 8 years	97.8	-
at 9 years	99.2	-
at 10 years	100.0	-
Mean (SD) in years *TTest: p= 0.09*	2.1 (2.0)	1.7 (1.3)

* Excludes the 10 respondents who had previously used both products

[11] Excluding the 10 respondents who had previously used both products

Figure 1.4.5 Survival distribution curve for DMPA and NET-EN



In order to determine the influence of multiple variables on discontinuation rates an analysis of maximum likelihood estimates was performed. The variables selected for the model were injectable product (DMPA or NET-EN), age, education and side effects (heavy bleeding, amenorrhoea, weight gain). The variables "heavy bleeding" and "age" were found to be independently associated with method discontinuation, although age was only marginally significant (Table 1.4.13). Those who experienced heavy bleeding and the younger women were more likely to discontinue the injectable method.

Table 1.4.13 Factors independently associated with injectable discontinuation

Variable	Risk Ratio	P value
Heavy bleeding	1.55	0.0016
Older Age	0.98	0.0595

1.4.3.2 Reasons for Discontinuation

Previous injectable users were asked to respond to a comprehensive list of possible reasons for discontinuing the injectable method. Up to five reasons were given by respondents. Side effects were most commonly cited as the reason for discontinuation, accounting for 54.5% and 46.1% of the reasons reported by DMPA and NET-EN users respectively (note that some respondents gave more than one reason). A significant difference was found between DMPA and NET-EN users in terms of the proportion reporting discontinuation due to side effects with more DMPA users giving this reason than NET-EN users (p=0.006). The menstrual disturbances amenorrhoea and heavy bleeding were the most frequent side effects leading to discontinuation. After these menstrual irregularities, the next most common reasons leading to discontinuation were "vaginal wetness" and weight gain, reported by similar numbers of respondents.

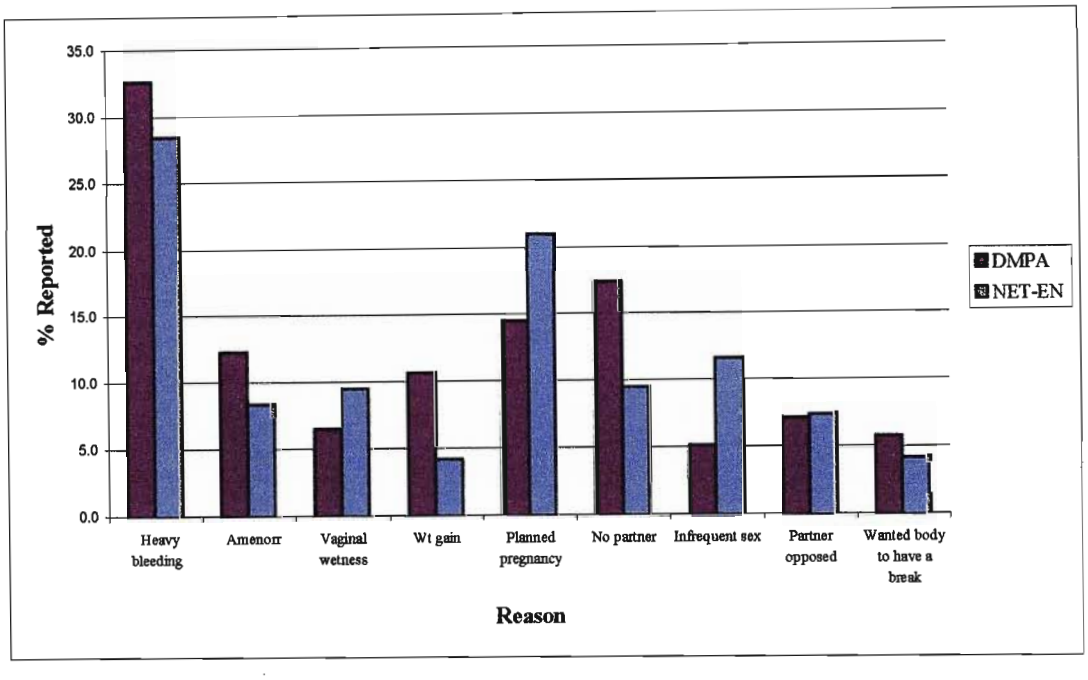
A common user related reason was "wanted to have a baby", especially for previous NET-EN users, with 21.1% of NET-EN discontinuers versus 14.5% of DMPA discontinuers giving this reason (Figure 1.4.6). No sexual partner and infrequent sex were also frequent user related reasons for discontinuation (Figure 1.4.6).

Similar proportions of DMPA and NET-EN users discontinued the method because of partner or family opposition. Only two women, both previous DMPA users, discontinued the method because they were concerned about a delay in return to fertility. Few reasons for discontinuation were related to health service provision (n=5). One woman discontinued DMPA because she believed that it caused HIV.

A compliance related reason for discontinuation was that of a "non-use segment" where a respondent discontinued the injectable to "give her body a break". This was a reason given by both DMPA and NET-EN users (Figure 1.4.6).

One previous DMPA user and 2 previous NET-EN users indicated that they discontinued the method as they became pregnant by mistake.

Figure 1.4.6 Main reasons for discontinuation of DMPA and NET-EN by previous injectable users



Heavy bleeding was significantly more likely to be given as a reason for discontinuation by previous users of both injectable products who discontinued in the first year of use (Cochran-Armitage statistic: -2.861, p=0.004; -2.283; p=0.02, for DMPA and NET-EN respectively). Younger DMPA users were also more likely to discontinue the method due to heavy bleeding than were older DMPA users (Cochran-Armitage statistic: -2.336,

p=0.019). Although this trend was also evident for NET-EN users, it was not statistically significant.

It is important to note that respondents reported up to five reasons for method discontinuation. The following proportions of respondents gave more than one reason for discontinuation:[12]

- Up to two reasons: 30.4% (41/135) of DMPA users; 18.7% (17/91) of NET-EN users
- Three or more reasons: 6.7% (9/135) of DMPA users; 3.3% (3/91) of NET-EN users
- Total giving more than one reason: 37.1% of DMPA users; 22.0% of NET-EN users (p=0.016).

As described earlier in this Chapter, 21 current users had previously used an IPC. Their reasons for discontinuation are similar to the reasons for discontinuation provided by respondents who were no longer using any injectable product as described above. The most common reason for discontinuation given by previous users of both products was heavy menstrual bleeding (n=10).

1.4.4 COST ANALYSIS OF DMPA AND NET-EN USE IN SOUTH AFRICA

The extensive use of the two IPCs in a rural area of South Africa is illustrated in the previous chapter. A cost analysis of the provision of IPCs is therefore essential if appropriate policies for the rational use of IPCs are to be developed. This analysis is undertaken here.

[12] Note: 3 DMPA and 5 NET-EN respondents did not give a reason for discontinuation or gave an inappropriate response.

1.4.4.1 Procedures Used to Analyze Supply Patterns and Cost

IPC Supply Patterns and Costs from Pharmaceutical Depots

Consumption figures of IPC stock issued from provincial pharmaceutical depots were requested from the Deputy Director, Procurement of the South African National Department of Health.[13] Data for DMPA and NET-EN were requested and made available for the KwaZulu-Natal (KZN), Gauteng and Free State Provincial pharmaceutical depots and for the Port Elizabeth depot, which serves the western part of the Eastern Cape Province. These four provinces (of nine South African provinces) represent over 50% of the total South African population. Gauteng has a mostly urban population and KZN and Eastern Cape are more rural. The following data were analysed for financial years 1997/8, 1998/9, and for 1/04/99 to 7/12/99 of the 1999/2000 financial year:

- Current and previous tender prices for DMPA and NET-EN.
- Position number on ABC (Pareto) analyses for DMPA and NET-EN. An ABC analysis is a method which ranks drugs according to their annual usage (unit cost times annual consumption). Class A items are the 10 to 20 % which account for 75 to 80% of the funds spent. Class B items have an intermediate contribution to total expenditure, whereas Class C items (the majority of items) account for a small percentage of funds spent. ABC analyses are used to identify priority cost drivers for intervention (Quick JD, 1997).
- Percentage of total depot expenditure on IPCs per financial year for each depot.
- Number of units of each item issued in the same time period per depot.

---

[13] J van den Berg (Deputy Director: Procurement, National Department of Health) and Mr T Odendaal (Systems Manager, Co-ordinating Committee for Medical Procurement) provided access to the data from the pharmaceutical depots and the initial Pareto analysis. A Gray (Senior Lecturer, Department of Experimental and Clinical Pharmacology, Nelson R Mandela School of Medicine) assisted with the analysis of these data. Their assistance is gratefully acknowledged.

- Total expenditure on DMPA and NET-EN for the time period 1 April 1999 to 7 December 1999.

Cost Analysis of IPC Utilisation Patterns in Hlabisa: A Case Study

The cost of providing DMPA or NET-EN was calculated on the basis of the prevalence of current use of these two products by respondents of the community-based survey undertaken in Hlabisa in 1998. The following analyses were undertaken:

- The ratio of NET-EN:DMPA use.
- The annual cost of providing DMPA or NET-EN to the 187 respondents who were currently using IPCs.
- Savings or increased costs if all respondents had used only one or other product.
- Projected cost for women using IPCs in the Hlabisa Sub-District.

1.4.4.2 Analysis of Supply Patterns and Cost

IPC Supply Patterns and Costs from Four Pharmaceutical Depots

IPC product costs

DMPA products issued at primary health care outlets in the three financial years analysed were Depo-Provera® and Petogen®, and NET-EN was available as Nur-Isterate®. Table 1.4.14 shows that the acquisition cost of a vial of both DMPA and NET-EN products increased every year, and that the cost of both DMPA products rose particularly steeply. In the 1999/00 financial year, the generic product Petogen® was almost the same price as Depo-Provera®, the innovator product. A vial of Depo-Provera® and Nur-Isterate® cost exactly the same in the 1999/00 fiscal year.

Table 1.4.14 Acquisition costs of IPCs: 1997/8, 1998/9, 1999/2000

Product	Cost per vial (South African Rands) 1997/8	1998/9	1999/2000
DMPA			
Depo-Provera® (Pharmacia Upjohn)	2.17	4.56	4.78
Petogen® (Pharmacare)	-- *	2.07	4.29
NET-EN			
Nur-Isterate® (Schering)	4.10	4.28	4.78

* tender not awarded

Since DMPA is given less frequently than NET-EN, cost per couple year of protection (CYP) provides a more accurate cost comparison of DMPA and NET-EN. Based on the 1999/2000 state tender price for Depo-Provera® and Nur-Isterate®, the cost per couple year was 28.68 South African Rands (ZAR) for Nur-Isterate® (six vials per year) and ZAR19.12 for Depo-Provera® (four vials per year). If the calculation was based on the Petogen® price, use of DMPA would have been even cheaper (ZAR17.16 per CYP). It should be noted that the cost of syringes, needles and swabs, personnel costs and client transport and time were not included in the calculations. These costs can be considerable and are obviously higher for NET-EN because it is administered more frequently.

Analysis of annual expenditure on DMPA and NET-EN

In all four depots, both IPCs consumed an important share of total drug expenditure (Table 1.4.15). A Pareto analysis shows that both DMPA and NET-EN appeared in the top ten in each year (based on actual volumes multiplied by constant 1999 prices), with the exception of NET-EN in KZN where it was19th in 1997/8, 1998/9 and 1999/2000. The items each accounted for between 0.55 and 2.73% of total spend in each year (Table 1.4.15).

Table 1.4.15 Pareto analysis of IPCs: 1997/8, 1998/9, 1999/00

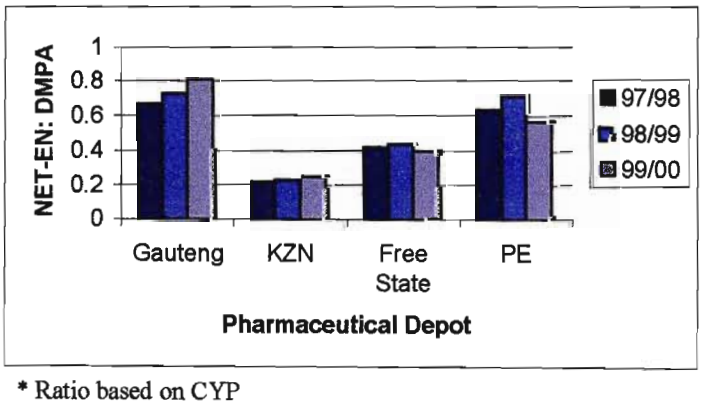
Pharmaceutical Depot	Rank* (% of Total Spend on Drugs) 1997/8	1998/9	1999/00
GAUTENG			
DMPA	3 (1.77)	4 (1.44)	4 (1.79)
NET-EN	2 (1.86)	3 (1.64)	2 (2.26)
KWAZULU-NATAL			
DMPA	4 (1.64)	6 (1.82)	4 (1.82)
NET-EN	19 (0.55)	19 (0.62)	19 (0.68)
FREE SATE			
DMPA	2 (1.99)	3 (2.25)	5 (2.73)
NET-EN	5 (1.31)	5 (1.55)	6 (1.73)
PORT ELIZABETH			
DMPA	3 (2.23)	6 (1.93)	3 (1.63)
NET-EN	4 (2.23)	4 (2.16)	4 (1.46)

* based on actual volumes multiplied by constant 1999 Depo-Provera® and Nur-Isterate® prices

Ratio of NET-EN:DMPA issued

The ratios of NET-EN:DMPA issued from the 4 depots, based on CYP rather than on number of vials issued, are shown in Figure 1.4.7. DMPA was increasingly used in Port Elizabeth where the ratio decreased from 0.64 in 1997/8 to 0.57 in 1999/00. In Free State the market share was more or less stable (0.42, 0.44, 0.40). A similar picture emerged in KZN (0.22, 0.23, 0.25), with some increase in NET-EN use. However, in Gauteng, while DMPA was still issued most, NET-EN use was clearly increasing (0.67, 0.73, 0.81).

Figure 1.4.7 Ratio of NET-EN:DMPA issued from the four pharmaceutical depots in 1997/8, 1998/9, 1999/00



* Ratio based on CYP

The ratio of NET-EN to DMPA based on volume of product (number of vials) issued and on CYPs is provided in Table 1.4.16. The NET-EN:DMPA ratio, based on volume issued, clearly shows that more vials of NET-EN were issued by the Gauteng Depot over the period being analysed. However DMPA is still more commonly used, as only 4 vials of DMPA are administered annually, compared to 6 vials for NET-EN.

Table 1.4.16 Ratio of DMPA and NET-EN issued: 1997-1999

Pharmaceutical Depot	Ratio Issued NET-EN: DMPA 1997/1998		Ratio Issued NET-EN: DMPA 1998/1999		Ratio Issued NET-EN: DMPA 1/4 to 7/31/99	
	Volume*	CYP#	Volume	CYP	Volume	CYP
Gauteng	1.01	0.67	1.10	0.73	1.21	0.81
KZN	0.33	0.22	0.34	0.23	0.37	0.25
Free Sate	0.63	0.42	0.66	0.44	0.61	0.40
Port Elizabeth	0.95	0.64	1.07	0.72	0.86	0.57

* Ratio based on number of vials issued; # Ratio based on couple years of protection (CYP)

Counting the Cost of IPC product choice

If all NET-EN clients in the 1999/2000 (annualised) had been given DMPA instead, the four depots together might have saved ZAR4.95 million. Conversely, if NET-EN had been issued to all DMPA clients, then the estimated additional cost in the same year for the four depots would have been R9.35 million. Savings and additional costs would be increased if other costs (surgical supplies, personnel costs, client transport etc.) were included. The savings are calculated on the annualised total CYP for Depo-Provera® and Nur-Isterate®. If the price of the cheaper generic preparation (Petogen®) had been used in the calculation, the savings would have been greater.

For the 1999/2000 financial year, possible savings on expected IPC drug expenditure were calculated assuming that all NET-EN users had been supplied with DMPA instead. The estimated percentage saved for this financial year, for each depot, is provided in Table 1.4.17. Likewise, the additional costs for a scenario where all DMPA users had been provided with NET-EN were calculated (Table 1.4.17). In KZN for example, a 9.0% saving (on product cost alone) could be effected by supplying DMPA only. On the other hand, if only NET-EN were available, the additional load on the expected annual IPC drug bill would have been 36.5% (ZAR2.9 million for the 1999/2000 annualised).

Table 1.4.17 Expected savings (by supplying only DMPA) or additional costs (by supplying only NET-EN) on expected expenditure on IPCs in the 1999/2000 fiscal year

Pharmaceutical Depot	% Savings	% Additional expenditure
Gauteng	18.3	22.6
KZN	9.0	36.5
Free Sate	12.6	31.1
Port Elizabeth	15.4	26.9

Cost Analysis of IPC Utilisation Patterns in Hlabisa: A Case Study

Of the 848 women interviewed, 187 (22.1%) were using an injectable contraceptive method, either DMPA or NET-EN. Forty-six per cent (86) of the IPC users were using DMPA and 54% (101) were using NET-EN. The ratio of NET-EN:DMPA users was thus 1.2 to 1. The Hlabisa Hospital provides health services including family planning services to the Hlabisa sub-district. It is the only health facility in the sub-district and other health facilities are far away across a game reserve. Thus almost all women living in the area attend the Hlabisa Hospital or its mobile clinics for their health care needs, including contraception, where this is required. An analysis of the Hlabisa Hospital family planning

clinic records from July 1998 to the end of June 1999 reveals that the ratio of NET-EN:DMPA (based on CYP) issued to women during that period was 1.1 to 1. This is consistent with the survey findings.

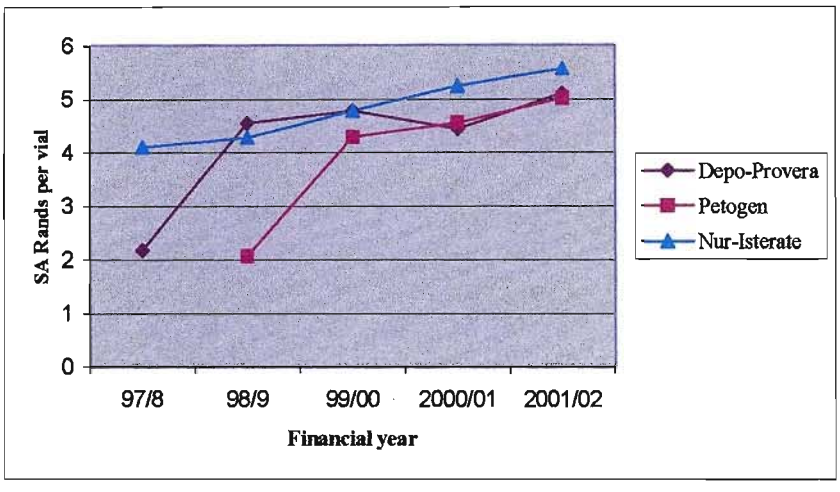
The annual cost of DMPA for the 86 survey respondents who were using it, based on the 1999/00 tender price of Depo-Provera®, would be ZAR1644 and the cost of an annual supply of NET-EN for the 101 survey users would be ZAR2897. The total annual cost for supplying IPCs to the 187 women would be ZAR4541. It is estimated that there are 3910 women of reproductive age living in the sub-district of Hlabisa. With an IPC user prevalence of 22.1%, 864 women were likely to be using an IPC. Of these, 467 would be using NET-EN and 397 would be using DMPA, which would cost the state ZAR20985 annually.

If IPC users in the district were only supplied with DMPA, the annual cost would be ZAR16520. If only NET-EN was provided, the annual cost would be ZAR24780. By supplying only DMPA, a saving of 21.3% could be achieved, but by providing only NET-EN, the cost would increase by 18.1%.

1.4.4.3 Rising Price of Generic DMPA Product and Net-En

The price of the generic DMPA product (Petogen®) increased markedly – from R2.07 in the 1998/9 financial year to R4.29 in the 1999/00 year. This represents a 107.2% increase in cost over a one-year period. In the 2000/01 financial year, Depo-Provera® was cheaper than Petogen® (Figure 1.4.8).

Figure 1.4.8 Acquisition costs of IPCs: 1997/8, 1998/9, 1999/00, 2000/01, 2001/02



The price of a Nur-Isterate® also continued to rise in the 2000/01 and 2001/02 fiscal years outstripping the cost of Depo-Provera® and Petogen® (Figure 1.4.8).

1.4.5 MAIN FINDINGS

Utilsation Patterns

Both injectable products were extensively used with over half the respondents having ever used one or other product. More current users of IPCs were using NET-EN than DMPA (ratio of NET-EN:DMPA use = 1.2:1).

User Characteristics

Age and education were independently associated with the injectable product used. Younger more educated women were more likely to be using NET-EN.

Reasons for Choosing the Injectable Method

- Health providers play an important role in contraceptive method choice. Health worker recommendation was one of the most frequent reasons given for choosing an IPC for current NET-EN users. For current and previous DMPA users and previous NET-EN users, the main reason was that IPCs were effective.
- IPCs are regarded as a convenient method by users of both products.
- A few current NET-EN users indicated that it was a good method for young women – a reason never put forward by DMPA users.
- Some DMPA (17.4%) and NET-EN (27.7%) users regarded amenorrhoea as a positive effect of IPCs, giving this as the reason for contraceptive method choice. Younger NET-EN users were significantly more likely to choose the method because it caused amenorrhoea.
- About a third of both product users chose the method because it was a private method that could be used without the knowledge of partners or others.

Reasons for Product Choice and Perceived Product Preference

- DMPA is regarded as the "stronger", more effective product and NET-EN as the "weaker" or "lighter" product.
- NET-EN is regarded as the product of choice for younger, nulliparous and/or unmarried women.
- NET-EN is regarded as less likely to delay return to fertility.
- Concern about side effects had little influence on product choice.
- Health worker recommendation was given as one of the most common reasons for product choice, particularly by NET-EN users.

Duration of Use

Some women used IPCs for long periods of time, with DMPA users more likely than NET-EN users to continue use beyond 5 years.

Reasons for Discontinuation

- Side effects, mainly amenorrhoea and heavy bleeding, were most commonly cited as the reason for discontinuation.
- Heavy bleeding was significantly more likely to lead to discontinuation in the first year of use.
- Younger DMPA users were more likely to discontinue use due to heavy bleeding. This trend was also seen for NET-EN users, but it was not statistically significant.
- Wanting to conceive and no sexual partner were also common reasons for discontinuation.
- Having a break (non-use segment) was sometimes given as a reason for discontinuation.
- Discontinuation was often a result of a number of reasons.

Cost Analysis

- IPCs accounted for a substantial share of the total state expenditure on drugs.
- Of the two IPCs available on the EDL, DMPA was a cheaper option than NET-EN at the time that the Pareto analysis was undertaken. Since then, the price of Nur-Isterate® has continued to escalate with the per vial price of Nur-Isterate® exceeding that of Depo-Provera® and Petogen® in the 2000/2001 and 2001/2002 financial years

- DMPA was supplied to more women from the four depots than NET-EN.
- In Gauteng, while DMPA was still used by more women, NET-EN use was clearly increasing. To a lesser extent, this is also true of KZN. Gauteng and KZN are the two most populous provinces, representing 18% and 21% of the population respectively (Statistics South Africa, 1998). A shift to the more expensive product therefore has important cost implications.
- Substantial savings could have been effected if more DMPA had been supplied. If only DMPA was made available, the savings for the 4 depots over the three-year analysis period was calculated to be 17%. In the Hlabisa sub-district, savings as high as 21% could have accrued.
- The price of the generic DMPA product was found to increase to the extent that there was little difference between the costs of generic and innovator products.

CHAPTER 1.5: RESULTS (III): EXPERIENCE OF SIDE EFFECTS WITH INJECTABLE CONTRACEPTIVE USE AND PERCEPTIONS OF EFFICACY AND REVERSIBILITY

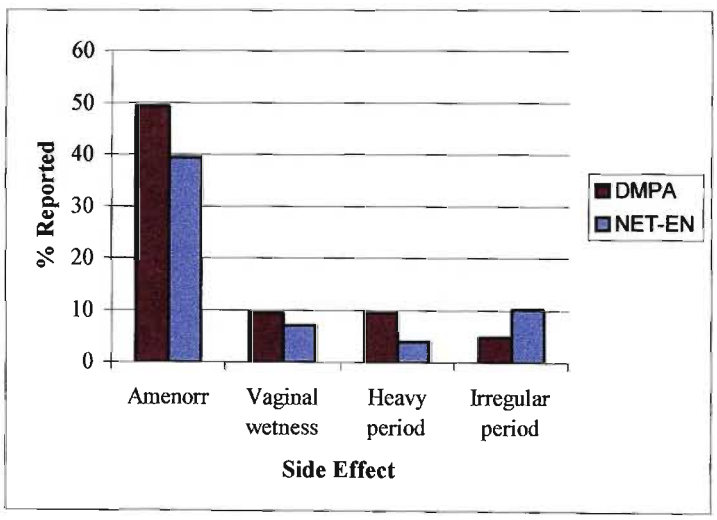
1.5.1 EXPERIENCE OF SIDE EFFECTS

In this chapter self reported side effects of IPC users and discontinued users are described. As can be seen from the literature review, little is known about side effects experienced by African women and few studies have compared the two injectable products. Many published reviews describe IPCs as a broad group, not differentiating between the two products available. The results presented here are based on a cross-sectional survey, not a randomized controlled trial. Nevertheless, some useful insights are obtained as these findings provide a direct comparison between side effects experienced by DMPA and NET-EN users at the time of use. IPC user and non-user perceptions of IPC efficacy and reversibility are also presented.

1.5.1.1 Side Effects Reported by Current Users

Current injectable users were asked to indicate what side effects, if any, they were experiencing with the injectable contraceptive method. They were first asked to respond to an open-ended question about their experience of side effects. The most frequently reported side effects were amenorrhoea, vaginal wetness, heavy bleeding and irregular bleeding (Figure 1.5.1) and no statistical differences were found between side effects reported by DMPA and NET-EN users.

Figure 1.5.1 Side effects most frequently reported by current DMPA and NET-EN users in response to an unprompted question



Respondents were subsequently prompted to respond to a list of 22 possible side effects. In responding to this list, the majority of women (88.4%) reported that they experienced at least one side effect and 7% reported 5 or more side effects. The side effects most commonly reported were amenorrhoea (62.5%), vaginal wetness (18.4%), weight gain (11.2%) and spotting (11.2%) (Table 1.5.1).

The side effect profile for DMPA and NET-EN users was similar (Table 1.5.1) and no significant differences were found between users of the two products in terms of their experience of side effects. The side effects most commonly reported by both product users were amenorrhoea, vaginal wetness and weight gain (Table 1.5.1 and Figure 1.5.2). The side effect profile for DMPA and NET-EN users was similar with no significant differences found in terms of their experience of side effects.

Table 1.5.1 Side effects reported by <u>current</u> NET-EN and DMPA users

Side Effect*	DMPA (%) (n=84)	NET-EN (%) (n=95)	P Value†	Total % (n=179)∞
Menstrual Irregularities				
Amenorrhoea#	67.5	58.9	0.240	62.5
Spotting	9.5	12.6	0.510	11.2
Heavy periods	8.3	7.4	0.792	7.8
Irregular periods	3.6	10.5	0.074	7.3
Longer periods	2.4	4.2	0.497	3.4
Dysmenorrhoea	1.2	1.1	0.930	1.1
Vaginal Wetness	22.6	14.7	0.175	18.4
Weight Gain	14.3	8.4	0.214	11.2
Loss of Libido	10.7	8.4	0.601	9.5
Dizziness	10.7	6.3	0.289	8.4
Headache	10.7	4.2	0.094	7.3
Nausea	9.5	3.2	0.077	6.1
Vaginal Discharge	8.3	3.2	0.132	5.6
Vaginal Discharge with odour	7.1	3.2	0.223	5.0
Delayed return to fertility	0.0	1.1	0.346	0.6
Vaginal dryness	0.0	0.0	-	0.0

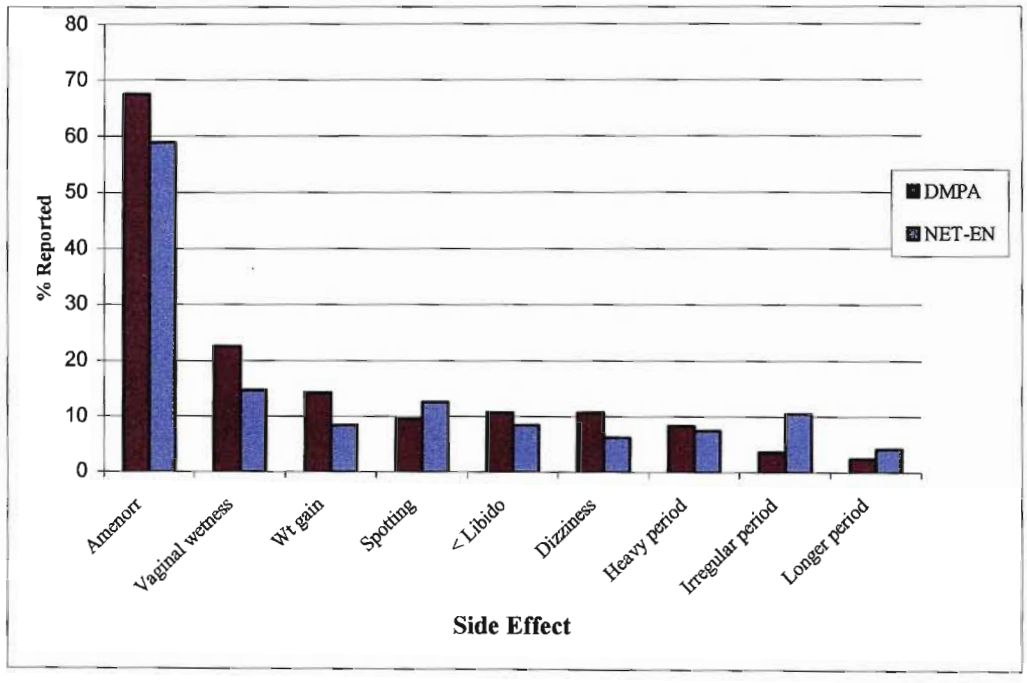
* Other side effects, reported by 5 or less respondents, were: hair falls out (2.8), depression (1.1), breast tenderness (1.1), sweating (0.6), bloating of abdomen (0.6), bloating of breasts (0.6).

† P values were determined using Chi-square (1 degree of freedom, significance tested at the 5% level).

∞Eight respondents had very recently started injectable use (< 3 months) and reported no side effects. They were therefore excluded from this analysis.

Includes thirty breastfeeding women. Although amenorrhoea was reported as a side effect of IPC use, it could have been lactational amenorrhoea.

Figure 1.5.2 Side effects commonly reported by <u>current</u> DMPA and NET-EN users in response to the administration of a set list of possible side effects



Many of the users of both DMPA (73.2%) and NET-EN (80.4%) who reported amenorrhoea as a side effect had been using the injectable for a year or more. By contrast, all (n=7) DMPA users and 1 of the 7 NET-EN users who reported experiencing heavy periods had been using the injectable for less than a year. A Cochran-Armitage Trend Test was used to analyse the experience of the most frequently reported side effects (amenorrhoea, heavy periods, vaginal moistness, and weight gain) over time for both products. Heavy bleeding was significantly more likely to occur amongst DMPA users in the first year of use (Cochran-Armitage statistic =-3.319; p=0.001). It is important to note however that the number reporting heavy bleeding was small. Although not significant, vaginal moistness was also decreasingly experienced over time by both DMPA and NET-EN users (DMPA: Cochran-Armitage statistic =-1.567; p=0.117; NET-EN: Cochran-Armitage statistic =-1.656; p=0.098). When combining the DMPA and NET-EN users so

that the sample size was larger (33), the Cochran-Armitage Trend test for decreased experience of vaginal moistness over time was significant (Cochran-Armitage statistic =-2.394; p=0.017).

Findings from the prompted list of possible side effects were consistent with the unprompted responses, but frequencies of reporting were higher especially for amenorrhoea and vaginal wetness (Figure 1.5.2). In response to an unprompted question, none of the women using contraceptive methods other than the injectable method reported any of the side effects most frequently experienced by injectable users.

The side effect vaginal wetness was frequently reported by respondents. As the literature review shows, this side effect is not clearly understood nor is it well documented. A detailed analysis of both survey and focus group respondents' experiences and perceptions of vaginal wetness was thus undertaken. This analysis was published in the journal *Social Science and Medicine* (2002, 55, 1511-1522) under the title 'Vaginal wetness: an underestimated problem experienced by progestogen injectable contraceptive users in South Africa'. A copy of the manuscript can be found on page xxxiv of this thesis, just after the abstract.

1.5.1.2 Side Effects Reported by Previous Users

In response to a list of 20 possible side effects, those most commonly reported by the previous users of both products were heavy periods, amenorrhoea, vaginal wetness and weight gain (Table 1.5.2 and Figure 1.5.3). The side effect profile for DMPA and NET-EN users was similar in most respects, but significant differences were found between DMPA and NET-EN in the reporting of loss of libido and longer periods. These two side

effects were not however the most common ones reported. DMPA users were more likely to report these two side effects than NET-EN users (Table 1.5.2). Not surprisingly, respondents who had used both methods previously almost always reported more side effects than those who had used either DMPA or NET-EN previously.

Table 1.5.2 Side effects most frequently reported by previous NET-EN and DMPA users in response to the administration of a set list of possible side effects

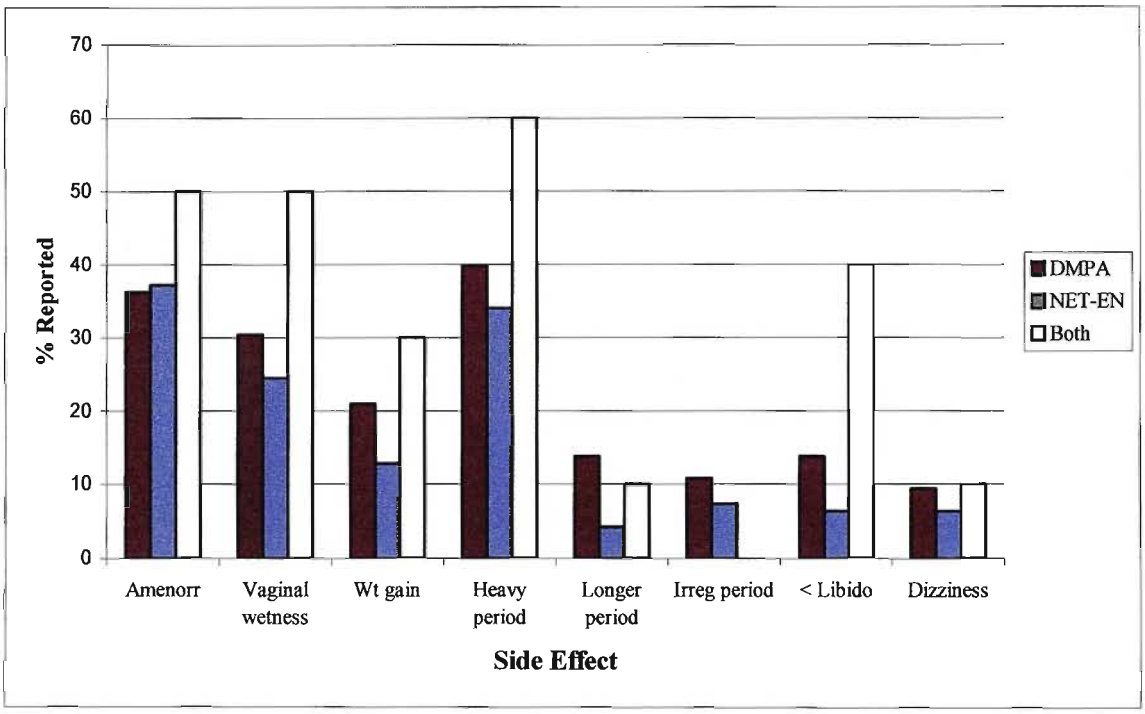
Side Effect*	DMPA (%) (n=138)	NET-EN (%) (n=94)	Both % (n=10)	Total % (n=242)
Menstrual Irregularities				
Heavy periods	39.9	34.0	60.0	38.4
Amenorrhoea	36.2	37.2	50.0	37.2
Longer periods†	13.8	4.3	10.0	9.9
Irregular periods	10.9	7.4	0.0	9.1
Dysmenorrhoea	7.2	2.1	10.0	5.4
Spotting	4.3	5.3	10.0	5.0
Vaginal Wetness	30.4	24.5	50.0	28.9
Weight Gain	21.0	12.8	30.0	18.2
Loss of Libido††	13.8	6.4	40.0	12.0
Dizziness	9.4	6.4	10.0	8.3
Headache	5.8	5.3	20.0	6.2
Nausea	8.0	2.1	10.0	5.8
Bloating of Abdomen	5.8	3.2	20.0	5.4
Delayed return to fertility	2.9	1.1	10.0	2.5
Vaginal dryness	2.9	1.1	0.0	2.1

* Other side effects were: hair falls out (2.1), depression (1.7), sweating (1.7%), breast tenderness (0.4), bloating of breasts (0.4%) (% based on DMPA + NET-EN users)

† Significant difference, p=0.017 (1df), comparing side effects reported by those who had previously only used DMPA or NET-EN

†† Significant difference, p=0.005 (2df), comparing side effects reported by those who had previously used DMPA or NET-EN or both.

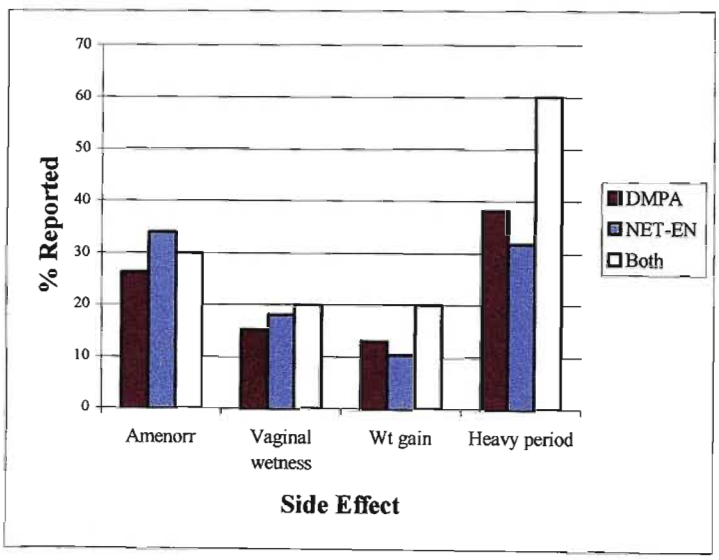
Figure 1.5.3 Side effects commonly reported by <u>previous</u> DMPA and NET-EN users in response to the administration of a set list of possible side effects



Up to 9 side effects were reported by both DMPA and NET-EN previous users. The mean number of side effects for previous DMPA users was 1.9 and for previous NET-EN users was 1.6. Although not significant, previous DMPA users experienced more side effects than previous NET-EN users (OR=1.08; 95%CI: 0.87,1.34).

As with current IPC users, respondents were first asked to respond to an open-ended question about their experience of side effects. Once again findings from this unprompted version of the question were consistent with the prompted responses for most side effects, but with lower frequencies of reporting (Figure 1.5.4 below). However, heavy bleeding was reported almost as frequently as in the prompted version of the question. No statistical differences were found between side effects reported by DMPA and NET-EN users.

Figure 1.5.4 Side effects most frequently reported by <u>previous</u> DMPA and NET-EN users in response to an unprompted question

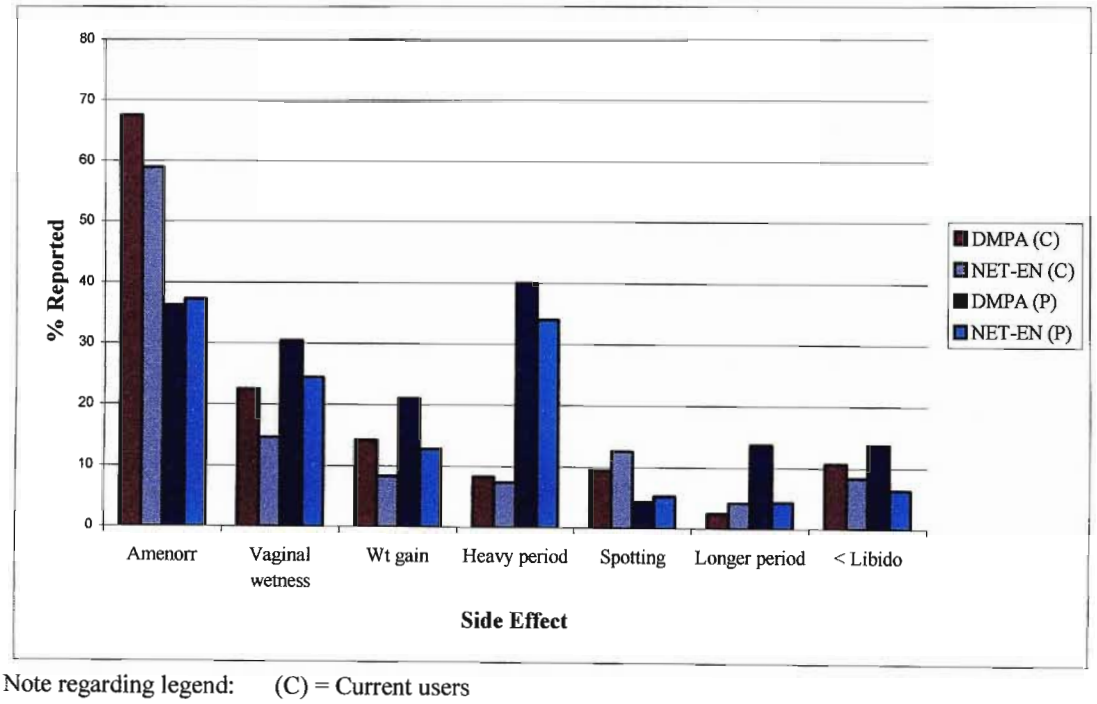


1.5.1.3 Comparison of Side Effects Reported by Current and Previous Users

In analysing responses to the set list of side effects, similar side effects were reported by current and previous users of both IPC products. However, whilst amenorrhoea was by far the most frequently reported side effect for current users of both DMPA and NET-EN, heavy bleeding was reported at very similar frequencies as amenorrhoea amongst

previous IPC users (Figure 1.5.5). Greater differences were thus reported by previous users compared to current users, than by users of the different products.

Figure 1.5.5 Comparison of side effects reported by current and previous DMPA and NET-EN users



Note regarding legend: (C) = Current users
(P) = Previous users

1.5.1.4 Side Effects Reported in Focus Group Discussions

The composition of the focus group interviews is provided in Table 1.5.3 below.

Table 1.5.3 Composition of focus groups

Type of Group	Number of Women (age range in years)	Number of Men (age range in years)
Sewing group	6 (34-59)	-
Gardening group	5 (26-35)	-
Community health workers	5 (34-47)	-
Nurses attached to the district hospital	8 (25-55)	-
Traditional healers	6 (35-60)	4 (48-74)
Church ministers	2 (47-48)	4 (37-75)
Taxi drivers	-	8 (24-48)
High school teachers	5 (23-37)	3 (26-28)
Primary school teachers	4 (23-33)	3 (26-33)
Parents	7 (30-60)	-
Members of a school governing board	3 (44-59)	3 (29-57)
Grade 12 secondary school girls	8 (17-24)	-
Grade 11 & 12 secondary school boys	-	8 (18-23)
Grade 11 & 12 secondary school girls & boys	4 (17-18)	4 (21-24)
Number of women of reproductive age (15-49 years)	50	-
TOTAL	**63**	**37**

During focus group interviews, the most commonly mentioned side effects of injectable contraceptives were: vaginal wetness (14 groups), delayed return to fertility (13 groups), heavy bleeding (12 groups), weight gain (12 groups) and amenorrhoea (10 groups). The side effects regarded as the worst were vaginal wetness (9 groups), heavy bleeding (7 groups) and amenorrhoea (1 group).

The problem of vaginal wetness with injectable contraceptive use was raised repeatedly in every focus group interview, and was raised spontaneously in the first instance. It came up repeatedly in the discussions with the group of high school teachers (women and men), with the group of high school girls, with the traditional healers (women and men), with the gardening group (women) and with the members of the school governing board (women and men). Some comments about the experience of vaginal wetness follow. Focus group participants, men and women, made frequent reference to the problems of "wetness" "coldness" and "tastelessness" with injectable contraceptive use. Coldness was used in the context of the female partner being perceived to be sexually unresponsive or losing her sexual appetite, and tastelessness as the female partner being sexually unappetizing or undesirable. Examples of comments made are[14]:

> "People using the injection used to complain about vaginal wetness. They say their partners do not enjoy sex with them and state that it all becomes a big dam. This vaginal wetness is associated with coldness and you eventually lose sex appetite" (woman from sewing group).

> "They say a lot of things like the injection makes one to be always wet and sometimes that their male partners complain that women who are using injection do not taste good....." (nurse). The group of nurses all agreed that women report experiencing vaginal wetness with injectable contraceptive use.

> " ..... truly speaking our children are finished by this injection, they are big in sizes, they are wet. There is another problem from the male side, I once overhead them talking saying

[14] All quotes have been translated from Zulu.

that it is much better to have sex with an old lady because she is not wet, teenagers are just swimming pools" (woman traditional healer).

"..... injection makes them gain weight, not that they are fat, the body is just full of water, and when having sex with such a person she is just a pool of water, you do not feel anything" (male church minister).

"They [men] also say we become cold, wet and the vagina opens, as it opens you are tasteless" (high school girl in the girls only group).

"..... a lot of men know that once she is wet she is using the pill or injection, so these days secret is out. Men can sense that the woman is using contraceptive method" (traditional leaders).

"The injection causes women to be wet and you as a man do not enjoy sex with such a woman to the extent that if it is your girlfriend and not a wife, you can be sure that she is from another man, she has been with someone else" (male member of the school governing board).

".....it [the injection] gets them into trouble; once she is wet the man would say she is having an affair" (female member of the school governing board).

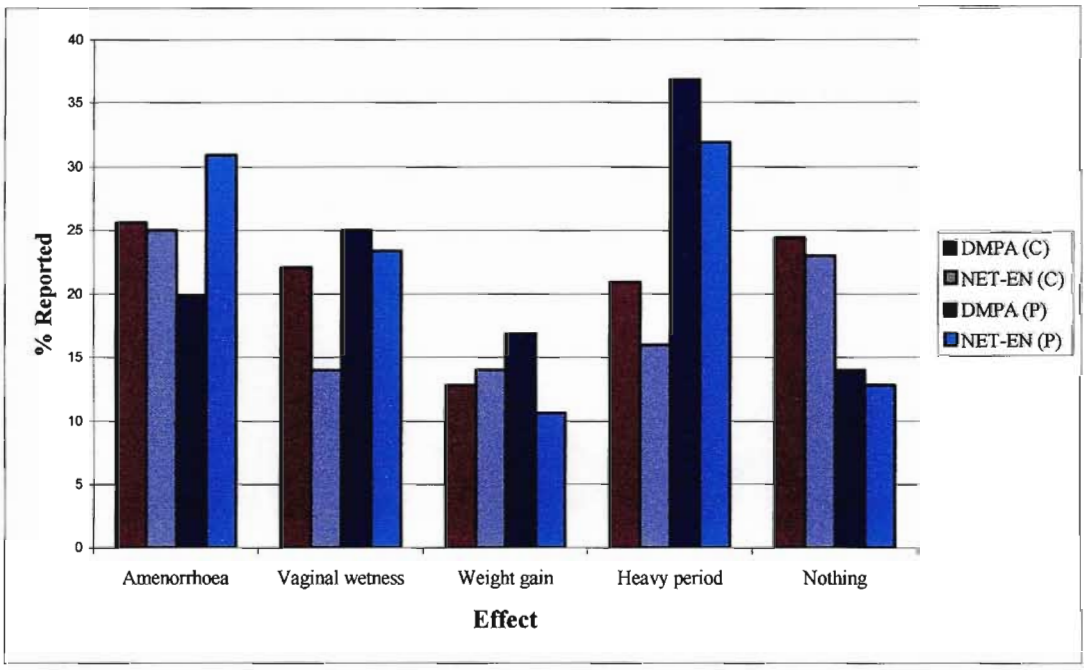
A more detailed description of side effects discussed in focus groups is documented in the publication mentioned earlier in this chapter (entitled 'Vaginal wetness: An underestimated problem experienced by progestogen injectable contraceptive users in South Africa').

1.5.1.5 What Respondents Liked Least about DMPA and NET-EN

Both current and previous users of DMPA and NET-EN reported similar dislikes about the injectable method, most commonly reporting amenorrhoea, heavy bleeding, vaginal wetness and weight gain as aspects they liked least. Amenorrhoea was the effect most disliked by current users and heavy bleeding was most disliked by previous users. Again, greater differences were reported by previous users compared to current users, than by users of the two different products.

The aspects liked least were consistent with the respondents' experience of side effects described earlier in this chapter (Figure 1.5.5). However, whilst heavy bleeding was much less commonly reported as a side effect by current users, many reported that this was what they liked least about the injectable (Figures 1.5.5 and 1.5.6). Current users reported that they disliked heavy bleeding almost as often as they reported a dislike for amenorrhoea.

Figure 1.5.6 Aspects liked least by current and previous DMPA and NET-EN users



Note regarding legend: (C) = Current users
(P) = Previous users

1.5.2 PERCEPTIONS OF EFFICACY AND REVERSIBILITY

This sub-section explores perceptions about the efficacy and reversibility of DMPA and NET-EN. The views of all survey respondents: current injectable users, previous users, those who have never used the injectable and of focus group participants are reported here.

1.5.2.1 Survey Findings

Survey respondents clearly regarded both injectable products to be effective as shown by the following findings:

- Efficacy was given as the characteristic current users and previous users liked most about both products, with this response given by 77.6% of current DMPA users,

76.2% of current NET-EN users, 75.2% of previous DMPA users and 77.5% of previous NET-EN users.

- When directly asked, 97.8% of current users believed that it was an effective method, with 2.2% not knowing whether or not it was effective.

Three previous IPC users discontinued use because they became pregnant by mistake – one was using DMPA and 2 were using NET-EN.

Perceptions of efficacy and reversibility were also illustrated when survey respondents were asked to state whether they thought women (in general) prefer DMPA or NET-EN, and why they thought this to be the case (Table 1.5.4). Most respondents (51.1%) thought that DMPA was the preferred product and the main reason given was its perceived effectiveness. DMPA was clearly regarded as "stronger" than NET-EN and NET-EN as "weaker' than DMPA. It should be noted however that many respondents, especially those who had never used an injectable contraceptive method, indicated that they did not know which was the preferred injectable product (Table 1.5.4).

NET-EN was perceived to be the preferred product for younger, nulliparous and/or unmarried women. This product was also considered not to delay return to fertility – a view held particularly by previous injectable users (34.0% - Table 1.5.4). That NET-EN is seen to be the preferred product for younger women is probably linked to the belief that it is the "weaker" of the two products and less likely to result in a delay in return to fertility. These findings are consistent with reasons given by current users for product choice which are reported in the previous chapter (Chapter 1.4, Table 1.4.11) and are

borne out by the age distribution of current DMPA & NET-EN users depicted in Figure 1.4.1 of Chapter 1.4.

Table 1.5.4 Reasons for injectable product preference

	Current Users (%) (n=180)	Previous Users (%) (n=242)	Never Used (%) (n=407)
♀ **Prefer DMPA (51.1%)**	56.7	66.5	39.6
Main reasons for preference			
Effective	51.0	48.4	76.8
"Stronger" than NET-EN	11.8	10.1	6.5
Convenient	32.4	35.8	7.1
Good for married ♀	2.0	-	-
♀ **Prefer NET-EN (20.0%)**	31.7	20.2	14.7
Main reasons for preference			
Effective	12.7	7.5	11.9
"Lighter" than DMPA	44.4	41.5	47.5
Convenient	1.6	9.4	3.4
No delay if want to conceive	14.3	34.0	6.8
Less side effects than DMPA	12.7	-	-
Safe	7.9	-	-
Right for those still wanting children; young ♀; unmarried ♀	4.8	9.4	11.9
Don't know which product is preferred (28.7%)	11.7	13.2	45.7

1.5.2.2 Findings from Focus Group Interviews

Participants of the focus group discussions corroborated the survey respondents' views about NET-EN being "weaker" or "lighter" than DMPA and the perceptions that NET-EN is intended for younger nulliparous women. Participants often alluded to their beliefs that NET-EN won't, or is less likely, to delay fertility or cause infertility than DMPA.

Which Contraceptive Method(s) were considered best for young women and which for older women?

Focus group participants were asked what contraceptive method(s) were considered "best" for younger or older women. Responses to this question were unprompted and discussants were free to mention any methods, including traditional or modern methods. Group participants had the following to say about DMPA and NET-EN:

> "Even with injection there is one for the young people, the one for 2 months[15]...." (female community health worker).

> "Nur[15] is better for young people because it is weaker than Depo[16] which is too strong..." (female high school teacher).

> "Girls say, Nur is suitable for young people and the Depo for the older people" (high school girl from group of girls and boys).

> "Injectables (Nur) [for younger women]" (high school boy in the boys only group).

> "Depo is good [for older women] because it stays a long time in the blood" (high school teacher).

> "Injection (Depo) [for older women] " (high school boy in the boys only group).

[15] The one for 2 months or "Nur" were terms often used in referring to NET-EN
[16] "Depo" was a term used in referring to DMPA.

"There is an injection for older people which they call it Depo, they say it is good for older people and to those who already have children because if you don't have one it makes you infertile" (high school girl in the girls only group).

The above comments show that DMPA was regarded as the more effective, stronger product, more suitable for older women. The view that DMPA is more likely to cause infertility was also expressed here. Also of note is that IPCs were often volunteered as the appropriate method ahead of other methods such as the condom or the traditional *ukusoma* (thigh sex) although this was not always the case.

Was DMPA or NET-EN regarded as the better product?

In response to a question about which was regarded as the better product, DMPA or NET-EN, the following comments were made:

"I think Depo is better because it stays a long time in the blood, whereas with Nur, if you did not take it when you were supposed to then you get pregnant" (female community health worker).

"Depo is better for older people" (female high school teacher).

"I think the two monthly Nur is right for the youth because I used to hear from girls saying that, it is weaker than Depo. That weakness is what makes it lighter than Depo making it have few dangers in one's body" (high school girl from group of girls and boys).

"What many people are saying is that, Depo is good for older people because it is strong, so for those who have many children or the ideal number of children, Depo is good. Because to them, getting a baby or not getting a baby is just the same" (high school boy from group of girls and boys).

"I heard that Nur is right for the youth and Depo is for adults" (female parent).

"To me, it is Nur, which is better, the two monthly because I used to hear that it was designed for young women and the Depo is for elder women and if you use it for a long time, you end up having no children" (female primary school teacher).

"Nur is better for young people" (female member of sewing group).

"Nur is lighter and you get children at anytime after stopping using it and Depo is bad because it make people to be infertile especially adults" (female member of sewing group).

"Depo is strong and they say it takes a long time in the blood system and I also heard that it is right for adults" (high school boy in the boys only group).

"Nur is right for the youth because of its weakness" (high school boy in the boys only group).

"I heard that Depo causes infertility" (high school girl in the girls only group).

"Depo is for older people whereas Nur is for young people" (high school girl in the girls only group).

"Depo is strong whereas Nur is weak" (high school girl in the girls only group).

Again, DMPA was regarded as more effective than NET-EN, more suitable for older women and more likely to cause infertility. On the other hand, NET-EN was seen to be the better product for younger women, still wanting to have children. The high school girl (comment 3 above) also believed that the "weakness" or "lightness" of NET-EN made it less harmful.

However, not all participants believed that one product is better than another as illustrated by the following comments. Note however that the nurse (third comment hereunder) does provide a restriction to the use of DMPA for those not having at least three children.

"What I can say about the injectables is that they are the same but the difference is in people's blood" (female high school teacher).

"There is no injection we can say is better; we think it depends on the blood of an individual. One can use Depo and encounter many problems and the other person can use the same injection and do not encounter problems" (female member of sewing group).

"Depo has been made to suit all ages, it can be someone with a child or without. It is good to everybody, the only difference comes in when people say, it has got side effects that is one, delays return of fertility. That is not right, we tell people that it is nine to twelve months one has to wait for the return of fertility before she can fall pregnant after stopping using Depo. However on the other hand, Nur takes three to six months, so we give everybody, young and old because, even those young girls, sometimes they are not

prepared to come to the family planning clinic every two months for Nur, that is why we give them Depo as well so that they can save transport money because some might be coming from afar, as long as the person is para 3, being a young girl or a married women, you get Depo" (female nurse).

Which injectable product was considered better for young women?

In response to a question which specifically explored whether DMPA or NET-EN was considered the better product for young women, or those without children the following comments were made:

"Nur is better because it is weak" (female high school teacher).

"Nur is better because Depo can cause sterility while with Nur you still can get pregnant after use" (all participants of the sewing group - all women - shared this view).

"Young people must take Nur and even at the clinics they used to be given Nur and even those who do not have babies must take Nur" (female community heath worker).

"Two monthly injection is better for those who do not have children because they can easily get pregnant when they want to" (female community health worker).

" They [women without children] must use Nur" (female parent).

"Nur [but] for those who do not have children yet. It is because the Nur is mild and the Depo is strong. It makes the return of fertility quicker and easily, whilst Depo delays fertility as it takes nine to twelve months" (female nurse).

"Nur is good and it is made for younger people" (female member of sewing group).

"It is Nur because it does not make people to be infertile" (female member of sewing group).

"People without children must also use Nur because it is weak and is right for those who are still looking to get children" (high school boy in the boys only group).

"Depo is good because young people used to go to the clinic once and they stay a long time without going to the clinic" (high school boy in the boys only group).

"I know two kinds of injection, the first one is Depo Provera, that one is given to a female who already have a child. The second one is Nur-Isterate which is given to school girls with no children" (unprompted comment was made by a member of the group of taxi drivers – all males).

All but one of these comments indicate that NET-EN was regarded as the better product for younger women or those without children. A member of the sewing group suggested that NET-EN was "made" for younger people. Once again, a frequent conclusion drawn was that NET-EN is weaker than DMPA and is therefore more appropriate for those (often young women) still wanting to have children. However, one of the high school boys regarded DMPA as the more convenient product for young women due to the longer interval between clinic visits.

Perceptions about reversibility

In addition to the references to the perceived effect of injectable products on fertility made above, opinions about the reversibility of DMPA and NET-EN were expressed as follows:

> "Pills are better because they prevent pregnancy and at the same time make you more fertile unlike Depo which can sterilise you" (female high school teacher).

> "Nur is best for teenagers because it does not disturb the cycle while Depo causes one not to menstruate and as a result one becomes infertile. But all the same I would say it depends with the blood of that person" (female high school teacher).

> "It depends on the period one has used an injection. If you have used an injection for longer period you definitely have to wait a long time come to get a child after you have stopped using it" (female high school teacher).

> "Even at the clinics they tell you that as you are taking Depo you will have some problems of getting a child by the time you want it" (female high school teacher).

> "Depo is good for the elder women. It is because, let us say you do not like to get babies anymore, then if you use the Depo, fertility returns after a long time or not to get it at all" (female nurse).

> "Other females end up not getting the child. ..... after using Depo" (female nurse).

"With Nur, one definitely gets the baby after using it and even sooner than expected if she has defaulted. Like one did not turn up on the specified date, she falls pregnant because the return of fertility is high and quick" (another female nurse).

"... there are a lot of people I can mention, who used the Depo when it was still new in the market, the people who were using it timeously, they never got children when they wanted them , they became sterile" (another female nurse).

"... with Depo it is very difficult to get babies after stopping using it. I once heard that if you using it maybe for six months and when you stop it let say you want a baby, maybe you have just got married, like you are twenty one years and your husband need a baby, you will go from doctor to doctor without getting the baby until you get sacked by the husband. And he will marry one who will get babies for him" (female primary school teacher).

"I heard that if you are a teenager and you want to start using a method you mustn't start using a Depo because it will make you infertile because it is very strong" (high school girl in the girls only group).

"It is not good to take a Depo for quite a long time you must give yourself a break so that it won't cause a problem of infertility" (high school girl in the girls only group).

"When it comes to sterility I would say it differs with people because I know of many people who used Depo and still got pregnant after stopping using it" (female high school teacher).

"I personally would like to differ [with those who say that Depo causes fertility problems] and stress the point that it differs with people, some get pregnant immediately they stop using injection and some wait for a long period" (female high school teacher).

With only two exceptions (see last two comments), all the comments made above reveal the perception that DMPA delays return to fertility or even results in infertility, whereas this is not the case with NET-EN.

In summary, in 11 of the 14 focus group discussions[17], the perception that NET-EN was a more appropriate injectable product for younger and/or nulliparous women was clearly enunciated. Further, DMPA was frequently referred to as the "stronger" product of the two and more likely to result in a delayed return to fertility. Within the groups, comments about the efficacy and reversibility of the two products were more often made by female members of the groups.

1.5.3 MAIN FINDINGS

Side effects

- Multiple side effects were experienced by users of both products.
- Similar side effects were most commonly reported, in similar frequencies, by users of both products.
- Amenorrhoea was the side effect most commonly reported by current users and heavy bleeding the most common amongst previous users.

[17] The three groups who did not make any comments about the differences between the two products were the church ministers, the traditional healers and the school governing board. These groups were unable to give their views on the two products as they were not familiar with them.

- Greater differences in the experience of side effects were found between current and previous users of IPCs than between users of the different products.
- Vaginal moistness was frequently reported as a side effect and appears to decrease as duration of use increases.
- Aspects liked least by both DMPA and NET-EN users were amenorrhoea, heavy bleeding, vaginal wetness and weight gain.
- Respondents regarded both products as highly effective, but DMPA is perceived to be "stronger" and more likely to delay return to fertility. As a consequence, NET-EN is regarded as the preferred method for younger, nulliparous and/or unmarried women.

CHAPTER 1.6: DISCUSSION AND CONCLUSIONS

1.6.1 INJECTABLE CONTRACEPTIVE PREVALENCE AND USE

Contraceptive prevalence in the rural area of KZN surveyed was only 30% compared to a national prevalence of 62% reported by the South African Demographic and Health Survey[18] (SADHS) which was conducted in the same year (Department of Health *et al,* 2002). Injectable progestogen-only contraceptives (IPCs) were widely used with over half the respondents in the survey having used the method at some time, and nearly three quarters, who were practicing contraception at the time of the survey, having used the injectable method. Use of injectables among those practising contraception was thus higher than that found in the SADHS for women living in non-urban areas and for residents of KwaZulu-Natal (KZN) as a whole. This suggests that injectable use among those practising contraception in deep rural areas may be higher than in urban and peri-urban areas of South Africa.

Consistent with the SADHS, the injectable method was most widely used by young women, with the highest prevalence amongst women in their teens and twenties. By contrast, a recent study conducted in Nigeria amongst secondary schoolgirls (aged 14-21 years) found that the most popular contraceptive was the rhythm method, followed by the oral contraceptive and withdrawal, used by 47%, 21% and 10% of sexually active respondents respectively (Okpani and Okpani, 2000). The injectable method was used by only 3% of these young women. In the Hlabisa study younger, more educated women in married or stable relationships were significantly more likely to be using the injectable method.

[18] Contraceptive prevalence: percentage of sexually active women currently using a contraceptive method.

Mean age at first contraceptive use was higher than mean age at first pregnancy. All but six of the IPC users had been pregnant at some stage, and their mean age of first contraceptive use was 3 years higher than the mean age of first pregnancy. Many women who had ever used the injectable method had only one child. On the other hand many who had never used the injectable method had no children. Having been pregnant was found to be strongly correlated with injectable contraceptive use (Odds Ratio=12). This suggests that contraceptive use commences some time after the first pregnancy, and, once respondents had at least one child, those seeking a contraceptive method were likely to opt for a very effective contraceptive method, the injectable.

Possible reasons put forward for young South African women initiating contraception only after the first pregnancy are:

- Demonstration of fertility will enhance marriageability as documented by Preston-Whyte (1990).
- Young women only receive adequate education about the need for contraception once they attend for ante-natal care or delivery services (Garenne *et al* 2000).

A recent study of age-specific fertility rates in the Agincourt sub-district, a rural area of South Africa, reports an atypical bi-modal pattern of fertility with underlying modes of premarital fertility among women aged 18-20 years, and marital fertility among women aged 28-30years (Garenne *et al* 2000). Pre-marital fertility accounted for 47% of births among women aged 12-26 years, but accounted for 21% of all births. A low incidence of contraceptive use before the first birth, particularly among adolescents, and high contraceptive uptake thereafter, are reasons the authors give for the high rate of pre-marital fertility. In the Hlabisa study a similar trend was observed with regard to initiation

of contraceptive use in relation to first birth. However, few women of any age were married, and this was especially true for injectable users (Table 1.3.3), with only three mothers under 25 years who were using the injectable being married. These low levels of marriage have important social and economic implications for women, as many have to fend for themselves or rely on extended families for support. The tendency for teenagers to conceive because they have unprotected sex is further illustrated in a study undertaken in Cape Town by Vundule *et al* (2001) where teenage pregnancy was found to be strongly associated with having sex without reliable contraceptive protection (Risk Ratio:24.35). Likewise Buga *et al* (1996) found that poor knowledge of contraceptives was a risk factor for unprotected sexual activity among Transkei (now Eastern Cape Province) school girls.

In the Hlabisa study, the main contraceptive method used by women who were under 20 years was the injectable method. A higher proportion of younger women were using the injectable contraceptive (84%) compared to the proportion of all the women surveyed who were using the injectable (74%). The Cape Town study on teenage pregnancy also found high rates of injectable contraceptive use amongst teenagers who had ever used contraception (Vundule *et al*, 2001). While Garenne *et al* (2000) note a pattern of low contraceptive use before adolescents delivered, followed by high use after delivery, these authors did not report which contraceptive methods were used.

Conclusions and Recommendations

The pattern of contraceptive usage in South Africa is unlike that found in most other countries in the world. This is important for policy makers, health planners, programme mangers and trainers to note, as, while contraceptive prevalence in South Africa is relatively high, there is great reliance on a single method (the injectable), which offers no

protection against HIV and other STIs. Attention should focus particularly on the method mix in deep rural areas, where injectable use may be even higher.

The contraceptive needs of young women should be addressed before their first pregnancy, as many sexually active young women are unprotected not only against unwanted pregnancy but also against sexually transmitted infections. The high rates of premarital fertility are cause for concern and should be further examined as they contribute to the social and economic vulnerability of women and children. Even after initiating contraceptive use, the injectable method, adopted by most young women, offers no protection against HIV/STIs, bearing in mind that women under 30 years of age are the hardest hit by HIV. Effective sexuality education programmes, which include information about contraceptive options, are urgently required for young women since they are particularly vulnerable to unplanned pregnancies and HIV/STIs.

1.6.2 METHOD MIX AND REASONS FOR CONTRACEPTIVE PRACTICE

The survey findings provide an extensive analysis of contraceptive use amongst rural KZN women. The pattern of low condom use and high injectable contraceptive use reported in this study is consistent with findings from the SADHS (Department of Health *et al,* 2002) which was conducted at the same time as the Hlabisa survey. Given the high prevalence of HIV in rural areas of KwaZulu-Natal, the low use of condoms for contraception requires attention. Only 11 women reported the male condom as their current method, and none were using the female condom. The practice of thigh sex, which may offer some degree of protection against HIV/STIs and pregnancy, was also low, with only 3 women reporting that they use this method. Since the teenage pregnancy

rate was also high, the need for effective, but appropriate, contraceptive methods is clearly evident.

Developing an understanding of why women choose a particular contraceptive method and recognising that many women do not need or wish to use a contraceptive method, and understanding their reasons why, are essential to the provision of effective advice about reproductive health, family planning and HIV/STI preventive measures. Findings from the Hlabisa survey provide this insight and are discussed below.

Understanding Method Choice

While studies undertaken in South Africa have examined contraceptive prevalence, contraceptive method mix, and reasons for method switching or discontinuation (Smit and Venter, 1993; Reproductive Health Task Force *et al*, 1994; Chimere-Dan, 1996; Bailie *et al*, 1997; Westaway *et al*,1997; Beksinska *et al*, 1998; Beksinska *et al*, 2001a; Smit *et al*, 2001; Department of Health *et al*, 2002), an extensive literature search revealed no published studies which describe reasons for method choice amongst South African users. This lack of data is addressed by the Hlabisa study. Health workers played an important role in women's decisions to use injectable contraceptives, with many injectable users indicating that they chose this method because it was recommended at the clinic. Only two women using other contraceptive methods gave this as a reason for method choice. While counselling and decision-making about appropriate contraceptive methods should take into account and address the dual risk of pregnancy and acquisition of HIV/STIs (Ott *et al*, 2002; Mantell *et al*, 2003), findings from the Hlabisa study suggest that there are many missed opportunities for counselling about barrier methods to minimize the dual risk of pregnancy and HIV acquisition. The need for South African family planning

providers to assist in HIV/STI prevention was documented early in the 1990s (Abdool Karim *et al*, 1992). However a recent survey in 89 South African public primary care clinics found that only 12% of women were protected from STI and pregnancy at last intercourse (Morroni *et al*, 2003) indicating that little progress has been made some ten years later.

Other reasons of note for choice of the injectable method were that it was a convenient and effective method that could be used secretly. The low use of condoms may be explained by their failure to meet these criteria to the extent that the injectable does. The need by some for secrecy particularly precludes the use of the condom which requires the co-operation of the partner. Since over 90% of injectable users reported no personal income, they are not in a strong position to negotiate condom use. For women who want to prevent pregnancy without their partners' knowledge, the injectable remains a rational choice. Where contraceptive efficacy is the criterion for method choice, women at risk of HIV acquisition could be counselled to use condoms in addition to their hormonal method. This "dual method" use approach is increasingly being advocated where appropriate and practiced (Stanton *et al*, 1996; Mantell *et al*, 2003; Morroni *et al*, 2003).

An important observation from this study is that at least 10 respondents had embraced the concept of dual protection against pregnancy and HIV/STIs, indicating that they were using the male condom or thigh sex because it provided protection against pregnancy and STIs.[19] This finding is encouraging as it may indicate that educational messages aimed at

[19] Since this study did not explicitly explore whether condoms were used concurrently with other methods of contraception for STI/HIV prevention, it is possible that the number of women practicing dual protection could have been higher. Exploration of dual protection practice was not an objective of this study and is beyond the scope of this thesis.

dual protection against unwanted pregnancy and HIV/STIs are reaching even remote rural areas of the country, or that women are recognising the need for dual protection.

Amenorrhoea is frequently reported as a side effect that women do not like, and often leads to method discontinuation (see Chapter 1.1). Yet, in the Hlabisa survey, while amenorrhoea was a reason for discontinuation for some women, nearly a quarter of injectable users, particularly the young NET-EN users, regarded amenorrhoea as a positive effect and chose the method for this reason. This may be an indication that younger women, who are often more educated, have a greater understanding of reproductive biology and do not regard the lack of menstruation associated with injectable use as a sign of pathology. It may also reflect a modernization of younger women who may be less concerned about the notion of womanhood embodied by menstruation. It is possible also that health providers give good counselling with regard to injectable side effects. It is clearly more convenient, especially for poor rural women with limited access to water, not to menstruate.

A recent study undertaken amongst family planning clinic clients and providers in China, South Africa, Nigeria and Scotland showed that the majority of Black African women, particularly those from Nigeria, liked menstruating (Glasier *et al*, 2003). These authors felt however that providers overestimate the importance of regular menstruation. In the Hlabisa study, whilst many women did not like amenorrhoea associated with IPC use, some women, particularly NET-EN users regarded amenorrhoea as a positive effect of the method. Providers should take this into account as it may affect their counselling approach.

Understanding Why Women are not Currently Practising Contraception

Few studies have explored reasons for non-use of contraception. The 1998 SADHS (Department of Health *et al* (2002) sought this information, but only amongst married women not using a method and not intending to use contraception in the future. The main reasons given by these women for non-use were: desire for more children, health concerns, and opposition to family planning on the part of the respondent or partner. For the older women, being menopausal, having had a tubal ligation and sub-fertility were also frequently given reasons. One other study on this topic, a qualitative study amongst 40 adolescents in the Northern Province of South Africa, was found (Wood *et al*, 1997). In this study, the main barriers to contraceptive use among the adolescents were the experience or fear of side effects, and harassment by clinic nurses, who regarded them to be too young to be sexually active (Wood *et al*, 1997). Vundule *et al* (2001) examined risk factors for teenage pregnancy, but regretted that they did not sufficiently explore reasons for not using contraceptives in this study. Developing an understanding of why women choose a particular contraceptive method and recognising that many women do not need or wish to use a contraceptive method, and why, are essential to the provision of effective advice about contraception and HIV preventive measures. The Hlabisa study explored reasons for non-use of contraception and findings assist in the development of pragmatic guidelines for counselling women about appropriate contraceptive options as suggested below.

Over two thirds of the Hlabisa women interviewed were not using a contraceptive method. Many had never been sexually active or were sexually inactive at the time, and these women were not at risk of unwanted pregnancy or infection. However nearly 40%

of the non-users were estimated to be at risk of an unplanned pregnancy and even more, including those who were pregnant or wanting to conceive, were at risk of acquiring HIV. Common reasons given for not practicing contraception were similar to the SADHS results with 'not needing a method' followed by being opposed to contraception and method related reasons e.g. side effects and health concerns. Unlike the study by Wood *et al* (1997) few women attributed non-use to service provision factors.

Many of the women had migrant partners who were absent for long periods of time and a reason put forward for not practising contraception was infrequent sexual intercourse. These women's contraceptive needs are intermittent and often unpredictable and they may be reluctant to use the injectable, with its poor side effect profile, continuously. For these women, provider counselling, which promotes injectable use, is inappropriate. Provided the partner was willing, the condom (male or female) may be a more appropriate contraceptive option for them, particularly as a dual protection method, since several studies have shown that migrants are at greater risk of being infected with HIV and other STIs (Lurie, 2000).

The "use a condom" message, which generally refers to male condoms, is also inappropriate for women whose partners refuse to use male condoms. The female condom was not widely available in South Africa at the time of the Hlabisa survey. However, the national female condom introductory strategy launched just prior to the survey, is being expanded to more public sector health facilities (Mqhayi *et al*, 2003). Preliminary evaluation of this introductory programme suggests that some women may be able to negotiate use of the female condom more easily than the male condom (Mqhayi *et al*, 2003). This will make this female controlled method more widely available. However, it

should be noted that two female condom acceptability studies undertaken in South Africa have reported a mixed reaction to the acceptability of the female condom (Sapire, 1995; Beksinska *et al*, 2001c). The cost of the female condom compared to the male condom is a barrier to widespread distribution of this method (J Wilson, Logistics Advisor: Chief Directorate HIV/AIDS and STIs, pers. comm., March 2003). Nevertheless, the female condom should be offered to those women who cannot negotiate use of the male condom.

Conclusions and Recommendations

The importance of individualized contraceptive counselling tailored to women's specific circumstances, including their risk of HIV/STI acquisition, is clear from this and other studies (Mantell *et al*, 2003). Health workers play an important role in decision-making about contraception, and are highly influential in the choice of the injectable method in South Africa. They may be happier to promote condom use over the injectable method, if they are reassured about barrier method efficacy. Promotion of the use of emergency contraceptive pills, as a back-up to condom use, may also result in increased likelihood of the promotion of condoms instead of injectables.

The choice of contraceptive methods available in public sector clinics is limited. The need for greater access to female controlled methods like the female condom, which also protect against HIV/STIs, should be addressed. A high priority for education intervention strategies are programmes which enhance women's ability to negotiate male condom use.

1.6.3 INJECTABLE CONTRACEPTIVE PRODUCT MIX

Although not extensively documented, it is claimed that there has been a shift away from the predominant use of DMPA in South Africa, to NET-EN, especially amongst younger, nulliparous women (Beksinska *et al*, 1998; Wood *et al*, 1997; Beksinska *et al*, 2001a). Prior to the Hlabisa study, no study in South Africa (and perhaps the world) has specifically examined the injectable product mix. The WHO's Medical Eligibility Criteria for Contraceptive Use classifies DMPA and NET-EN together (World Health Organization, 2000). The Primary Health Care Essential Drugs List for South Africa provides no guidelines with respect to the circumstances under which DMPA rather than NET-EN should be prescribed, or vice versa(National Department of Health,1998).

In the Hlabisa survey, both injectable products were extensively used, with more respondents using NET-EN than DMPA. The main predictor for NET-EN use was younger age. This trend seemed largely to be based on the perception that NET-EN was the "weaker" of the two products and would be less likely to result in delayed fertility for those still wanting to have children. DMPA was clearly regarded as the more effective ("stronger") product. This perception was inextricably linked to perceptions about method reversibility and was shared by many of the household survey respondents and by participants of the focus group discussions which included community health workers, nurses and teachers. Further, health workers appeared to play an important role in decision-making about which IPC product was provided. These findings are consistent with results from a study undertaken in the Northern Province of South Africa where providers were found to recommend NET-EN for younger women based on their perception that DMPA use may result in permanent infertility, whilst NET-EN was considered ".... less strong and 'usually reversible' " p. 13 (Wood *et al*, 1997).

As illustrated in the literature review (Chapter 1.1), both IPC products are demonstrably highly effective and there is no reason to provide one product over another on the basis of efficacy. Further, there is no evidence that one product has a better safety profile than the other. Although menstrual irregularities are reported in the literature to occur more often with DMPA than with NET-EN, in the Hlabisa study side effects appeared to have had little influence on whether DMPA or NET-EN was used. While return to fertility is reported by some reviewers to be more rapid with NET-EN (Fraser and Weisberg, 1982; Howard *et al*, 1985), others (Bigrigg *et al*, 1999) have suggested that there is no delay in return to fertility with DMPA use if one considers the methodological bias of early studies, which did not take into account the date of the last DMPA injection.

Age as a criterion for prescribing one or other IPC product on the basis of reversibility is also not supported by the literature. Some policy documents and publications specifically debunk the notion that IPCs should be restricted according to age. For instance, Lande (1995, p.7) recommends that: "Providers may need to reassure clients and the public that injectables do not cause infertility but to note that women should expect a wait of some months after stopping injectables to become pregnant. Service policies based on a fear of infertility - in particular, age and parity restrictions - can be dropped". In the first edition of the WHO Medical Eligibility Criteria for Contraceptive Use (World Health Organization, 1996) the only restriction made in relation to age and IPC use, was that 'For women under 16 years of age, there are theoretical concerns regarding hypo-oestrogenic effects due to POC use" p.54 (POC refers to Progestogen-only contraceptives). This restriction was applied to IPCs in general, not to one or other product. In the second edition of the WHO Medical Eligibility Criteria for Contraceptive

use (World Health Organization, 2000) this restriction has been revised as follows: "For women under 18 years of age, there are theoretical concerns regarding hypo-oestrogenic effects particularly due to DMPA use." and, "For women greater than age 45, there are theoretical concerns regarding hypo-oestrogenic effects particularly due to DMPA use, and whether these women will regain bone mass after discontinuation of DMPA." (Progestogen-only contraceptives - p.1). The WHO does not however advise that NET-EN rather than DMPA should be used by women under 18 years or over 45 years. Further, for these younger and older women, DMPA and NET-EN are assigned the same medical eligibility category (2), where the advantages of using a method are considered to outweigh the theoretical risks (2000). The WHO applies no restriction to the use of progestogen-only contraceptive methods by nulliparous women. The South African Department of Health's National Contraception Policy Guidelines (2001, p.25) specifically states that: "Young clients should not be prevented from using **either** DMPA or NET-EN because of their age."

A cost analysis of the supply patterns of IPCs from four pharmaceutical depots showed that they accounted for a substantial share of the total state expenditure on drugs in South Africa. Of the two IPCs available on the South African Essential Drugs List (National Department of Health, 1998), DMPA is a cheaper option than NET-EN, even if only considering acquisition costs. The analysis showed that if all NET-EN clients had been given DMPA, between 9% and 18% of the expected annual drug bill for IPCs could have been saved per depot.

In highlighting key issues in financing family planning services in Sub-Saharan Africa, Janowitz *et al* (1999, p.64) make the following statement "Given limited resources, the

universal provision of methods based on demand and without regard to cost will restrict the number of individuals whose need for family planning services can be met". The balancing of needs and resources becomes even more challenging when attempting to meet reproductive health needs more broadly. For instance, in developing countries like South Africa many drugs such as antiretrovirals for HIV treatment are not available through the public sector since they are not affordable. Despite the growing demand for access to the female condom, distribution by the Department of Health is currently limited to 214 of approximately 5,000 public sector clinics across the country (M Beksinska, Director, Reproductive Health Research Unit, pers. comm., May 2003) because of the high cost of the female condom compared to the male condom. The price of the female condom is about 55 US cents while the cost of the male condom is 2-3 US cents. Careful analysis of current expenditure on drugs is thus required so that resources can be allocated to meet changing therapeutic needs.

Rational use of drugs cannot be based on financial criteria alone and clinical criteria, such as efficacy, reversibility, acceptability of side effects, discontinuation patterns and safety must also be considered. The World Health Organization's general criteria - safety, affordability, necessity and efficacy (SANE) - for inclusion on the Model List of Essential Drugs (EDL) (Kanji, 1992) provide a useful basis upon which to make decisions about drug selection and rational use. If one were to embrace the WHO promoted Essential Drugs concept (Kanji, 1992) the decision about which IPC to supply should be made on cost since DMPA and NET-EN have comparable efficacy and safety profiles. Based on the cost analysis presented in this paper, DMPA should be the product selected. However, reducing contraceptive options, flies in the face of progressive reproductive health policies which promote expansion of contraceptive choice. For instance, the WHO "is giving

priority to improving access to high-quality care in family planning through a variety of strategies" (World Health Organization, 2000, p.2), and lists one of these strategies as "promoting the widest availability of different contraceptive methods so that people may select what is most appropriate to their needs and circumstances", p2. The Programme of Action adopted at the International Conference on Population and Development held in Cairo in 1994 recommended that family planning programmes should "Recognize that appropriate methods for couples and individuals vary according to their age, parity, family-size preference and other factors, and ensure that women and men have information and access to the widest possible range of safe and effective family-planning methods in order to enable them to exercise free and informed choice" (United Nations Population Information Network, 1994, p.39/132). The Population Council's approach to contraceptive introduction in developing countries involves an assessment of the context of contraceptive use in that country, on the basis of which "recommendations for upgrading contraceptive services - which could include introducing new methods, improving the utilisation of existing ones, and/or removing one or more from the method mix" (Population Council, 1996, p.1).

The injectable contraceptive method is an important option in South Africa, since some women choose this method because its use does not require partner knowledge or consent (Kaufman, 1997). In cases where side effects such as amenorrhoea are particularly problematic with DMPA, NET-EN may be a good alternative. By providing NET-EN explicitly as a second-line option, the range of contraceptive products would be restricted, but not reduced. Such a policy should not be considered to overly restrict choice since, even in the western world only one product (usually DMPA) is available.

Arising out of these findings, a Cochrane systematic review of DMPA and NET-EN is underway. The Fertility Regulation Group of the Cochrane Collaboration has accepted a proposal from the author of this thesis for a review to be undertaken. The registered title is: *A comparison between the progestogen-only injectable contraceptives depot medroxyprogesterone acetate and norethisterone oenanthate for contraceptive use.* The protocol is currently being developed and the review will be submitted as a master's dissertation by Dr B Draper, under the supervision of Margaret Hoffman, in the Department of Public Health of the University of Cape Town.

Also of importance in regard to health care costs is that, while use of generic drugs is promoted in the South African National Drug Policy (Department of Health, 1996) as a cost-containing mechanism, the price differential between the generic and innovator DMPA products, appeared to be almost negligible. The rising cost of generic medicines is documented in an editorial in the British Medical Journal which states, in relation to the United Kingdom National Health System: "... these price rises threaten to undermine the development of primary care groups and suggest that the market for generic drugs can no longer remain unregulated." (Walley and Burrill, 2000, p.131).

Conclusions and Recommendations

There is no reason to provide one injectable product over another on the basis of efficacy, reversibility, discontinuation or safety. In the Hlabisa study side effects appeared to have had little influence on whether DMPA or NET-EN was used. Providing IPCs on the basis of age is not appropriate or cost effective. Training of health workers and counselling of clients to correct this misconception is clearly required. Where clients require immediate return to fertility upon discontinuing contraception, neither IPC preparation is ideal. Since

DMPA is a cheaper option than NET-EN, health worker training about the rational use of injectable contraceptives should include consideration of the cost implications of prescribing one product over another. DMPA should be considered as the first option, but where DMPA is not well tolerated, NET-EN should be available as a second option. The price of the generic DMPA product in relation to the innovator product should be further investigated. Consideration should be given to encouraging the registration of the combined injectable contraceptive in South Africa, which has a better side effect profile than the IPCs (Kaunitz *et al*, 1999). This would be an expensive option thus combined injectable contraceptives should only be provided where side effects with the IPCs are intolerable. A better contraceptive option, especially for young people, might however be the male or female condom with back up of emergency contraceptive pills to provide dual protection against unwanted pregnancy and HIV and other sexually transmitted infections.

1.6.4 DISCONTINUATION RATES AND REASONS

Most discontinuation rates are derived from clinical trials, women attending health facilities and clinic record reviews, thus data from women lost to follow-up are seldom included in the analysis. In the Hlabisa study women were randomly selected at household level and discontinuation rates were calculated on all discontinuers in the selected sample. Cultural, religious and personal attitudes influence perceptions about injectable use and especially menstrual side effects. Generalization of findings from international discontinuation studies to South African users may not be appropriate. Since unwanted pregnancy and teenage pregnancy rates in South Africa are high (Smit *et al*, 2001; Department of Health *et al*, 2002), it is important to have data on local discontinuation rates and to develop an understanding about reasons for discontinuation of the most commonly used contraceptive method.

The discontinuation rates for injectable contraceptive use were high among the rural Hlabisa women who had previously used the method. Notably, more women respondents had discontinued IPCs than were current users, and few previous users were found to be using another contraceptive method with hardly any (n=28; 16%) protected against pregnancy. One reason for the low contraceptive prevalence in discontinued injectable users may be the limited choice of methods available in public clinics.

Cumulative discontinuation rates of DMPA and NET-EN at two years (68% and 78% respectively) were higher than the discontinuation rate (41%) reported in a study on urban injectable users in Soweto Johannesburg (Beksinska *et al*, 2001a). However the Soweto figure did not include those lost to follow-up. There are no published discontinuation rates for injectable users among rural South African women. The Hlabisa discontinuation rates were similar to those reported in the WHO two year multinational comparative randomized trial which compared the two injectable products in 13 centres (n=3172) (Table 1.1.4, World Health Organization, 1983). However, in the WHO study, the rates varied widely between regions with discontinuation rates in the two sub-Saharan African countries reported to be 62% (Nigeria) and 92% (Zambia) after two years of use.

Despite the high discontinuation rates after two years, some Hlabisa women had used IPCs for long periods of time. As in the Soweto study, no difference was found in continuation rates for DMPA and NET-EN amongst Hlabisa IPC users. However DMPA users were more likely to continue using the method for longer periods (beyond five years). Since the NET-EN users were younger, one could speculate that more stopped using the method, after shorter periods of use, to have a baby. Women who experienced heavy bleeding and those who were younger were more likely to discontinue the method.

Reasons for discontinuation amongst previous IPC users were similar to those reported in the literature with side effects, particularly amenorrhoea and heavy bleeding most commonly cited. As in other studies, heavy bleeding was commonly the cause for discontinuation in the first year of use and amongst younger users. One reason for discontinuation rarely reported in the literature, but fairly commonly reported in the Hlabisa study was the experience of "vaginal wetness". Only one other study, also a South African study has ever documented a 'watery discharge' as a reason for discontinuation (Beksinska *et al*, 2001b). This was reported as a reason for discontinuation less frequently than vaginal wetness reported by rural Hlabisa injectable users (4 % versus 8%). Weight gain and vaginal wetness were the third and fourth most common reasons for discontinuation. The experience of vaginal wetness is explored more fully in the next sub-section.

"Taking a break"[20] was reported as a reason for IPC discontinuation in the Hlabisa survey. Temporary discontinuation has been documented in studies undertaken in Johannesburg, South Africa (Beksinska *et al* 1998; Beksinska *et al*, 2001a). It has also been reported in IPC studies undertaken in Kenya and the USA (Sekadde-Kigondu *et al*, 1996; Potter *et al*, 1997; Polaneczky and Liblanc, 1998; Potter, 1999) and for oral contraceptive use (Forest and Silverman, 1989, Sekadde-Kigondu *et al*, 1996). It has been suggested that temporary discontinuation be regarded as an adherence problem, which could lead to an unwanted pregnancy. It may occur because some women want to see menses (Beksinska *et al* 1998; Department of Health *et al,* 2002) and may be encouraged by an incorrect belief that the method provides protection as long as women are amenorrhoeic (Beksinska *et al*, 2001a). It may also occur where women are advised that it

[20] Sometimes referred to in the literature as a non-use segment (Beksinska *et al*, 1998).

could take up to year to conceive after discontinuing the injectable and thus mistakenly believe that they are protected against pregnancy for a year after injection (Potter, 1999).

Three respondents in the Hlabisa study reported that they stopped using the injectable as they became pregnant. Reasons for these cases of method failure were not explored, but could indicate an adherence problem, with defaulters returning late for the next scheduled injection appointment. Other studies amongst South African injectable users have found that women do return late for their next scheduled dose (Dickson-Tetteh *et al*, 'Profile of women accessing termination of pregnancy services under the new legislation' unpublished observations, cited in Beksinska *et al*, 2001a, p.12), and may be under the impression that the method is protecting them as long as they are amenorrhoeic. A delay in returning for the next injection would be more likely to affect the efficacy of NET-EN than of DMPA.

Injectables were often discontinued for more than one reason with respondents reporting up to five reasons and significantly more DMPA users giving more than one reason. It is simplistic therefore to assume that discontinuation is based on only one reason.

Conclusions and Recommendations

Discontinuation rates for injectable contraceptive use among rural women were high. Even though contraceptive prevalence in South Africa is high, so are the rates of teenage and unwanted pregnancies. Counselling to improve rates of continuation and adherence to dosing regimens could impact positively on unwanted pregnancy rates. More data on discontinuation patterns among South African users is needed as so few studies have been undertaken. Further studies should take care to define discontinuation criteria clearly,

differentiating between poor adherence and discontinuation. The experience of vaginal wetness as a reason for discontinuation also needs to be explored further. The multiplicity of reasons for discontinuation is seldom commented on in the literature, but is important to take into account when counselling injectable users. Discontinuation rates with DMPA and NET-EN are not different and should not form the basis for advising use of one rather than other.

1.6.5 SIDE EFFECTS WITH INJECTABLE CONTRACEPTIVE USE

The Hlabisa study provides the first comprehensive account of the experience of side effects amongst South African IPC users. Uniquely, it documents the experience of current and discontinued users of both DMPA and NET-EN users. It is evident from the previous section that side effects are instrumental in decisions to discontinue the method and a good understanding of the undesirability of side effects experienced by South African users is crucial for effective method counselling.

In general, the side effect profile experienced by the Hlabisa injectable users was similar to those reported in other studies. Users experienced many side effects with the method, but despite this, it continues to be the most popular method. Amenorrhoea was the most commonly experienced side effect among current users and heavy bleeding most common amongst previous injectable users. Heavy bleeding was also a more frequently mentioned side effect than amenorrhoea in focus group discussions. This suggests that injectable users are more likely to discontinue use because of heavy bleeding rather than because of amenorrhoea. Side effects reported by DMPA and NET-EN users were similar. In fact, greater differences were reported between previous and current users than by users of the different products.

Unlike other studies, a side effect translated from the vernacular as "vaginal wetness", was a frequently reported side effect by both current and previous IPC users in the Hlabisa study. It was also found to be what many of the women liked least about using the method. Consistent with findings from the study by Beksinska *et al* (2001b) it seemed to be experienced more often in the first few months of use. It was also a recurrent theme in focus group discussions and was identified as the worst side effect in the majority of focus group discussions. Vaginal wetness is a side effect that is not well accepted in the study area, and may result in method discontinuation. Many comments made in focus group interviews convey the negative way in which vaginal wetness is regarded and the negative impact it may have on the enjoyment of sexual intercourse and on relationships. It is noteworthy that some survey respondents who did not report it as a side effect (41%) were clearly concerned about the possibility of experiencing it, as they listed this as a reason for least liking the injection.

This side effect is discussed in some detail here as there is little reference to it in the literature. More detail is also provided in a paper on these findings published in *Social Science and Medicine* (copy included in the section after the abstract on page xxxiv of this thesis). Vaginal wetness was reported separately from vaginal discharge, and vaginal discharge with an unpleasant odour, the latter two being reported less often. Whilst the nature of the difference in the experience of vaginal wetness and vaginal discharge was not explicitly explored in the survey, different Zulu phrases were used in referring to vaginal wetness and vaginal discharge. The distinction was identified in the development

and translation of the interview schedule prior to commencing the survey and has been corroborated with Zulu/English translators subsequently (Z Gwamanda, Medical Research Council, M Kubeka, R Ngcamu, Africa Centre for Population Studies and Reproductive Health, pers. comm., September 1998; W Dlamini, D Msweli, Medical Research Council, pers. comm., October, 2000). The approximate English translations of Zulu concepts or commonly used phrases (in brackets) were:

- Increased vaginal moisture or wetness (*Ukubamanzi*)
- Vaginal discharge (*Ukuphuma koketshezi ebulilini bowesimame*)
- Vaginal discharge with unpleasant odour/smell (*Ukuphuma koketshezi olunephunga elibi*).

Respondents in the survey were not asked to describe vaginal wetness, however reproductive health workers suggested that it is of a watery consistency (N Ntuli, Research Nurse, Medical Research Council, pers.comm., September 1999) and discussants in the focus groups also described it as a watery substance which occurs in excessive quantities. Vaginal discharge reported by injectable users is also described as watery by Beksinska *et al* (2001b). Female participants in a study described by Brown *et al* (1993a) distinguish between three types of vaginal secretions - (i) secretions which occur in small amounts at certain stages of the menstrual cycle and during sexual arousal; (ii) excessive secretions described as 'too much water', resulting in a 'wet vagina'; and (iii) unusual discharges resulting from infections. The second type of secretion described by Brown *et al* (1993a) is consistent with the description of vaginal moistness which the KZN focus group respondents associate with injectable contraceptive use. As described in the literature review (Chapter1.1) early studies, the Petogen® product brochure and the more recent study in Soweto, South Africa (Beksinska *et al*, 2001b) describe vaginal discharge as a side effect, whereas respondents in the Hlabisa survey differentiate

between vaginal wetness and vaginal discharge, both of which are reported as side effects. It is not clear whether the early reports of vaginal discharge, and the vaginal wetness reported in the present study, are analogous. Whether either of these effects is in reality a consequence of injectable contraceptive use is also unclear, and if so the mechanisms by which they occur are not understood.

According to almost half the respondents in the Hlabisa survey, men regard women who use the injectable contraceptive as "wet", "cold" and/or "tasteless. Women also stated that the reason men dislike the injectable was because they believe that women who use it misbehave. Injectable users are clearly concerned about the response of their male partners to vaginal wetness thought to be produced by injectable use. Likewise, in focus group discussions, women using the injectable method were frequently described as wet, cold and/or tasteless and were sometimes perceived as being unfaithful or promiscuous. This notion can only serve to deepen the disempowerment experienced by many South African rural women. Beksinska *et al* (2001b) also reported that men disliked the increased vaginal discharge which they linked to injectable use. Since some South African men may prefer dry sex the perception that the injectable contraceptive increases vaginal wetness may be problematic for women who use it.

Previous studies have shown that women in many parts of Central and Southern Africa have a preference for "dry sex"[21,22] (Brown *et al*, 1993a; Brown *et al*, 1993b; Civic and Wilson, 1996; Morar and Abdool Karim, 1998; Beksinska *et al*, 1999; Brown *et al*,

[21] The practice of dry sex is defined as the drying, tightening, and sometimes warming of the vagina for sexual intercourse (Brown *et al*, 1993a; Dallabetta *et al*, 1995; Beksinska *et al*, 1999).
[22] Only some of these studies were conducted exclusively amongst commercial sex workers and the practice of dry sex is not restricted to commercial sex workers.

2000). For instance, in a study undertaken in Zaire (now the Democratic Republic of Congo), Brown *et al* (1993b) found that "Both men and women expressed a definite preference for dryness and tightness, saying that when a woman's vagina is moist or large, neither she nor her partner experience full sexual pleasure" p.97. Further, Beksinska *et al* (1999) found that 60% of men and 46% of women surveyed in Orange Farm, South Africa expressed a preference for dry sex. One of the main reasons for practising dry sex given by both men and women respondents was that it shows that the woman is not promiscuous. Another reason given, but only by women, was "for partner satisfaction" (Beksinska *et al*, 1999). Where dry sex practices are preferred women resort to potentially harmful measures to dry, tighten and warm their vaginas (Baleta, 1998; Beksinska *et al*, 1999). Injectable contraceptive users who perceive that use of the injectable results in increased wetness may well resort to these practices.

Increased vaginal wetness linked with the most popular contraceptive method used in South Africa, is clearly a problem which must be regarded seriously. At this stage there is no explanation for this side effect widely reported by women in the Hlabisa study as well as by family planning service providers. It is possible that, even if women from western countries have experienced vaginal wetness with injectable use, it may not have been reported or documented, since in these countries, increased vaginal moistness may not be regarded as a problem. One would in fact expect the anti-oestrogenic properties of progestogen to result in vaginal dryness, which is a documented, though rarely reported side effect (Guillebaud, 1993; Nelson, 1996). One possible explanation for the reported wetness is that the women who report this problem have sexually transmitted infections (STI's). However, the nature of the wetness does not, for the most part, appear to fit the description of an infection. Another possible explanation is that vaginal wetness,

attributed to progestogen injectable contraceptive use, is a perception that has grown and spread over time, possibly fueled by men's concerns about loss of control of their partner's fidelity and fertility if she uses the injectable contraceptive.

Conclusions and Recommendations

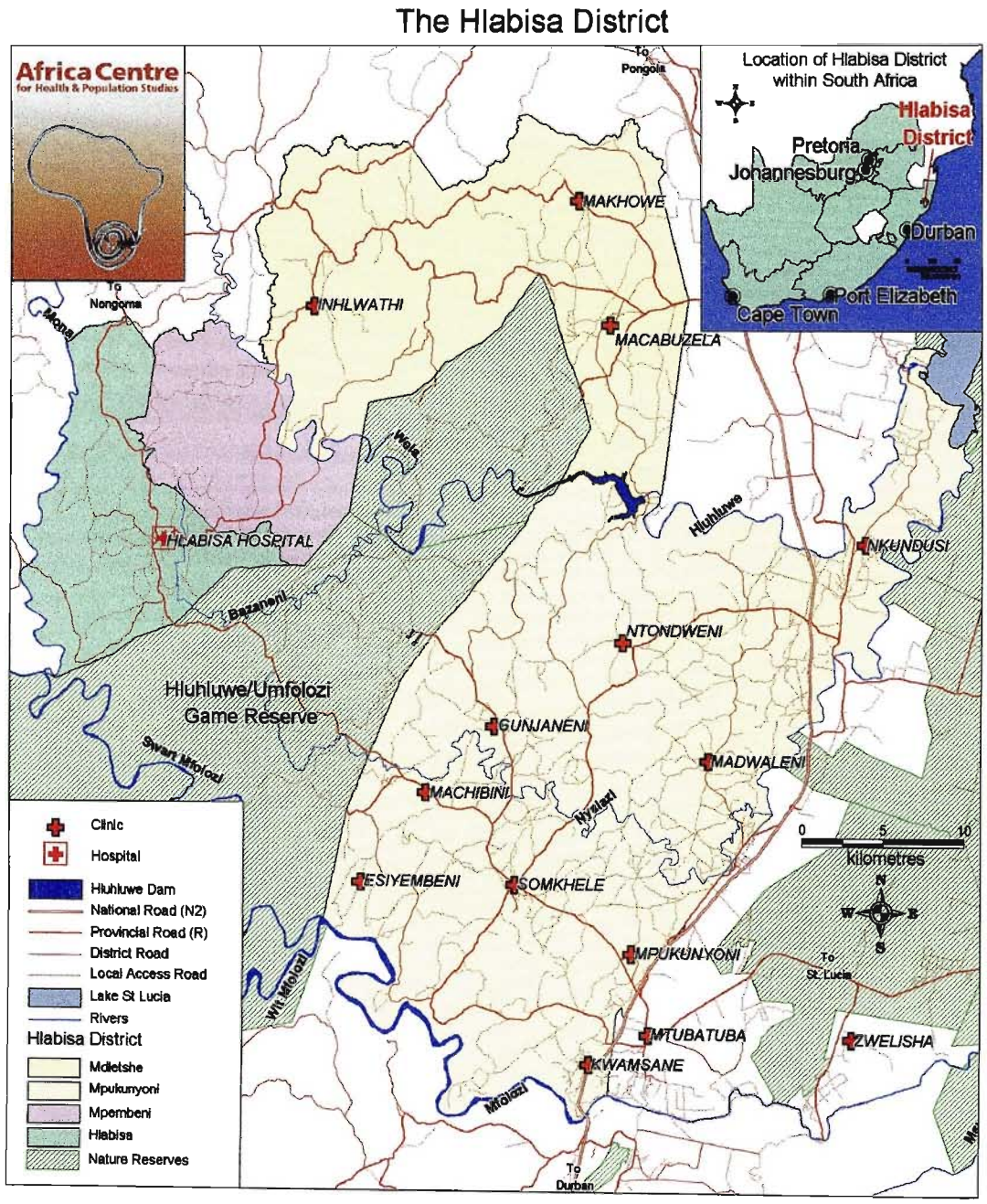
Consistent with findings from other studies, many side effects, particularly menstrual disturbances were experienced by users of both injectable products. Unlike other studies however, this study has found that vaginal wetness is a commonly reported side effect of progestogen-only injectable contraceptive. This side effect appears to be particularly disturbing in terms of the way in which men view women who use it. Yet, despite this undesirable effect, women continue to use the injectable method, mainly because they find it a convenient and effective method which can be hidden from their partners. Whilst vaginal wetness can only be classified as a subjective side effect at this stage, further investigations are needed. It is also an issue that must be addressed by health workers responsible for counseling women who use this method of contraceptive. Wright (2003) recently reviewed the published findings on vaginal wetness from the Hlabisa study and recommended that health workers should be aware that the perception that injectables cause vaginal wetness can affect acceptability and lead to discontinuation.

A study is being developed to explore the nature and possible etiology of vaginal wetness, how it may differ from the vaginal discharge reported by respondents, and whether it is a consequence of a vaginal infection or a relatively transient problem that resolves for most women on continued use.

Appendices to Section 1

APPENDIX 1.2.1

Map of the Hlabisa district showing the Hlabisa sub-district and Hlabisa Hospital



Source: F Tanser & B Gijsbertsen, Geographical Information Systems (GIS) Unit, Africa Centre for Health and Population

Appendix 1.2.2

- Patient information sheets for individual interviews (English and Zulu)
- Patient information sheets for focus group discussions (English and Zulu)

Africa Centre
for Population Studies and Reproductive Health

INFORMATION TO HOUSEHOLDERS ABOUT THIS RESEARCH STUDY ON THE USE OF THE CONTRACEPTIVE INJECTION

WHO IS DOING THE STUDY ?
This study is being undertaken by researchers from the Departments of Pharmacy and Pharmacology of the University of Durban-Westville and the Africa Centre for Population Studies and Reproductive Health

WHAT IS THE STUDY ALL ABOUT ?
We know that many women have worrisome problems when they use the injection. We hope that by doing this research we will be able to lessen these problems and in this way help women who wish to use the injection.

HOW WILL THE STUDY BE DONE ?
We need to ask you questions about family planning methods you may have used. We especially want to know what you think about the use of the contraceptive injection. We would like to ask you some questions even if you have never used the injection or other ways of delaying pregnancy, so that you can tell us what you think about these methods. We would also like to find out how much you weigh so that we can find out about whether people who are using the injection gain weight, compared to those who do not use the injection.

WHY IS THE STUDY IMPORTANT ?
What we find from this study could improve the life of many women who use the injection. We believe that this is a very important study and without your help it can't be done.

RESEARCHERS' PROMISE :
The people doing this study promise that no-one will be told anything about you. Nobody will be told what your particular answers to the questions are, as your name will not be used. We will not even ask you what your name is.

THANK YOU VERY MUCH FOR YOUR HELP

Jenni Smit
(Senior Lecturer, Pharmacy Department, University of Durban-Westville)

Mtubatuba Office: +27-35-5500158 ; P O Box 198, Mtubatuba, 3935, South Africa; # +27-35-5501674; e-mail: gagel@mrc.ac.za

The Africa Centre for Population Studies and Reproductive Health is a recently established international research centre established and funded by the Wellcome Trust of the United Kingdom. It is a consortium of three major South African academic institutions, namely the Medical Research Council of South Africa, the University of Natal and the University of Durban-Westville and is based in KwaZulu-Natal, South Africa.

INCAZELO KUBASEBENZISI MJOVO MAYELANA NOCWANINGO NGOKUSEBENZA KOMJOVO WOHLELOMNDENI

UBANI OZOQHUBA LOLUCWANINGO ?
Lomsebenzi wokucwaninga uzoqhutshwa ngabacwaningi bomnyango wezokuthakwa nokukhishwa kwemithi yokwelapha eNyuvesi yase- Durban-Westville.

LUZOSIZA NGANI LOLUCWANINGO ?
Siyazi ukuthi abesifazane abaningi bahlanga- bezana nezinkinga eziningi ezibakhathazayo uma besebenzisa umjovo. Sinethemba lokuthi ngokwenza lolucwaningo sizokwazi ukunciphisa lezizinkinga, ngalendlela kusizakale labo besifazane abafuna ukusebenzi- sa umjovo.

LUZOKWENZWA KANJANI LOLUCWANINGO ?
Sifisa ukuthatha igazi lokusampulisa iziqubu ezintathu kuwena ukuze sazi ukuthi kwenzekani emzimbeni wakho uma ukade ujova. Kuzomele sithole isampula Legazi Kuwena namhlanje ngaphambi kokuba ujove bese siphinda sicele ukuba ubuye esikhathini esiyinyanga sithathe elinye isampula legazi. Kuyodingeka ubuye ezinyangeni ezimbili ukunikeza isampula legazi lokugcina.

Siyazi ukuthi sikunikeza umthwalo odulele Kodwa uyobe usisize Kakhulu uma uvuma ukuba yingxenye yaloluhlelo. Ukukubonga ngokusisiza, siyokunika isipho esincane mhlazane ufika okokugcina. Sikholwa ukuthi lolucwaningo lungolubaluleke kakhlulu Kanti lungeka lwaba yimpumelolo ngaphandle Kosizo lwakho.

KUNGANI LOLUCWANINGO LUBALULEKILE ?
Sikholwa ukuthi konke esiyokuthola ocwaningweni kungasiza ukwenza ngcono izimpilo zabesifazane abaningi abasebenzisa umjovo ukuhlela.

ISETHEMBISO SABACWANINGI :
Abantu abazobe benza loluwaningo bayakuthembisa ukuthi akukho muntu oyotshelwa utho ngawe noma badlulisele phambili loko obatshele khona. Igama lakho ngeke lisetshenziswe nangengozi, akekho futhi oyotshelwa ukuthi uyeza kulomtholampilo noma uyajova.

OKUFANELE UKWENZE ?
Uma uzimisele ukuba ingxenye yalolucwaningo, sicela :

- Usayinda imvume kulelipheshana elihambisana nalencwadi
- Uphendule imibuzo ozoyibuzwa ngumhlengikazi eMtholampilo
- Uvumele umhlengikazi athathe isampula legazi
- Uphinde uze kulomtholampilo wohlelomndeni ngalezi zinsuku ezilandelayo :
  ....., .../...../98
  ....., .../...../98

SIYALUBONGA USIZO LWAKHO

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INFORMATION TO FOCUS GROUP PARTICIPANTS ABOUT THIS RESEARCH STUDY ON THE USE OF THE CONTRACEPTIVE INJECTION

WHO IS DOING THE STUDY ?
This study is being undertaken by researchers from the Departments of Pharmacy and Pharmacology of the University of Durban-Westville and the Africa Centre for Population Studies and Reproductive Health

WHAT IS THE STUDY ALL ABOUT ?
We know that many women have worrisome problems when they use the injection. We also know that some men have worries about women using it. We hope that by doing this research we will be able to lessen these problems and in this way help women who wish to use the injection.

HOW WILL THE STUDY BE DONE ?
We want to have a discussion about family planning methods you or your relatives and friends may have used. We especially want to know what you think about the use of the contraceptive injection. We would like to ask you to tell us your views even if you have never used the injection or other ways of delaying pregnancy. We especially want to know about problems or worries people have about using the injectable contraceptive.

WHY IS THE STUDY IMPORTANT ?
What we find from this study could improve the life of many women who use the injection. We believe that this is a very important study and without your help it can't be done.

RESEARCHERS' PROMISE :
The people doing this study promise that we will not tell anyone anything about you personally. Nobody will be told what your particular answers to the questions are, as your name will not be used.

THANK YOU VERY MUCH FOR YOUR HELP

Jenni Smit
(Senior Lecturer, Pharmacy Department,
University of Durban-Westville)

Sihle Ngcamu

INCAZELO KUBASEBENZISI MJOVO MAYELANA NOCWANINGO NGOKUSETSHENZISWA KOMJOVO WOHLELOMNDENI

Ubani ozoqhuba lolucwaningo ?

Lomsebenzi wokucwaninga uzoqhutshwa ngabacwaningi bomnyango wezokuthakwa nokukhishwa kwemithi yokwelapha eNyuvesi yase-Durban-Westville ibambisene ne-Africa Centre for Population Studies and Reproductive Health ezinze eMtubatuba.

Luzosiza ngani lolucwaningo ?

Siyazi ukuthi abesifazane abaningi bahlangabezana nezinkinga eziningi ezibakhathazayo uma besebenzisa umjovo. Sinethemba lokuthi ngokwenza lolucwaningo sizokwazi ukunciphisa lezizinkinga, ngaleyondlela kusizakale labo besifazane abafuna ukusebenzisa umjovo.

Luzokwenziwa kanjani lolucwaningo ?

Sifisa ukukubuza imibuzo ngezindlela zokuhlela umndeni osuwake wazisebenzisa. Sifisa ukuzwa ikakhulukazi uvo lwakho ngokusetshenziswa komjovo njengendlela yokuhlela. Sizocela ukukubuza imibuzo noma ngabe awukaze uwusebenzise umjovo noma yiyiphi-ke indlela yokuvikela ukukhulelwa yikhona sizozwa olwakho uvo ngalezizindlela. Sifisa futhi ukuthola isisindo sakho yikhona sizokwazi ukubona ukuthi ngabe abantu abasebenzisa umjovo bayakhuluphala yini uma beqhathaniswa nalabo abangawusebenzisi.

Lubaluleke ngani lolucwaningo ?

Sikholwa ukuthi konke esiyokuthola kulolucwaningo kungasiza ukwenza ngcono izimpilo zabesifazane abasebenzisa umjovo. Sikholwa ukuthi lolucwaningo lubaluleke kakhulu ekanti ngaphandle kosizo lwakho lungeze lwenzeka.

Isethembiso sabacwaningi

Abantu abazobe benza lolucwaningo bayakuthembisa ukuthi akukho muntu oyotshelwa utho ngawe noma badlulisele phambili lokho obatshele khona. Igama lakho ngeke lisetshenziswe nangengozi.

SIYALUBONGA USIZO LWAKHO

Jenni Smit and Sihle Ngcamu
University of Durban-Westville

APPENDIX 1.2.3

DATA COLLECTION INSTRUMENTS

- Community-based survey composite interview schedule
- Focus group interview schedule
- Individual interview schedule for focus group participants
- Record of focus groups
- Family planning clinic record of contraceptive units

Injectable Contraceptive Usage: A Community-Based Study

COMPOSITE INTERVIEW SCHEDULE

(Font reduced and spacing removed to reduce document size)

BLACK QUESTION NUMBERS = Questions common to all subsamples
YELLOW QUESTION NUMBERS = Questions for current users only
BLUE QUESTION MUMBERS = Questions for previous users only
GREY QUESTION NUMBERS = Questions only for ♀ who had never used IC

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1. Respondent Number: ☐☐☐

Demographic data

2. How old are you? ***(state in years or give date of birth)***: .....

3. Residential Status:

(a) Do you <u>sleep</u> in this house for four nights a week or more?

Yes ☐
No ☐

(b) In the last three months, have you stayed (slept) in this house for at least 50% of the time

Yes ☐
No ☐

4. Are you married or single?

(a) Current Marital Status

Marital Status	✓	Length of relationship *(as perceived by the respondent)*
Married – by civil, religious or traditional/customary ceremony		.....
Single: in stable relationship currently		.....
Single: casual relationships currently		
Single: no relationship now, but has had previous relationships		
Single: never had a relationship		
Other *(explain)*		

(b) Are you or have you ever been divorced?

Yes ☐
No ☐

(c) Are you or have you ever been widowed?

Yes ☐
No ☐

(d) If you are in a <u>relationship</u>, does your husband or partner <u>sleep</u> in this house for four nights a week or more?

Yes ☐
No ☐

<u>IF NO</u>, How often does your husband or partner return to Hlabisa?

.....

<u>IF NO</u>, Where does your husband or partner stay (sleep) when he is away?

.....

(e) **If you are in a relationship, does your husband or partner stay (sleep) in this house for at least 50% of the time**

Yes ☐
No ☐

IF NO, How often does your husband or partner return to Hlabisa?

.....

IF NO, Where does your husband or partner stay (sleep) when he is away?

.....

5. What is your religion? ***(be as specific as possible)***

.....

6. What is your level of education?

No Formal Schooling	☐
Schooled up to Standard 1 (Grade 3)	☐
Standard 2 (Grade 4) to Standard 5 (Grade 7)	☐
Standard 6 (Grade 8) to Standard 8 (Grade 10)	☐
Standard 9 (Grade 11) to Standard 10 (Grade 12)	☐
Tertiary (University/Technikon/College)	☐

7. Household size: How many people live in this house who share or contribute to household resources? (only include those who sleep in the house for at least 7 nights in a year; also include children) .....

8. What is your occupation?

(a)

Employed (formal sector)	
Employed (informal sector or self employed)	
Scholar	
Student	
Pensioner/ retired	
Housewife	
Unemployed	
Other (explain)	

IF EMPLOYED,

(b) What is your job? ***(actual job/job title)***

.....

Reproductive and Contraceptive History and Practice

9. Have you ever been pregnant?

Yes ☐
No ☐

If YES,

(i) How old were you when you were first pregnant? ..... (years)
(ii) How many times have you been pregnant? .....
(iii) How many live births have you had ? .....

10. How many living children do you have? .....

What is their sex and age?

	Age	Age	Age	Age	Age	Age	Age	Age	Age
Girls									
Boys									

11. Are you pregnant now?

Yes ☐
No ☐
Don't know ☐

If YES, how many months pregnant are you? .....

12. Have you ever had difficulty in getting pregnant

Yes ☐
No ☐
Don't know ☐

13. Have you used any method or way to delay or prevent getting pregnant <u>at any time</u> in your life, including now?

Yes ☐
No ☐

If YES,

(a) How old were you when you first used a contraceptive method? .....(years)

(b) What method did you <u>FIRST</u> use? ***(Don't read list but probe if necessary)***

METHOD	**For how long used (years & months)**
Pill/ Oral Contraceptive ***(state brand name if possible)***	
Injection: 2 monthly, Nur-Isterate	
Injection: 3 monthly, Depo Provera; Petogen ***(state brand name if possible)***	
Intrauterine contraceptive device: IUCD/IUD/coil/loop	
Emergency Contraceptive Pill (ECP)	
Quinine	
Diaphragm/cap	
Vaginal cream/foam/douche/spermicide/jelly	
Male condom	
Female condom	
Withdrawal, coitus interruptus	
Ukusoma, thigh sex	
Rhythm/Calendar method	
Body Temperature Method	
Breastfeeding	
Herbs/ remedy ***(state which)***	
Abstinence ***(state which)***	
Female sterilisation/tubal ligation (*state how long ago)*	
Male sterilisation/vasectomy	
Other ***(state which)***	

Current Contraceptive Practice

14. Are you <u>currently</u> (now) using a way or a method to avoid or prevent getting pregnant?

Yes ☐
No ☐

If <u>YES</u>, answer Questions 15-29

If <u>NO</u>, what are the main reasons for <u>not</u> using a method? ***(After answering this question, go on to question 38). (Don't read out. More than one reason may be ticked)***

Never been sexually active	
Sexually inactive/ no partner	
Infrequent sex	
Pregnant	
Want to get pregnant	
Menopausal	
Had hysterectomy/tubal ligation	
Infertile	
Breastfeeding	
Respondent is opposed to contraceptive use	
Husband/partner is opposed to contraceptive use	
Relatives/friends are opposed to contraceptive use	
Religious reasons	
Respondent knows no contraceptive method	
Respondent does not know where to go to get contraceptives	
Too far to go to the health facility	
Health reasons or concerns (*explain*)	
Fear of side effects *(explain)*	
Inconvenient to use (*explain*)	
Interferes with body's natural processes	
Costs too much	
Other *(explain)*	

QUESTIONS 15 to 29 below FOR CURRENT CONTRACEPTIVE USERS ONLY (i.e. for those who answered YES to question 14 above)

15. What method are you currently using and for how long have you used it?

METHOD	For how long used (years & months)
Current method is the same as the first method used	
Pill/ Oral Contraceptive *(state brand name if possible)*	
Injection: 2 monthly, Nur-Isterate	
Injection: 3 monthly, Depo Provera; Petogen *(state brand name if possible)*	
Intrauterine contraceptive device: IUCD/IUD/coil/loop	
Emergency Contraceptive pill (ECP)	
Quinine	
Diaphragm/cap	
Vaginal cream/foam/douche/spermicide/jelly	
Male condom	
Female condom	
Withdrawal, coitus interruptus	
Ukusoma, thigh sex	
Rhythm/Calendar method	
Body Temperature Method	
Breastfeeding	
Herbs/ remedy *(state which)*.....	
Abstinence *(explain)*	
Female sterilisation/tubal ligation (*state how long ago)*	
Male sterilisation/vasectomy	
Other *(state which)*	

If the respondent is using the injectable contraceptive, go to question 16 on page 4 of the yellow questionnaire

Injectable Contraceptive Use

16. What injectable contraceptive method are you currently using and for how long have you used it?

METHOD	For how long used (years & months)
2 monthly, Nur-Isterate	
3 monthly, don't know which brand	
3 monthly, Depo Provera (Depo)	
3 monthly, Petogen	
Other (*state which)*.....	

17. (a) Why did you decide to use the injectable contraceptive rather than another method of contraception?

.....

17. (b) Why did you decide to use this contraceptive method?

.....

18. Did you choose this method for any of the following reasons? ***(Read the list and tick more than one reason if necessary)***

You only have to have Depo Provera (Depo) every 3 months or 12 weeks Yingoba udinga ukujova emva kwezinyanga ezintathu kuphela	
You only have to have Nur-Isterate every 2 months or 8 weeks Yingoba udinga ukujova emva kwezinyanga ezimbili kuphela	
You don't want your partner to know you use contraception Awufuni ukuthi umngani wakho azi ukuthi uyahlela	
You don't want your friends or relatives to find out that you use contraception Awufuni ukuthi abangani nezihlobo zakho zazi ukuthi uyahlela	
Your friend or relative recommended it Yiyona ndlela eyanconywa abangani nezihlobo	
It was recommended for you at the clinic Yiyona ndlela eyanconyelwa wena emtholampilo	
Its an effective way to prevent pregnancy (it works) Yiyona ndlela esebenzayo yokuvikela ukukhulelwa	
Its a very safe way to prevent pregnancy (it doesn't cause harm) Yiyona ndlela ephephile yokuvikela ukukhulelwa	
You don't have a period when you're using it Awuyi esikhathini uma usebenzisa lendlela	
It suits you as there are few problems or side effects Iyangichaza ngoba izinkinga zincane engihlangabezana nazo	

19. Are you satisfied with this contraceptive method?

Yes ☐
No ☐
Unsure ☐

Explain your answer

.....

20. Who advised you to use this method?

Health worker	
Partner	
Relative	
Friend	
Teacher	
No-one	
Other (*state who)*	

21. How often do you go to the clinic or hospital to get the injectable contraceptive?

Every two months	
Every three months	
Other (state how often)	

22. Explain why you prefer the injectable you use ***(i.e. the two monthly rather than the three monthly injectable contraceptive; or the three monthly rather than the two monthly injection)*** .....
.....

23. Approximately when (approximate date) did you last go to the clinic to get the injectable contraceptive: ...../...../.....

24. When did you start using the injectable contraceptive? (years and months)
.....

25. What side effects or problems have you experienced with the injectable contraceptive?

.....

26. Have you experienced any of the following side effects? (*Read the list and tick more than one option if necessary*)

SIDE EFFECT	NOW *(±last 3 months)*	BEFORE *(e.g. When first used)*
No period/menstruation Ukungayi esikhathini		
Heavy periods Ukopha kakhulu		
Longer periods Ukuya esikhathini izinsuku ezingaphezulu kwezijwayelekile		
Spotting Ukopha kancane phakathi nenyanga		
Irregular periods Ukuya esikhathini ngezikhathi ezingafani		
Painful periods Ukuzwa ubuhlungu uma usesikhathini		
Headache Ukuphathwa ikhanda		
Dizziness Ukuphathwa isiyezi		
Sweating Ukujuluka		
Nausea Ukucanuzela kwenhliziyo		
Weight gain Ukukhuluphala		
Bloating of abdomen Ukukhukhumala kwesisu		
Bloating of breasts Ukukhukhumala kwamabele		
Breast tenderness Ukudumba nobuhlungu kwamabele		
Increased vaginal moisture or wetness Ukubamanzi		
Vaginal discharge Ukuphuma koketshezi ebulilini bowesimame		
Vaginal discharge with unpleasant odour (smell) Ukuphuma koketshezi olunephunga elibi		
Vaginal dryness Ukoma		
Hard to get pregnant after stopping the injection Ubunzima bokukhulelwa emva kokuyeka umjovo		
Loss of libido/don't feel like sex Ukuzizwa ungathandi ukuya ocansini		
Depressed mood/feel sad & unhappy Ukukhathazeka emoyeni		
Hair falls out Ukwephuka kwezinwele		

27. Over the last 12 months, have you had a break in your contraceptive use for any reason?

Yes ☐
No ☐
Can't remember ☐

If YES:

(a) Why did you have a break? ***(Record all reasons given)***

REASON	✓
Became pregnant (*by mistake, unplanned)*	
Wanted to get pregnant/ wanted more children	
Sexually inactive/no partner	
Infrequent sex (*explain)*.....	
Wanted to menstruate	
Wanted body to have a rest from contraception	
Health Reasons (explain)	
Other (explain)	

(b) For approximately how long did you have a break in using it?

..... (years and months)

28. Over the last 2 years have you had a break in using the injectable contraceptive. In other words, have you stopped using it and then started again?

Yes ☐
No ☐
Can't remember ☐

If YES:

(a) Why did you have a break? ***(Record all reasons given; don't read list but probe if necessary)***

REASON	✓
Became pregnant (*by mistake, unplanned*)	
Wanted to get pregnant/ wanted more children	
Sexually inactive/no partner	
Infrequent sex (*explain)*.....	
Wanted to menstruate	
Wanted body to have a rest from contraception	
Health Reasons (*explain*)	
Other (*explain*)	

(b) For approximately how long did you stop using it?

.....

29. Where do you go to get the injectable contraceptive? ***(Write the name or place of the health facility; more than one option can be ticked)***

	NAME OR PLACE OF HEALTH FACILITY
State Hospital	
General Clinic (not mobile)	
Family Planning Clinic (not mobile)	
Mobile Clinic	
Community Health Worker	
Pharmacy/Chemist	
Private Hospital	
Private Doctor/Gynaecologist	
Other (explain)	

30. Does your partner know you are using the injectable contraceptive?

Yes ☐
No ☐
Don't know ☐

IF NO, why not?

.....

31. Who made the decision to use the injectable contraceptive?

Yourself	
Your partner	
Joint decision between myself and partner	
Clinic sister or doctor	
Joint decision between myself and clinic nurse or doctor	
Mother	
Aunt	
Grandmother	
Other relative (state which)	

32. Will you continue to use the injectable contraceptive?

Yes ☐
No ☐

IF NO,

(a) Why not? ***(Do not read list, but probe if necessary)***

REASON	
❖ Want to get pregnant	❖
Partner is leaving/will not be sexually active	
Partner will not be around very much so I will infrequently have sex	
Want to menstruate	
Gained a lot of weight	
Want body to have a rest from contraception	
Interferes with body's natural processes	
Don't like the side effects I experience (*explain*)	
Health Reasons (*explain*)	
Worried that it may delay return to fertility	
Want to change to another method	
Going to have a hysterectomy/tubal ligation	
Menopausal	
Partner not happy with the method (*explain*)	
Use not recommended by family or friends	
Change of method recommended by health worker	
Religious reasons	
Too far to go to the health facility to get the injectable contraceptive	
Other (*explain*)	

❖ **If pregnancy is the reason**, ask respondent if she would be willing to allow follow-up to see how long it takes for her to get pregnant?

Yes, willing to allow follow-up ☐
No ☐

IF YES: Name of respondent .....
Address of respondent .....

IF NO

(b) What method will you use instead?

None/no method	
Pill/ Oral Contraceptive	
Another type/brand of Injection (state which one)	
Intrauterine contraceptive device: IUCD/IUD/coil/loop	
Emergency Contraceptive pill (ECP)	
Quinine	
Diaphragm	
Vaginal cream/foam/douche/spermicide/jelly	
Male condom	
Female condom	
Natural method (e.g. Withdrawal, coitus interruptus, rhythm, calendar	
Traditional (e.g. Ukusoma, thigh sex, herb)	
Breastfeeding	
Abstinence	
Female sterilisation/tubal ligation	
Male sterilisation/vasectomy	
Don't know	
Other **(state which)**	

33. What do you like most about using the injectable contraceptive?

.....

34. What do you like least about using the injectable contraceptive?

.....

Previous Contraceptive Practice

35. (a) What contraceptive method did you use last, i.e. before you started using the injection?

METHOD	For how long used (years & months)
None/have only ever used the injectable	
Pill/ Oral Contraceptive	
A different type of Injection (state which)	
Intrauterine contraceptive device: IUCD/IUD/coil/loop	
Emergency Contraceptive pill (ECP)	
Quinine	
Diaphragm/cap	
Vaginal cream/foam/douche/spermicide/jelly	
Male condom	
Female condom	
Withdrawal, coitus interruptus	
Ukusoma, thigh sex	
Rhythm/Calendar method	
Body Temperature Method	
Breastfeeding	
Herbs/ remedy *(state which)*	
Abstinence *(state which)*	
Female sterilisation/tubal ligation *(state how long ago)*	
Male sterilisation/vasectomy	
Other *(state which)*	

(b) Why did you change from this method to the injectable contraceptive method?

.....

Possible reasons could include (don't read out this list):

i) ***Stopped the method to get pregnant and then started the injectable after the birth of the baby***
ii) ***Got pregnant by mistake (method failure) and started the injectable after the birth of the baby***
iii) ***Wanted body to have a break from contraceptive use***
iv) ***Interferes with body's natural processes***
v) ***Side effects – find out what these were***
vi) ***Health reasons or concerns e.g. harmful or dangerous to use***
vii) ***Change of method recommended by health worker***
viii) ***Religious reasons***
ix) ***Partner not happy with method – find out why***
x) ***Use not recommended by family or friends***
xi) ***Method no longer available/ couldn't get method/out of stock***
xii) ***To far to go to get the method/lack of access***
xiii) ***Difficult or inconvenient to use***
xiv) ***Unpleasant or painful to use***
xv) ***Messy to use***
xvi) ***Puts one off sex***
xvii) ***Difficult to remember to take***
xviii) ***Have to use each time one has intercourse***
xix) ***Other***

36. What other contraceptive methods have you used <u>previously</u>? *(More than one can be ticked)*

METHOD	✓	YEARS & MONTHS USED
None/ have only only ever used the injection		
Pill/ Oral Contraceptive		
Injection: 2 monthly, Nur-Isterate		
Injection: 3 monthly, Depo Provera; Petogen		
Intrauterine contraceptive device: IUCD/IUD/coil/loop		
Emergency Contraceptive pill (ECP)		
Quinine		
Diaphragm/cap		
Vaginal cream/foam/douche/spermicide/jelly		
Male condom		
Female condom		
Withdrawal/coitus interruptus		
Ukusoma/thigh sex		
Rhythm/calendar method		
Body Temperature method		
Breastfeeding		
Herbs/remedy (*state which)*		
Abstinence (*explain)*		
Female sterilisation/tubal ligation (state how long ago)		
Male sterilisation/vasectomy		
Can't remember		
Other *(state which)*		

37. For each method listed in question 36 above, explain why you stopped using the method.

METHOD	REASONS STOPPED USING

Possible reasons could include(don't read out this list):

i) ***Became pregnant (by mistake or unplanned)***
ii) ***Wanted to get pregnant/wanted to have more children***
iii) ***Sexually inactive/no partner***
iv) ***Infrequent sex***
v) ***Menopausal***
vi) ***Had a hysterectomy/tubal ligation***
vii) ***Wanted to menstruate***
viii) ***Wanted body to have a break from contraceptive use***
ix) ***Interferes with body's natural processes***
x) ***Side effects – find out what these were***
xi) ***Health reasons or concerns e.g. harmful or dangerous to use***
xii) ***Change of method recommended by health worker***
xiii) ***Religious reasons***
xiv) ***Partner not happy with method – find out why***
xv) ***Use not recommended by family or friends***
xvi) ***Method no longer available/ couldn't get method/out of stock***
xvii) ***To far to go to get the method/lack of access***
xviii) ***Difficult or inconvenient to use***
xix) ***Unpleasant or painful to use***
xx) ***Messy to use***
xxi) ***Puts one off sex***
xxii) ***Difficult to remember to take***
xxiii) ***Have to use each time one has intercourse***
xxiv) ***Other***

38. What methods have you used previously? *(More than one can be ticked)*

METHOD	✓	YEARS & MONTHS USED
None/Never used a contraceptive method		
Only ever used one method which is the first metohd		
Pill/ Oral Contraceptive		
Injection: 2 monthly, Nur-Isterate		
Injection: 3 monthly, Depo Provera; Petogen		
Intrauterine contraceptive device: IUCD/IUD/coil/loop		
Emergency Contraceptive pill (ECP)		
Quinine		
Diaphragm/cap		
Vaginal cream/foam/douche/spermicide/jelly		
Male condom		
Female condom		
Withdrawal/coitus interruptus		
Ukusoma/thigh sex		
Rhythm/calendar method		
Body Temperature method		
Breastfeeding		
Herbs/remedy (*state which)* ……		
Abstinence (*explain)*…… ……		
Female sterilisation/tubal ligation (*state how long ago)*		
Male sterilisation/vasectomy		
Other ***(state which)*** ……		

39. For each method listed in question 38 above, explain why you stopped using the method.

METHOD	REASONS STOPPED USING
Injectable *(provide a detailed explanation for this method)*	

Possible reasons could include:

xx) ***Became pregnant (by mistake, unplanned)***
xxi) ***Wanted to get pregnant/wanted to have more children***
xxii) ***Sexually inactive/no partner***
xxiii) ***Infrequent sex***
xxiv) ***Menopausal***
xxv) ***Had a hysterectomy/tubal ligation***
xxvi) ***Wanted to menstruate***
xxvii) ***Wanted body to have a break from contraceptive use***
xxviii) ***Interferes with body's natural processes***
xxix) ***Side effects – find out what these were***
xxx) ***Health reasons or concerns e.g. harmful or dangerous to use***
xxxi) ***Change of method recommended by health worker***
xxxii) ***Religious reasons***
xxxiii) ***Partner not happy with method – find out why***
xxxiv) ***Use not recommended by family or friends***
xxxv) ***Method no longer available/ couldn't get method/out of stock***
xxxvi) ***To far to go to get the method/lack of access***
xxxvii) ***Difficult or inconvenient to use***
xxxviii) ***Unpleasant or painful to use***
xxxix) ***Messy to use***
xl) ***Puts one off sex***
xli) ***Difficult to remember to take***
xlii) ***Have to use each time one has intercourse***
xliii) ***Other***

Previous Injectable Contraceptive Use

40. Did you decide to give up using the injectable contraceptive for any of the following reasons?
(Read the list and tick more than one reason if necessary)

I became pregnant by mistake Ngakhulelwa ngephutha	
I wanted to get pregnant Ngangifuna ukukhulelwa	
I no longer had a sexual partner and did not need contraception Angisenaye engangikade ngithandana naye futhi ngingasadingi kuhlela	
My partner was not around very much/infrequent sex *(explain)* Engithandana naye wayengekho eduze / angiyi njalo ocansini (chaza) ……	
I wanted to menstruate Ngangifuna ukuya esikhathini	
I gained weight/ Ngangikhuluphala	
I wanted to give my body a break from using the injection Ngangifuna ukuphumuza umzimba wami ekusebenziseni umjovo	
It interfered with my body's natural processes Kwakuphazamisa ukusebenza ngokwemvelo komzimba wami	
I did not like the side effects I experienced *(explain)* Angizithandanga izinkinga engahlangabezana nazo (chaza)……	
I thought it was unhealthy *(explain)* Ngangicabanga ukuthi akunayo impilo (chaza)……	
I thought it would make me infertile Ngangicabanga ukuthi kuzongiqeda inzalo	
I wanted to change to another method *(state which method)* Ngangifuna ukushintshela kwenye indlela ……	
The health worker recommended that I change to another method *(state which method)* Isisebenzi sezempilo sangincomela ukuthi ngishintshele kwenye indlela(shono ukuthi iyiphi) ……	
I had a tubal ligation/ Ngaboshwa amashubhu	
I had a hysterectomy/ Ngakhishwa isibeletho	
I was menopausal/ Ngangingasayi esikhathini	
My partner did not want me to go on using it *(explain)* Engithandana naye wayengasafuni ukuthi ngiqhubeke nokusebenzisa umjovo(chaza) ……	
Use was not recommended by family or friends Ukuwusebenzisa kwakunganconyiwe umndeni noma abangani	
Religious reasons/ Izizathu zenkolo	
The health facility was too far to go to get the injection regularly Umtholampilo wawukude kakhulu ukuba ngiye kothola umjovo ngesikhathi enginqunyelwe sona	

41. (a) When did you stop using the injectable contraceptive? ……..

(b) <u>For how long</u> did you use the injectable contraceptive method? ……

(c) Why did you choose the injectable contraceptive method at the time?

……

(d) What side effects or problems did you experience with the injectable contraceptive when you were using it?

……

(e) Did you experience any of the following side effects? ***(Read the list and tick more than one option if necessary)***

SIDE EFFECT	
No period/menstruation ukungayi esikhathini	
Heavy periods ukopha kakhulu	
Longer periods ukuya esikhathini izinsuku ezingaphezulu kwezijwayelekile	
Spotting Ukopha kancane phakathi nenyanga	
Irregular periods ukuya esikhathini ngezikhathi ezingafani	
Painful periods ukuzwa ubuhlungu uma usesikhathini	
Headache Ukuphathwa ikhanda	
Dizziness Ukuphathwa isiyezi	
Sweating Ukujuluka	
Nausea Ukucanuzela kwenhliziyo	
Weight gain ukukhuluphala	
Bloating of abdomen ukukhukhumala kwesisu	
Bloating of breasts Ukukhukhumala kwamabele	
Breast tenderness ukudumba nobuhlungu kwamabele	
Increased vaginal moisture or wetness Ukubamanzi	
Vaginal dryness ukoma	
Hard to get pregnant after stopping the injection ubunzima bokukhulelwa emva kokuyeka umjovo	
Loss of libido/don't feel like sex ukuzizwa ungathandi ukuya ocansini	
Depressed mood/feel sad & unhappy Ukukhathazeka emoyeni	
Hair falls out ukwephuka kwezinwele	

42. After stopping use of the injectable contraceptive, did you use another method?

Yes ☐
No ☐
Can't remember ☐

If YES, what method did you change to? ***(Don't read list but probe if necessary***

Pill/ Oral Contraceptive *(state brand name if possible)*.....	
Another type/brand of Injection *(state which one)*	
Intrauterine contraceptive device: IUCD/IUD/coil/loop	
Emergency Contraceptive pill (ECP)	
Quinine	
Diaphragm	
Vaginal cream/foam/douche/spermicide/jelly	
Male condom	
Female condom	
Natural method (e.g. withdrawal, coitus interruptus, rhythm, calendar	
Traditional (e.g. ukusoma, thigh sex, herb)	
Breastfeeding	
Abstinence	
Female sterilisation/tubal ligation	
Male sterilisation/vasectomy	
Other (state which)	

IF YES, why did you choose to use this method?

.....

43. Did your partner know you were using the injectable contraceptive?

Yes ☐
No ☐
Don't know ☐

44. Will you ever use the injectable contraceptive again?

Yes ☐
No ☐
Maybe ☐

Explain your answer

.....

45. What did you like most about using the injectable contraceptive?

.....

46. What did you like least about using the injectable contraceptive?

.....

NOW I AM GOING TO ASK YOU SOME QUESTIONS ABOUT OTHER PEOPLE'S USE AND OPINIONS OF THE INJECTABLE CONTRACEPTIVE

47. (a) What do you think is the most popular method of contraceptive used?

.....

(b) Why do you think this method is popular?

.....

48. Do you think the injectable contraceptive is used by

Very many women	Many women	A fair number of women	Few women	Very few women

49. Do any of your close friends or relatives use the injectable contraceptive?

Many	
Few	
None	
Don't know	

50. Why do you think women choose to use the injectable contraceptive?

.....

51. Why do you think women choose <u>NOT</u> to use the injectable contraceptive?

.....

52. Do women prefer the two monthly or the three monthly injection?

Two monthly (Nur-Isterate)	
Three monthly (Depo-Provera, Petogen)	
Don't know	

Explain your answer

.....

53. Do <u>you</u> think the injectable contraceptive is a good method of contraception?

Yes ☐
No ☐
Don't know ☐

IF YES OR NO, explain your answer

.....

54. Do <u>men</u> think the injectable contraceptive is a good method of contraception?

Yes ☐
No ☐
Don't know ☐

IF YES OR NO, explain your answer

.....

55. Do your friends and relatives think the injectable contraceptive is a good method of contraception?

Yes ☐
No ☐
Don't know ☐

IF YES OR NO, explain your answer

.....

56. Do you think the injectable contraceptive is effective (does it work properly)?

Yes ☐
No ☐
Don't know ☐

IF YES OR NO, explain your answer

.....

57. Do you think the injectable contraceptive is safe (not harmful)?

Yes ☐
No ☐
Don't know ☐

IF YES OR NO, explain your answer

.....

58. Do you think the injectable contraceptive is suitable for young women or girls to use?

Yes ☐
No ☐
Don't know ☐

IF YES OR NO, explain your answer

.....

59. Do you think <u>YOU</u> will ever use the injectable contraceptive?

Yes ☐
No ☐
Maybe ☐

IF NO, why not? .....

60. Do you know of or have you heard of any side effects or problems experienced by people using the injectable contraceptive? (*Read list and tick more than one if necessary*)

SIDE EFFECT	
No period/menstruation ukungayi esikhathini	
Heavy periods ukopha kakhulu	
Irregular periods ukuya esikhathini ngezikhathi ezingafani	
Other problems with periods or menstruation izinkinga ngokuya esikhathini	
Headache Ukuphathwa ikhanda	
Weight gain Ukukhuluphala	
Bloating of abdomen and breasts Ukukhukhumala kwesisu nababele	
Increased vaginal moisture or wetness Ukubamanzi	
Vaginal discharge Ukuphuma koketshezi ebulilini bowesimame	
Vaginal discharge with unpleasant odour (smell) Ukuphuma koketshezi olunephunga elibi	
Vaginal dryness Ukoma	
Hard to get pregnant after stopping the injection Ubunzima bokukhulelwa emva kokuyeka umjovo	
Loss of libido/don't feel like sex Ukuzizwa ungathandi ukuya ocansini	
Depressed mood/feel sad & unhappy Ukukhathazeka emoyeni	
Nausea/Ukucanuzela kwenhliziyo	

Medical History

NOW I AM GOING TO ASK YOU SOME QUESTIONS ABOUT YOUR HEALTH

61. Do you smoke ? Yes ☐ No ☐

62. Are you breastfeeding

Yes ☐
No ☐

63. What medicines do you use regularly? ***(Write the name of the medicine and what it is used for)***

.....

64. Are you taking medicines to treat TB

Yes ☐
No ☐
Don't know ☐

IF YES,

(a) Are you taking Rifampicin

Yes ☐
No ☐
Don't know ☐

(b) Which injectable contraceptive are you using?

Nur-Isterate	
Depo Provera (Depo)	

(c) How often to you go to the clinic or hospital to get the injectable contraceptive?

Every two months/ 8 weeks	
Every three months/ 12 weeks	

Possible TB medicines are:
Rifampicin
Isoniazid, INH
Pyrazinamide
Ethambutol
Streptomycin

65. Do you have any medical problems? ***(Give more than one answer if necessary)***

Condition	Details/Explanation
Cardiovascular (high blood pressure; heart attach; angina; chest pain, high cholesterol; fats; stroke)	
Hepatic (liver)	
Kidney	
Tuberculosis, TB	
Cancer	
Diabetes (Sugar)	
Headache	
Epilepsy	
Gynaecological (e.g. problems with periods)	
Other (explain)	

66. How much did you weigh when you first started using the injectable contraceptive ..... kilograms.

IF RESPONDENT CAN'T GIVE A FIGURE, ASK HER IF HER WEIGHT WHEN SHE FIRST STARTED USING THE INJECTION WAS (Tick only one):

Much less than now	
Less than now	
The same as now	
More than now	
Much more than now	
Can't remember	

67. Income Level:

(a) How much do you yourself earn per month (*gross*)?

No income	
R 1 - R 500 per month	
R 501 - R1000 per month	
R1001 - R2000 per month	
R2001 – R3000 per month	
R3001 – R4000 per month	
Over R4001 per month	
Don't want to answer	

(b) What is your household income level *(roughly)*?

No income	
R 1 - R 500 per month	
R 501 - R1000 per month	
R1001 - R2000 per month	
R2001 – R3000 per month	
R3001 – R4000 per month	
Over R4001 per month	
Don't want to answer	
Don't know	

(c) What are the sources of your household income?

.....

68. MEASURE RESPONDENT'S WEIGHT (in Kilograms) .....

69. MEASURE RESPONDENT'S HEIGHT (in Centimeters) .....

70. Do you have any of the following menstrual/bleeding problems? (*Read list, more than one can be ticked)*

No period/menstruation ukungayi esikhathini	
Heavy periods ukopha kakhulu	
Irregular periods ukuya esikhathini ngezikhathi ezingafani	
Other problems with periods or menstruation Izinkinga ngokuya esikhathini	
Other *(explain)*	
None/No Problems	

THANK YOU VERY MUCH FOR YOUR HELP

TO BE COMPLETED BY INTERVIEWER

Date of interview .....

Name of interviewer .....

Length of Interview (how long did it take?) .....

Home Language of Respondent .....

Interview Conducted in:

Zulu ☐
English ☐
Combination of English & Zulu ☐

Race of Respondent <u>if not African</u> .....

****

Checked by: ..... **On (date):** .....

****

GENERAL INTERVIEWER COMMENTS ABOUT THE INTERVIEW
(INTERVIEWER TO WRITE AS MUCH AS SHE WANTS)

FOCUS GROUP INTERVIEW SCHEDULE

Themes for Focus Group Discussions: Injectable Contraceptive

THEME 1

What are your views and opinions about contraception and contraceptive methods

- Do you approve or disapprove?
- What methods are most used?
  - Which is most popular?
  - Which is least popular?
  - What traditional methods are used?
  - What unusual methods are used?
- What methods are best?
  - For young people
  - For older people
- How would you like to improve existing methods?

THEME 2

What do you think about the injectable contraceptives

- Which is better, Depo or Nur?
- Which is best for young people?
- Which is best for people without children?
- What don't you like about the injectable?
- What do you like about the injectable?
- How popular is the injectable contraceptive?
- What do men think about women using it?
- Why do many women use it?
- Do women tell their partners that they use it?

THEME 3

What problems or side effects do people who use the injectable contraceptive have?

Probe for:

- *Menstrual problems like no period, heavy bleeding etc.*
- *Vaginal wetness*
- *Delayed return to fertility*
- *Weight gain*
- *Which problem in the worst, no period, heavy period or wetness?*

THEME 4

Some women say that they experience wetness or moistness in the vagina from the injectable. Do these women use anything to reduce the wetness or dry out the vagina?

- What do women do or use to "dry" the vagina?
- How do they use these substances?

THEME 5

Is the injection is a good contraceptive method to use when many people have AIDS?

THEME 6

What are the views of the community leaders and elders about the use of contraceptives

- Especially by young women
- What do you think young people should do?

What are the views of the church about the use of contraceptives

- Especially by young women
- What do you think young people should do?

GENERAL

Is there anything else you can tell us about the use of the injectable contraceptive?

INDIVIDUAL INFORMATION: FOCUS GROUP PARTICIPANTS

1. **Group Reference Number** _____

2. **Age** _____

3. **Gender** **Female** Y
   Male Y

4. **Current Marital Status**

Married – by civil, religious or traditional/customary ceremony	
Single: in stable relationship currently	
Single: casual relationships currently	
Single: no relationship now, but has had previous relationships	
Single: never had a relationship	

5. **Occupation**

Employed (formal sector)	1
Employed (informal sector or self employed)	2
Scholar	3
Student	4
Pensioner/ retired	5
Housewife	6
Unemployed	7
Other (explain)	8

6. **Level of Education**

No formal schooling	1
Schooled up to Standard 1 (Grade 3)	2
Standard 2 (Grade 4) to Standard 5 (Grade 7)	3
Standard 6 (Grade 8) to Standard 8 (Grade 10)	4
Standard 9 (Grade 11) to Standard 10 (Grade 12)	5
Tertiary (University/Technikon/College)	6

7. **Number of living children** _____

8. **Are you or your partners currently using a contraceptive method?**
   Yes Y **No** Y

   If Yes, **what method are you using** _____
   (see list below)

Pill/ Oral Contraceptive (brand not specified)	01
Triphasil	02
Ovral	03
Microval	04
Nordette	05
Other Pill (named)	06
Other Pill (unspecified)	07
Injection: 2 monthly, Nur-Isterate	08
Injection: 3 monthly (brand not specified)	09
Depo Provera	10
Petogen	11
Intrauterine contraceptive device: IUCD/IUD/coil/loop	12
Emergency Contraceptive Pill (ECP)	13
Quinine	14
Diaphragm/cap	15
Vaginal cream/foam/douche/spermicide/jelly	16
Male condom	17
Female condom	18
Withdrawal, coitus interruptus	19
Ukusoma, thigh sex	20
Rhythm/Calendar method	21
Body Temperature Method	22
Breastfeeding	23
Herbs/ remedy	24
Abstinence	25
Female sterilisation/tubal ligation	26
Male sterilisation/vasectomy	27
Other: Brewer's Yeast	28
Other: Rope	29
Other: Flagyl	30
Other: Shell/Snail's Shell	31
Other: Essence of Life	32
Other: Hysterectomy	33
Other	34

RECORD OF FOCUS GROUPS

TYPE OF GROUP *(e.g. sewing, church etc.)*	DATE	NO. OF PEOPLE IN THE GROUP *(don't include facilitators)*	NAME OF FACILITATOR 1	NAME OF FACILITATOR 2	VENUE	TIME STARTED	TIME ENDED

Family Planning Clinic Record of Contraceptive Units Issued

Number of Units dispensed each month for each method issued

Product	Number of Units dispensed each month: July 1998 to June 1999											
	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	March	April	May	June
Depo-Provera												
Petogen												
Nur-Isterate												
Ovral												
Nordiol												
Nordette												
Triphasil												
Biphasil												
Micoval												
Egen-C												
Female condom												
Male Condom												
IUD												
Other*												
Other*												
Other*												

* Specify

SECTION 2

THE PHARMACOKINETICS OF

DEPOT MEDROXYPROGESTERONE ACETATE

LIST OF TABLES: SECTION 2

LIST OF FIGURES: SECTION 2

CHAPTER 2.1 LITERATURE REVIEW AND OBJECTIVES

2.1.1 PHARMACOLOGY OF DEPOT MEDROXYPROGESTERONE ACETATE

Pharmacokinetics is defined as the study of the time course of drug absorption, distribution, metabolism and excretion (Benet *et al*, 1996). Mathematical models are used to describe these processes in order to condense the data by estimation of drug pharmacokinetic parameters such as clearance (CL), volume of distribution (V), half-life ($t_{½}$), and rate of absorption. In addition, mathematical modelling may allow exploration of mechanisms and be used to make predictions (Bourne, 1995). It is widely recognised that a high priority should be placed on understanding the pharmacokinetic variability of drugs (Whiting *et al*, 1986), and the assessment of pharmacokinetic parameters of contraceptives is regarded by Sang (1994, p..219) to be "of critical importance in assessing contraceptive efficacy of depot medroxyprogesterone acetate (DMPA), side-effects and menstrual bleeding patterns". However, Fotherby (1990) draws attention to the lack of attention paid to the pharmacokinetics of contraceptive steroids in most textbooks and monographs. He attributes this to the difficulty in deriving and interpreting pharmacokinetic parameters for gestogens.

Whilst some pharmacokinetic studies of DMPA have been published, studies for long-acting injectable agents used by South African women, are entirely lacking. The previous section of this thesis highlighted the efficacy of DMPA and the poor side effect profile experienced by users of DMPA. Given its extensive use in South Africa, the lack of pharmacokinetic data for South African women is a glaring omission since international studies suggest that regional and population differences exist in the pharmacokinetics of steroidal contraceptives (Fotherby *et al*, 1980b; Sang, 1994; Garza-Flores *et al*, 1994). Over

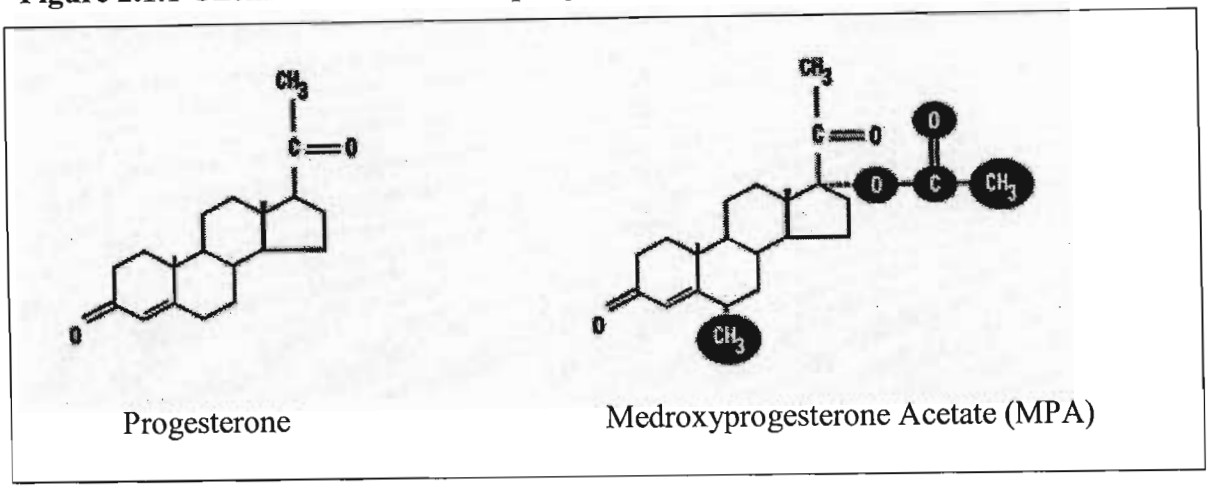
20 years ago Fotherby *et al* (1980b) recommended that studies investigating these differences be conducted in countries where injectables are widely used, yet no such studies have been undertaken in South Africa.

The pharmacokinetics of DMPA are reviewed below. This review is a prelude to the presentation of data from a population pharmacokinetic study undertaken amongst DMPA users in Durban, South Africa. Whilst use of norethisterone oenanthate (NET-EN) is increasing, especially amongst younger women (Beksinska *et al*, 2001a), DMPA is still the most commonly used injectable (see copy of paper by Smit *et al* (2001) in Section 1 of this thesis, page xxv). Due to high drug assay costs, data collection was confined to DMPA users. Hence this review is restricted to DMPA studies. Reference is only made to NET-EN pharmacokinetic studies where these studies have relevance to DMPA pharmacokinetics.

2.1.1.1 Chemistry

Medroxyprogesterone acetate (MPA) is a chemical derivative of 17α-hydroxyprogesterone (6α-methyl-4-pregnen-3,20-dione-17α-yl-acetate) (Figure 2.1.1) (Benagiano and Primerio, 1983a; Garza-Flores *et al*, 1992). MPA and progesterone have similar structures, but MPA has an additional methyl group at C-6 and an acetoxy group (OCOCH3) at C-17 (Kaunitz and Rosenfield, 1994), resulting in greater potency and a longer half-life (Theron and Grobler, 1998). Babcock *et al* (1958, p.2905) first synthesized it and described it as a "progestational agent of exceptional potency". MPA (C24H34O4) has a molecular weight of 386.5 (Benagiano and Primerio, 1983a; Martindale, 2002; USP DI, 2002) and solubility in water of less than 1mg/ml (Benagiano and Primerio, 1983a).

Figure 2.1.1 Chemical structures of progesterone and medroxyprogesterone acetate



Progesterone Medroxyprogesterone Acetate (MPA)

2.1.1.2 Mechanism of Action of DMPA

DMPA inhibits ovulation by suppressing the release of pituitary gonadotrophins, resulting in the abolition of the mid-cycle surge of lutenizing hormone (LH) and follicle stimulating hormone (FSH) (Mishell *et al*, 1968; Mishell *et al*, 1972; Kirton and Cornette, 1974; Schwallie, 1974; Jeppsson and Johansson, 1976; Garza-Flores *et al*, 1992; Mishell, 1996; Clark *et al*, 2001). Basal LH and FSH levels are reported to remain around luteal phase levels (Goldzieher *et al*, 1970; Mishell *et al*, 1972; Jeppsson *et al*, 1977; Ortiz *et al*, 1977).

Although published studies of the effect of DMPA on circulating hormones are sparse, some studies have investigated the plasma concentrations of hormones achieved with DMPA, and have related these to the effect on follicular and luteal activity and on ovulatory function. This information is summarized in Table 2.1.1. At a dose of 150mg administered intramuscularly every 3 months, DMPA has been shown to be effective as a contraceptive for at least 90 days (Ortiz *et al*, 1977; Koetsawang *et al,* 1979; Fotherby *et al,* 1980a; Bassol *et al*, 1984; Lan *et al*, 1984; Jeppsson and Johansson, 1976; Mishell,

1996) and ovulation is reported to resume when MPA blood concentrations decline to less than 0.1ng/ml (Ortiz *et al*, 1977). MPA exerts secondary contraceptive effects at endometrial and cervical levels (Garza-Flores *et al*, 1992; Mishell, 1996; Clark *et al*, 2001).

Table 2.1.1 Effect of DMPA on ovulatory function

	Reference
• MPA levels >0.1ng/ml: Ovulation inhibited • MPA levels of 0.1-0.2ng/ml: Threshold MPA concentrations expected to exert a contraceptive effect • MPA levels <0.1ng/ml: Resumption of ovulation	Ortiz *et al*, 1977 Rahimy *et al* 1999b Ortiz *et al*, 1977
• Progesterone level >3ng/ml: Resumption of normal ovulatory pattern • Progesterone levels of at least 4.0ng/ml: Evidence of ovulation • Progesterone levels ≥4.7ng/ml: Confirmation of ovulation • Progesterone levels ≥3ng/ml; Oestradiol levels ≥150pg/ml: Indicative of luteal and follicular activity respectively • Significant correlation between the concentration of MPA in blood and the return of follicular and luteal function	Ortiz *et al*, 1977 Fotherby *et al*, 1980b Siriwongse *et al*, 1982 Rahimy *et al* 1999b Fotherby *et al*1980a Rahimy *et al* 1999b Fotherby *et al* 1980a
• For inhibition of ovulation in initial injection cycle: DMPA should be administered within 5 - 7 days of onset of menses	Siriwongse *et al*, 1982 Kaunitz 1994

2.1.1.3 Absorption and Serum Medroxyprogesterone Acetate Concentrations after Injection of DMPA

The recommended dose of DMPA for contraception is 150mg every 12-13 weeks by the intramuscular route (Pharmacia and Upjohn, 1993; Martindale, 2002; USP DI, 2002).

When administered as an aqueous microcrystalline suspension into the deep gluteal or deltoid muscle, MPA is slowly absorbed from the intramuscular site. The prolongation of hormonal activity is a result of this formulation as described by Babcock *et al* (1958). MPA blood concentrations are determined by the rate of absorption from the surface of the microcrystals at the absorption site, the degree of protein binding in the bloodstream, the rate of hepatic metabolism and enterohepatic circulation, and the rate of urinary excretion of water-soluble metabolites (Fraser and Weisberg, 1981; Fotherby and Koetsawang, 1982b; Theron and Grobler, 1998). Drug formulation and crystal size may influence effectiveness (Garza-Flores *et al*, 1992) and it has been suggested that massage of the site of the injection can enhance absorption (Theron and Grobler, 1998). Following intramuscular injection of DMPA there is an initial high release of progestogen into the bloodstream, followed by a fall in MPA concentrations according to first-order release rates (Kirton and Cornette, 1974). Prolonged circulating levels of active progestogen are a result of delayed absorption from the injection site due to the low solubility of the microcrystals. This is reported to extend protection beyond the 3 month dosing interval (Kaunitz, 1994).

Early published studies have determined serum or plasma concentrations of MPA after intramuscular injection of 150mg of depot medroxyprogesterone acetate (DMPA) (Kirton and Cornette, 1974; Jeppsson and Johansson, 1976; Jeppsson *et al*, 1977; Ortiz *et al*, 1977; Shrimanker *et al*, 1978; Koetsawang *et al,* 1979; Fotherby *et al,* 1980a; Fotherby *et al* 1980b; Bassol *et al*, 1984; Lan *et al*, 1984). However, these studies used a variety of different assay techniques and, in all but three (Jeppsson *et al*, 1977; Koetsawang *et al,* 1979; Jeppsson and Johansson, 1976), MPA levels were reported after only one dose. In addition, the sample sizes were small and none of the populations studied were African.

MPA can be detected in the systemic circulation within 30 minutes of injection and levels rise steadily to contraceptive levels within 24hours (Ortiz *et al*, 1977; Mishell, 1996; Kaunitz, 2000). Following injection of DMPA, blood concentrations of MPA are reported to peak within 3 weeks (Ortiz *et al*, 1977; Fotherby *et al,* 1980b; Jeppsson and Johansson, 1976; USP DI, 2002). A summary of peak levels reported is provided in Table 2.1.2. Cornette *et al* (1971) reported that intramuscular injection of MPA resulted in fluctuating blood levels that were maximal at 2-15 days post injection and Jeppsson and Johansson (1976) measured peak levels during the first week after injection. Fotherby *et al* (1980b) reported peak concentrations, between 1 and 7ng/ml, within three weeks of DMPA injection in a study undertaken amongst 4 Indian and 4 Swedish women. In an earlier study with 3 subjects, maximal MPA concentrations of 10-25ng/ml were achieved between 5 and 20 days following intramuscular injection of 150mg of DMPA (Kirton and Cornett, 1974). It has been suggested that the higher serum levels reported in this study could be because the assay (RIA) used measured additional substances as well (Ortiz *et al*, 1997; Mishell, 1996). Higher peak serum concentrations were also reported by Fotherby *et al* (1980a). Mishell (1996) suggested that the lack of an initial plateau and relatively rapid decline in MPA levels in Fotherby's study could have been due to manipulation of the injection site. This could also explain why higher peak levels of MPA were recorded (Fraser and Weisberg, 1981; Mishell, 1996).

Kirton and Cornette (1974) found that MPA concentrations decreased to 5-10ng/ml by 30 days after DMPA administration. MPA concentrations are reported to remain fairly constant in the range of 1.0-1.5ng/ml for the 2 to 3 months post injection (Ortiz *et al*, 1977) and MPA is reportedly absorbed at a relatively constant rate over a 2 to 3 month

period. Levels then decrease gradually to 0.2ng/ml by the sixth month and eventually to undetectable levels of less than 0.02ng/ml by up to nine months (Ortiz *et al*, 1977; Lan *et al*, 1984; Mishell, 1996).

Reported findings on MPA levels after injection of DMPA are summarized in Table 2.1.2 and discussed in subsequent sub-sections. While these studies often reported peak, plateau and/or trough MPA levels and/or the time after injection at which MPA concentrations were still detectable, none reported pharmacokinetic parameter values of MPA. Nevertheless many of these studies were referred to as pharmacokinetic studies.

Table 2.1.2 Summary of relevant findings on MPA serum levels from key DMPA studies

Study	Peak MPA Conc.	Plateau or Trough MPA Conc.	Min detectable MPA Conc.	Effect of MPA on endogenous progesterone levels
Cornette *et al*, 1971 n=3 Determination of the conc. of MPA (Provera) after i/m administration	Fluctuating blood levels maximal at 2-15 days post inj.	Not reported	Not reported	Ovulatory status not returned beyond the 4th month post treatment as indicated by serum progestin levels
Kirton and Cornette, 1974 n=3 Examined relationship between peripheral concs. of MPA & progesterone after a single i/m inj. of 150mg of DMPA. Blood sampled prior to inj & post inj on Mon, Wed, Fri for 9 specimens, then weekly until return of ovulation	10-25ng/ml 5-20 days post inj.	5-10ng/ml by 30 days post inj. thereafter gradual ↓ for rest of study (260 days)	0.5ng/ml levels >0.5ng/ml found in all 3 subjects up to 185 days post inj.	Progesterone levels ↓ MPA conc. when progesterone rise first detected: 5.1, 0.8, <0.5ng/ml @ 203, 238 & 245 days post inj.
Jeppsson and Johansson, 1976 n=2 Measured MPA blood levels after i/m inj of 150mg DMPA	Maximum levels within first week after inj. Peak levels: **Subject 1**: ±4ng/ml (after 1st ever dose of DMPA) **Subject 2**: ±3ng/ml (after 20th inj. of DMPA)	Trough levels (at end of 12 week dosing period): **Subject 1**: 0.5ng/ml at end of 12 week dosing period **Subject 2**: 1ng/ml at end of 12 week dosing period	Not applicable – all had detectable conc.	<0.5ng/ml during treatment
Jeppsson *et al*, 1977 n=11 Women on long term treatment (6-18 doses) with DMPA 150mg i/m every 12th week. Blood samples taken 6-15 days after inj. & 12 weeks after inj.	One week after inj. 3.57±0.51ng/ml – the article doesn't indicate if this is the peak level	0.6±0.1ng/ml at end of 12 week dosing period	Not applicable – all had detectable concs.	<0.6ng/ml one week after inj. and at end of dosing period

Table 2.1.2 Continued

Study	Peak MPA Conc.	Plateau or Trough MPA Conc.	Min detectable MPA Conc.	Effect of MPA on endogenous progesterone levels
Ortiz *et al*, 1977 n=3 Measured serum MPA & ovarian function after 150mg of DMPA i/m. MPA levels measured daily x2 weeks, then 3x a week for 3mths, then weekly until undetectable	1-3ng/ml within 24h	◦ 1-1.5ng/ml for 2-3 mths ◦ 0.5ng/ml in 4^{th}-5^{th} mth. ◦ 0.2ng/ml in 6^{th} mth.	Undetectable @ <0.02ng/ml ± 7.5 – 9 mths after inj.	Rise in progesterone (luteal activity) only occurred when MPA <0.1ng/ml, 7-9 mths after inj.
Shrimanker *et al*, 1978 N=10 (Thai) Measured serum MPA 7 & 75 days after 150mg DMPA given i/m	7 days post inj.: Range: 1.75-9.0ng/ml Mean (SD): 3.56ng/ml (2.46)	75 days post inj.: Range: 0.680-2.600ng/ml Mean (SD): 1.25ng/ml (0.62)	Not reported	Not reported
Koetsawang *et al*, 1979 N=21 (Thai) Serum MPA levels measured 90 days after i/m DMPA 10 received only one inj. 90 days prior to blood sampling; 11 had received 8 consecutive doses	Not measured	**Levels 90 days post inj.** After 1^{st} ever dose: Range: <0.10-1.28ng/ml, Mean: 0.61ng/ml. After 8 consecutive doses: Range: 0.12-2.56ng/ml, Mean: 0.90ng/ml	2 had levels <0.1ng/ml 90 days post inj.	Not measured
Fotherby *et al*, 1980a n=20 (Thai) Measured MPA levels after different DMPA doses (25, 50, 100 150mg) on days 4-6 of cycle. Blood sampled 2x weekly for 1 cycle prior to & after inj for 6mths	For 150mg dose: Mean (SD): 8.3ng/ml (3.16)	No initial plateau, & relatively rapid decline.	Days MPA detectable with 150mg dose: Mean (SD): 92ng/ml (44.2)	Progesterone levels did not rise until MPA <100pg/ml, initial rise of progesterone 3.5 mths. after inj. of 150mg of DMPA

Table 2.1.2 Continued

Study	Peak MPA Conc.	Plateau or Trough MPA Conc.	Min detectable MPA Conc.	Effect of MPA on endogenous progesterone levels
Fotherby *et al*, 1980b [Only MPA findings summarized] n=8 (4 Indian & 4 Swedish) Comparative pilot study on PK & PD properties of DMPA & NET-EN. DMPA given on day 1-5 of cycle Blood sampled weekly 1 cycle prior to & after inj. until resumption of ovulation or 6mths post inj.	Highest concentrations in 1st 3 weeks: 1-7ng/ml	Not specifically reported	Undetectable <100pg/ml at 120-200 days post inj. except in 2 slow absorbers	Not specifically reported
Bassol *et al* (1984) n=20 (Mexican) Subjects randomly assigned to 4 groups & different DMPA doses given to each group (25, 50, 100 150mg) DMPA given on day 4-6 of cycle. Blood sampled 2 weekly for 6mths	Not specifically reported Graphically presented data indicate levels ± 1ng/ml with dose of 150mg	Not reported	MPA remained detectable after 140 days with 150mg dose	Not specifically reported
Lan *et al* (1984) n=8 (Swedish) Single dose (150mg) of DMPA given MPA levels measured 3 times a week during pre-treament (control) cycle, then daily during post inj. weeks 14-17, 22-25, and 30-33.	Not measured	MPA levels @ 14th week post inj. ranged from 0.9-2.24 nmol/L*	MPA was undetectable between 17 & 24 weeks in 4 cases, and after week 33 in 4 cases. (lower level of detection = 250pmol/L*)	Progesterone profiles suggested that ovulation occurred between 20 and 49 weeks. Based on progesterone profiles, ovulation was judged to have occurred in 7 of the women when MPA levels were undetectable; in one woman MPA levels were very low, but still detectable

Conc.=concentration; inj.=injection; i/m= intramuscular; mth=month; PK=pharmacokinetic; PD=pharmacodynamic
*1 nmol/L=0.3865ng/ml

2.1.1.4 Distribution and Metabolism

MPA circulates in the blood bound by protein, especially serum albumin (Akpoviroro *et al* 1981; Pérez-Palacios *et al*, 1981; Garza-Flores *et al*, 1992; Martindale, 2002). It has a low affinity for sex hormone-binding globulin (SHBG) (Garza-Flores *et al*, 1992; Gibbon and Swanepoel, 1995) and is also not bound to corticosteroid-binding globulin (Akpoviroro *et al,* 1981; Pérez-Palacios *et al*, 1981; Garza-Flores *et al*, 1992). These authors point out that the way in which MPA is transported in the blood is unusual and differs from that of natural progesterone. It is however unclear why MPA differs from progesterone in this way.

Unchanged MPA is the active molecule, and is responsible for the contraceptive effect of DMPA (Akpoviroro *et al* 1981; Garza-Flores *et al*, 1992). MPA is metabolized in the liver and excreted mainly as glucuronide conjugates in the urine and faeces (Martindale, 2002; USP DI, 2002).

Ohtsu T *et al* (1998) conducted a study comparing the pharmacokinetics of high oral doses of MPA (1200mg), administered daily to women being treated for cancer, versus lower doses (600mg). Intersubject variability in the pharmacokinetic parameters (area under the concentration versus time curve, peak plasma concentration, mean minimum steady-state concentration) was found. The authors speculated that MPA is metabolised in a similar way to progesterone by the cytochrome P450 system. They point out that marked interindividual variability in P450 of the small bowel and liver has been reported, and endogenous and exogenous factors (such as age, blood pH, concomitant diseases and drug therapy, meal preparation procedure, nutritional habits and smoking) are thought to

contribute to P450 system heterogeneity. If MPA is metabolized by the cytochrome P450 system it might explain the interindividual variability in the pharmacokinetics of MPA.

Population differences in the metabolism of contraceptive steroids have also been suggested (Fraser and Weisberg, 1981). However, in an extensive review of DMPA which was published in 1981, these authors pointed out that, given that DMPA had been available for a considerable length of time, surprisingly little is known about its metabolism and excretion. Over two decades later, there is still very little published on the metabolism of DMPA.

The efficacy of DMPA may be impaired by the concomitant administration of enzyme-inducing agents such as rifampicin, phenytoin, meprobamate and alcohol. In cases where these drugs are used with DMPA it is recommended that DMPA be administered every 8 weeks instead of every 12 weeks (Gibbon, 2000; National Department of Health, 1998).

2.1.1.5 Elimination

MPA is rapidly cleared from the bloodstream and its prolonged presence in the blood is said to be due to slow release from the injection site (Ortiz *et al*, 1977). Gupta *et al,* (1979) reported a high metabolic clearance rate of 1668 liters per 24 hours after 50 μCi [^{3}H]medroxyprogesterone acetate was administered intravenously. This is lower than for progesterone but still shows rapid metabolism (Fraser and Weisberg, 1981). In the studies summarized in Table 2.1.2 the half-life ($t_{½}$) of DMPA is not provided. However, Garza-Flores *et al* (1994) described a highly variable DMPA half-life in reviewing unpublished data from some of these studies, with $t_{½}$ varying from 24.1days to 112.2 days (Table 2.1.3). The $t_{½}$ was reported to vary between population groups, with a shorter $t_{½}$ for Thai

women than for the Mexican women (Table 2.1.3). Likewise the area under the curve (AUC) was also highly variable between studies and populations (Table 2.1.3).

Table 2.1.3 Mean pharmacokinetic parameters of DMPA (150mg) in 3 studies undertaken among Thai and Mexican women

Study (n)	T_{max} (days)	C_{max} nmol/L (≈ng/ml)*	t½ (days)	AUC nmol.day/L	T_c (days)
Thai (10 thin)	7.0±3.2	16.5±6.1 (6.4)	27.4±22.8	606±307	160±73
Thai (10 obese)	8.6±4.9	18.2±15.7 (7.0)	30.2 ±18.1	582±326	145±42
Mexican (5 thin)	22.4±14.5	2.3±0.9 (0.9)	56.4 ±42.8	96±22	171±95
Mexican (5 obese)	8.8±3.0	2.4±0.8 (0.9)	112.2±117.8	93±25	305± 274
Thai (5)	-	21.5±8.3 (8.3)	24.1±23.6	558±79	92±44
Mexican (4)	-	3.4±5.2 (1.3)	62.5±23.7	259±152	187± 85
Thai (14)	8.0±3.7	25.9±16.3 10.0	24.3±18.1	606±352	143±78

Adapted from Garza-Flores *et al* (1994). Primary data from these studies appear to be unpublished
*1 nmol/L=0.3865ng/ml
C_{max}=maximum serum concentration; t½=half-life; AUC=steady-state area under the serum concentration-time curve; T_c=time to reach serum concentration below limit of detection (<0.259)

According to the USP DI (2002) and the US approved physician prescribing information published on the manufacturer's website (Pharmacia and Upjohn, 1999), the apparent t½ for the 150mg intramuscular dose is approximately 50 days. The t½ after oral administration is reported to be 30days (USP DI 2002).

Trough levels of MPA and time taken for MPA levels to become undetectable, as reported in the published literature, are summarised in columns three and four of Table 2.1.2. Most of these studies clearly illustrate that MPA concentrations above the level required for contraceptive efficacy (0.1ng/ml) were attained up to and beyond the DMPA dosing interval of 12-13 weeks. Circulating levels of MPA could be detected up

to 9 months following injection of DMPA (Table 2.1.2). For instance, Kirton and Cornette (1974) found that, at the time that a rise in progesterone serum concentrations was first detected, MPA concentrations in the study's 3 subjects were 5.1, 0.8, and <0.5ng/ml and occurred at 203, 238 and 245 days after injection of MPA. Levels above the minimal detectable concentration of 0.5ng/ml were found in all 3 subjects up to 185 days post injection. Ortiz *et al* (1977) reported that MPA became undetectable (<0.02ng/ml) seven and a half to nine months post injection. Kirton and Cornette (1974) concluded that a single intramuscular dose of 150mg of DMPA inhibited formation of a functional corpus luteum for ≥200 days. Similarly, Lan *et al* (1984) deduced that DMPA suppressed ovulation for at least four to five months.

However in one study (Fotherby *et al* 1980a), MPA was detectable for more than 100 days in only 1 of 5 women who received 150mg of DMPA, it was detectable for about 90 days in 2 subjects and was undetectable by days 55 and 64 in 2 subjects. The authors of this study pointed out that their findings were not consistent with other studies which had shown detectable levels of MPA for 200 days or more. Nevertheless, luteal function was inhibited in all five subjects for longer than the 90 day dosing interval. Mishell (1996) commented on the different pattern of MPA clearance found in the Fotherby *et al* study (1980a) and speculated that the differences could be attributed to manipulation of the injection site, causing more rapid dispersion of MPA.

Four studies have reported specifically on serum or plasma MPA levels at the end of the DMPA dosing interval. In the first study of two women, the MPA levels 12 weeks after injection were reported to be approximately 0.5ng/ml in a woman who had had one previous injection, and 1.0ng/ml in a woman who had received her 20th injection

(Jeppsson and Johansson, 1976). The second study of 11 women who had received between 6 and 18 injections, found a mean (SD) MPA level of 0.6 (±0.1)ng/ml 84 days after the last injection (Jeppsson *et al*,1977). In the third study, amongst Thai women who had received only one injection (n=10) 90 days earlier, plasma MPA levels ranged between <0.10ng/ml and 1.28ng/ml, with a mean of 0.61ng/ml. In those who had received 8 consecutive doses (n=11) the range was 0.12ng/ml to 2.56ng/ml, with a mean of 0.90ng/ml. The difference between the group receiving multiple injections and the group receiving only one injection was not statistically significant (Koetsawang *et al,* 1979). The fourth study by Lan *et al* (1984) MPA levels of 8 Swedish women ranged between 0.9 and 2.24 nmol/L (≈0.35-0.87ng/ml)14 weeks after injection.

2.1.1.6 Variability

Large intraindividual, interindividual and interpopulation differences in pharmacokinetic parameters of contraceptive steroids have been reported (Aedo *et al*, 1985; Garza-Flores *et al*, 1994; Sang, 1994). The variability has been attributed to factors such as body weight or size, ethnic differences in fat distribution and storage of steroid in fat cells, levels of protein such as sex hormone binding globulin, genetic factors, dietary factors and drug interaction or disease.

Interindividual Variability

Koetsawang *et al* (1979) describes the interindividual variability in 21 Thai women, whose MPA levels were found to vary from 100 to 2560 pg/ml, (mean = 897 pg/ml) 90 days after DMPA injection. Fotherby *et al* (1980b) found that DMPA became undetectable by between 120 and 200 days after injection in all but 2 of 8 women studied. Levels in these 2 women were still detectable beyond 200 days after injection and it was

postulated that these 2 women, an Indian and a Swede, absorbed DMPA very slowly. Several review articles also comment on the interindividual variability of MPA levels in DMPA users (Sang, 1994; Kaunitz, 2000). Sang (1994) cites personal communication with Dr Odlind of Uppsala University, Sweden, who found a significant negative correlation between peak value and body weight ($p<0.05$), and area under the curve (AUC) and body weight ($p<0.02$), in a pharmacokinetic study of women using two DMPA preparations (Gestapuran depot and Depo-Provera). Lan *et al* (1984) also comment on the interindividual variation in return of ovulation, metabolism and elimination of MPA amongst the 8 Swedish women they studied. However, in this study no correlation was found between the obesity index of the subjects and the time taken for MPA levels to become undetectable.

Rahimy *et al* (1999b) studied the pharmacokinetics of the combined injectable containing 25mg of MPA and 5mg of estradiol cyprionate (Lunelle^{TM}) administered every 28 days. They found that trough levels at the end of the dosing interval were consistently above the threshold MPA concentrations of 0.10-0.20ng/ml necessary to suppress ovulation. However the authors of this paper did not recommend lowering the dose of MPA because of substantial interindividual variability in levels of MPA, especially at the end of the dosing interval (range of individual concentrations at day 28 after the third monthly injection: 0.24-0.71ng/ml). Rahimy *et al* (1999a) found that while MPA tended to be absorbed more quickly by thin women, the average trough MPA levels were higher in thin than in obese women ruling out the possibility of reduced efficacy in thinner women.

Interpopulation Variability

Evidence of differences in interpopulation MPA metabolic clearance rates and disposition has been shown (Garza-Flores *et al*, 1992; Garza-Flores *et al*, 1994; Sang, 1994). A study amongst 20 Thai women (Fotherby *et al*, 1980a) showed a significant difference in the length of DMPA induced ovarian suppression at all four dosing regimens used, compared with a similar study undertaken amongst 20 Mexican women by Bassol *et al* (1984). A longer delay in resumption of ovulation was observed in the Mexican women. The radioimmunoassay method described by Shrimanker *et al* (1978) was used in both studies (Fotherby *et al*, 1980a; Bassol *et al*, 1984).

Ovulation was inhibited in all Mexican women for at least 3 months, even at the 25mg dose. The authors point out that this was in keeping with the longer disappearance of MPA from the serum in this population (Bassol *et al*, 1984). Garza-Flores (1994) and Sang (1994) reviewed MPA data on Thai and Mexican women and conclude that, for Thai women, the serum MPA peak was significantly higher and reached earlier, serum concentrations of MPA decreased more quickly and ovulation returned sooner. Sang (1994) comments further that these differences could not be explained by body weight differences only.

In the study amongst four Swedish and four Indian women, progesterone levels amongst the Indian women suggested an early return of some luteal function within 73 days with MPA levels > 600pg/ml (Fotherby *et al*1980b). The Swedish women did not ovulate until more than 156 days after injection when MPA levels were undetectable. However the Indian women ovulated within 73 days of injection when MPA levels were still over 0.6ng/ml. No significant differences were found between the two groups for time taken

for plasma MPA to be undetectable, however differences in return to luteal function were significant (Fotherby *et al* 1980b). Few other studies comparing interpopulation variability have been published and the Fotherby *et al* (1980a) and Bassol *et al* (1984) studies are cited repeatedly in reviews of the pharmacokinetics of DMPA (Garza-Flores *et al*, 1992; Garza-Flores *et al*, 1994; Sang, 1994).

Findings from a large randomized multicentred comparative trial on the use-effectiveness of 200mg of NET-EN and 150mg DMPA, with both preparations given every 12 weeks, showed that the body weight of NET-EN users who became pregnant was significantly lower than those who did not conceive (World Health Organization, 1977). In this study, 24 NET-EN users (n=832) and 4 DMPA users (n=846) became pregnant. As a result of these findings, the NET-EN dosing interval was reduced to every 2 months and studies on the influence of weight on the pharmacokinetics of DMPA and NET-EN were undertaken. In a review of the studies amongst DMPA users of different populations, no significant differences were observed between fat and thin women, but a tendency for the thin women to absorb the hormone more rapidly was found (Garza-Flores *et al*, 1994). However peak values of MPA were found to be "almost an order of magnitude greater in Thai women than in Mexican women, and the area under the curve was some six-fold greater" p.72 (Garza-Flores *et al*, 1994). The reviewers of these studies (Garza-Flores *et al*, 1994) postulated that differences in fat distribution and adipocytic metabolism are a major influence on the pharmacokinetics of the long-acting hormonal contraceptives and explain the pharmacokinetic differences between Thai and Mexican women. A WHO study on the combined injectable containing 25mg of MPA and 5mg of estradiol cyprionate (HRP112) also found differences in the pharmacokinetics of MPA between Mexican and Thai women. The implications for South African women are important, given their morphology.

Since no significant differences were found in serum levels of MPA when DMPA was given in doses of 100 or 150mg, the possibility of reducing the dosage of DMPA from 150mg to 100mg, especially for Mexican women, was considered (Garza-Flores *et al*, 1994). This led to a multi-centred study comparing the efficacy and side effects of doses of 100 and 150mg of DMPA (World Health Organization, 1988). Little difference was found between the 2 groups. However, because of the occurrence of 2 pregnancies in the 100mg group (n=609), there was a reluctance to reduce the dose. Garza-Flores *et al* (1994) in reviewing these findings suggested that improved formulation of DMPA may, in the future, result in dose reduction. The 2 women, 1 from Jamaica and 1 from the Philippines, who conceived whilst taking 100mg of DMPA had a Quetelet's Index[23] of 16.7 and 21.3 respectively. These values suggest that these 2 women were thin as they are consistent with the Quetelet's indices found in women classified as thin in Fotherby and Koetsawang's (1982b) study of the metabolism of DMPA amongst thin and obese women. It is of note however that Fotherby and Koetsawang (1982b), in comparing the thin (n=10) and obese (n=10) women, found no difference in serum levels of DMPA, nor in the rate of return of ovarian, follicular and luteal function.

Garza-Flores *et al* concluded that, despite the small sample sizes and wide interindividual variability, Thai women irrefutably absorb DMPA more rapidly, resulting in higher peak serum concentration levels and more rapid elimination than Mexican women. They suggest that these differences appear to be due to "ethnic difference in fat distribution and the behaviour of fat cells in steroid storage" (Garza-Flores *et al*, 1994, p. 81).

[23] Quetelet's Index: weight divided by the square of height (W/H^2)(Fotherby and Koetsawang, 1982b, RM61)

Differences were also observed between Thai and Mexican women in regard to the pharmacokinetic parameters of MPA when given in combination with estrogen. Thai women exhibited higher peak serum concentrations, which also occurred earlier (WHO 1987). In reviewing these findings, Garza-Florez (1994) calls for further study of population differences in MPA pharmacokinetics.

2.1.1.7 Combination Progestogen/Oestrogen Injectables

In reviewing the pharmacokinetics of DMPA it is appropriate to note that there are published studies on the pharmacokinetics of combined progestogen/oestrogen injectables, including a number of studies undertaken in the 1980s. They comprise a combination of synthetic progestogens and short or medium acting oestrogen, and are administered on a monthly basis. Amongst these were studies published by Fotherby *et al* (1982a), Aedo *et al* (1985) and the World Health Organization (1987). Some pharmacokinetic parameters for MPA were reported in these two studies (see Table 2.1.4).

Table 2.1.4 Comparison of mean pharmacokinetic parameters of MPA reported in studies of combined progestogen/oestrogen injectables

Pharmacokinetic Parameters	**Aedo *et al* 1985** 8 Swedish ♀	**WHO 1987** 7 Thai ♀ 8 Mexican ♀	**Zhou *et al* 1998** 9 Chinese ♀	**Rahimy *et al* 1999b** 14 US ♀
	Cycloprovera	HRP112	Cyclofem®	Lunelle™
Dose	25mg MPA & 5mg estradiol cyprionate	25mg MPA & 5mg estradiol cyprionate	25mg MPA & 5mg estradiol cyprionate per 0.5ml (post 6th injection)	25mg MPA & 5mg estradiol cyprionate per 0.5ml (post 3rd injection)
T_{max} (days)	not reported	2.3 (Thai) 7.8 (Mexican)	4.3	3.5
C_{max} (ng/ml)	1.12*	3.6 (Thai) 1.5 (Mexican)	2.14*	1.25
$C_{day\ 28}$ /trough (ng/ml)	0.28*	not reported	0.93*	0.47
$t_{½}$ (days)	14#	12.1/15.4	12#	14.7

Notes: *Values converted from nmol/L (1 nmol/L=0.3865ng/ml); # $t_{½}$ reported in Rahimy *et al*, 1999b
T_{max}= time to reach maximum concentration; C_{max}=maximum serum concentration; AUC=steady-state area under the serum concentration-time curve; $C_{day\ 28}$ = trough; $t_{½}$=half-life

Relevant findings on MPA pharmacokinetics from 2 recent studies of the combined injectable contraceptives, Cyclofem® and Lunelle™ are summarized in Table 2.1.5 and Table 2.1.6.

It should be noted that the recommended contraceptive dose of MPA for the combined injectable agents is much lower (25mg) than for the MPA-only injectables (150mg), and that they are given in combination with oestrogen (Zhou *et al*, 1998; Rahimy *et al*, 1999b) on a monthly basis. Despite the lower dose of MPA in combined injectables, similar peak MPA concentrations to the DMPA-only products were found (Tables 2.1.2, 2.1.4, 2.1.5 and 2.1.6). Studies on combined injectables (MPA/estradiol cyprionate) give a half-life for MPA ranging from 12 to 15.4 days (Table 2.1.4).

Table 2.1.5 Summary of mean pharmacokinetic parameters of MPA after the 6th injection of Cyclofem®

Study	T_{max} (day)	C_{max} (nmol/L)*	AUC_{0-28} (nmol·day/L)*	MRT (days)	$C_{day\ 28}$ [trough] (nmol/mL)
Zhou *et al* 1998 n=9 (Chinese) Cyclofem® given i/m every month for up to a year Dose: 25mg MPA & 5mg estradiol cyprionate/0.5ml Blood sampled immediately prior to injection & on days 1,3,5,7,14, 21, 28 during 1st, 6th, 12th treatment cycle	4.3 ±2.2	5.54 ± 1.79 (≈ 2.14 ng/ml) Wide inter-individual variation	95.45 ± 26.56 Wide inter-individual variation	12.77 ± 0.47	2.43 ± 0.70 (≈ 0.93ng/ml)

T_{max}= time to reach maximum conc.; C_{max}=maximum serum conc.; AUC=steady-state area under the serum concentration-time curve; MRT=mean residence time, indicating the duration necessary for 63.5% of a given dosage to leave the body from time of administration: MRT=AUMC/AUC; AUMC=area under the moment curve; C_{day28}=day 28 serum conc

Table 2.1.6 Summary of steady-state pharmacokinetic parameters of MPA after the 3rd monthly injection of Lunelle™

Study	T_{max} (day)	C_{max} (ng/ml)	AUC_{0-28} (ng·day/ml)	$t_{½}$	$C_{day\ 28}$ (ng/ml)
Rahimy *et al*, 1999b n=16 (US); 14 completed study; 13 white, 1 black Lunelle™ given i/m every 28 days x 3 months. Dose: 25mg MPA & 5mg estradiol cyprionate/0.5ml Blood sampled on days 3-7,12,14, 18,21,28 prior to inj. Then days 1,29,57 after first inj. Then days 58,60,62,64,67,69,71,75,78,85 and weekly until day 141.	Mean: 3.5 SD: 2.9 Range:1-10	Mean: 1.25 SD: .33 Range: 0.94-2.17	Mean: 21.51 SD: 3.98 Range:14.44-27	Mean: 14.7 SD: 7.8 Range: 6.2-36.0 Took 63-84 days to drop below 0.1-0.2ng/ml (i.e. to fall below the lower limit of quantitation)	Mean: 0.47 SD: 0.14 Range:0.24-0.71

T_{max}= time to reach maximum concentration; C_{max}=maximum serum concentration; AUC=steady-state area under the serum concentration-time curve; $t_{½}$=half-life; $C_{day\ 28}$ = trough (post 1st dose); SD= Standard Deviation

2.1.2 DETERMINATION OF PHARMACOKINETIC PARAMETERS

A number of methods can be used to estimate pharmacokinetic parameters including compartmental modelling and noncompartmental methods. With compartmental modelling methods there are two broad approaches: the traditional methods using rich experimental data, and the alternative population approaches which use sparse routine patient data (Sheiner and Beal, 1980a).

2.1.2.1 The Traditional Approach

Traditionally, pharmacokinetic studies involve a small number of subjects with a relatively large number of plasma concentration values (Whiting and Kelman, 1985). A limitation of this approach is that the numbers of representative patients may be insufficient and results may be imprecise with a biased estimate of variability (Whiting and Kelman, 1985). Traditional pharmacokinetic studies are also known as the standard two-stage (STS) approach (Sheiner and Beal, 1980b) when attempting to relate parameter values to other patient factors such as weight. The pharmacokinetic parameters of an individual are calculated by analysing data collected from that individual using weighted or un-weighted non-linear regression with the least-squares criterion. Least-squares regression is used to calculate the relationship between the pharmacokinetic parameters and physiological factors (Sheiner and Beal, 1980a; Sheiner and Beal, 1980b).

2.1.2.2 The Population Approach

The alternative approach, a population approach, can be successfully used to estimate population pharmacokinetic data from sparse clinical data, obtained from a large number of

individuals, during routine care (Sheiner *et al* 1977, Sheiner and Beal, 1980a, Sheiner and Grasela, 1991; Whiting and Kelman, 1985). Typically one or two concentration values are obtained for each subject. This approach provides results which are highly representative of the subjects being studied with the population being the unit of analysis rather than the individual (Whiting and Kelman, 1985).

- "The principle aim of population pharmacokinetic analysis is to account for the inherent kinetic variability within a population of patients in terms of readily identifiable factors which may be physiological, pathological, environmental or genetic." (Whiting *et al*, 1986, p.398). Population pharmacokinetics describes this variability in terms of fixed effects (true pharmacokinetic variability) and random effects (inter- and intra-individual variability) (Whiting *et al*, 1986) in the form of nonlinear mixed effect modelling.

Data required for population pharmacokinetic analysis include:

- Kinetic data: dose, route of administration, dosage interval, whether steady-state has been achieved, details of dosage history, concentration measurements and time(s) since previous dose (Whiting *et al*, 1986).
- Demographic data: age, sex, weight, height, race, patho-physiologic status, nutritional status, smoking habits, alcohol consumption, co-medication, biochemical and haematological indices (Whiting *et al*, 1986).

The population approach to estimating the pharmacokinetic parameters of DMPA allows for the use of data collected from women routinely using the injectable contraceptive, thus generating pharmacokinetic parameters more likely to be representative of injectable users.

Further, as the subjects are comprised of women from the general population, the possibility of a chance discovery of a previously unknown influence exists. The population approach is also a more ethical approach as the women recruited into the study are likely to have chosen to use the method prior to recruitment and few blood samples are required per subject (Whiting *et al*, 1986; Wählby, 2002).

The main limitations of the population approach are:

- A sophisticated statistical approach is required to analyse the data
- Bias may be introduced due to the effects of unknown concomitant variables (e.g. an undisclosed drug interaction) that are correlated with included variables
- Model misspecification may lead to erroneous results (Sheiner *et al* 1977; Sheiner and Beal, 1980a).

Sang (1994) has highlighted the need for population pharmacokinetic studies of steroidal contraceptives in order to assess regional or population differences. He questioned the clinical significance of comparisons made between regions or populations where a population approach has not been adopted and stresses the importance of collecting data in the population actually using the contraceptives. An extensive literature search has revealed no published population pharmacokinetic studies of injectable hormonal contraceptives. In South Africa, studies of this kind are of particular importance since injectable methods are extensively used, particularly by African women. In addition, and unlike most other places in the world, injectables are widely advocated for use in young women.

Population pharmacokinetics describe the pharmacokinetic variability of drugs in terms of mixed effects, that is, a combination of fixed and random effects (Whiting *et al* 1986):

- Fixed effect parameters consist of mean values of pharmacokinetic parameters such as drug clearance (CL), volume of distribution (V_d), absorption rate constant (KA) and bioavailability (F), as well as the relationship to patient factors such as weight, age and creatinine clearance.
- Random effect parameters quantify the interindividual error and the residual error.

Pharmacokinetic analyses have advanced due to the development of appropriate computer software capable of analysing population pharmacokinetic data (Whiting *et al*, 1986). One such programme, NONMEM (Nonlinear Mixed Effects Model) (Beal and Sheiner, 1980; Beal and Sheiner, 1992) is discussed here, as this programme was used to test models describing MPA pharmacokinetic behaviour in the present study. The statistical model used in the NONMEM programme is based on the premise that individual pharmacokinetic parameters of a patient population arise from a distribution which can be described by the population mean and the interindividual variance (Whiting and Kelman, 1985).

Non-linear mixed effects models consist of three sub-models (Wählby, 2002):

- The structural or pharmacokinetic sub-model describing the main tendency in the data.
- The statistical sub-model which includes the models for interindividual and residual variability.
- The covariate sub-model describing relationships between covariates and model parameters by means of fixed effects parameters.

Each sub-model is selected separately and the model building process usually proceeds in a step-wise fashion (Beal and Sheiner, 1992; Ette and Ludden, 1995).

NONMEM can also be used to investigate the possibility of inter-occasion variability (IOV) which occurs when a parameter (e.g. clearance) varies within subjects between study occasions (Karlsson and Sheiner, 1993). Failure to identify IOV may result in model misspecification, biased parameter estimates and false co-variate relationships (Karlsson and Sheiner, 1993).

2.1.3 OBJECTIVES

As discussed in the above review few studies have been undertaken on the pharmacokinetics of DMPA. Sample sizes are small and assays have been inconsistent or not specific, sometimes measuring other substances in addition to DMPA. Despite the widespread use of DMPA in South Africa there are no published pharmacokinetic parameters for DMPA amongst South African DMPA users or amongst African DMPA users. Several international studies highlight the interindividual variability in the pharmacokinetics of DMPA. Interpopulation variability has been suggested by some researchers and has been attributed to differences in fat distribution and fat cell storage of MPA amongst different ethnic groups, with women with heavier builds showing a tendency to have more prolonged MPA levels and longer delays in resumption of ovulation than women of a lighter build. These population differences are less important when considering the efficacy of DMPA in the standard dosing regimen, but may be important considerations for those women who experience intolerable side effects with DMPA, like menstrual disturbances and/or a long delay in return to fertility.

Since South African DMPA users tend to be of a heavy build, it is possible that at the recommended dose, DMPA may remain in the body for longer periods of time than expected.

While there have been no population pharmacokinetic studies of MPA, this approach may be particularly useful in estimating pharmacokinetic parameters for this substance. Accordingly the objectives of this study were to:

- Measure MPA levels in South African DMPA users
- Use the population approach to:
  - determine the pharmacokinetic parameters, clearance and volume of distribution
  - investigate the possible influence of covariates such as weight, BMI and ethnicity on the pharmacokinetic parameters of MPA.

CHAPTER 2.2 METHODS

This study was undertaken at family planning clinics in Durban, South Africa amongst women routinely attending for family planning services.

2.2.1 ETHICAL APPROVAL AND CONSENT

The study was approved by the ethics committees of the University of Durban-Westville (Ethics approval Number 96014B) and the Nelson R Mandela School of Medicine of the University of Natal (Ethics clearance number H150/00). Permission to conduct the study at Durban local health authority family planning clinics was obtained from the Durban City Medical Officer of Health, the Deputy Medical Officer of Health, and the Chief Nursing Sister of the Durban City Health Department.

Prior to commencing the study, workshops were held with all nursing staff of the three clinics involved to develop the interview schedule. They received comprehensive training about the study objectives, protocol and procedures. Women who were requested to participate in the study were provided with verbal and written information about the study (in English and/or Zulu). They were assured that participation was voluntary and that all information would be confidential. Each study participant signed a consent form provided by the Durban City Health Department in accordance with the local health authority protocol for research being conducted at their facilities. They were assured that they could terminate participation in the study at any stage without their subsequent management being compromised. Client information sheets and instructions to family planning nursing staff involved in the study are shown in Appendix 2.2.1. All information collected has been stored and used in a manner which ensures the protection of participants' rights to confidentiality, anonymity and privacy.

2.2.2 STUDY POPULATION

Study participants were recruited at three municipal family planning clinics in Durban. Quota sampling (Bernard, 1994) was used to select the three clinics, Lancer's Road, Chatsworth and Bluff, in order to ensure a spread of ethnic groups (African, Indian, Coloured and White). After consultation with internationally recognised pharmacokineticists, and taking into account practical considerations such as the need for minimal disruption of the clinic and the high cost of the blood assays, a sample size of 120 was decided on (40 women per clinic). Only women who were already acceptors (new or current users) of the depot medroxyprogesterone acetate (DMPA) product Depo Provera® (Pharmacia & Upjohn) were eligible for recruitment. Starting in October 1996, all acceptors attending the clinics were invited to participate in the study. Clients were recruited until the target of 40 women per clinic was reached and by the end of November 1996, 122 Depo Provera® users had been recruited.

2.2.3 DRUG ADMINISTRATION

The dosage regimen for DMPA at the clinics is 150mg every 12 weeks given by intramuscular injection into the gluteal or deltoid muscle.

2.2.4 DATA COLLECTION

The study involved the collection of:

- Demographic data including: age, weight, height, race, pathophysiologic status, nutritional status, smoking habits, co-medication, blood pressure measurements, biochemical and haematological indices, and side effects experienced with DMPA use.
- Drug information including: dose, dosage interval, time since previous dose, duration of use.

- Blood samples to assay for MPA.

The client interviews were conducted and blood samples drawn by the clinic nurses. The interview schedule can be found in Appendix 2.2.2. Data collection was completed in March 1997. Blood samples were drawn from each woman every four weeks over a period of 4 months. For repeat users of DMPA, the first sample was drawn on the day of return to the clinic for their next dose, that is approximately 12 weeks after their last dose. Thereafter, they were requested to return to have further samples taken four and eight weeks later. For new users, blood samples were drawn on the day of recruitment and four and eight weeks after receiving their first injection. In the case of early study recruits, a fourth blood sample was drawn 12 weeks after recruitment. Even if a women returned early or late for her scheduled appointments, a blood sample was taken. A detailed interview was conducted with each woman at each visit (Appendix 2.2.2). Where necessary, the study clinic staff followed-up telephonically to remind clients to return to have blood samples taken. Participants were given a ZAR20 grocery voucher at each blood sampling appointment to cover transport costs. Cash reimbursement could not be provided for security reasons.

On the day of sampling blood samples were stored in the clinic refrigerator. They were then collected from the family planning clinics on a daily basis by research staff, and transported to the university laboratory in cooler boxes. After centrifuging at 3700 revolutions per minute for 10 minutes, the resultant serum was stored at –70°C, until couriered in dry ice by DHL Worldwide Express to Immunometrics Ltd., London, United Kingdom for analysis. The samples were packed in dry ice with the assistance of FARMOVS Research Centre at the University of the Free State.

2.2.4.1 Exclusions

The following subjects were excluded:

- one woman from whom the clinic sister was unable to draw a blood sample
- three first-time users who did not return for further appointments thus no serum samples were obtained
- insufficient samples were available for four women (Immunometrics,1999: MPA laboratory assay results, Final Report)
- the interview schedule for one woman was lost by the clinic staff

Thus nine women were excluded, leaving 113 women in the study.

2.2.5 MPA ANALYSIS

MPA was measured using a Tritium-labelled radioimmunoassay (RIA) with charcoal separation developed for the World Health Organization Special Programme of Research in Human Reproduction,[24] as described by Ashan *et al* (1998). The analytical work was performed by Immunometrics Ltd., London, United Kingdom in 1999, and detailed in a report from which relevant extracts on the quality control and assay procedures employed are provided below:

2.2.5.1 Summary of RIA

Calibration: Steroid-free human serum with preservative containing medroxyprogesterone acetate solution (concentration of MPA solution added to serum

[24] Recognising the difficulty in interpreting results from different studies, the World Health Organization's Task Force on the Long Acting Systemic Agents for Fertility Regulation has produced standardised protocols and matched reagents for radioimmunoassay of synthetic progestagens [Ashan *et al, 1998]*.

confirmed by UV Absorbance).

Analytical sensitivity: 96 pmol/L. Defined as 3 x SD of measurement of zero dose, i.e. lowest dose analytically distinguishable from zero.

Detection limit: 102 pmol/L (0.04ng/mL). This is the lowest level for which Immunometrics Ltd consider the assay provides a reliable quantitative result, and is the lowest point on the standard curve.

Cross reaction: (Estimated at 50% suppression of zero binding)

Compound	*% Cross- Reaction*
Medroxyprogesterone acetate	100
17α-hydroxy-6 α -methylprogesterone	0.02
6-dehydroprovera (megestrol acetate)	9.5
6β-hydroxyprovera	64.6
20α-dihydroprogesterone	None detected
20β-dihydroprogesterone	None detected
17α-hydroxyprogesterone	None detected

Precision: *Intra-assay*:
% Coefficient of variation (CV) of duplicate dose
(Calculated by data processing programme from all assays performed for Study)

101 pmol/L	21.0%
233 pmol/L	10.0%
535 pmol/L	5.7%
1231 pmol/L	4.5%
2143 pmol/L	4.9%
4925 pmol/L	7.3%

Inter-assay:
Experimental % CV measured using QC pools
(Each pool included twice in each assay, data from 11 assays)

300 pmol/L	8.8%
750 pmol/L	6.9%
2000 pmol/L	6.5%

The full assay protocol and reagent batches used in this study are documented in the Final Report Appendices (Immunometrics, 1999).

2.2.5.2 Quality Control Materials

In all assay batches, medroxyprogesterone acetate was measured in 3 different Quality Control (QC) Pools which cover the range of the standard curve. QC pools were prepared by addition of medroxyprogesterone acetate solution to steroid-free human serum.

2.2.5.3 Quality Control and Acceptance Criteria

Data processing programme

Beta-counts measured were entered into the Data Processing Programme — the programme used was the WHO Immunoassay Program, written by PR Edwards (Department of Molecular Endocrinology, University College London Medical School, London). Results were calculated in pmol/L.

All data entry stages were checked for all data points, and any errors corrected.

Standard curve fitting

Each point of the standard curve was measured in duplicate in every assay. The standard curve was fitted from the data using a single-binding site model. All points of the standard curve were used in curve fitting, and none were dropped in order to improve the curve fit.

Subject samples and QC pools

Samples were stored at -20^{0}C until analysis. Samples were identified by study number and date of visit. All subject samples and QC pools were assayed in duplicate. Any duplicate results identified by the data processing programme as poor replicates (defined as observed SD more than three times the SD predicted at that dose) were re-assayed until results met this limit. Of all samples in the study, 7 were identified as poor replicates and re-assayed.

Dose estimates above the highest standard are not reported. 15 study samples gave results above the highest standard dose. These samples were re-assayed after dilution in zero standard (steroid-free human serum).

Three samples with high results within the standard range (near the highest standard dose) were assayed at several dilutions (i.e., 1:2, 1:4, 1:8 sample:zero standard by volume) to establish linearity of results on dilution.

The dilution of the high samples was selected so that the diluted result fell within the most precise dose range of the precision profile, i.e., approximately 800 to 2500 pmol/L. This was the 1:5 dilution. Reported results were corrected for dilution.

All samples from a subject (except poor replicates or high dose samples as specified in the previous paragraphs) were assayed in the same assay batch to minimise the effects of between batch bias.

QC pools were assayed in duplicate at the beginning and end of each assay. Three pools were used in this study. Target values and acceptance criteria are listed in Table 2.2.1.

QC pools were prepared by adding a solution of medroxyprogesterone acetate to steroid-free human serum. The MPA concentration of the solution added was confirmed by UV Absorbance. The target values were set according to the concentration of MPA added. The acceptance criteria were set as a percentage of the target value.

Table 2.2.1 MPA QC Pools: Target values and acceptance criteria

Batch #	Target Value	Acceptance Limit: Set at ±15% of Target
H1717	300	255-345
H1718	750	637-863
H1719	2000	1700-2300

2.2.5.4 Assay Acceptance Criteria

Assays were accepted if (1) the mean values of the four replicates per QC pool in an assay were within the acceptance limits or (2) at least five out of six QC results were within acceptance limits.

Within-batch drift was also calculated for the three QC pools by the Data Processing Programme. This monitors whether there is a significant change in the QC pools results at the beginning and end of the assay. Within-batch drift was not flagged as significant by the software for any batches in this study, and none of the batches exceeded the in-house acceptability limit of ±15%.

2.2.6 DATA ANALYSIS

MPA serum concentrations and demographic data were captured using Microsoft® Excel. Where values were missing, the median was used. Data were checked for outliers and encoding errors using Xpose (version 3.007). Two subjects were excluded from analysis on the basis of this checkout. One had been using another injectable product norethisterone oenanthate (NET-EN) and was excluded as it was thought that this might have affected her MPA serum level. The second exclusion was made as it appeared that the woman had returned within 14 days of receiving her last dose, possibly as she wished to be recruited into the study.

Data were analysed in two ways:

- First the serum concentrations were analysed, focusing particularly on measurements taken at the end of the dosing interval (the trough levels).
- Second a population pharmacokinetic analysis was undertaken in order to estimate pharmacokinetic parameters for DMPA and to investigate the influence of covariates on the pharmacokinetic parameters.

2.2.6.1 Serum MPA Level Analysis Focusing on Trough Levels

Serum levels were analysed and are briefly described in the results chapter (2.3). Most levels were measured at the end of the dosing period when women returned for their next dose. Hence, trough serum levels, which provide information related to product efficacy, were analysed in detail. MPA serum concentrations and demographic data were analysed using Microsoft® Excel 2002. In all, trough serum MPA levels were measured in 97 DMPA users. A manuscript describing the results of this analysis has been accepted by

the Journal *Contraception* for publication. A copy of this paper can be found on page xlvi of this thesis after the abstract.

2.2.6.2 Population Pharmacokinetic Analysis

The Non-linear Mixed Effects Modelling computer programme (NONMEM) Version 5, level 1, described in the previous chapter was employed (Sheiner and Beal, 1994) in conjunction with a Compaq Visual Fortran Optimizing Compiler, Version 6.6 (Compaq, copyright 2001).

To identify a pharmacokinetic model which best describes the pharmacokinetic parameters of MPA, **structural models** were selected from the NONMEM PREDPP[25] library. Interindividual variation in clearance (CL) and volume of distribution (V), as well as residual variability and inter-occasion random effects were modelled with exponential error models (**statistical model**). Estimates were obtained for the following:

- the population mean of the pharmacokinetic parameters, CL and V
- variance of the interindividual random effects (etas) of CL (η^{CL}) and volume of distribution (η^{V})
- variance of the residual error (EPS, ϵ) (e.g. drug assay errors, model misspecification)
- standard errors of the parameter estimates
- inter-occasion random effects (π), and
- the objective function value (OFV) which is equal to minus twice the log-likelihood of the data.

[25] PREDPP stands for "Pred for Population Pharmacokinetics. It is a PRED ("prediction") subroutine for use with NONMEM and is specialized to the kinds of predications which arise in pharmacokinetic data analysis (Boeckmann *et al*, 1994, p.4).

A NONMEM data file was constructed in Microsoft® Excel 2002 using a comma delimited (.csv) file format. The data file parameters and the first 15 client records of the data file are shown in Appendices 2.2.3 and 2.2.4 respectively.

Xpose (version 3.007) was used for model building and diagnostics. Xpose is an S-PLUS based model building aid for population analysis using NONMEM (Jonsson and Karlsson, 1998a, (http://www.biof.uu.se/Xpose accessed 8/29/02). It facilitates data set checkout, exploration and visualization, model diagnostics, candidate covariate identification and model comparison.

Graphics were used in exploratory data analysis to examine distribution and correlation between covariates.

Estimation Method

Initially, the default first order method (FO) in NONMEM was used to estimate the typical values of the population parameters. The FO method makes expansions around the population average predicted value by using first-term Taylor series expansion in the approximation (Beal and Sheiner, 1992). Thereafter, the First Order Conditional Estimation (FOCE) method was used as it was considered to be more accurate since random interindividual variability was large. It has been recently reported that use of appropriate conditional estimation methods give a better agreement between nominal and true *p* values when using the likelihood ratio test for assessing nested models (Wählby *et al* 2001; Gobburu and Lawrence, 2002; Wählby *et al* 2002).

The Structural (Pharmacokinetic) Model

Two models from the NONMEM PREDPP library were selected to take into account the slow absorption of MPA from the intramuscular site of administration:

Model one: A one compartment linear model parameterized in terms of clearance (CL) and volume of distribution (V), using the programme subroutines ADVAN1 TRANS2. DMPA is administered by the intramuscular route and is slowly absorbed from intramuscular sites after administration, thus MPA blood concentrations are controlled by the rate of absorption from the surface of the microcrystals at the absorption site. It is possible for NONMEM-PREDPP to estimate the input rate of a constant-rate drug delivery system (e.g. sustained release tablet, implant). Accordingly, the RATE data item was assigned the value -2 (Boeckmann *et al*, 1994) and an additional pharmacokinetic parameter, duration of input (D1), was included in the model. Based on time to reach peak MPA levels after intramuscular injection of DMPA documented in the literature (see Table 2.1.2, previous chapter), a sensitivity analysis was carried out to determine a suitable value for D1. Various fixed values of D1 were tested and attempts were also made to estimate its value.

Model two: A one compartment linear model with first order absorption parameterized in terms of absorption, volume, and clearance, using the programme subroutines ADVAN2 TRANS2. This subroutine was selected because, in addition to the central compartment, it specifies a depot compartment where the dose goes and from which the drug enters the central compartment by a first order process (Boeckmann *et al* 1994).

In both models a scale parameter S=V/1000 was entered so that the units of the predicted responses match the data.

Since the drug is absorbed from a depot compartment, the estimated clearance and volume are apparent, CL/F and V/F respectively, where F=bioavailability.

The Statistical Model

Inter-individual differences (deviations of the drug's apparent clearance [CL/F] and apparent volume [V/F] of each individual from the population mean values) were estimated using the exponential, error model. This model was selected as it is appropriate for pharmacokinetic parameters which generally show a log normal distribution.

The residual error, which accounts for the difference between the observed concentrations and those predicted by the regression model, was estimated using exponential, additive and combined error models (Boeckmann *et al* 1994). The possibility of inter-occasion variability was also investigated.

Correlation between CL/F and V/F was tested with the BLOCK(2) option in the $OMEGA record as described by Boeckmann *et al*, (1994) and, alternately, by including a bioavailability term fixed to one, but with interindividual variability included.

Statistical model selection was based on goodness of fit, graphical analysis, the size of the individual variability, the residual errors and the relative standard errors of the parameters.

Covariate Modelling

Covariate modelling is an iterative process with the basic model (structural and statistical) forming the basis for identifying potential covariates (Wählby, 2002). Potential covariates can be tested within NONMEM, but this is very time-consuming. Thus methods which lessen the number of covariates to be tested in NONMEM are often employed. Covariates identified by these methods can be included in the model by stepwise forward inclusion, or all identified variables are combined as the full model and covariates are then tested using stepwise backward deletion (Wählby, 2002). An automated procedure where the covariate model is built within NONMEM in a stepwise fashion can also be used to identify potential covariates (Wählby, 2002).

In line with the covariate screening procedures described above, covariate modelling was undertaken in two ways in this study:

(i) Covariate selection with generalized additive modelling (GAM).

Starting with the basic model, covariate influences were explored using the GAM method (Mandema *et al*, 1992) as implemented in Xpose (Jonsson and Karlsson, 1998a). Linear and nonlinear models are tested on the parameters from a basic model run without covariates. Using GAM, model discrimination was made by undertaking a univariate analysis of covariate effect on CL/F and V/F. Plausible covariates identified by GAM were tested in NONMEM. This was done in a stepwise fashion, singly and in combination, on CL/F and V/F respectively.

The covariates tested in this way were:

- The continuous covariates age, weight, height, duration of use of DMPA, creatinine, alkaline phosphatase, gamma GT, aspartate transaminase, alanine aminotransferase, total bilirubin, conjugated bilirubin
- The categorical covariates race and smoking

(ii) Covariate selections using a step-wise automated procedure within NONMEM.

Identification of covariates was also carried out using an automated procedure in NONMEM (Jonsson and Karlsson, 1998b) which allows for covariate testing within NONMEM runs. This process involves a stepwise testing of linear and non-linear relationships in a forward inclusion (ΔOFV of 3.84, p=0.05) and backward exclusion (ΔOFV of 10.83, p=0.001) procedure. For each covariate and pharmacokinetic parameter, a hierarchical set of possible models was defined. For categorical covariates this set was either no relation or a shift in the intercept, and for continuous covariates it was no relation (first level), a linear relation (second level) or a non-linear relation (third level). The latter was modelled as a continuous piecewise linear relation with two different slopes, one for each side of the median value of the covariate.

The stepwise search for a covariate relation started at the naive model, that is the model without covariates. A series of non-linear mixed effect models were fitted to the data. In the first step, each parameter-covariate relation at the second level in the hierarchical set of models was added to the start model, one at a time, and its statistical significance was assessed. The parameter-covariate relation, for which the lowest p value was obtained, was retained in the model. In the second step each parameter-covariate relation, as given by the next possible level in the hierarchical set of models, was tried in the new model

and its statistical significance was assessed. This continued until no more statistically significant parameter-covariate relations were found. After the forward inclusion of parameter-covariate relations, a backward elimination followed. This was essentially the reverse of the forward inclusion. In each step, the next lower model in the hierarchical set of models replaced each parameter-covariate relation in the model. The least important relationship (giving the lowest change in OFV), given that it was not statistically significant, was dropped in favour of the simpler model. This continued until no more terms could be dropped.

The covariates tested in this way were:

- The continuous covariates age, weight, height, duration of use of DMPA, creatinine, alkaline phosphatase, gamma GT, aspartate transaminase, alanine aminotransferase, total bilirubin, conjugated bilirubin.
- The categorical covariates race and smoking. Since there were relatively few Indian, White and Coloured women (n=38), these women were grouped together and tested versus Africans as the reference group (n=73).

The advantage of this method is that all selected covariates are tested singly and in combination within NONMEM runs. Further, the covariate model is built for all parameters at the same time, it can handle covariates that vary over time and is not dependent on the quality of the posterior Bayes estimates of the individual parameter values (Jonsson & Karlsson, 1998b). This method does not, however, take into account covariate interactions.

Model Evaluation

NONMEM was used to identify which fixed effects had the most significant influence on MPA apparent CL/F and apparent V/F, and which regression model best described the data. The value of the OFV, a goodness-of-fit statistic, was used to compare the validity of successive models. Minimizing the objective function is equivalent to maximizing the probability (likelihood) of the data. The ΔOFV between two nested models is approximately Chi-square distributed, and the improvement in goodness of fit of the model, due to introduction or elimination of parameters, can be assigned significance levels as follows (Wählby, 2002):

ΔOFV=3.84, $p<0.05$

ΔOFV=6.63, $p<0.01$

ΔOFV=10.83, $p<0.001$

Degrees of freedom (df) in each of the above = 1, where the number of df is equal to the number of differing parameters

According to Boeckmann *et al* (1994) a fall in OFV of 4 shows that the new model (where a single new parameter is introduced and where no existing ones are eliminated) has substantially improved the overall goodness of fit. It is usual to apply significance levels of 0.05 (ΔOFV=3.83 or more) for forward inclusion of parameters and 0.001 (ΔOFV=10.83 or more) on backward elimination.

Successive models were also evaluated by means of the relative standard errors of the estimates and on the basis of graphical analysis which provides an important mechanism for judging goodness-of-fit (Wählby *et al*, 2001).

The goodness of fit of the final model was assessed by means of the following graphical analysis:

- Distribution of weighted residuals (WRES): If the model chosen is appropriate, the data will be randomly distributed.
- Population predictions (PRED) versus observed values (DV): Gives an impression of how well the model can predict data (Karlsson, 1998). Substantial and systematic deviations from the line of identity suggest that there are problems with the fit (Boeckmann *et al*, 1994).
- Individual predictions (IPRE) versus DV: A general diagnostic tool which is better for rich than sparse data and better for the assessment of the structural than the statistical model (Karlsson, 1998).
- Individual plots of observed concentrations, individual concentration predictions and final model concentration predictions.
- Individual weighted residuals (IWRES) versus individual predictions (IPRE): A statistical model diagnostic which should show no trend in the magnitude of IWRES (Karlsson, 1998).
- Weighted residuals (WRES) in relation to time after dose: A structural model diagnostic. For a good model fit, the residuals should be scattered evenly around the zero line (Karlsson, 1998).
- Plots which examined relationships between observed values and predicted values, in relation to time after dose.

2.2.7 STUDY LIMITATIONS

Although this study included many more subjects than previous studies on MPA concentrations and/or pharmacokinetic parameters, the following limitations should be noted:

- The dataset contained few peak MPA measurements, so little light was shed on the time taken to reach peak values, or the MPA value at peak level.
- There were relatively few Indian (n=28) and White (n=9) women and only one Coloured woman, making it difficult to draw conclusions about these three races.

CHAPTER 2.3 RESULTS

2.3.1 CHARACTERISTICS OF DMPA USERS

In all, data from 111 DMPA users were analysed. The characteristics of these DMPA users are provided in Table 2.3.1 and their clinical chemistry is reported in Table 2.3.2. They were 28 years old on average, with a mean weight of 62 kg. Most were African and only a few, mainly white women were smokers. While some had used DMPA for many years, the mean duration of use was three years. Five women had elected to use DMPA on the day of recruitment into the study and 11 had been using it for only one dosing cycle (i.e. 12 weeks).

Table 2.3.1 Characteristics of DMPA users

Characteristic			
	Mean (SD)	**Median**	**Range**
Age (years)	28 (5.8)	27	17-42
Weight at recruitment (kg)	62 (11.8)	61	37-105
Height (meters)*	1.6 (8)	1.6	1.4-1.8
Body mass index (BMI)[+]based on weight at recruitment	25.2 (4.8)	24.5	15.4-39.0
Duration of use (years)[#]	3.2 (3.4)	2	0-20
	N (%)		
Race			
African	73 (65.8)		
Indian	28 (25.2)		
Coloured[†]	1 (0.9)		
White	9 (8.1)		
Smokers	8 (7.2)		

*The heights of 16 women were not recorded at the clinic. The mean and median heights were calculated in 2 ways. First by excluding the subjects with missing values (n=95) and second by using the median height for the missing values. In both calculations, the mean and median obtained was the same as that reflected in the table above.

[+]Body mass index was calculated as weight (kilograms), divided by height (meters) squared. This median height was used for the missing height values in the BMI calculation

[#]The duration of use of one woman was not recorded

[†]Mixed race

Table 2.3.2 Serum clinical chemistry of DMPA users

Test	Mean (SD)	Median	Range	Laboratory Reference Range
Creatinine (umol/L)	81 (8)	80	58-115	63-115
Alkaline phosphatase (U/L)	143 (41)	139	14-290	68-212
Gamma GT (U/L)	13 (8)	11	3-48	8-37
Aspartate transaminase (U/L)	15 (10)	13	5-100	0-25
Alanine aminotransferase (U/L)	16 (15)	12	6-134	0-29
Total bilirubin (umol/L)	8.2 (3.9)	7.6	1.8-23.2	2-17.0
Conjugated bilirubin (umol/L)	1.8 (1.1)	1.7	0.1-5.4	0.1-8.5

Few women were taking concomitant medication:

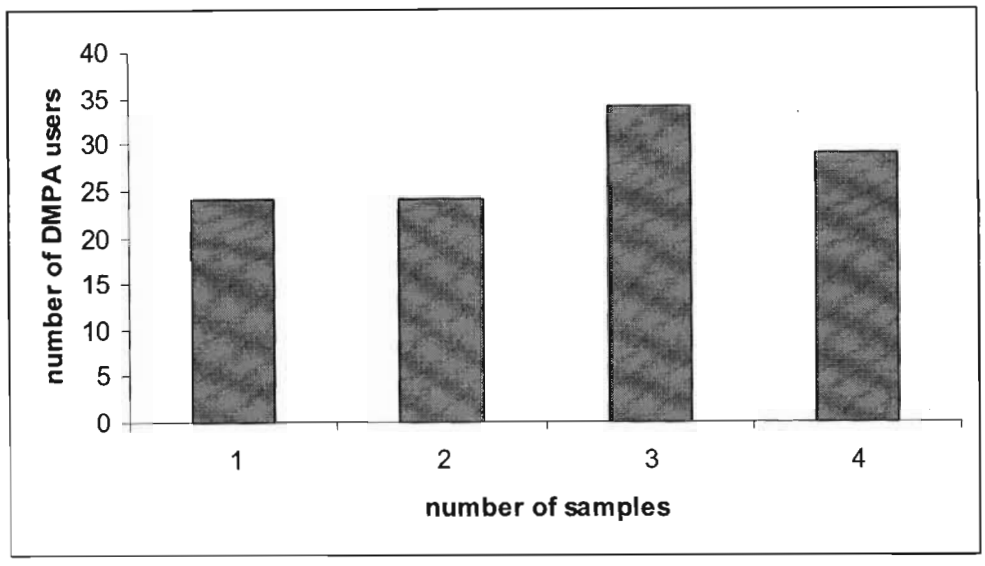
- one woman was taking an oral anticonvulsant, carbamazepine, for epilepsy at a dose of 300mg daily
- three women were taking antihypertensive medication
- one woman was taking an oral hypoglycaemic drug and one was using insulin.
- one woman had used Ovral® for heavy bleeding with DMPA use, and
- one woman had used Premarin® for 7 days.

2.3.2 SERUM SAMPLES AND SAMPLING TIMEFRAME

A total of 291 serum concentrations were analysed from the 111 DMPA users. Sixteen of these women had been using the injectable for one or less dosing cycles. In these cases the levels were assumed not to be at steady state.

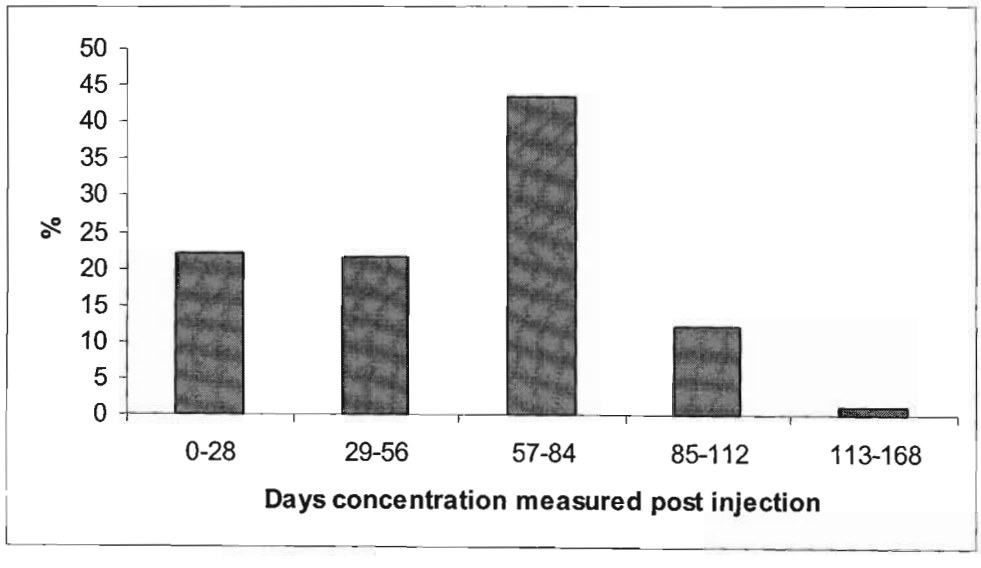
The median number of samples taken per woman was three with a range of one to four (Figure 2.3.1).

Figure 2.3.1 Number of samples analysed per woman



Concentrations were measured between 4 and 168 days post injection, with most measurements (25.4%) occurring just before the next dose was due, that is 84 days after injection. The frequency distribution of concentration measurements according to the length of time after the last dose is shown in Figure 2.3.2.

Figure 2.3.2 Proportion of measurements according to time after last dose



2.3.3 SERUM MPA LEVELS FOCUSING ON TROUGH LEVELS

Only 3 measurements were taken during the time period after injection when peak levels were likely to occur. These measurements were obtained at days 4, 7 and 20 and were 3.51ng/ml (race: Indian; BMI: 15.6), 4.15ng/ml (race: African; BMI:22.77) and 4.27ng/ml (race: African; BMI: 23.88) respectively. The mean MPA concentration of measures taken between 29 and 56 days post injection was 1.42ng/ml (median: 1.38ng/ml; range:0.49 to 3.50ng/ml). Most levels were measured at the end of the dosing interval and these levels are described below in detail.

2.3.2.1 Trough Levels

Trough serum MPA levels were measured in 97 of the 111 DMPA users. Ninety-five of the women returned between 11 and 14 weeks of receiving their last dose. The remaining three returned more than 14 weeks after their last injection and were classified as "defaulters" in keeping with clinic policy.

Demographic data and serum MPA levels of the 94 African, Indian and White women returning between 11 and 14 weeks after their last dose are presented in Table 2.3.3. On recruitment into the study, 12% of these had had one dose of DMPA, 7% two doses, 5% three doses and the remainder had been using DMPA for a year or more. Sixty-four were Africans, 24 were of Indian descent, and six were White. The mean and median MPA levels were 0.88ng/ml (Table 2.3.3). The MPA level of one woman was below the minimum level of detection (0.04ng/ml).[26]

[26] Where this value was included in determining a mean value, the level was set at 0.02ng/ml, that is half the limit of quantitation.

Table 2.3.3 Demographic data and trough MPA levels

	Age (years) n=94	Weight (kg) n=94	BMI* n=80[+]	MPA level (ng/ml) n=94
Mean	28	62	25.4	0.88
Median	27	61	24.3	0.88
Range	17-42	38-106	15.4-39.4	<0.04-1.77

*Body mass index was calculated as weight (kilograms), divided by height (meters) squared.
[+]The heights of 14 women were not recorded

Serum MPA levels in relation to the time after the last injection are presented in Figure 2.3.3. Levels of those who returned up to a week early, or up to two weeks late, were similar to those returning exactly 84 days after their previous dose. The large interindividual variability is well illustrated by the wide range of levels, particularly in the large group who returned at 84 days. MPA levels in these 55 women ranged between <0.04ng/ml and 1.53ng/ml (median: 0.90ng/ml; mean [SD]: 0.86[0.31]ng/ml). The MPA levels of the three defaulters who returned 109, 112 and 168 days after their last dose were 0.77ng/ml, 0.74ng/ml and 0.29ng/ml respectively.

Figure 2.3.3 Trough MPA levels in relation to dosing interval by ethnic group

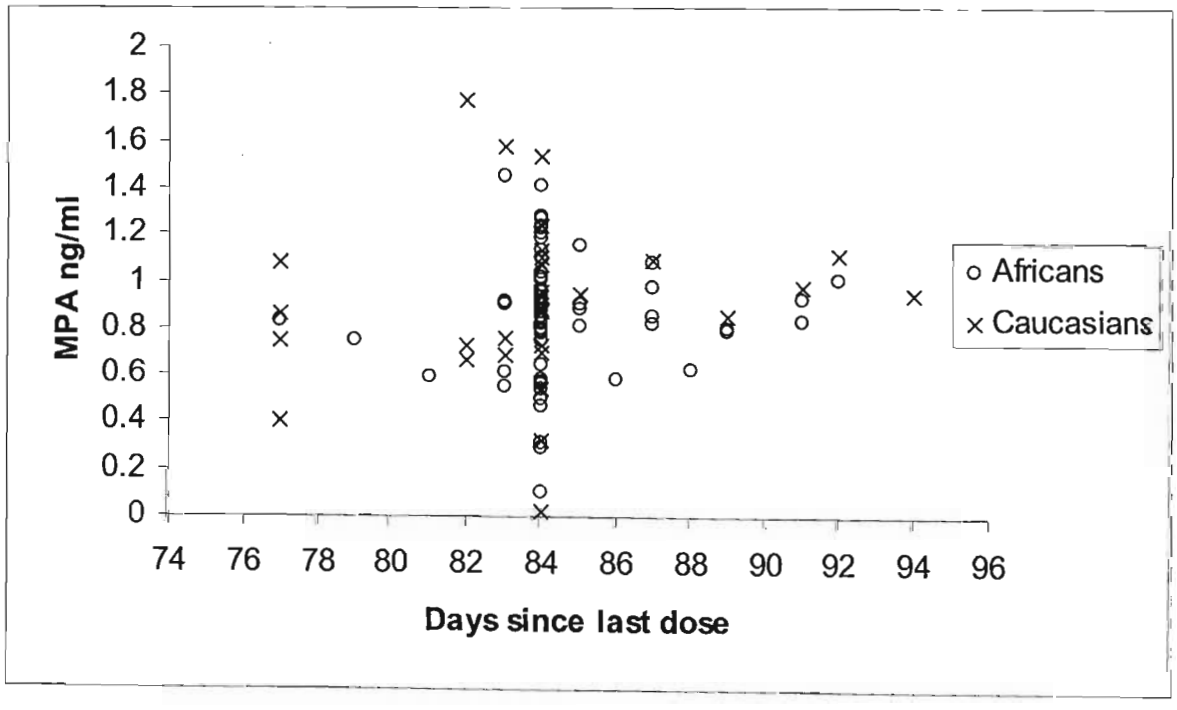


Figure 2.3.3 also shows that the trough MPA levels of Africans and Caucasians were similar. In the group returning at 84 days, the median (range) MPA levels were 0.90 (0.10-1.40)ng/ml and 0.90 (<0.04-1.53)ng/ml for Africans (n=41) and Caucasians (n=14) respectively. Although widely varied within each ethnic group, BMIs were similar between groups with a median (range) BMI of 25.8 (17.4-39.4) for African women (n=51) and 23.6 (15.4-33.8) for Caucasians (n=29). The MPA levels of subjects with a BMI less than 25 were similar to those with a BMI of 25 or more (Table 2.3.4).

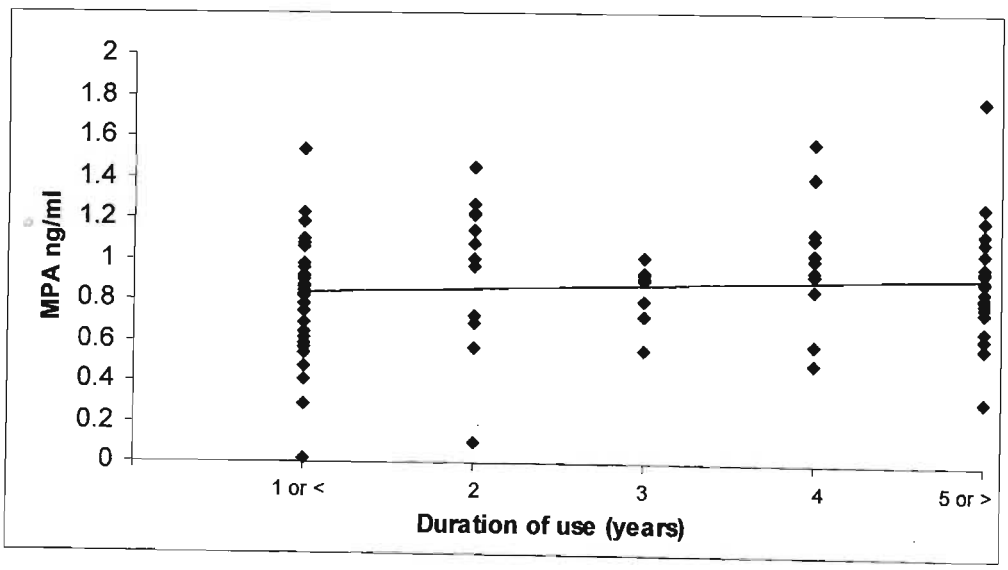
Table 2.3.4 Trough MPA levels of women with different BMIs

	MPA level (ng/ml)			
	n	Mean	Median	Range
BMI < 25	43	0.85	0.85	<0.04-1.58
BMI ≥ 25	37	0.88	0.88	0.31-1.45

Desirable BMI range is 19-24 [17]

There was a slight trend (Pearson's Product Moment=0.13) towards higher MPA levels at the end of the dosing interval with longer duration of use (Figure 2.3.4). However, wide interindividual variability was evident irrespective of length of use.

Figure 2.3.4 Trough MPA levels in relation to duration of use (n=93)



2.3.4 POPULATION PHARMACOKINETIC ANALYSIS

2.3.4.1 The Pharmacokinetic Data File

The pharmacokinetic data file was constructed as described in Chapter 2.2. All errors identified in the data run checkout were corrected. The first 15 client records of this data file are shown in Appendix 2.2.4. Because there were so few women taking concomitant medication in each group, the influence of concomitant drugs was not tested in the population analysis.

2.3.4.2 Estimation Method

Initially, the default first order method (FO) in NONMEM was used (run 2, Run Record in Appendix 2.3.1) to estimate the typical values of the population parameters. Thereafter, the First Order Conditional Estimation (FOCE) method was used (run 3, Run Record in Appendix 2.3.1). Although the parameter estimates are not dissimilar (run 2 and 3), FOCE gives smaller standard error of estimates. FOCE was thus used for all subsequent runs.

2.3.4.3 Model Building

A summary of the main runs constructed during the model building process is provided in Appendix 2.3.1.

The Structural (Pharmacokinetic) Model

Since the drug is absorbed from a depot compartment, the estimated clearance and volume are apparent, that is CL/F and V/F, where F=bioavailability. Two one compartment structural models were tested, both parameterized in terms of apparent volume and apparent clearance. The first model assumed a zero order infusion with first

order elimination while the second assumed first order absorption and first order elimination. The models produced similar objective function values (OFV) (Table 2.3.5) and similar values for CL/F and V/F (Appendix 2.3.1). The first model was chosen for further covariate analysis as the covariance matrix was estimated giving standard errors of parameter estimates.

Table 2.3.5 Summary of key decisions taken in model building

Question	OFV	Δ OFV	Conclusion	Reference
Should the FO or FOCE estimation method be used? FO FOCE	 -216.262 -227.481		 No Yes • Recent literature on *p* value (see previous chapter: 2.2.6.2) • Variability parameters appear to be more precisely estimated	 Run 2 Run 3
Structural Model				
Which NONMEM Subroutine? • ADVAN1 TRANS2 (CL/F; V/F; D1) • ADVAN2 TRANS2 (CL/F; V/F; Ka)	 -233.462 -233.161		 Yes - Covariate Matrix No	 Run 8 Run 11
What value should be assigned to duration of input (D1)? • Literature indicates that MPA values likely to peak within a week of administration	-233.462 -233.345	↓5.981	D1=4 • Sensitivity test indicates that D1=4 gives best OFV D1 estimated as 4.2	Run 8 Run 4
Statistical Model				
• Should the combined (additive and proportional) residual error model be used?	-241.970	↓8.508	Yes	Run 12 vs run 8
Is inter-occasion variability on CL/F and V/F significant?	-247.931	↓5.961	No • Small improvement in OFV • Little change in parameters (CL/F & V/F) • Large standard errors on IOV for CL/F (190%) & V/F (54%)	Run 16 vs run 12
Is there correlation between CL/F and V/F? • Block (2) included • Block (2) removed • Bioavailability term=1 with IIV included	 -241.970 -193.794 -209.067	 ↑48.176 ↑32.903	Yes 101% correlation IIV on V/F very small; estimates of IIV on CL/F not precise	 Run 12 Run 13 vs run 12 Run 14 vs run 12

OFV=objective function value; ΔOFV=difference in objective function value; NONMEM=Non-linear Mixed Effects Modelling; FO=the first-order estimation method in NONMEM; FOCE=the first-order conditional estimation method in NONMEM; CL/F= apparent clearance; CL/V=apparent volume; F=bioavailability; D1=duration of input; Ka=first order absorption rate function; IOV=inter-occasion variability; IIV=interindividual variability.

Based on the time to reach peak MPA documented in the literature (see Table 2.1.2 in Chapter 2.1), D1 was initially set at 7 days. A sensitivity analysis was carried out to determine a suitable value for fixing D1 (the duration of input as described in Chapter 2.2). Attempts were made to estimate the value of D1 and various fixed values of D1 were also tested. Table 2.3.6 provides a summary of the NONMEM runs carried out for the sensitivity analysis. Where D1 was estimated, it was found to be 4.2 days and the best OFV was obtained for run 8 where D1 was fixed at 4 days. The pharmacokinetic parameters (CL/F and V/F) and variability parameters obtained were similar in the runs indicating that the value of D1 did not have much influence. Accordingly, this fixed value, D1=4, was selected for subsequent modelling.

Table 2.3.6 Sensitivity analysis: Duration of input (D1)

Run #	D1 (days)	OFV	CL/F (L/day)	V/F (L)
3	7	-227.481	1110	90000
4	Estimated (4.12)	-233.345	1090	90200
5	10	-200.348	1130	91500
6	5	-232.612	1100	89600
7	3	-233.334	1080	89100
8	4	-233.462	1090	89600

The Statistical Model

The exponential error model was selected to estimate the interindividual differences as this model is appropriate for pharmacokinetic parameters which generally show a log normal distribution.

The residual errors were estimated by means of proportional and combined (additive and proportional) models. Based on an improvement in the OFV of 8.508 (run 12 versus run 8: Table 2.3.5 and Run Record Appendix 2.3.1), the residual errors were estimated by the combination model as depicted by the following equation:

$$Y = F \cdot (1+\varepsilon_{ij,1}) + \varepsilon_{ij,2}$$

Where Y is the observed concentration and F is the corresponding model predicted value. ε (or eps) are the residual error terms for the *i*th individual and the *j*th concentration.

The possibility of inter-occasion variability (IOV) was also investigated (run 16, Table 2.3.5 and Run Record, Appendix 2.3.1). The IOV on CL/F was found to be 6.4% and on V/F was 18%. However, a relatively small improvement in the OFV (5.961), very little change in the parameters (CL/F and V/F), and large standard errors on IOV for CL/F (190%) and V/F (54%) were obtained (Table 2.3.5). It was thus concluded that inclusion of inter-occasion random effects did not offer much improvement in the model fit. Also, for most women in the data set, information for only one dose interval was available.

As described in the Methods Chapter (2.2), correlation between CL/F and V/F was taken into consideration by utilizing the Block (2) option, resulting in a 101% correlation between CL/F and V/F. When the correlation was removed, the OFV increased by 48.176, indicating a worse fit (run 13 versus run 12: Table 2.3.5 and Run Record in Appendix 2.3.1). An alternate strategy to using the Block (2) involved the inclusion of a bioavailability term fixed to one, but with interindividual variability added. This strategy produced an OFV that increased by 32.903 compared with the Block (2) option (run 14 versus run 12: Table 2.3.5 and Run Record in

Appendix 2.3.1), again indicating a worse fit. In addition, the interindividual variability on V/F became very small and interindividual variability on CL/F was not precisely estimated (run 14 versus run 12: Run Record in Appendix 2.3.1). The model including the correlation in the form of a Block (2) option was thus considered to be the most suitable model for covariate model building.

Covariate Modelling

(i) Covariate selection with generalized additive modelling (GAM).

The GAM on both CL/F and V/F indicated that weight and smoking may be significant covariates. However neither proved significant when tested in NONMEM (run 19-22 of Run Record in Appendix 2.3.1).

(ii) Covariate selections using a step-wise automated procedure within NONMEM.

Two covariate batches were created for the step-wise automated procedure as the number of covariates to be tested exceeded the number of data items NONMEM can accommodate:

- The first batch included the covariates: race, smoking, age, weight, duration of use, alkaline phosphatase, gamma GT and total bilirubin.
- The second batch included the covariates: race, height, creatinine, aspartate transaminase, alanine aminotransferase, and conjugated bilirubin.

As race on V/F was found to be a marginally significant covariate in the first batch, it was also included in the second batch.

In the first batch of the automated covariate testing procedure only race was identified as a significant covariate for V/F (ΔOFV of -4.9) in the forward inclusion procedure. However it was rejected on backward elimination (ΔOFV of 4.9) as shown in Table 2.3.7.

Table 2.3.7 Identification of significant covariates in the automated covariate testing

ROUND	MODEL	OFV	Δ OFV[a]	COMMENT
Base (Run12)	No covariate relations	-241.970	-	Basic model
Batch 1				
Forward inclusion (ΔOFV of 3.84 for nominal p=0.05)				
1	RACE on V/F	-246.871	-4.901	Retain
2	AGE on V/F	-250.655	-3.784	Do Not Retain
Backward elimination (ΔOFV of 10.83 for nominal p=0.001)				
3	Minus RACE on V/F	-241.970	4.901[b]	Do Not Retain
Batch 2				
Forward inclusion (ΔOFV of 3.84 for nominal p=0.05)				
1	RACE on V/F	-246.871	-4.901	Retain
2	CREA* on CL/F	-250.343	-3.472	Do Not Retain
Backward elimination (ΔOFV of 10.83 for nominal p=0.001)				
3	Minus RACE on V/F	-241.970	4.901[b]	Do Not Retain

[a] For the forward inclusion the Δ OFV is the OFV of the statistically most significant model in each step minus the OFV of the statistically most significant model in the former step. [b] Difference in OFV between this model and the best model in round 1.
* See Appendix 2.2.3 for covariate abbreviations as entered in the data file

The race covariate indicated that V/F was 22% larger for women who were not African. This parameter was estimated at 0.22 with a standard error of 0.58 (run 24, Run Record, Appendix 2.3.1).

Serum creatinine on its own was a significant covariate for CL/F (ΔOFV of -4.8) in the first forward round of the second batch. In the second round, when included with race, it was no longer significant (ΔOFV of -3.5) and was therefore not retained.

The results of univariate analyses from Round 1 for both batches are shown in Table 2.3.8.

Table 2.3.8 also shows that the covariates weight and smoking were not significant, although they were identified by generalized additive modelling (see (i) above) as covariates which might be relevant. (See Appendix 2.2.3 for covariate abbreviations as entered in the data file)

Table 2.3.8 Univariate analysis of covariate effect on apparent clearance and apparent volume

Hypothesis	OFV	Δ OFV	*p* value	Conclusion	Reference
Basic model	-241.97				Run 12
Did CREA influence CL/F?	-246.757	-4.787	<0.05	Yes	vs 12
Did height influence CL/F?	-244.721	-2.751	>0.05	no	vs 12
Did race influence CL/F?	-244.711	-2.741	>0.05	no	vs 12
Did weight influence CL/F?	-244.495	-2.525	>0.05	no	21 vs 12
Did AST influence CL/F?	-244.398	-2.428	>0.05	no	vs 12
Did ALT influence CL/F?	-243.142	-1.172	>0.05	no	vs 12
Did CBIL influence CL/F?	-242.815	-0.845	>0.05	no	vs 12
Did ALKP influence CL/F?	-242.414	-0.444	>0.05	no	vs 12
Did GAMA influence CL/F?	-242.392	-0.422	>0.05	no	vs 12
Did BMI influence CL/F?	-242.391	-0.421	>0.05	no	17 vs 12
Did age influence CL/F?	-242.322	-0.352	>0.05	no	vs 12
Did TBIL influence CL/F?	-242.298	-0.328	>0.05	no	vs 12
Did smoking influence CL/F?	-242.107	-0.137	>0.05	no	19 vs 12
Did duration of use influence CL/F?	-242.014	-0.044	>0.05	no	vs 12
Did race influence V/F?	-246.871	-4.901	<0.05	Yes	24 vs 12
Did CREA influence V/F?	-244.295	-2.325	>0.05	no	vs 12
Did ALKP influence V/F?	-244.006	-2.036	>0.05	no	vs 12
Did AST influence V/F?	-243.433	-1.463	>0.05	no	vs 12
Did smoking influence V/F?	-243.366	-1.396	>0.05	no	20 vs 12
Did CBIL influence V/F?	-243.256	-1.286	>0.05	no	vs 12
Did age influence V/F?	-243.063	-1.093	>0.05	no	vs 12
Did height influence V/F?	-242.96	-0.99	>0.05	no	vs 12
Did ALT influence V/F?	-242.693	-0.723	>0.05	no	vs 12
Did BMI influence V/F?	-242.29	-0.32	>0.05	no	18 vs 12
Did weight influence V/F?	-242.157	-0.187	>0.05	no	22 vs 12
Did TBIL influence V/F?	-242.143	-0.173	>0.05	no	vs 12
Did GAMA influence V/F?	-242.013	-0.043	>0.05	no	vs 12
Did duration of use influence V/F?	-242.006	-0.036	>0.05	no	vs 12

Although the covariate BMI was not included in the stepwise automated procedure, the influence of race and BMI on V/F was tested in NONMEM (run 23, Run Record, Appendix 2.3.1) resulting in a ΔOFV of -1.52 (run 23 vs run 24, Run record Appendix 2.3.1) which was not significant.

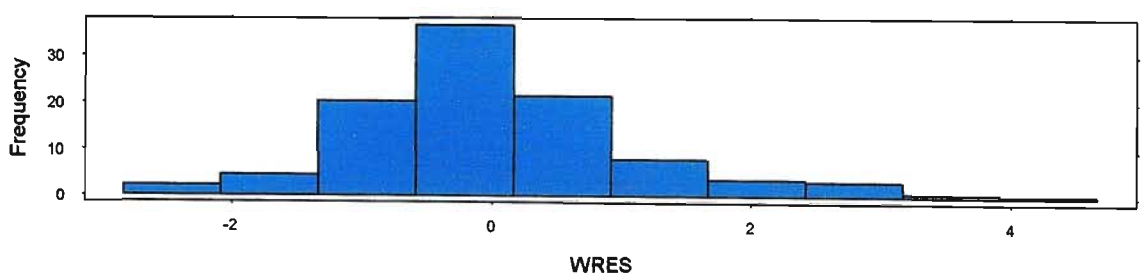
Final Population Pharmacokinetic Model

The final population pharmacokinetic model had no covariates on CL/F or V/F as none were found to be significant at a *p* value of 0.001 on backwards deletion.

The goodness of fit of the final model was assessed by means of graphical analysis as shown in Figures 2.3.5, 2.3.6, 2.3.7 and 2.3.8.

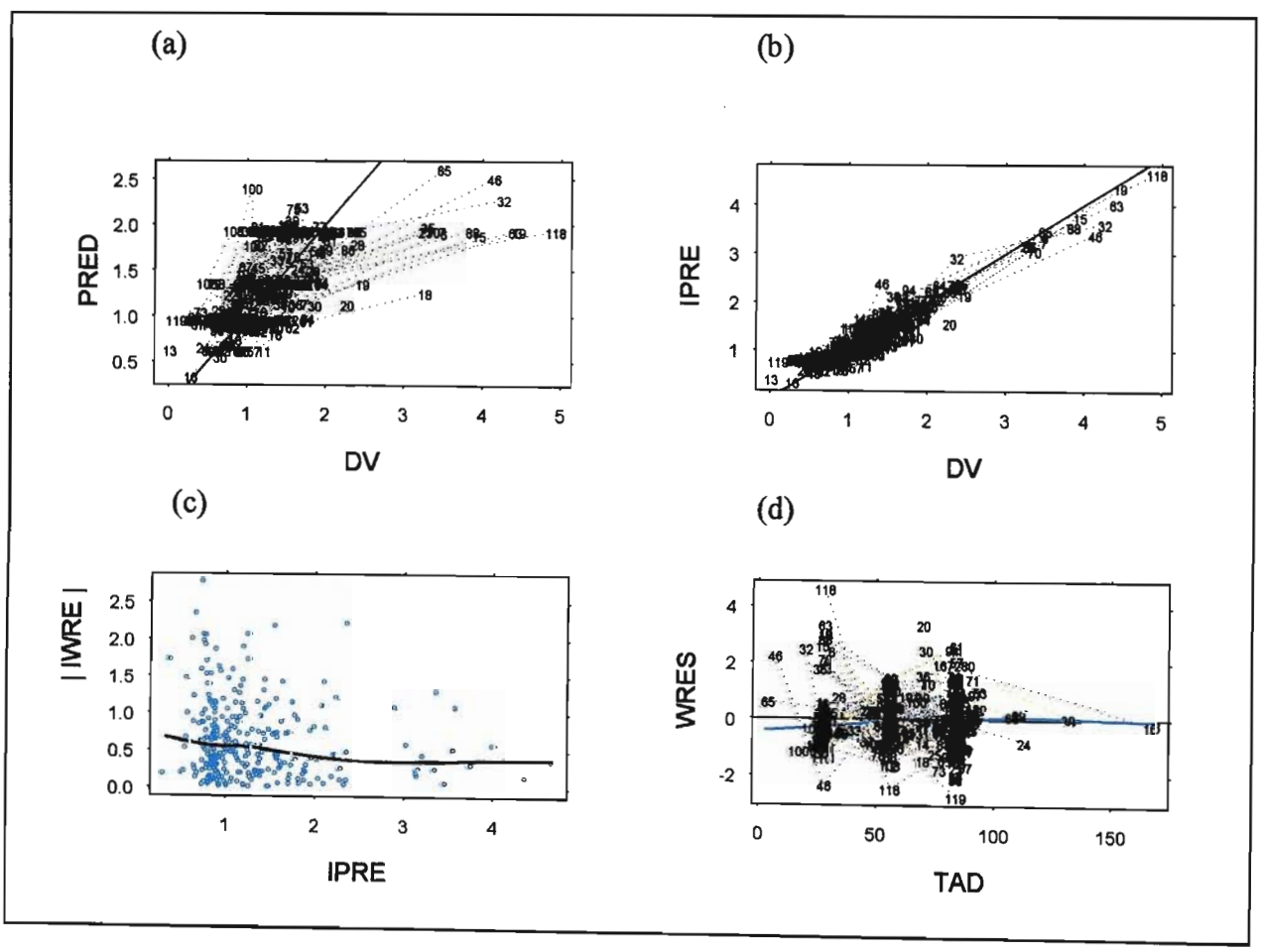
The frequency distribution of weighted residuals associated with the final model was randomly distributed as shown in Figure 2.3.5.

Figure 2.3.5 Frequency distribution of weighted residuals (WRES)



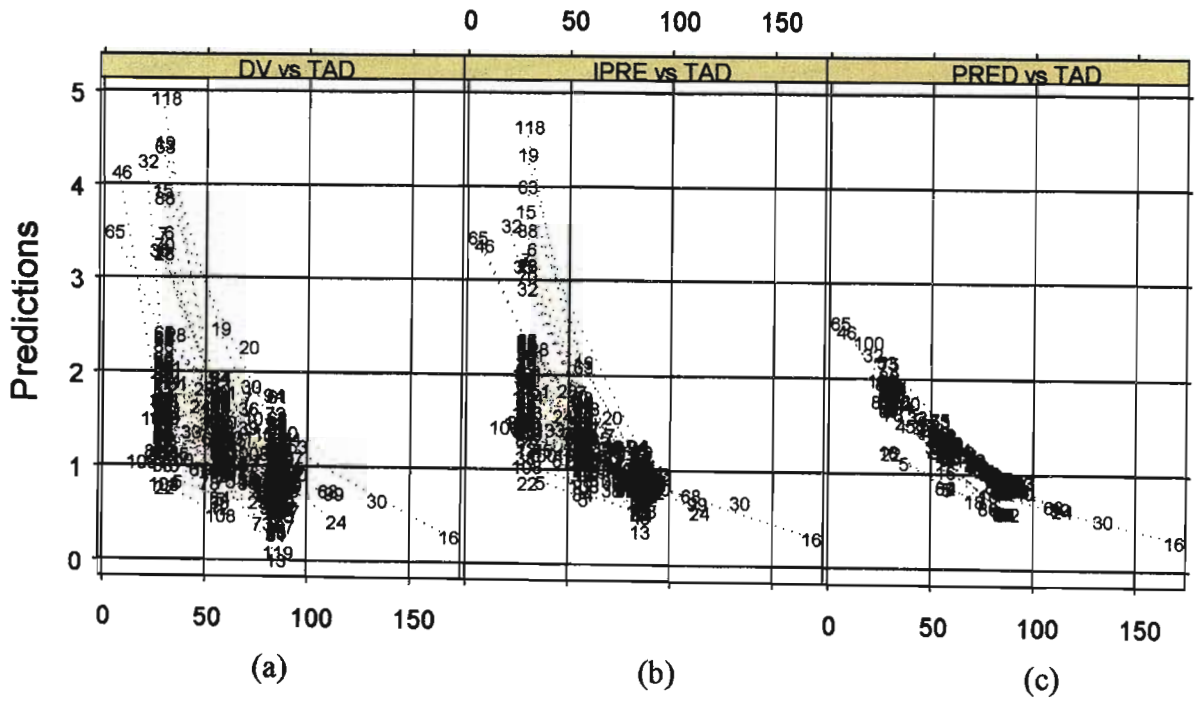
The relationship between the measured concentrations and those predicted for the final model are shown in Figure 2.3.6 (a) and (b). Concentrations measured early in the dosing cycle are less accurately predicted than concentrations measured later. Figure 2.3.6 (c) shows the individual weighted residuals (IWRES) versus the individual predictions indicating a reasonable statistical model as there does not appear to be a trend in the magnitude of IWRES. Figure 2.3.6 (d) shows the weighted residuals (WRES) versus time after dose indicating that concentrations measured within the first month of administration of the dose are less accurately predicted than concentrations measured later in the dosing cycle.

Figure 2.3.6 Scatterplots:
(a) Predicted (PRED) versus observed concentrations (ng/ml)
(b) Individual predictions (IPRE) versus observed concentrations (ng/ml)
(c) Individual weighted residuals (IWRES) versus individual predictions (IPRE)
(d) Weighted residuals (WRES) versus time



The relationship between the measured concentrations and individual predictions and those predicted for the final model, in relation to time are shown in Figure 2.3.7. While concentrations measured within the first month after administration of the dose are not well predicted by the model, concentrations measured later in the dosing cycle are more accurately predicted. This is further illustrated by the individual plots of measured concentrations, individual concentration predictions and final model concentration predictions in relation to time after dose (see for instance ID:6 and ID:15 in Appendix 2.3.2).

Figure 2.3.7:
(a) Measured concentration (DV) (ng/ml) versus time after dose (TAD) (days)
(b) Individual predictions (IPRE) (ng/ml) versus time after dose (days)
(c) Model predictions (PRED) (ng/ml) versus time after dose (days)



In sum, although higher concentrations measured within the first month of administration of the dose are less accurately predicted than concentrations measured later in the dosing cycle, the structural and error models are reasonable. There is however insufficient information about concentrations early in the dosing cycle to explain the weak prediction of these observed concentrations in some women.

The final model estimates for CL/F and V/F were 1080 (95% CI: 994, 1166) L/day and 86200L (95 %CI: 68246, 104154) respectively. The parameter estimates obtained for the final population pharmacokinetic model are summarized in Table 2.3.9. The mean predicted population half-life ($t_{½}$=0.693xV/CL) was calculated to be 55.31days.

Table 2.3.9 Final population pharmacokinetic model and its parameter estimates

Parameter	Value	RSE %
CL/F	1080 (L/day)	4.1
V/F (L)	86200 L	11
IIV		
V/F	71 %	19
CL/F	33 %	23
Correlation	101%	22
Residual Error		
Additive	0.202 ng/ml	20
Proportional	16.2 %	26

RSE=Relative standard error

CHAPTER 2.4 DISCUSSION

An extensive search of the literature indicates that this is the first study on the pharmacokinetics of depot medroxyprogesterone acetate (DMPA) amongst African women using DMPA, and the first ever population pharmacokinetic analysis of DMPA. The study has described serum concentrations of medroxyprogesterone acetate (MPA) amongst 111 South African women (African, Indian, Coloured and White) using Depo-Provera®. MPA serum levels are discussed first in this chapter, focusing particularly on levels at the end of the dosing period (trough levels), since most measurements were taken when women returned to the clinic for their next dose. Secondly, findings from the population pharmacokinetic analysis of MPA are discussed.

2.4.1 SERUM MPA LEVELS

MPA levels were found to be similar to those reported in previous studies. The mean trough level of 0.88ng/ml, measured for 94 women, was comparable to mean trough levels reported by Jeppsson and Johansson, (1976), Jeppsson *et al* (1977), and Koetsawang *et al* (1979) where means ranged from 0.6ng/ml to 0.9ng/ml.

Most studies have found MPA levels at the end of the three month dosing period to be above the level at which ovulation is reported to resume (0.1ng/ml) (Kirton and Cornette, 1974; Jeppsson *et al*, 1977; Ortiz *et al*, 1977; Koetsawang *et al* 1979; Fotherby *et al* 1980b). In this South African study, with the exception of one undetectable level (<0.04ng/ml), all MPA levels between 11 and 14 weeks after the dose were above this level. Even the MPA levels of three defaulters, two who returned 4 weeks late and one 12 weeks late, were still above 0.1ng/ml. In four of five women studied, Fotherby *et al* (1980a) reported undetectable levels by days 55, 64, 87 and 87 post injection respectively

(minimum detectable level >0.1ng/ml) and, in a study by Koetsawang *et al* (1979), two of 21 women had levels of less than 0.1ng/ml at the end of the dosing period. It should be noted, however, that the assay used in these two earlier studies was less sensitive (0.1ng/ml) than that of this South African study where the lower limit of quantitation was 0.04ng/ml. In addition, assays used in early studies varied. More recently, recognising the difficulty in interpreting results from different studies, the World Health Organization's Task Force on the Long Acting Systemic Agents for Fertility Regulation has produced standardised protocols and matched reagents for radioimmunoassay of synthetic progestogens (Ashan *et al*, 1998). These procedures were used in this South African study and should be used in future studies to improve standardization and between-centre comparability of assay results.

Wide interindividual variability in serum MPA levels has been noted in previous studies (Fotherby *et al*, 1980a; Fraser and Weisberg, 1981; Sang 1994). Findings from this South African study, based on a much larger sample size than those of previous studies, also show wide interindividual variability with trough MPA levels ranging from <0.04 to 1.77ng/ml and levels measured between 29 and 56 days post injection ranging from 0.49 to 3.5ng/ml.

The possibility of MPA levels increasing with successive injections has also been investigated, by a few researchers. For instance, the study undertaken in Thailand by Koetsawang *et al* (1979) reported a higher mean plasma level at the end of the dosing period for those receiving multiple injections than that of those receiving a single dose, although the difference was not significant. Fraser and Weisberg (1981) in reviewing these findings, suggested that no significant difference was found because of the wide

interindividual variation within each group and recommended further investigation. In an early review of Depo-Provera® studies, Schwallie (1974) presented data (Depo-Provera Protocol 9A) which showed no accumulation of MPA when comparing median serum levels after the first and fifth injection period. This South African study demonstrated a slight tendency towards increased MPA levels at the end of the dosing interval with longer duration of use. However the wide interindividual variability precluded the possibility of determining whether or not this was a real trend. In addition, this study, like that of Koetsawang *et al* (1979) was cross-sectional. A prospective study, which follows DMPA use in the same women over time would be required to determine if accumulation actually occurs.

The possible influence of weight, BMI and ethnicity on MPA levels has been studied (Fotherby *et al*, 1980b; Fotherby and Koetsawang, 1982; Bassol *et al*, 1984; Garza-Flores *et al*, 1994; Sang, 1994). In one of these studies which compared the rate of uptake and metabolism of DMPA in obese and thin women, no difference in MPA serum levels was found between the two groups (Fotherby and Koetsawang, 1982). However another study reported a tendency for DMPA to be absorbed more rapidly in thin than in obese women (Garza-Flores *et al*, 1994). Bassol *et al* (1984) reported a longer delay in resumption of ovulation in Mexican than in Thai women, which they considered to be in keeping with the longer time for disappearance of MPA from the serum of the Mexican women. In another study undertaken amongst Indian and Swedish women (Fotherby *et al*, 1980b), luteal activity was found to return later in the Swedish women, but no difference was found between the two populations in time taken for plasma MPA to become undetectable. In this study of African, Indian, and White South Africans, serum MPA

levels at the end of the dosing interval were not found to vary according to weight, BMI or ethnicity.

Although few concentrations (n=3) were measured in this South African study in the time period after injection when peak levels were likely to occur, these measurements (3.51ng/ml at day 4 post injection; 4.15ng/ml at day 7 post injection; 4.27ng/ml at day 20 post injection) were consistent with peak concentrations reported in most of the literature (see Table 2.1.2).

More recent studies on the pharmacokinetics of the combination progestogen/oestrogen injectables suggest differences in the pharmacokinetics of MPA based on weight and ethnicity (WHO, 1987; Rahimy *et al*, 1999a). Rahimy *et al* (1999a) found that MPA tended to be absorbed more quickly by thin women, and that trough levels were higher in thin than in obese women. Similarly, the WHO study (1987) found higher peak MPA levels were attained in Thai than in Mexican women. It is possible that pharmacokinetic differences, based on weight and ethnicity, may occur in the absorption phase of MPA and may manifest at peak levels. Conclusions cannot be drawn from this South African study as few peak levels were measured.

Further studies examining peak levels are needed to investigate weight and ethnic variability with MPA, as this could explain why some women demonstrate a poorer side effect profile with DMPA use. Based on this analysis of trough levels and on literature findings, it seems unlikely that weight or population differences in pharmacokinetics affect efficacy of DMPA.

2.4.2 POPULATION PHARMACOKINETIC ANALYSIS

As already discussed, a few studies have described serum MPA levels, including maximum (peak) and minimum (trough) concentrations, half-life ($t_{\frac{1}{2}}$) and the steady-state area under the serum-concentration time curve (AUC), after intramuscular injection of 150mg of DMPA. However, as noted, these studies are limited; the sample sizes were small, a variety of different assay techniques were used, MPA levels were often investigated after only one dose and none studied levels in African women. Further, an extensive search has yielded no published studies, using either compartmental or noncompartmental methods, which describe the pharmacokinetic parameters clearance (CL) and volume of distribution (V) for MPA after injection of 150mg of DMPA. Since values for CL and V are not described, relationships between these parameters and subject characteristics are also not documented.

This is the first time that a pharmacokinetic model has been developed to describe the population pharmacokinetics of MPA.

A one compartment model, parameterized in terms of apparent clearance and apparent volume, adequately described MPA concentrations in the later part of the dose interval. However, higher concentrations measured within the first month, were not well described, with observed measurements being higher than those predicted by the model. Wade *et al*, (1994) explain that simple (parsimonious) pharmacokinetic models may appropriately be used for a variety of reasons such as where data obtained at steady state are insufficient to characterize a distribution phase. Since, in this South African study, too few measurements were made early in the dosing cycle there is a weak prediction of high concentrations in some women, and it is appropriate that the most parsimonious model be

used. A more complex model for the input function may provide a better definition of the absorption phase, and it is possible that a two compartmental model may better describe concentrations early in the dosing cycle. In order to better define the absorption phase, a study which measures serum MPA levels at least every week for the first four weeks after injection would have to be carried out.

When the nature of the data prevents characterization of the whole model, parts of the model, often input, can be fixed according to the best *a priori* information (Wade *et al*, 1993). The MPA model developed here included an input rate parameter (D1), which was fixed at 4 days, based on the literature and after performing a sensitivity analysis to determine the most suitable value as suggested by Wade *et al* (1993).

DMPA is administered by the intramuscular route and is slowly absorbed from the intramuscular site. As the elimination is not true MPA elimination, but is rate limited by absorption, the model is a 'flip-flop' model with the absorption rate from the depot site being determined and not the true elimination (Gibaldi and Perrier, 1975).

As discussed previously, the possible influence of weight, BMI, ethnicity and duration of use on MPA levels has been studied (Fotherby *et al*, 1980b; Fotherby and Koetsawang, 1982; Bassol *et al*, 1984; WHO, 1987; Garza-Flores *et al*, 1994; Sang, 1994; Rahimy *et al*, 1999b). While these covariates were found to affect MPA levels in some studies, no differences were found in others. Moreover, the sample sizes of the studies were often too small for findings to be conclusive.

In this South African study trough MPA levels of DMPA users were not found to vary according to weight, BMI or ethnicity. The possible influence of covariates including weight, BMI and duration of use, were further tested in the population analysis. No significant relationships were found between the covariates tested and pharmacokinetic parameters. In testing the influence of ethnicity on CL/F or V/F, and CL/F and V/F, the race covariate was found to have a marginally significant influence on V/F. However a study with a larger sample size would be needed to determine if race is a statistically significant variable. Studies on the pharmacokinetics of the combination oestrogen/progestogen injectables seem to suggest that differences in the pharmacokinetics of MPA based on weight and ethnicity may occur in the absorption phase of MPA and may manifest at peak levels rather than at trough levels (World Health Organization, 1987; Rahimy *et al*, 1999b). A study examining peak levels would be required to investigate weight and ethnic variability with MPA and to define whether or not these covariates may explain why some women demonstrate a poorer side effect profile with DMPA use.

Interindividual variability (IIV) in both CL/F (33%) and V/F (71%) was found. The IIV for CL/F and V/F was not explained by any of the covariates. While wide IIV in the pharmacokinetics of contraceptive steroids, including MPA, has been emphasized (Gupta *et al,*1979; Koetsawang *et al*, 1979; Fotherby *et al*, 1980b; Fotherby, 1983; Fotherby, 1990; Shenfield and Griffin, 1991; Sang 1994; Rahimy *et al*, 1999b; Kaunitz, 2000), no population pharmacokinetic analyses of contraceptive steroids have previously been published to allow for comparison. However the IIV of MPA on CL/F and V/F found in this study was not dissimilar to those of other drugs reported in the pharmacokinetic

literature (Lalonde *et al*, 1996; Bruno *et al*, 1997; Mould *et al*, 2002; Staatz *et al*, 2002; Csajka *et al*, 2003).

This study was not designed to collect data for the assessment of inter-occasion variability (IOV) as for most women, information for only one dose interval was collected. Nevertheless, the possibility of IOV was investigated, but the inclusion of inter-occasion random effects did not offer much improvement to the model. Karlsson and Sheiner (1993, p.735) warn that if IOV is ignored, "predictable biases occur in parameter estimates and previously nonexistent period effects are found". It is recommended therefore that the future study, proposed earlier, be designed as a longitudinal study which includes a number of dosing intervals and measures both peak and trough MPA levels.

Pharmacokinetic parameters

This is the first study which has yielded values for apparent clearance and apparent volume of distribution for MPA after intramuscular injection of 150mg of DMPA. The values derived are 1080L/d and 86200L respectively. Since this is the first contribution to the literature on CL and V values of MPA it is difficult to determine the validity of these values. Only one published study which records a value for the CL of MPA was found in the literature (Gupta *et al*, 1979). This study determined the mean metabolic clearance rate (MCR) of MPA from the steroid disappearance curve after a single intravenous injection of [^{3}H]MPA (50 μCi) and found it to be 1668 ± 146 (SEM) litres per day.

Studies undertaken on the combined progestogen/oestrogen injectable products which are given once a month report 0-28 day AUC values. If one calculates the clearance values (CL=dose/AUC) one can obtain a value for clearance: The average $AUC_{0\text{-}28}$ for MPA

after the third monthly injection of 25mg MPA/5mg estradiol cyprionate was determined by Rahimy *et al* (1999b), using noncompartmental methods, to be 21.51ng/day/ml giving a mean value for CL of 1162L/day. Zhou *et al* (1998), on a model-independent basis, estimated the average $AUC_{0\text{-}28}$ for MPA after the 1st dose (25mg MPA/5mg estradiol cyprionate) to be 21.58ng/day/ml and after the 6^{th} dose to be 36.89ng/day/ml (≈95.45nmol·day/L). The mean values for CL calculated from the $AUC_{0\text{-}28}$ values are 1158 and 678L/day respectively. These values for CL, especially the CL value reported by Rahimy *et al* (1999b) are similar to the CL/F determined in this present study.

The average V/F for MPA estimated in this present study seems large and there are no published values for MPA volume of distribution with which to compare it. In the study by Gupta *et al* (1979) described above, it was reported that V_0 could not be accurately estimated due to the variable finite time required to take the early samples and thus they were unable to estimate the volume of distribution. A possible explanation for the large V/F is that, since MPA is slowly absorbed from the intramuscular site, absorption and elimination are taking place concurrently earlier in the dosing interval. The study proposed earlier, with more measurements taken in the absorption phase, may estimate V/F better.

The apparent half-life of MPA determined in the present study ($t_{½}$/F=55.3 days) was similar to the half-life of MPA for Mexican women in two of three studies cited by Garza Florez *et al* (1994): $t_{½}$=56.4days (n=5) and $t_{½}$=62.5days (n=4). The half-life values cited by these authors across the three studies (including Thai and Mexican women) were highly variable ranging from 24 to 112 days (see Table 2.1.3 in Chapter 2.1). The USP DI (2002) and the US approved physician prescribing information published on the

manufacturer's website (Pharmacia and Upjohn, 1999) report an apparent $t_{½}$ for the 150mg intramuscular dose of approximately 50 days -- very similar to the South Africa study finding.

In summary, this is the first study which estimates the pharmacokinetic parameters apparent clearance (CL/F) and apparent volume of distribution (V/F) for MPA after injection of 150mg of DMPA. The population pharmacokinetic model, developed using Non-linear Mixed Effects Modelling (NONMEM), is simple. The development of more complicated models would require more data for each individual, particularly in the absorption phase. The CL/F estimated was in accordance with the little published information available. The influence of covariates on CL/F and V/F of MPA were also investigated, but no significant covariates were identified and findings from some previous studies suggesting that weight, BMI or ethnicity influence the pharmacokinetics of MPA were not confirmed. Based on this analysis of largely trough levels and on literature findings, it seems unlikely that weight or population differences in pharmacokinetics affect efficacy of DMPA. Further investigation of the effect of covariates on peak levels is needed. It is recommended that a longitudinal study be undertaken with serum MPA levels measured at least every week for the first four weeks after injection. Since norethisterone oenanthate is also widely used in South Africa and elsewhere, a similar pharmacokinetic study of norethisterone oenanthate should be carried out.

Appendices to Section 2

APPENDIX 2.2.1

- Instructions to family planning clinic providers
- Client information sheet – English
- Client information sheet – Zulu

INSTRUCTIONS TO FAMILY PLANNING CLINIC NURSING STAFF

RESEARCH STUDY ON DEPO-MEDROXYPROGESTERONE ACETATE

AIMS AND OBJECTIVES OF THE STUDY

Aim : To undertake a preliminary investigation of the population pharmacokinetics of Depo-medroxyprogesterone acetate.

Objectives : (i) To assess the variation in the pharmacokinetics of DMPA.
(ii) To establish relationships between physiological, pathological, environmental or genetic factors and kinetic parameters of DMPA.

DURATION OF STUDY: October to December 1996/January 1997

SELECTING CLIENTS

Number to be selected: **At least 40** clients who use the injectable contraceptive to be selected

These 40 women to be selected in the first month of the study (Oct. 96), on days and at times when it is convenient for staff.

Follow up visits to be arranged for 4 weeks time and 8 weeks time.

Select those most likely to be able to return - e.g. those who live nearby.

Anyone can be selected, irrespective of whether or not they have had the injection before. Women of any age, race, weight etc. can be selected.

If someone not initially selected comes back to the clinic before her next dose of the injection is due (for example because of some problem being experienced), it would be very useful to include her in the study and take a blood sample. She should also be asked to return for two more samples if this is possible.

INFORMATION/EXPLANATIONS FOR CLIENTS

1. Give an information pamphlet to the client
2. Fill in return dates on the information pamphlet
3. Ask the patient to sign the consent form (the consent form should be retained at the clinic)

Points to be highlighted include:

- That a blood sample will have to be taken
- That the client should return in 4 weeks time and in 8 weeks time (fill in dates on information pamphlet given to clients).
- That they will have to answer some questions.
- That the information they give will be regarded as strictly confidential.
- That they will receive a small "gift" for participating in the study.
- That we are most grateful for their help.

INTERVIEWING CLIENTS AND FILLING IN THE QUESTIONNAIRE

A short questionnaire has been provided for interviewing each client selected. The questions should be self explanatory, but if you experience any problems please let us know.

- Only one questionnaire has been designed to include the first time a blood sample is taken (pages 1 - 4) and the second visit (page 5) and the third visit (page 6). The questionnaires should therefore be retained and accessible for the duration of the study.

RECORDING INFORMATION ON CLIENT CLINIC RECORD

- Coloured stickers are provided to stick on the client clinic card to identify them as subjects in this study
- Client return dates i.e. after 4 weeks and 8 weeks should also be recorded on the client clinic record.

BLOOD SAMPLING

Collection :

- Blood samples should be collected in 2 x 7ml plain tubes to be provided by the City Health Department (CHD).
- 21 gauge needles should be used (to be provided by University of Durban Westville [UDW])

Labeling blood tubes :

The following information should be recorded on the label of each blood sample taken :

1. Client name
2. Client Clinic No.
3. Clinic name - i.e. Township, Bluff or Lancer's Road.
4. Date of collection
5. Time of collection

Storing blood samples in the clinic :

Blood samples should be stored in the clinic fridge (**not freezer**) until transportion to the next destination.

Transporting blood samples :

- The blood samples must be transported in cooler boxes to be provided by the CHD.
- Samples from Chatsworth and Bluff Clinics must be transported to Lancer's Rd Clinic within 24 hours of being collected. CHD will arrange (Audrey Clarke or Louise Barnaschone) for the bloods to be taken to Lancer's Rd, Clinic.
- UDW staff will collect blood samples from all three clinics from Lancer's Rd Clinic on a daily basis.

CONTACT PHONE NUMBERS

Jenni Smit : Dept of Pharmacy, UDW, PB X54001, Durban 4000
Phone : 8202891(office), 8202358 (secretary), 237810 (home)
0832697475 (cell phone)
Fax : 8202792
e-mail : weah96@pixie.udw.ac.za

Lynn McFadyen : Dept. of Pharmacology, UDW, PB X54001, Durban 4000
Phone : 8202720 (office), 815733 (home)

FEEDBACK ON RESULTS

On completion of this study, a seminar on the findings will be held for participating CHD Staff. Copies of the research report and any publications will be made available the City Health Department.

We would like to take this opportunity to thank City Health Department staff very much for all their assistance in this study. It is very much appreciated.

Jenni Smit
(Senior Lecturer, Pharmacy Dept.)

Lynn McFadyen
(Ass. Professor, Pharmacology Dept.)

INFORMATION TO CLIENTS ABOUT THIS RESEARCH STUDY ON THE USE OF THE CONTRACEPTIVE INJECTION

WHO IS DOING THE STUDY ?
This study is being undertaken by researchers from the Departments of Pharmacology and Pharmacy of the University of Durban-Westville.

WHAT IS THE STUDY ALL ABOUT ?
We know that many women have worrisome problems when they use the injection. We hope that by doing this research we will be able to lessen these problems and in this way help women who wish to use the injection.

HOW WILL THE STUDY BE DONE ?
We would like to take three blood samples from you which will tell us what happens in your body when you get an injection. We will have to take a blood sample from you **to-day** just before you get your injection, and then we would like to ask you if you would **please** come back **in one month** so we can take another blood sample. It will be necessary for you to come back again in **two months' time** for the last measurement.

We know that this is more trouble for you. But you would really be helping us a lot if you would agree to do it. To say thank you to you for helping us, we will give you a small gift on your last visit to us. We believe that this is a very important study and without your help it can't be done.

WHY IS THE STUDY IMPORTANT ?
What we find from this study could improve the life of many women who use the injection.

RESEARCHERS' PROMISE :
The people doing this study promise that no-one will be told anything about you or about anything you tell us. **Your name will not be used at all and no-one will be told that you come to this clinic or that you use the injection.**

WHAT YOU HAVE TO DO ?
If you are willing to participate in this study, will you please :

- sign the consent form attached to this letter
- answer some questions that the clinic sister will ask you
- allow the clinic sister to take a blood sample
- return to this family planning clinic on the following dates :
  .....day, .../...../96
  .....day, .../...../96

THANK YOU FOR YOUR HELP

Jenni Smit
(Senior Lecturer, Pharmacy Dept.)

Lynn Mc Fadyen
(Ass. Prof, Pharmacology Dept.)

ZULU TRANSLATION OF CLIENT INFORMATION

INCAZELO KUBASEBENZISI MJOVO MAYELANA NOCWANINGO NGOKUSEBENZA KOMJOVO WOHLELOMNDENI

UBANI OZOQHUBA LOLUCWANINGO ?
Lomsebenzi wokucwaninga uzoqhutshwa ngabacwaningi bomnyango wezokuthakwa nokukhishwa kwemithi yokwelapha eNyuvesi yase- Durban-Westville.

LUZOSIZA NGANI LOLUCWANINGO ?
Siyazi ukuthi abesifazane abaningi bahlanga- bezana nezinkinga eziningi ezibakhathazayo uma besebenzisa umjovo. Sinethemba lokuthi ngokwenza lolucwaningo sizokwazi ukunciphisa lezizinkinga, ngalendlela kusizakale labo besifazane abafuna ukusebenzi- sa umjovo.

LUZOKWENZWA KANJANI LOLUCWANINGO ?
Sifisa ukuthatha igazi lokusampulisa iziqubu ezintathu kuwena ukuze sazi ukuthi kwenzekani emzimbeni wakho uma ukade ujova. Kuzomele sithole isampula Legazi Kuwena namhlanje ngaphambi kokuba ujove bese siphinda sicele ukuba ubuye esikhathini esiyinyanga sithathe elinye isampula legazi. Kuyodingeka ubuye ezinyangeni ezimbili ukunikeza isampula legazi lokugcina.

Siyazi ukuthi sikunikeza umthwalo odulele Kodwa uyobe usisize Kakhulu uma uvuma ukuba yingxenye yaloluhlelo. Ukukubonga ngokusisiza, siyokunika isipho esincane mhlazane ufika okokugcina. Sikholwa ukuthi lolucwaningo lungolubaluleke kakhlulu Kanti lungeka lwaba yimpumelolo ngaphandle Kosizo lwakho.

KUNGANI LOLUCWANINGO LUBALULEKILE ?
Sikholwa ukuthi konke esiyokuthola ocwaningweni kungasiza ukwenza ngcono izimpilo zabesifazane abaningi abasebenzisa umjovo ukuhlela.

ISETHEMBISO SABACWANINGI :
Abantu abazobe benza loluwaningo bayakuthembisa ukuthi akukho muntu oyotshelwa utho ngawe noma badlulisele phambili loko obatshele khona. Igama lakho ngeke lisetshenziswe nangengozi, akekho futhi oyotshelwa ukuthi uyeza kulomtholampilo noma uyajova.

OKUFANELE UKWENZE ?
Uma uzimisele ukuba ingxenye yalolucwaningo, sicela :

- Usayinda imvume kulelipheshana elihambisana nalencwadi
- Uphendule imibuzo ozoyibuzwa ngumhlengikazi eMtholampilo
- Uvumele umhlengikazi athathe isampula legazi
- Uphinde uze kulomtholampilo wohlelomndeni ngalezi zinsuku ezilandelayo :
  ....., .../...../96
  ....., .../...../96

SIYALUBONGA USIZO LWAKHO

Jenni Smit
(Senior Lecturer, Pharmacy Dept.)

Lynn Mc Fadyen
(Ass. Prof, Pharmacology Dept.)

APPENDIX 2.2.2

INTERVIEW SCHEDULE FOR DMPA USERS ATTENDING FAMILY PLANNING CLINICS

POPULATION PHARMACOKINETICS OF DEPO-MEDROXYPROGESTERONE ACETATE

INTERVIEW SCHEDULE FOR DMPA USERS

PART I : FIRST BLOOD SAMPLE

Client to return on : .....day,...../...../96.
.....day,...../...../96.

SECTION 1 : CLASSIFICATION

1. Client No: .....

2. Date : ...../...../96 Time : .....

3. Clinic : Township Centre ☐ Lancers Rd ☐ Bluff ☐

SECTION 2 : PERSONAL DETAILS

4. Name : .....

5. Phone (for follow-up) .....

6. Address :
.....
.....
(if unable to get an exact address, indicate general area of residence e.g. Bayview, Brighton Beach, Fynnlands, Clairwood, Merebank, Durban Central, Umlazi, Inanda, KwaMashu, Berea, etc.)

7. Date of birth : ..... *(or age in years if date of birth is unknown)*

8. Race : African ☐ Indian ☐ Coloured ☐ White ☐

9. Individual Income :

R 0 - R 500 per month	
R 501 - R1000 per month	
R1001 - R2000 per month	
Over R2000 per month	

SECTION 3 : QUESTIONS RELEVANT TO THE USE OF THE CONTRACEPTIVE INJECTION

10. How many children do you have? .....

11. Do you smoke ? Yes ☐ No ☐

12. Why have you decided to use the injectable contraceptive method ?
(don't prompt client)

.....

.....

.....

.....

.....

13. Which of the following are the reasons you are using the injection?
(*more than one box can be ticked)*

I only have to have it every 3 months	
My partner does not know I use contraception	
My friends/relatives don't not know I use contraception	
My friend/relative recommended it	
It was recommended for me at the clinic	
Its a very safe way to prevent pregnancy	
I don't have a period when I'm using it	
It suits me (few problems/side effects)	
other (state which)	

14. What problems or side effects have **you** had since your last injection/visit . *(don't prompt client).*

.....
.....
.....
.....
.....
.....

15. Which of the following side effects or problems have **you** had when taking the injection?*(more than one box can be ticked)*

no period/menstruation	
heavy and or longer period	
spotting	
irregular periods	
painful periods	
headaches	
dizziness	
sweating	
nausea	
weight gain	
bloating of abdomen and breasts	
vaginal moisture increased	
vaginal dryness	
hard to get pregnant after I stop the injection	
loss of libido/don't feel like sex	
depressed mood/feel sad & unhappy	
My hair falls out	
I worry that it may cause cancer	
other (give details)	

16. What other medicines are you using now ?
*(list **all** medications mentioned as specifically as possible*)

.....
.....
.....
.....

SECTION 4 : RELEVANT MEDICAL HISTORY

17. Weight at commencement of injection use .....kg

18. History of relevant medical problems

Condition	Details
Cardiovascular	....
Hepatic	....
Diabetes	....
Headache	....
Recorded problems with inject contraceptive	....

SECTION 5 : USE OF CONTRACEPTIVE INJECTION

19. Brand of contraceptive injection given to-day : Depo Provera ☐
Petogen ☐

20. Date when injectable **last** used : ...../...../.....

21. Brand of contraceptive given at **last visit** : Depo Provera ☐
Petogen ☐
None given ☐

22. Date when injectable **first** used : Specify date of commencement .....
or
Duration of treatment..... years, ...months

SECTION 6 : MEASUREMENTS TO BE TAKEN

23. Weight to-day: .....kg

24. Height : .....cms

25. Blood Pressure .....

26. **OTHER COMMENTS :** .....
.....
.....
.....
.....
.....

PART II : SECOND BLOOD SAMPLE

27. Date : ...../...../96 Time : .....

28. Name : .....

29. Phone (*if changed since first blood sample was taken)* : .....

30. Address (*if changed since first blood sample was taken*):
.....
.....

31. What side effects or problems have **you** had since your last injection/visit ? *(don't prompt client)*
.....
.....
.....
.....
.....
.....

32. What other medicines are you using now ? *(list **all** medications mentioned as specifically as possible*)
.....
.....
.....
.....

USE OF CONTRACEPTIVE INJECTION

33. Brand of contraceptive injection given to-day : Depo Provera ☐
(if given at all) Petogen ☐

34. Date when injectable **last** used : ...../...../.....

MEASUREMENTS TO BE TAKEN

35. Weight to-day: .....kg

36. Blood Pressure .....

37. **OTHER COMMENTS :** .....
.....
.....
.....

PART III: THIRD BLOOD SAMPLE

38. Date : ...../...../96 Time : .....

39. Name : .....

40. Phone (*if changed*) : .....

41. Address (*if changed*):
.....
.....

42. What side effects or problems have **you** had since your last injection/visit ? *(don't prompt client)*
.....
.....
.....
.....
.....

43. What other medicines are you using now ? *(list **all** medications mentioned as specifically as possible*)
.....
.....
.....
.....

USE OF CONTRACEPTIVE INJECTION

44. Brand of contraceptive injection given to-day : Depo Provera ☐
(if given at all) Petogen ☐

45. Date when injectable **last** used : ...../...../.....

MEASUREMENTS TO BE TAKEN

46. Weight to-day: .....kg

47. Blood Pressure .....

48. **OTHER COMMENTS:** .....
.....
.....
.....

BLOOD SAMPLE ON RETURN DATE FOR INJECTION

1. Date : ...../...../96 Time : .....

2. Name : .....

3. Phone (*if changed*) : .....

4. Address (*if changed*):
.....
.....

5. What side effects or problems have **you** had since your last injection/visit ? *(don't prompt client)*
.....
.....
.....
.....

6. What other medicines are you using now ? *(list **all** medications mentioned as specifically as possible*)
.....
.....
.....
.....

USE OF CONTRACEPTIVE INJECTION

7. Brand of contraceptive injection given to-day : Depo Provera ☐
(if given at all) Petogen ☐

8. Date when injectable **last** used : ...../...../.....

MEASUREMENTS TO BE TAKEN

9. Weight to-day: .....kg

10. Blood Pressure .....

11. **OTHER COMMENTS :** .....
.....
.....
.....

THANK YOU VERY MUCH!

APPENDIX 2.2.3

PHARMACOKINETIC DATA FILE PARAMETERS

PHARMACOKINETIC DATA FILE PARAMETERS

A NONMEM data file was constructed with the following parameters (abbreviation in parenthesis): The first 15 client records of this data file are shown in Appendix 3.2.5

Patient number (ID)

Days since dose based on the number of days a dose was given before recruitment into the study (TIME). *[In many cases, the woman would already have been on DMPA and the first blood level, taken on recruitment into the study, would reflect the concentration relating to her previous injection about 84 days ago. In some cases, the woman was a first time user, and hence on recruitment her level would be zero]*

Serum MPA concentration in ng/ml (DV)

Event identification (EVID): 0=observation event, 1=dose event

Steady-state (SS): 1=steady-state, 0=not yet at steady-state

Interdose interval (II)

Dose of DMPA in mg/ml (AMT)

Dose rate (RATE). *[-2=IV infusion of unknown rate or duration. The unknown rate or duration is modelled in the NONMEM analysis]*

Age in years (AGE)

Weight in kg (WT)

Race (RACE). 1=African, 2=Indian, 3=Coloured, 4=White

Smoking (SMOK). 0=nonsmoking, 1=smoker

Serum creatinine levels in umol/L (CREA)

Serum alkaline phosphatase levels in U/L (ALKP)

Serum gamma GT levels in U/L (GAMA)

Serum aspartate transaminase levels in U/L (AST)

Serum alanine aminotransferase levels in U/L (ALT)

Serum total bilirubin levels in umol/L (TBIL)

Serum conjugated bilirubin levels in umol/L (CBIL)

Whether taking anticonvulsant drugs (EPID)

Whether taking antihypertensive drugs (BPD)

Whether taking drugs for diabetes (DIAD)

Whether taking Ovral® (OV)

Whether taking Premarin® (PREM)

Height in centimeters (HT)

Duration of use of DMPA in years (DUR)

Body mass index (BMI)

APPENDIX 2.2.4

PHARMACOKINETIC DATA FILE RECORDS

(First Fifteen Client Records Only)

APPENDIX 2.2.4

Pharmacokinetic data file (first 15 clients only)

# ID	TIME	ug/l DV	EVID	SS	II	mg AMT	RATE	AGE	WT	RACE	SMOK	CREA	ALKP	GAMA	AST	ALT	TBIL	CBIL	EPID	BPD	DIAD	OV	PREM	HT	DUR	BMI
1	0	0	1	1	84	150	-2	20	60	4	0	69	156	17	14	71	12.8	3.9	0	0	0	0	0	0	170	1	20.76
1	87	1.083	0	0	0	0	0	20	60	4	0	69	156	17	14	71	12.8	3.9	0	0	0	0	0	0	170	1	20.76
2	0	0	1	1	84	150	-2	33	70	1	0	78	154	17	20	21	4.6	1.3	0	0	0	0	0	0	153	2	29.9
2	84	0.967	0	0	0	0	0	33	70	1	0	78	154	17	20	21	4.6	1.3	0	0	0	0	0	0	153	2	29.9
3	0	0	1	0	0	150	-2	29	67	1	0	86	153	8	17	12	3.4	0.6	0	0	0	0	0	0	-99	0	27.18
3	83	0.611	0	0	0	0	0	29	67	1	0	86	153	8	17	12	3.4	0.6	0	0	0	0	0	0	-99	0.2	27.18
3	83	0	1	0	0	150	-2	29	67	1	0	86	153	8	17	12	3.4	0.6	0	0	0	0	0	0	-99	0.2	27.18
3	132	1.465	0	0	0	0	0	29	66	1	0	86	153	8	17	12	3.4	0.6	0	0	0	0	0	0	-99	0.4	27.18
3	139	1.197	0	0	0	0	0	29	66	1	0	86	153	8	17	12	3.4	0.6	0	0	0	0	0	0	-99	0.4	27.18
3	167	1.064	0	0	0	0	0	29	66	1	0	86	153	8	17	12	3.4	0.6	0	0	0	0	0	0	-99	0.5	27.18
4	0	0	1	1	84	150	-2	25	66	1	0	80	142	9	14	12	9.6	2.7	0	0	0	0	0	0	165	1	24.24
4	89	0.783	0	0	0	0	0	25	66	1	0	80	142	9	14	12	9.6	2.7	0	0	0	0	0	0	165	1	24.24
4	89	0	1	0	0	150	-2	25	66	1	0	80	142	9	14	12	9.6	2.7	0	0	0	0	0	0	165	1	24.24
4	118	1.948	0	0	0	0	0	25	67	1	0	80	142	9	14	12	9.6	2.7	0	0	0	0	0	0	165	1	24.24
5	0	0	1	0	0	150	-2	32	59	4	1	58	198	20	22	38	7.2	1.7	0	0	0	0	0	0	157	0	23.94
5	36	0.851	0	0	0	0	0	32	56	4	1	58	198	20	22	38	7.2	1.7	0	0	0	0	0	0	157	0.1	23.94
5	57	0.667	0	0	0	0	0	32	57	4	1	58	198	20	22	38	7.2	1.7	0	0	0	0	0	0	157	0.2	23.94
6	0	0	1	1	84	150	-2	25	53	1	0	75	170	13	14	19	6.9	2.8	0	0	0	0	0	0	162	0.2	20.2
6	78	0.743	0	0	0	0	0	25	53	1	0	75	170	13	14	19	6.9	2.8	0	0	0	0	0	0	162	0.4	20.2
6	78	0	1	0	0	150	-2	25	53	1	0	75	170	13	14	19	6.9	2.8	0	0	0	0	0	0	162	0.4	20.2
6	109	3.502	0	0	0	0	0	25	53	1	0	75	170	13	14	19	6.9	2.8	0	0	0	0	0	0	162	0.5	20.2
6	161	0.685	0	0	0	0	0	25	55	1	0	75	170	13	14	19	6.9	2.8	0	0	0	0	0	0	162	0.7	20.2
7	0	0	1	1	84	150	-2	32	70	1	0	89	101	8	9	12	8.7	2.1	0	0	0	0	0	0	155	4	29.14
7	84	1.004	0	0	0	0	0	32	70	1	0	89	101	8	9	12	8.7	2.1	0	0	0	0	0	0	155	4	29.14
7	84	0	1	0	0	150	-2	32	70	1	0	89	101	8	9	12	8.7	2.1	0	0	0	0	0	0	155	4	29.14
7	112	3.486	0	0	0	0	0	32	68	1	0	89	101	8	9	12	8.7	2.1	0	0	0	0	0	0	155	4	29.14
7	140	1.521	0	0	0	0	0	32	69	1	0	89	101	8	9	12	8.7	2.1	0	0	0	0	0	0	155	4	29.14
7	154	1.734	0	0	0	0	0	32	67	1	0	89	101	8	9	12	8.7	2.1	0	0	0	0	0	0	155	0	24.97
8	0	0	1	0	0	150	-2	34	60	1	0	89	148	18	15	15	16.8	3.3	0	0	0	0	0	0	155	0.2	24.97
8	84	0.471	0	0	0	0	0	34	60	1	0	89	148	18	15	15	16.8	3.3	0	0	0	0	0	0	155	0.2	24.97
8	84	0	1	0	0	150	-2	34	60	1	0	89	148	18	15	15	16.8	3.3	0	0	0	0	0	0	155	0.3	24.97
8	112	1.986	0	0	0	0	0	34	61	1	0	89	148	18	15	15	16.8	3.3	0	0	0	0	0	0	155	0.4	24.97
8	140	1.345	0	0	0	0	0	34	65	1	0	89	148	18	15	15	16.8	3.3	0	0	0	0	0	0	155	0.5	24.97
8	165	0.998	0	0	0	0	0	34	64	1	0	89	148	18	15	15	16.8	3.3	0	0	0	0	0	0	163	2	17.69
9	0	0	1	1	84	150	-2	21	47	2	0	78	113	11	10	7	4.6	0.9	0	0	0	0	0	0	163	2	17.69
9	83	0.686	0	0	0	0	0	21	47	2	0	78	113	11	10	7	4.6	0.9	0	0	0	0	0	0	155	1	24.56
10	0	0	1	1	84	150	-2	21	59	2	1	71	114	16	9	10	6.3	1.8	0	0	0	0	0	0	155	1	24.56
10	84	0.877	0	0	0	0	0	21	59	2	1	71	114	16	9	10	6.3	1.8	0	0	0	0	0	0	155	1	24.56
10	84	0	1	0	0	150	-2	21	59	2	1	71	114	16	9	10	6.3	1.8	0	0	0	0	0	0	155	0	22.48
10	156	1.527	0	0	0	0	0	21	60	2	1	71	114	16	9	10	6.3	1.8	0	0	0	0	0	0	155	0.2	22.48
11	0	0	1	0	0	150	-2	25	54	2	0	66	129	8	15	14	12.5	3	0	0	0	0	0	0	155	0.2	22.48
11	84	1.228	0	0	0	0	0	25	54	2	0	66	129	8	15	14	12.5	3	0	0	0	0	0	0	155	0.3	22.48
11	84	0	1	0	0	150	-2	25	54	2	0	66	129	8	15	14	12.5	3	0	0	0	0	0	0	155	0.4	22.48
11	112	1.853	0	0	0	0	0	25	52	2	0	66	129	8	15	14	12.5	3	0	0	0	0	0	0	-99	0.2	22.31
11	140	1.105	0	0	0	0	0	25	55	2	0	66	129	8	15	14	12.5	3	0	0	0	0	0	0	-99	0.5	22.31
12	0	0	1	1	84	150	-2	18	55	1	0	74	130	5	11	8	14.1	3.9	0	0	0	0	0	0	-99	0.5	22.31
12	84	0.819	0	0	0	0	0	18	55	1	0	74	130	5	11	8	14.1	3.9	0	0	0	0	0	0	-99	0.6	22.31
12	84	0	1	0	0	150	-2	18	55	1	0	74	130	5	11	8	14.1	3.9	0	0	0	0	0	0	-99	0.6	22.31
12	112	1.237	0	0	0	0	0	18	57	1	0	74	130	5	11	8	14.1	3.9	0	0	0	0	0	0	-99	0.7	22.31
12	140	0.577	0	0	0	0	0	18	55	1	0	74	130	5	11	8	14.1	3.9	0	0	0	0	0	0	165	0	18.73
12	161	0.758	0	0	0	0	0	18	55	1	0	74	130	5	11	8	14.1	3.9	0	0	0	0	0	0	165	0.2	18.73
13	0	0	1	0	0	150	-2	17	51	4	1	79	140	9	11	11	10.4	2.8	0	0	0	0	0	0	150	5	22.22
13	84	0.02	0	0	0	0	0	17	51	4	1	79	140	9	11	11	10.4	2.8	0	0	0	0	0	0	150	5	22.22
14	0	0	1	1	84	150	-2	28	50	2	0	77	226	33	15	21	11.8	1.9	0	0	0	0	0	0	150	5	22.22
14	84	1.131	0	0	0	0	0	28	50	2	0	77	226	33	15	21	11.8	1.9	0	0	0	0	0	0	150	5	22.22
14	84	0	1	0	0	150	-2	28	50	2	0	77	226	33	15	21	11.8	1.9	0	0	0	0	0	0	150	5	22.22
14	154	0.88	0	0	0	0	0	28	55	2	0	77	226	33	15	21	11.8	1.9	0	0	0	0	0	0	150	2	28.44
15	0	0	1	1	84	150	-2	37	64	1	0	87	94	9	14	12	8.2	0.3	0	0	0	0	0	0	150	2	28.44
15	92	1.003	0	0	0	0	0	37	64	1	0	87	94	9	14	12	8.2	0.3	0	0	0	0	0	0	150	2	28.44
15	92	0	1	0	0	150	-2	37	64	1	0	87	94	9	14	12	8.2	0.3	0	0	0	0	0	0	150	2	28.44
15	119	3.956	0	0	0	0	0	37	63	1	0	87	94	9	14	12	8.2	0.3	0	0	0	0	0	0	150	2	28.44

APPENDIX 2.3.1

RUN RECORD:

SUMMARY OF MAIN RUNS CONSTRUCTED DURING THE MODEL BUILDING PROCESS

RUN RECORD: SUMMARY OF MAIN RUNS CONTRUCTED DURING MODEL BUILDING PROCESS

Run	Comments	Termination	OFV	CL/F (L/day)	V/F (L)
1	1. Run 1 (thesis) based on run Lyn2 estimation of residual variability datdmpa26 2. Structural Model One compartment D1=7 days 3. Covariate model None 4. Interindividual variability Exp etas on CL & V - Correlation between 5. Residual variability Proportional - not fixed 6. Other	MINIMIZATION SUCCESSFUL	-216.262	1020	67600
2	1. Run 2 (thesis) = Lyn3 - Removed all unnecessary code and added COV step datdmpa26 2. Structural Model One compartment D1 fixed at 7 days 3. Covariate model None 4. Interindividual variability Exp etas on CL & V & Correlation 5. Residual variability Proportional -	MINIMIZATION SUCCESSFUL	-216.262	1020	67600
3	1. Run 3 (thesis)=Lyn3 - Removed all unnecessary code and added COV step Use FOCE estimation method - usually standard these days (or FOCE with interaction) datdmpa26 2. Structural Model One compartment D1 fixed at 7 days 3. Covariate model None 4. Interindividual variability Exp etas on CL & V & Correlation 5. Residual variability Proportional - note different parameterisation of sigma!	MINIMIZATION SUCCESSFUL	-227.481	1100	90000
4	1. Run 4 (thesis)=Lynn 6 based on run 5 - D1 estimated plus eta Use FOCE datdmpa26 2. Structural Model One compartment D1 estimated 3. Covariate model None 4. Interindividual variability Exp etas on CL & V & Correlation & D1 5. Residual variability Proportional - 6. Other	MINIMIZATION SUCCESSFUL	-233.345	1090	90200
5	1. Run 5 (thesis) =lyn8 - Check fixed value of D1 Use FOCE datdmpa26 2. Structural Model One compartment D1 fixed at 10 days 3. Covariate model None 4. Interindividual variability Exp etas on CL & V & correlation 5. Residual variability Proportional -	MINIMIZATION SUCCESSFUL	-200.348	1130	91500
6	1. Run 6 (thesis) = lyn9 - Check fixed value of D1	MINIMIZATION	-232.612	1100	89600

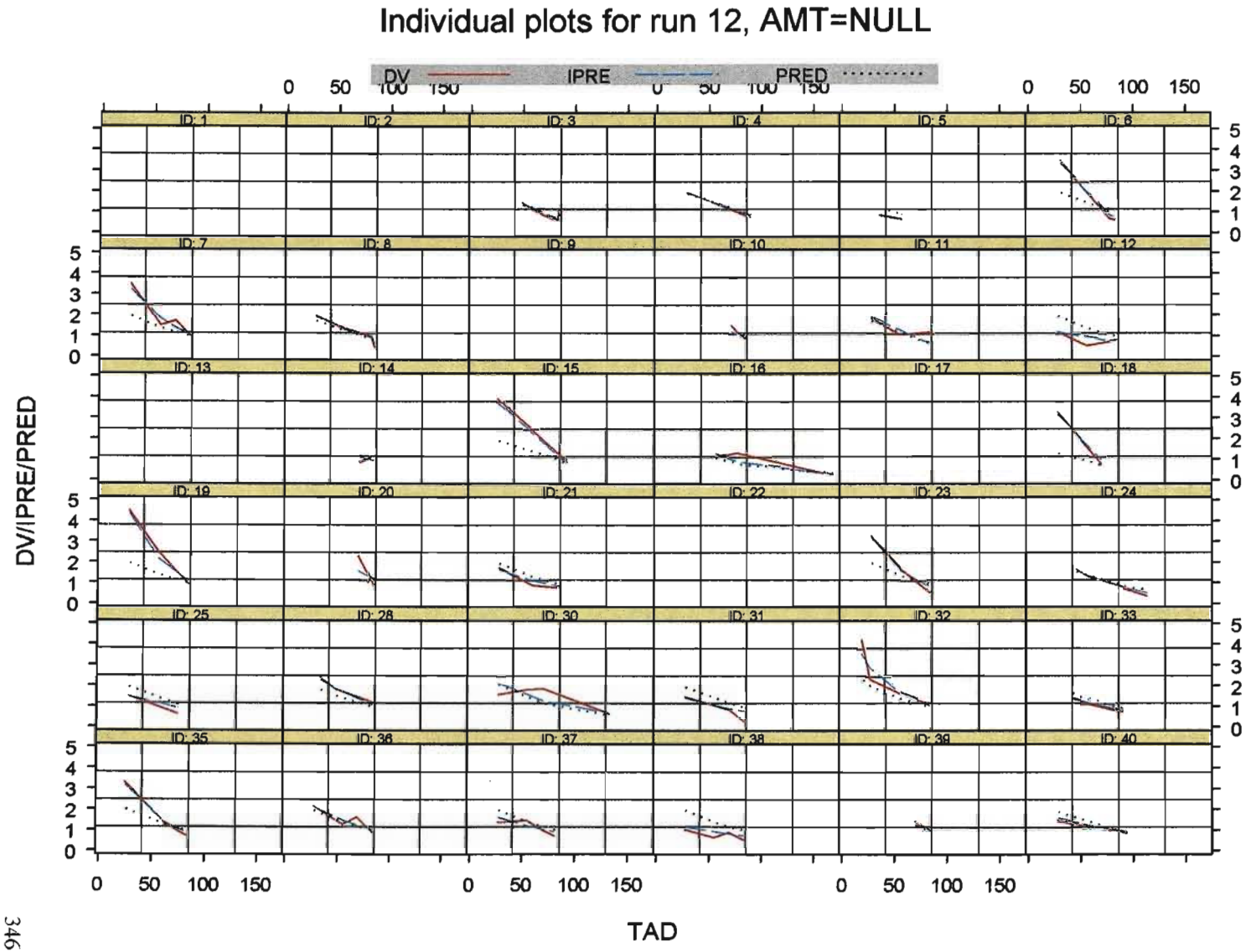
	Use FOCE datdmpa26 2. Structural Model One compartment D1 fixed at 5 days 3. Covariate model None 4. Interindividual variability Exp etas on CL & V & Correlation 5. Residual variability Proportional -	SUCCESSFUL			
7	1. Run 7 (thesis) =lyn10 - Check fixed value of D1 Use FOCE datdmpa26 2. Structural Model One compartment D1 fixed at 3 days 3. Covariate model None 4. Interindividual variability Exp etas on CL & V & Correlation 5. Residual variability Proportional -	MINIMIZATION SUCCESSFUL	-233.334	1080	89100
8	1. Run 8 (thesis)=lyn11 - Check fixed value of D1 Use FOCE datdmpa26 2. Structural Model One compartment D1 fixed at 4 days 3. Covariate model None 4. Interindividual variability Exp etas on CL & V 5. Residual variability Proportional -	MINIMIZATION SUCCESSFUL	-233.462	1090	89600
9	1. Run 9 (thesis) =lyn14 - Check fixed value of D1 Use FOCE datdmpa26 2. Structural Model One compartment model with first order absorption 3. Covariate model None 4. Interindividual variability Exp etas on CL & V & Correlation 5. Residual variability Proportional -	MINIMIZATION SUCCESSFUL	-232.952	1060	87400
10	1. Run 10 (thesis) =lyn15 based - estimating ka Use FOCE datdmpa26 2. Structural Model One compartment model with first order absorption - upper bound on ka 3. Covariate model None 4. Interindividual variability Exp etas on CL & V & Correlation 5. Residual variability Proportional -	MINIMIZATION SUCCESSFUL	-233.159	1080	88500
11	1. Run 11 (thesis)=lyn16 - eta on ka Use FOCE datdmpa26 2. Structural Model One compartment model with first order absorption - 3. Covariate model None 4. Interindividual variability Exp etas on CL & V & Correlation & ka 5. Residual variability Proportional -	MINIMIZATION SUCCESSFUL	-233.161	1080	88400

12	1. Run 12 (thesis) =lyn17- Use FOCE datdmpa26 2. Structural Model One compartment D1 fixed at 4 days 3. Covariate model None 4. Interindividual variability Exp etas on CL & V & correlation 5. Residual variability Proportional and additive -	MINIMIZATION SUCCESSFUL	-241.970	1080	86200
13	1. Run 13 (thesis)=lyn18 Use FOCE datdmpa26 2. Structural Model One compartment D1 fixed at 4 days 3. Covariate model None 4. Interindividual variability Exp etas on CL & V No correlation 5. Residual variability Proportional and additive -	MINIMIZATION SUCCESSFUL	-193.794	1000	63900
14	1. Run 14 (thesis) =lyn19 Use FOCE datdmpa26 2. Structural Model One compartment D1 fixed at 4 days 3. Covariate model None 4. Interindividual variability Exp etas on CL & V no correlation Eta on F1 5. Residual variability Proportional and additive -	MINIMIZATION SUCCESSFUL	-209.067	1040	70300
15	1. Run 15 (thesis) lyn23 Use FOCE datdmpa26iov.csv 2. Structural Model One compartment D1 fixed at 4 days 3. Covariate model None 4. Interindividual variability Exp etas on CL & V 5. Residual variability Proportional and additive -	MINIMIZATION SUCCESSFUL	-247.931	1090	88400
16	1. Run 16 (thesis)= lyn24 Use FOCE datdmpa26iov.csv 2. Structural Model One compartment D1 fixed at 4 days 3. Covariate model None 4. Interindividual variability Exp etas on CL & V 5. Residual variability Proportional and additive -	MINIMIZATION SUCCESSFUL	-247.931	1090	88300
17	1. Run 17 (thesis) based on run12 (thesis) Use FOCE datdmpa27.csv 2. Structural Model One compartment D1 fixed at 4 days 3. Covariate model BMI on CL 4. Interindividual variability Exp etas on CL & V & correlation 5. Residual variability Proportional and additive -	MINIMIZATION SUCCESSFUL	-242.391	1070	83600
18	1. Run 18 (thesis) based on run12 (thesis) Use FOCE datdmpa27.csv 2. Structural Model One compartment D1 fixed at 4 days	MINIMIZATION SUCCESSFUL	-242.290	1080	84400

	3. Covariate model BMI on V 4. Interindividual variability Exp etas on CL & V & correlation 5. Residual variability Proportional and additive -				
19	1. Run19 based on 12 (thesis) Use FOCE 2. SMOK on CL	MINIMIZATION SUCCESSFUL	-242.107	1080	85900
20	1. Run20 based on 12 (thesis) Use FOCE 2. SMOK on V	MINIMIZATION SUCCESSFUL	-243.366	1080	84800
21	1. Run21 based on Run 12 (thesis) 2. WT on CL	MINIMIZATION SUCCESSFUL	-244.495	1080	86800
22	1. Run21 based on Run 12 (thesis) 2. WT on V	MINIMIZATION SUCCESSFUL	-242.157	1080	85800
23	1. Run23 based on VRACE GAM1 & 2	MINIMIZATION SUCCESSFUL	-248.391	1070	75400
24	1. Run24 based on VRACE GAM1 & 2 RACE on V ONLY	MINIMIZATION SUCCESSFUL	-246.871	1080	79900

APPENDIX 2.3.2

INDIVIDUAL PLOTS OF MEASURED CONCENTRATIONS, INDIVIDUAL CONCENTRATION PREDICTIONS AND FINAL MODEL CONCENTRATION PREDICTIONS IN RELATION TO TIME AFTER DOSE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DV
IPRE
PRED
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ID: 3
ID: 4
ID: 5
ID: 6
ID: 7
ID: 8
ID: 9
ID: 10
ID: 11
ID: 12
ID: 13
ID: 14
ID: 15
ID: 16
ID: 17
ID: 18
ID: 19
ID: 20
ID: 21
ID: 22
ID: 23
ID: 24
ID: 25
ID: 28
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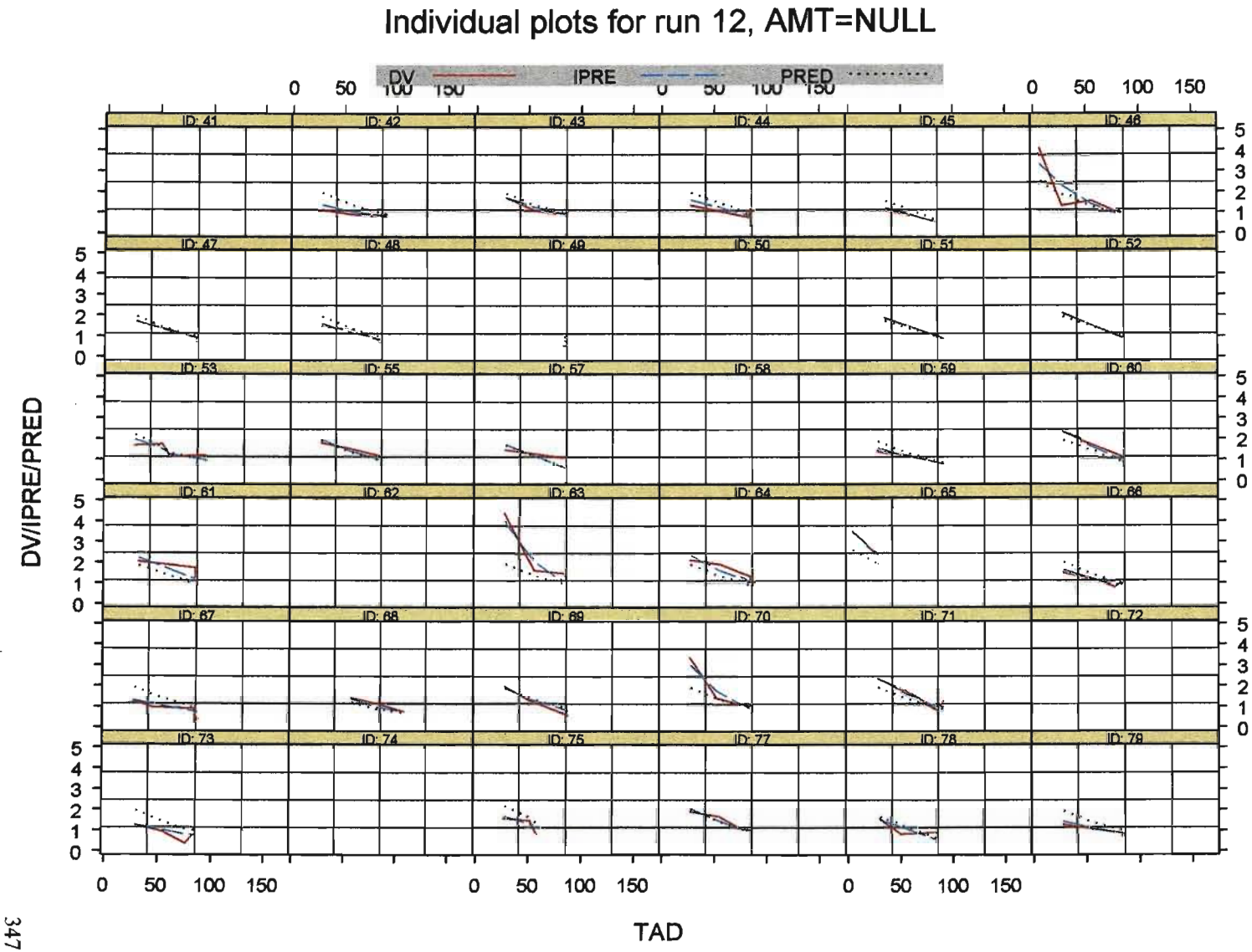
ID: 38
ID: 39
ID: 40
DV/IPRE/PRED
TAD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DV
IPRE
PRED
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ID: 43
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ID: 45
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ID: 47
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ID: 49
ID: 50
ID: 51
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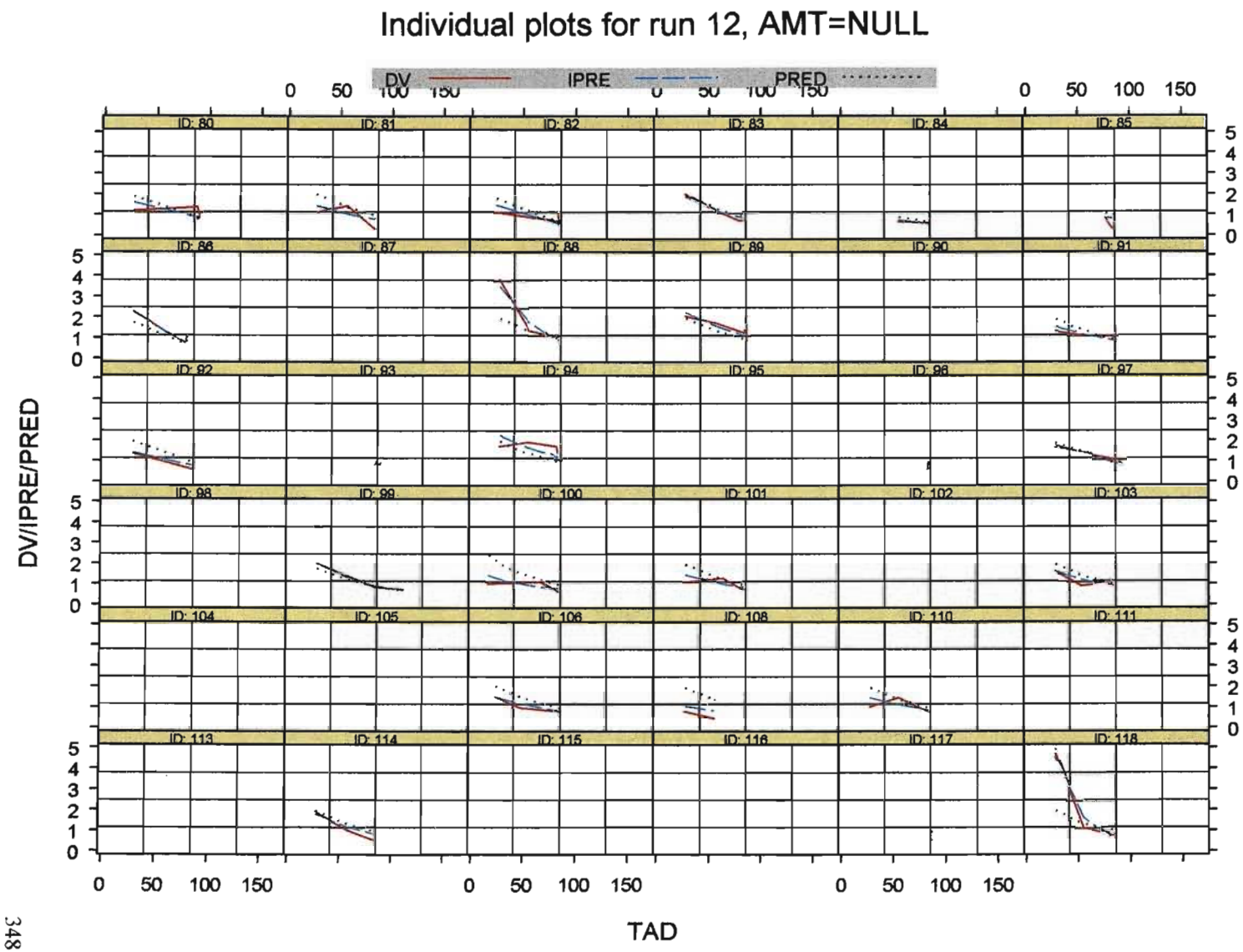
ID: 77
ID: 78
ID: 79
DV/IPRE/PRED
TAD


Individual plots for run 12, AMT=NULL
DV
IPRE
PRED
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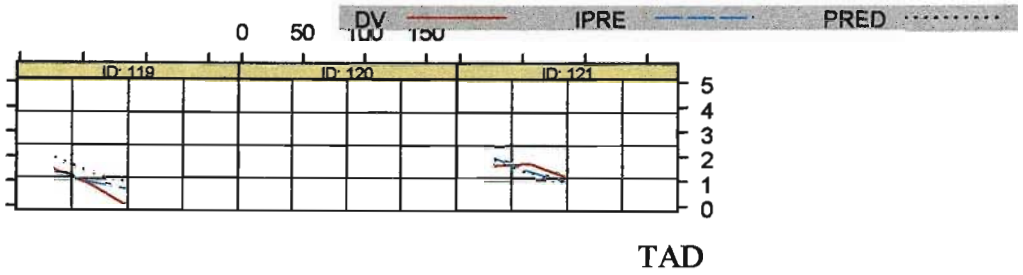
ID: 113
ID: 114
ID: 115
ID: 116
ID: 117
ID: 118
DV/IPRE/PRED
TAD

Individual plots for run 12, AMT=NULL



TAD

RECOMMENDATIONS FOR RATIONAL PROVISION OF INJECTABLE CONTRACEPTIVES

Contraceptive Method Mix

- Attention should be directed at the disproportionate reliance on a single contraceptive method (the progestogen-only injectable), which offers no protection against HIV and other STIs. Attention should focus particularly on the method mix for young people and for people living in rural areas, where injectable use is especially high.
- The choice of contraceptive methods available in public sector clinics is limited. The need for greater access to female controlled methods like the female condom, which also protect against HIV/STIs, should be addressed.
- The findings documented in this thesis provide a comprehensive account of injectable contraceptive use at a time when new health policies, specifically the National Contraception Policy Guidelines (Department of Health, 2001) were being developed and implemented. In this time period, the full impact of the HIV/AIDS pandemic was only just being realised. This thesis provides important baseline data on contraceptive use and should be used to measure whether recommended changes in the method mix occur.

Injectable Contraceptive Product Mix

- Age as a criterion for providing one injectable product over another on the basis of reversibility is not appropriate or cost effective. Training of health workers and counselling of clients to correct the misconception that NET-EN is the better product for young women, on the basis of reversibility, is required. This recommendation has been

published in *BMC Health Services Research* (copy included after the abstract on page xxv of this thesis) and is already been implemented by contraception trainers and programme managers (M. Moss, Changing Attitudes to Contraception: Contraception update 2003 – Satellite Symposium, 11 July, 2003).

- Since DMPA is a cheaper option than NET-EN, provider training about the rational use of injectable contraceptives should include consideration of the cost implications of prescribing one or other product. DMPA should be considered as the first option, but where DMPA is not well tolerated, NET-EN should be available as a second option.

Counselling

- Counselling about contraceptive options should be tailored to women's specific circumstances, including their risk of HIV/STI acquisition. Health workers play an important role in decision-making about contraception, and are highly influential in the decision to use the injectable method. They should be encouraged and supported to promote barrier methods where these are more appropriate. For instance, training about of the use of emergency contraceptive pills, as a back-up to condom use, may increase likelihood of the promotion of condoms instead of injectables where providers have concerns about shifting women from the more effective injectable method. Promotion of dual method use (e.g. male or female condom plus hormonal method) is another strategy which could be encouraged.
- The perception that injectables cause vaginal wetness can affect acceptability and lead to discontinuation. Health workers should be aware of this and should counsel women appropriately.

- Counselling to improve rates of continuation and adherence to dosing regimens could impact positively on unwanted pregnancy rates. Clients should be told about the likelihood of amenorrhoea, especially with longer duration of use and advised against "taking a break" or returning late for their next dose. They should also be informed that they may experience heavy bleeding in the first few injection cycles, but should be told that this side effect is likely to diminish with longer duration of use.
- Although amenorrhoea is a problem for some women, others see it as an advantage of the injectable method. Counselling about this side effect should take this into account.
- The multiplicity of reasons for discontinuation is seldom commented on the literature, but is important to take into account when counselling injectable users.

Focus on young women

- Many sexually active young women do not practice contraception until after their first pregnancy. The contraceptive needs of young women should be addressed **before** their first pregnancy, also taking into account their need for protection against HIV and other STIs

Pharmacokinetics of DMPA

- Although some previous studies suggest that weight, body mass index or ethnicity influence the pharmacokinetics of medroxyprogesterone acetate, this was not found in the pharmacokinetic analysis of the influence of covariates on apparent clearance and apparent volume of distribution for medroxyprogesterone acetate. This information should be communicated to the research community and to health providers.

Further research

- More data on discontinuation patterns among South African users are needed. Further studies should take care to define discontinuation criteria clearly, differentiating between poor adherence and discontinuation.
- Whilst vaginal wetness can only be classified as a subjective side effect at this stage, further investigations are needed. A study is being developed to discover more information about the nature and possible etiology of vaginal wetness, how it may differ from the vaginal discharge reported by respondents, and whether it is a consequence of a vaginal infection or a relatively transient problem that resolves for most women on continued use.
- Future Demographic and Health Surveys should collect information on which injectable product is being used (i.e. DMPA or NET-EN). The next SADHS is scheduled to take place in the latter part of 2003 and, on the basis of the recommendation of the author of this thesis, this disaggregated information will be collected. A study is also proposed in Western Cape Province family planning clinics to investigate the injectable product mix. This study will adopt a similar methodology as that used in this thesis and the author of this thesis as been invited to be a collaborator.
- A systematic Cochrane review comparing DMPA and NET-EN in regard to side effects, efficacy, discontinuation, reversibility and safety is underway. This review will focus particularly on the effects of the two injectables on bone mineral density.
- Forthcoming findings from prospective studies of the effect of DMPA and NET-EN on bone mineral density should be carefully considered. Depending on the outcome,

appropriate recommendations for South African users, particularly younger women (under 18 years) and older women (over 45 years) should be made.

- A clinic-based study which investigates the influence of providers on contraceptive method choice is needed.
- A comprehensive cost effective analysis of DMPA versus NET-EN should be undertaken. This should include, in addition to product costs, a costing of personnel time in providing each of the two products; an analysis of the content and quality of provider counseling; time taken for counseling; time taken and cost incurred for clients to get to the clinic; and cost of materials such as needles, syringes and swabs.
- A pharmacokinetic/pharmacodynamic study should be undertaken to investigate medroxyprogesterone acetate levels in relation to ovulation and side effects.
- Since norethisterone oenanthate is also widely used in South Africa and elsewhere, a pharmacokinetic study of norethisterone oenanthate should be carried out.

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