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An Audit of Couples attending the Infertility Unit at Inkosi Albert Luthuli Central Hospital (IALCH), Durban.

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953022013

A dissertation submitted in fulfilment of the requirements for the degree of Masters in Medicine (MMed) - Obstetrics and Gynaecology

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September 2011

DECLARATION

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TABLE OF CONTENTS

PRESENTATIONS

J V Jogessar, JS Bagratee. The Success Rate of Infertility Treatment at Inkosi Albert Luthuli Central Hospital (IALCH), Durban. Is there a need for Assisted Reproductive Technology (ART)?

1. Department of Obstetrics and Gynaecology. Nelson R Mandela School of Medicine. Research Day; 6 August 2008.

   Winner – Best Registrar Presentation

2. National Registrars Research Day, Cape Town; 15 August 2008.

3. Oral presentation – South African Society of Obstetricians and Gynaecologists (SASOG), Cape Town; 5 – 7 October 2008

4. Oral Presentation – International Federation of Gynaecology and Obstetrics (FIGO), Cape Town; 4 – 9 October 2009

ACKNOWLEDGEMENTS

I wish to thank the following people whose assistance made it possible to complete this study:

Professor Jayanthilall Bagratee, my teacher and mentor, for his guidance throughout my postgraduate training and for his excellent supervision during this study.

Mrs Sandy Dayaram of the Medical Research Council, Durban for her assistance with statistical analyses.

Mrs Tanya Esterhuizen for her valued input and statistical analyses.

Mrs Pam Moonsamy of AME for her assistance in retrieving information from the IALCH Medicom Database.

Dr M Joshua, the medical manager at IALCH, for allowing me to conduct this study at the hospital.

My wife, Dr Nicolene Moonsamy, and my son Dhruv, for their unwavering patience and encouragement.

Finally, my parents, for their selflessness and constant support in my every endeavour.

ABSTRACT

An audit of Couples attending the Infertility Unit at Inkosi Albert Luthuli Central Hospital (IALCH), Durban

Objectives

To determine the patient profile, causes of infertility and the success rates of medical and surgical treatment of infertility thus emphasizing the need for assisted reproductive treatment

Methods

Data was obtained retrospectively from the medical records of 281 couples that presented to Inkosi Albert Luthuli Central Hospital Infertility Unit between January 2004 and December 2006. Information was recorded on a structured proforma and data analysed using SPSS version 15.0

Results

The causes of infertility were anovulation (32.7%), tubal factor (30.3%), male factor (11.7%), endometriosis (7.8%), uterine factor (4.3%) and unexplained infertility in 7.1% of cases. Couples with both male and female factors contributed to 6.1% of infertility cases. Twenty two percent of patients with severe male factor and tubal infertility could not be offered any treatment because of the unavailability of assisted reproductive technology (ART). The pregnancy rate was 24.3% after medical treatment and 14.3% after surgery. When both

modalities were employed, the pregnancy rate was 26%. The overall pregnancy rate was 16% with 84% of couples requiring further treatment.

Conclusion

Anovulation and tubal factors were the major causes of infertility. This audit illustrates that the majority of couples (84%) require gonadotrophins and / or assisted reproductive services to achieve conception. A dedicated infertility unit should provide a full range of services including ART. A significant proportion of couples are denied this health service in the public sector in KwaZulu Natal.

CHAPTER 1

Introduction

In third world countries and South Africa in particular, where family planning has become synonymous with contraception; infertility and childlessness is often a neglected aspect of family planning.[1] Apart from the inability to bear children, women often suffer negative consequences such as stigmatisation, ostracism, abuse and economic deprivation due to local socio-cultural beliefs.[2] In Africa, children fulfil important roles for both parents and society. Children serve to fulfil perceived gender roles and to confer social status in the community. Apart from satisfying a spiritual directive to procreate, children also assist in domestic tasks and offer security in old age. At death children also ensure the continuity of family lines, ensure a proper funeral and secure property rights.[3] Low self-esteem, depression and feelings of guilt can contribute to marital difficulties, polygamy, divorce and abandonment. [4]

The prevalence of infertility has been estimated at 10 to 20% but appears to be rising due to increasing male and female genito-urinary infections.[5] The changing roles of the modern woman and the deferment of marriage and pregnancy along with the associated decrease in fecundity associated with age have resulted in an increase in infertility rates.[6] A previous audit of infertility in Durban revealed an average age of participants of 31 years with 25% over the age of 35 years.[7] Lifestyle factors including age, weight, alcohol consumption, cigarettes and recreational drug use impacts negatively on reproductive performance in both males and females.[8] Increasing public awareness of the availability of infertility services might also contribute to the apparent increase in prevalence.[7] The rising incidence of and

changing attitudes toward divorce have also led to more women seeking reversal of tubal sterilization procedures.[8]

Inkosi Albert Luthuli Central Hospital (IALCH) has the only infertility unit in the public sector in KZN that was specifically requisitioned for that purpose. Although currently underutilised, IALCH has the infrastructure in terms of an IVF laboratory and reproductive theatre, a theatre slate, a dedicated clinic, subspecialists in feto-maternal and reproductive medicine, ultrasonographers, radiographers, radiologists, urologists, geneticist, a genetic counselor, dietician, psychologists and social workers. Although the clinic is able to offer couples a wide range of medical and surgical services, assisted reproductive technology (ART) is currently unavailable to patients from the province due largely to the financial constraints and other health concerns of the provincial government.

This audit will ascertain the success rate of currently available medical and surgical treatment of infertility and highlight the dire need for ART. It will also determine the causes of infertility delineate the patient profile of couples attending the infertility clinic.

CHAPTER 2

Background and Literature Review

2.1 Epidemiology

Due to international differences in definitions of infertility, the prevalence is between 4% to 14%, accounting for nearly 80 million women.[9] The classical clinical definition is the inability to fall pregnant after one year of regular sexual intercourse with no contraceptive measures taken.[6] Because couples may conceive after 12 months without treatment, the World Health Organisation (WHO) suggests two years of unprotected intercourse as the preferred definition.[10]

Primary infertility is diagnosed when no prior conception has occurred, and secondary infertility when there has been a confirmed previous pregnancy. In sub-Saharan African women (excluding South Africa) primary infertility rates were previously estimated to be below the biologically expected minimum of 4%.[11] This was attributed to younger age of marriage with early childbearing due to local socio-cultural beliefs and attitudes. Recent changes in socio-economic trends in many parts of Africa have resulted in an increase in this prevalence. [9]

Countries in Southern Asia, Latin America and north Africa have a 15% to 25% prevalence of secondary infertility, whilst in the "infertility belt" of sub-Saharan Africa, this exceeds 30%.[9] High rates of infertility were initially attributed to dietary factors such as iodine and selenium deficiencies and to environmental factors such as aflatoxins and occupational exposure to pesticides, industrial chemicals and heavy metals.[11] Lifestyle factors such as cigarette

smoking, alcohol consumption and obesity that negatively impact on reproductive success are also becoming increasingly prevalent in developing countries. However the primary cause of secondary infertility in developing countries is pelvic infections caused by sexually transmitted disease with resulting damage to the fallopian tube. [9]

Fecundability is described as the probability of pregnancy within a single menstrual cycle and is estimated at 20 to 25% in a normal couple.[12] Fecundity is the probability of achieving a live birth within a single cycle, which normally ranges from 0.15 to 0.20 per month.[13]

2.2 Ovulatory factor Infertility

Ovulatory disorders account for 20% to 25% of infertile women.[6] The WHO classifies these into three distinct groups. Hypogonadotrophic hypogonadism accounts for 10% and results in decreased gonadotrophins and estrogen with normal prolactin levels. Amenorrhoea results from failed follicular development. Hypothalamic-pituitary dysfunction (85%), as seen in polycystic ovarian syndrome (PCOS), causes anovulatory oligo-amenorrhea. Hypergonadotrophic hypogonadism (ovarian failure) causes increased gonadotrophins, hypogonadism and decreased estrogen and accounts for 4% to 5% of ovulatory disorders.[14]

2.2.1 Ovarian Reserve

Reproductive ageing is determined by a gradual decrease in the quantity and quality of oocytes. Being a physiological rather than a pathological process, age cannot be deemed causative of infertility. By 20 weeks of intrauterine life, germ cells within the fetal ovaries

multiply to reach 6 to 8 million. These germ cells are found in the primordial follicles consisting of an oocyte surrounded by granulosa cells. Oocytes undergo apoptosis and decreases continuously. At birth only approximately 2 million germ cells remain. By puberty this figure will drop to around 400 000. Only 10% of these will develop into mature oocytes during a woman's reproductive years. By the age of 37 years only 10 000 oocytes remain and when only 1000 remain, at a mean age of 45 years, menstrual regularity is lost and ovulation becomes infrequent.[15] When numbers drop below 1000, menopause occurs.[16]

Studies comparing chromosomal abnormalities in IVF embryos in older and younger women have revealed that the loss of oocyte quality is related to an increase of meiotic non-disjunction and aneuploidy of the early embryo at higher female ages.[16] This loss of quality is thought to mark the end of the fertile period, while the loss of quantity results in menstrual irregularity and menopause.

Age is an important determinant of reproductive success because it is a predictor of ovarian reserve in both natural and ART cycles. [17] This decline in fecundability is a direct reflection of the increased oocyte age.[18] Oocyte donation programs in the United States reveal that when embryos produced from oocytes retrieved from younger women were transferred to older recipients, pregnancy rates approximated those of the younger women highlighting the importance of the age of the oocyte and not the recipient .[19]

2.2.2 Polycystic Ovary Syndrome and Infertility

Polycystic ovary syndrome (PCOS) is an endocrine disorder causing excessive androgen secretion with abnormal insulin activity. It can result in several health complications including infertility, menstrual dysfunction, hirsutism, acne, obesity and metabolic syndrome. Long term consequences included an increased risk of developing type 2 diabetes mellitus, endometrial carcinoma and cardiovascular disease.[20]

At a joint consensus meeting of the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) in Rotterdam in 2003, PCOS was redefined. Oligo-ovulation and/or anovulation, biochemical and /or clinical hyperandrogenism, and ultrasound features of at least 12 ovarian follicles, 2 to 9 mm in diameter with an ovarian volume of 10cm³, with the exclusion of other aetiologies were included as part of the criteria with two out of three being necessary to confirm the diagnosis.[21,22] Whilst earlier diagnostic criteria estimated the prevalence at 6.5% to 8%,[20] it now ranges between 20% to 33%.[21]

PCOS may result in a peripheral insulin resistance characterised by a 35 to 40% decrease in insulin mediated glucose uptake.[22] Insulin resistance also contributes to hyperandrogenism and gonadotrophin abnormalities that encourage infertility. High levels of insulin decrease circulating steroid hormone binding globulin (SHBG) levels, thereby increasing the availability of testosterone. Insulin is also a co-factor that stimulates LH action on theca cells in the ovary increasing adrenal androgen synthesis. [20]

Women with PCOS typically have chronic anovulation with normal FSH and E2 levels.[15] A PCOS consensus workshop hosted by ESHRE and ASRM in Greece, 2007 recommended preconception counseling and emphasised the importance of lifestyle including weight reduction, diet, exercise and avoidance of smoking and alcohol consumption. The first line of treatment for ovulation induction remains clomiphene citrate (CC). Gonadotrophins or laparoscopic ovarian drilling (LOD) were advocated as second line interventions with third line management being in-vitro fertilization (IVF). It was suggested that metformin be limited to those with glucose intolerance. Further trials were recommended for newer induction agents such as aromatase inhibitors.

Lifestyle modification in women with PCOS, including dietary modification and exercise, has shown to improve ovulation rates in natural and assisted cycles and a weight loss of 5% has beneficial effects on the hormonal milieu.[23] Lifestyle changes are the first modality of treatment and results in significant improvement in menstrual abnormalities and fertility rates with a reduction in hyperandrogenism and hyperinsulinaemia and correction of gonadotrophin pulsatile secretion.[24] However achieving and maintaining weight loss is often difficult in obese PCOS women.[25] Moreover, 10% to 30% of women with PCOS have a low or normal BMI, and weight loss is not a therapeutic option.[26]

Clomiphene citrate is a selective estrogen receptor modulator (SERM) used to treat women with oligo-anovulation caused by hypothalamic-pituitary dysfunction for over 40 years.[27] It is the primary treatment for induction of ovulation in such cases, as is seen in those with PCOS. It antagonizes the negative feedback of estrogen on the hypothalamic pituitary axis thereby stimulating FSH production.[20] Approximately 75% to 90% of anovulatory women will ovulate and 35% to 40% will conceive[27] with a 30% live birth rate.[25] Approximately 70% to 85% of conceptions occur within the first three cycles with more than 70% ovulating with

doses of 50 to 100mg.[27] Treatment is usually commenced with 50mg daily cycle for 5 days. Similar ovulation rates have been observed if started on day 2 or day 5. [20] If ovulation is not achieved the dose is increased to 100mg and 150mg in subsequent cycles. [20] Those that do not ovulate to 150mg of CC daily after 6 months are considered CC resistant, whilst those that ovulate and do not fall pregnant have clomiphene failure. Both require second line intervention.[27]

The half life of CC is 5 to 7 days but isomers of the drug can be detected in the blood and adipose tissue for up to 4 to 5 weeks especially in those women that had larger doses for longer periods of time. [20] Clomiphene citrate may, therefore, contribute to infertility due to its antiestrogenic effect on the endometrium and cervix resulting in decreased quality and quantity of cervical mucus and thinning of the endometrium. [20] This may explain the low pregnancy rate (35 – 40%) despite the relatively high ovulation rates (75 - 90%).[27]

Gonadotrophin stimulation is recommended as the next step in treating anovulation in women who are resistant to CC. The drug can cause an increase in follicle production that can precipitate ovarian hyperstimulation syndrome (OHSS) especially at higher doses.[28] The cumulative live birth rate is approximately 60% after 6 cycles and the multiple pregnancy rate has been estimated at between 10% to 25%.[25] Although effective, gonadotrophins are costly and require intense monitoring of ovarian response.

The mechanism by which laparoscopic ovarian drilling works is uncertain. It may restore ovulatory cycles by increasing the sensitivity of the ovary to gonadotrophin stimulation by modifying autocrine and paracrine factors within the ovary. Spontaneous ovulation occurs in more than two-thirds of women and this is attributed to an associated decrease in LH and

testosterone concentrations.[15] Marked obesity (BMI > 35kg/m²), greatly elevated hyperandrogenism and duration of infertility longer than three years predict resistance to LOD. However, when comparing LOD to gonadotrophins in women with CC resistant PCOS, there was no difference in the miscarriage and cumulative live birth rates.[28] There is also a decrease in the multiple pregnancy rates.[28] Moreover, LOD is an invasive procedure and anaesthetic and surgical complications, adhesions and premature ovarian failure can occur and the procedure is usually limited to those patients in which other ovulation induction methods have failed.[25]

Letrozole and anastrozole are aromatase inhibitors that increase follicular development by directly suppressing the synthesis of estrogen resulting in a decrease on its negative feedback on the hypothalamic pituitary axis, causing an increase in FSH. [25] Pregnancy rates are comparable to CC. [29] Unlike CC. there are no anti-estrogenic effects on the endometrial lining and cervical mucus and it allows for monofollicular growth.[30] Initial doubts regarding the teratogenic potential of letrozole were raised following the findings of 150 congenital abnormalities after ovulation induction with letrozole compared to 36 000 spontaneous live births, [31] prompting the manufacturer to issue a warning to physicians. These findings were later refuted by Tulandi et al (2010) who found a 2.4% (14/514) incidence of congenital and chromosomal abnormalities following conceptions with letrozole compared to 4.8% (19/397) with clomiphene citrate.[32] Current evidence suggests that aromatase inhibitors are a potential alternative to CC for induction of ovulation and with FSH for ART.[30]

Metformin is a biguanide that lowers glucose without causing increased insulin levels and hypoglycemia.[33] It reduces hepatic gluconeogenesis, which is increased in insulin resistant states.[34] Apart from improving peripheral insulin sensitivity and reducing intestinal glucose absorption, metformin in obese PCOS patients was found to lower abdominal obesity.[34]

Pasquali et al (2000) showed that in PCOS women with abdominal obesity, long-term treatment with metformin in association with a hypocaloric diet induced a greater reduction of body weight and abdominal fat when compared to a placebo.[34] Apart from a significant improvement in hirsutism and menstrual irregularities, there was also a decrease of serum insulin, testosterone, and leptin concentrations.[33] It also decreases insulin concentrations, decreases GnRH-stimulated LH release, decreases androgen production from the ovaries, causes a 44% decrease in free testosterone levels and a rise in SHBG thereby improving ovulation.[26] Derangements in lipid profile and prothrombotic factors also improved with metformin.[33] A similar effect was seen in PCOS women with BMI less than 24 kg/m². [26] The findings of Tang et al in a 2010 Cochrane analysis[35] concurred with two earlier meta-analyses which confirmed that when compared to a placebo, metformin alone can increase the ovulation rate. However, there is no evidence that it improves live birth rates either when used alone or with CC.[36,37] Its use in clinical practice, therefore, remains limited.

This was confirmed by two large randomized controlled trials (RCTs) published in 2006 found no significant differences in rate of ovulation (64% vs. 72%) and ongoing pregnancy rate (40% vs. 46%) when comparing CC plus a placebo to CC plus metformin.[38,39] The trials concluded that metformin was not an effective addition to CC as the primary method of ovulation induction. Whilst CC remains an effective inducer of ovulation in PCOS, the efficacy of metformin alone or in combination remains controversial.[25]

Thiazolidinediones are insulin-sensitisers that increase glucose uptake mainly in adipose and muscle. The drug binds to nuclear receptors that result in the activation of genes that encode insulin action.[26] Troglitazone, prior to being withdrawn for fatal liver hepatoxicity, was the first thiazolidinedione, and was shown to decrease circulating insulin, decrease LH, reduce hyperandrogenism and increase the ovulation rate in women with PCOS.[26]

Pioglitazone and rosiglitazone have shown similar results including improvements in menstrual cyclicity.[26] Pioglitazone compared to metformin in obese women with PCOS was as effective in improving insulin sensitivity but was associated with an increase in BMI. [40]

In-vitro fertilisation (IVF) is the remaining option in anovulatory women with PCOS who fail to conceive with other measures. Gonadotrophins are usually used to stimulate the ovaries prior to ultrasound guided aspiration of oocytes. The eggs are fertilised with spermatozoa in the laboratory with embryo transfer into the uterus usually occurring on day 3 after egg retrieval. For women under 35 years, there is 30 to 35% live birth rate per IVF cycle with the success rate decreasing with increasing oocyte age. [20]

2.2.3 Premature Ovarian Failure

Premature ovarian failure (POF) is a common cause of infertility in women, and is characterised by amenorrhoea, hypo-oestrogenism and elevated gonadotrophin levels in women under the age of 40 years.[41] The condition occurs in 1 to 3% of women and is as a result of a decreased development or an inadequate preservation of the overall pool of ovarian follicles with resultant early menopause.[42] In 0.1% of women POF will occur prior to the age of 30 years.[43] There is a premature cessation of menses and accompanied elevated gonadotrophin concentration (FSH > 40iu/L).[42]

In the majority of cases no direct cause can be attributed. Autoimmune factors with anti – ovarian antibodies are seen in 10% [43] Iatrogenic causes include chemo-radiation therapy or oophorectomy and cigarette smoking is associated with early menopause.[41] A genetic cause

occurs in 20 to 30% of cases with an increased risk if there was also maternal affectation. X chromosome abnormalities have been isolated in approximately 5% while mutations in autosomal genes are currently under investigation.[43]

2.2.4. Hyperprolactinaemia and Infertility

Common hypogonadal gynaecological manifestations of hyperprolactinaemia include infertility, decreased libido, galactorrhea and oligo-amennorhea. Visual changes and headaches are usually due to mass effect caused by a pituitary or hypothalamic micro or macroadenoma.[44] Other differential diagnoses include ingestion of drugs that deplete dopamine or act as a receptor antagonist, polycystic ovary syndrome (PCOS), hypothyroidism and hepatic and kidney failure.[44] Hyperprolactinaemia may be associated with ovulatory factor infertility by causing a disruption in the hypothalamus-pituitary-ovarian axis. Hyperprolactinemia causes reproductive dysfunction in 9% to 17% of women whilst the incidence in ovulatory infertile women occurs in 3.8% to 11.5%.[14] After a repeat prolactin level has confirmed the increase and other causes have been ruled out, a magnetic resonance imaging (MRI) is performed to exclude an intracranial pathology, especially in the presence of typical symptoms. Treatment with bromocriptine is followed by commencement of ovulation in 90% of patients within 6 weeks.[15] Magnetic resonance imaging is now the modality of choice in assessment of the hypothalamo-pituitary axis with superior soft tissue discrimination even in the absence of contrast when compared to CT scan.[45]

2.2.5 Thyroid disease and Infertility

Both hypo- and hyperthyroidism can cause menstrual irregularities and ovulation dysfunction. Asymptomatic hypothyroidism can occur in up to 7% of the general population. Thyrotoxicosis can cause anovulation in up to 21.5% of patients.[46] In severe hypothyroidism, oligo-amenorrhea and anovulation can occurs in 23.4%.[46] Clinical hypothyroidism occurs in 1.3 to 5.1% of infertile women, and sub-clinical hypothyroidism in 0.88 to 11.3% [14] In mild dysfunction ovulation and conception can occur. However, there is an increased rate of miscarriages, stillbirths and prematurity. Evidence suggests that preconceptual treatment results in resolution of ovulatory dysfunction and an increased live birth rate.[14]

2.2.6 Low BMI, Exercise, Chronic Disease and Infertility

Hypogonadotrophic hypogonadism is defined as anovulation in the presence of low serum LH, FSH and E2 levels.[47] A similar hormonal profile is evident in patients who are anovulatory secondary to hypothalamic dysfunction caused by a very low BMI (<18 kg/m²), anorexia nervosa, malnutrition or those undergoing rigorous athletic training. Amenorrhea and ovulation also occurs in those with chronic disease such as renal failure and acquired immunodeficiency syndrome (AIDS).[47] Osteopenia and osteoporosis are often also associated with these disorders. In one study increased caloric intake and weight gain resulted in resumption of menses in 90% of women with spontaneous conception in 73% of participants.[47]

2.3 Tubal Factor Infertility

In Africa the commonest cause of tubal infertility has been attributed to sexually transmitted infection (STI), namely chlamydia and gonorrhea[11] that prevents conception by scarring of the fallopian tubes and causing intraluminal and peritubal adhesions. Seventy percent of cases of pelvic inflammatory disease (PID) in sub-Saharan Africa can be related to STIs with the remainder attributed to abortion and unsafe delivery practices.[11] The risk of infertility increases with increasing episodes of PID; 12% after one episode, 23% after two episodes and 53% after three episodes.[14] History of previous pelvic surgery has also been isolated as an important risk factor for tubal infertility.[48] It was estimated that tubal factors account for 14% infertility in women in the United Kingdom.[49] A local Durban study attributed tubal factors in 78% of infertility patients.[7]

Hysterosalpingography (HSG) is the initial diagnostic tool used to evaluate tubal patency and has a sensitivity of 90% to 100% in evaluating PID related tubal occlusion.[48] Uterine leoimyomas, synechiae, polyps and anatomical abnormalities of the uterus can also sometimes also be detected.

The laparoscopy and dye test is an additional diagnostic modality used to assess tubal and peritoneal disease. Like HSG, it involves chromopertubation, the instillation of dye through the cervix, such that spillage from the fimbriae is directly visualized. It is usually considered before HSG in symptomatic females as it allows for diagnosis and treatment at the same time. Intramural and subserosal leiomyoma, peritubal adhesions and endometriosis can be assessed and surgically managed. Although the detection and treatment of pathology

missed by HSG may not increase live birth rates, there is an 18% false positive rate with a further 34% having additional pelvic pathology.[50]

As success rates for ART continue to improve, the indications for tubal microsurgery are becoming increasingly limited. However, in countries where access to ART is limited, tubal surgery is routinely performed. One case series reporting on women with proximal tubal occlusion who had undergone tubo-cornual anastomosis achieved a live birth rate of 27% and 47% after 1 and 2 years respectively.[51] A cohort study with three year follow up revealed a 29% pregnancy rate in those who had tubal surgery compared to 12% in those without surgery. [52] The severity of pelvic disease was a major determinant in the live birth rate. [51]

A 2010 Cochrane metanalysis found no advantage or disadvantage when comparing the various surgical techniques used in tubal infertility.[53] There was no improvement in pregnancy rates with the use of CO_2 laser for adhesiolysis or salpingostomy compared to standard surgical technique using diathermy or scissors.[53] Similarly there was no advantage of laparoscopy over laparotomy.[53] At salpingostomy there also no advantage when using a prosthesis or with the different types of salpingostomy used (Bruhat vs Cuff).[53] Pregnancy rates were also similar when using the operative microscope compared to the magnifying lenses (loupes).[52] However the number of trials in this meta-analysis was small with the authors recommending further RCTs.[53]

Furthermore, a meta-analysis of fourteen studies concluded that IVF pregnancy rates were markedly lower in cases where hydrosalpinx was present.[54] Prior pelvic surgery, endometriosis and PID can all result in distal tubal disease. Hydrosalpinx results from luminal secretions that accumulate within the occluded fallopian tube. Apart from this

physical blockage, the fluid contains substances that impair implantation. Distal tubal disease can be corrected by the lysis of fimbrial adhesions (fimbrioplasty), by dilatation of the fimbrial phimosis, or by the creation of a new tubal opening (salpingostomy or neosalpingostomy).[54] Apart from dense pelvic or adnexal adhesions, poor prognostic factors for pregnancy after tubal surgery include a hydrosalpinx greater than 30mm in diameter, thickened tubal walls, patients with both proximal and distal tubal disease and the absence of visible fimbriae. [48]

2.4 Male factor Infertility

Male factor infertility accounts for up to 30% of infertility and may play a contributory role in 40% of couples.[6] The pathology encompasses defective production or transport of sperm including sexual dysfunction. [55]

The World Health Organisation (WHO) bases the reference criteria for semen quality on populations of fertile men. Although it has a sensitivity of 89.6%, it has poor specificity. A single sample analysis will falsely identify about 10% of men as abnormal, but repeating the test reduces this to 2% and improves this specificity.[14] The WHO (1999) lower reference values included: volume, 2 millilitres; liquefaction time, 60 minutes; ph, 7.2; sperm concentration, 20 milliion spermatozoa per millilitre; sperm number, 40 million per ejaculate; grade a motility, 50% within 60 minutes; grade b motility, 25% within 60 minutes; morphology, 15% normal forms; vitality, 75% live forms and white blood cells, 1 million per millilitre.

A strict criteria of sperm morphology was described by Kruger et al (1986).[56] A head of 5 to 6 μm in length, 2.5 to 3.5 μm in width, a smooth shape and well defined acrosome compromising 40 to 70% of the head in the absence of neck, mid-piece or tail defects are considered normal. Greater than 14% of such sperm are present in normally fertile men. [56]

Problems with application and interpretation of the 1999 WHO reference values with issues surrounding the imprecisely defined reference populations and standards of the analytical methodologies of the laboratories used, along with a general lack of consensus, prompted the development of new reference values published in 2010. [57] The values were based on international semen samples of 4500 men whose partners had a time to pregnancy of less than 12 months.[57] The lower reference values included: semen volume, 1.5ml; total sperm number 39 million per ejaculate; sperm concentration 15 million per millilitre; vitality, 58% live; progressive motility, 32%; total (progressive and non-progressive) motility, 40% and morphologically normal forms, 4.0%.[57]

Other hormonal investigations include serum FSH concentrations, which increase with worsening impairment of spermatogenesis, whilst testosterone, prolactin and thyroid function tests are done if clinically warranted. Scrotal and trans-rectal ultrasound can be done to investigate the presence of varicoceles, testicular tumours and prostatic lesions respectively. Urinalysis and urethral swabs may detect Chlamydia.[55]

Approximately 20% of male factor infertility may be treatable.[55] Lifestyle modification including weight loss, exercise and avoidance of smoking, alcohol, and use of illicit drugs will improve spermatogenesis. Hypogonadotrophic hypogonadism can be treated with either gonadotrophins or GnRH analogues with up to 50% success rate. [55] Some forms of erectile

dysfunction can be treated with combination psychotherapy and medical treatment (e.g. sildenafil). Viable sperm can be isolated from the urine of those with retrograde ejaculation and used for intra-uterine insemination (IUI) or intracytoplasmic sperm injection (ICSI). Glucorticoids can be administered to those with sperm autoimmunity and pregnancies have occurred in 40% of treated couples but the side effects of steroids can be dangerous. [55] Sperm washing to remove antibodies and IUI or ICSI is another alternative. Ciprofloxacin and doxycycline are commonly prescribed for infectious causes while surgery is limited to those with varicoceles and vasal obstruction. [55]

The most common indications for ICSI include oligozoospermia, azoospermia, teratozoospermia, asthenozoospermia, necrospermia and low fertilisation rate after IVF with normal sperm parameters. Sperm can be retrieved via epididymal biopsy if necessary and successfully injected into a metaphase II oocyte with pregnancy rate per ICSI cycle of 25 to 35% and live birth rate of 20 to 30%. [55]

2.5 Endometriosis

Endometriosis is the presence endometrial glands and stroma in locations outside the uterus. [58] A laparotomy or laparoscopy is needed for histological diagnosis and staging of the disease. Endometriosis affects 10% of women in the reproductive age group.[59] Approximately 25% to 50% of infertile women have endometriosis and 30% to 50% of women with endometriosis are infertile.[13] In untreated women with endometriosis and infertility, fecundity is reduced from 0.15 to 0.2 (in normal couples) to 0.02 to 0.10.[13]

Ovarian suppression, routinely used for pain in endometriosis, is not indicated for the treatment of infertility. Hormonal treatment does not improve the fecundity of infertile women with stage I/II endometriosis.[60] When comparing pregnancy rates, danazol,[61,62] gonadotropin releasing hormone agonists (GnRH-a),[63] and progestins[43] were no better than expected management in stage I/II endometriosis. A meta-analysis comparing medical treatment to no treatment or placebo, found a common odds ratio for pregnancy of 0.85 (95% CI 0.95 - 1.22).[64] There is little published evidence on medical treatment for more severe disease.

The surgical treatment of minimal to mild endometriosis has also been highly controversial.[65] This entails the destruction of the endometriotic implants, adhesiolysis and removal of ovarian endometriomas either at laparotomy or laparoscopy.[66] Similar outcomes in terms of recurrence and adhesion formation were found if either electro-cautery or laser ablation are employed.[65] The Canadian Collaborative Group demonstrated a beneficial effect with the live birth rate in the resection/ablation group being 29% and 17% in the group that received no treatment. [66] The treatment group experienced an increase in the fecundity rate. There was an increased chance of pregnancy (OR 2.03, 95% CI 1.28 – 3.24) and ongoing pregnancy after 20 weeks (OR 1.95, 95% CI 1.18 – 3.22).[66] However, patients in this study were not blinded as to whether treatment had occurred and surgery was limited to ablation of blue-black lesions and adhesiolysis only.

In stage III/IV endometriosis, the aim is to restore anatomical relations of the tube and ovary, ablate implants and remove ovarian endometriomas.[67] Cystectomy of endometriomas greater than 4cm in diameter is the preferred procedure and is associated with a greater improvement in fertility compared to incision and drainage where the remaining pseudocapsule often results in recurrence[60] Surgery for severe endometriosis increases the probability of pregnancy by 45% after laparotomy and 63% after laparoscopy, respectively. [65]

Paradoxically, endometriosis surgery is more efficient in moderate/severe endometriosis compared to minimal/mild endometriosis.[65]

Medical therapy either before or after surgery does not enhance fertility.[60] Whilst medical treatment is used in the management of endometriosis related pain, it may, in fact, unnecessarily delay conventional fertility therapy. Whilst preoperative medical therapy may assist by decreasing the size and vascularity of implants and minimise blood loss and the extent of surgery necessary, there was no improvement in fertility. [60] Medical treatment after surgery for severe disease was proposed to treat microscopic and residual disease. Postoperative medical management also did not affect fertility rates.[13]

After surgery for mild/moderate endometriosis, if ovarian stimulation with IUI fails, IVF is recommended. In-vitro fertilisation is also recommended for those with severe disease or those with gross distortion of the tubes and ovary. [67]

2.6 Unexplained Infertility

Unexplained infertility occurs in 15 to 30% of couples in which ovulation is confirmed, there is adequate sperm production and tubal patency has been established.[68] Couples with this disorder often have diminished and delayed fecundity. Although conception can occur spontaneously, in the absence of any correctable abnormality, management is empiric. After a period of ovulation induction with timed intercourse, IUI and ART are the next management possibilities.[69]

In the only RCT in which IUI was evaluated against intercourse in patients with unexplained infertility, conceptions occurred in 4.1% compared to 2.4% [69] Clomiphene citrate compared to intercourse alone results in just one additional pregnancy per 40 cycles.[68] However the current evidence on these 2 managements when used in combination is contradictory, and requires a RCT evaluating placebo, CC, IUI and combined CC/IUI.[69] The ESHRE Multicentre Trial determined pregnancy rates of 15.2% per cycle using gonadotrophins, 27.4% per cycle with combination gonadotrophins and IUI, and 25.7% in IVF cycles.[70] Combination gonadotrophin/IUI therapy was found to be superior to CC/IUI and the use of ICSI was found to have no advantage over conventional IVF.[68]

2.7 Uterine Factors

2.7.1 Uterine Leiomyomas and Infertility

Uterine fibroids are present in 20% to 50% of women between 14 and 45 years and the incidence increases until the time of menopause.[71] Although associated with infertility in 5% to 10%, when other causes are excluded, fibroids are solely responsible in only 2% to 3%.[72]

Leiomyomas may contribute to infertility by interrupting the passage of sperm by distorting the uterine cervix or blocking the tubal ostia. An enlarged, deformed uterus may interfere with sperm transport by altering uterine contractility. Furthermore, decreased vascularity, an altered endometrial cavity and the persistence of blood clots can interfere with implantation and cause recurrent miscarriages.[72]

For those desirous of fertility, open myomectomy is the most common surgical procedure employed. It is, however, associated with significant operative and postoperative morbidity including the risk of blood transfusion, damage to internal organs, conversion to hysterectomy and infection leading to tubal compromise [73] Depending on the site of incision, posterior adhesions occur in 94% of cases while anterior uterine adhesions occur in 55%.[72] Furthermore, the recurrence rate is 15% and the risk of uterine rupture 1%.[73] Gonadotrophin releasing hormone analogues prior to surgery have not been found to reduce adhesions.[72] After myomectomy live birth rates range from 40% to 50% with retrospective analyses revealing a decrease in recurrent miscarriage rates from 41% to 19%.[72]

Laparoscopic myomectomy is another alternative that has shown comparable pregnancy rates to the open procedure. Laparoscopy offers shorter hospitalisation, faster recovery, fewer adhesions, reduced risk of haemorrhage with better cosmesis. However, patients need to be well selected based on the position and size of the fibroids and concern has been expressed regarding the integrity of the uterine scar. [73]

Hysteroscopic myomectomy is the procedure of choice for intracavitary myomas, particularly in view of the impact of intracavitary distortion on IVF success.[72] Hysteroscopic removal of submucous fibroids improves pregnancy rates and avoids uterine scarring, minimises adhesion formation and has few complications. The procedure is also advocated where no other obvious cause of infertility exists.[73]

GnRH analogues prior to myomectomy have been shown to decrease estimated blood loss intraoperatively, but although it may reduce the size of the fibroid, it does not make surgery easier or reduce complication rates. It may, however, cause a distortion of tissue planes and

predispose to recurrence by rendering fibroids too small to identify at surgery.[72] Routine medical treatment of leiomyomata is not indicated for those desirous of fertility.

Although available studies have yielded conflicting results regarding the removal of fibroids prior to ART, there is consensus that the location and size of the fibroids are important and that intramural and intracavitary myomas that cause distortion of the endometrial cavity should be removed. [71]

CHAPTER 3

Aims, Methods and Statistics

The infertility unit at the quaternary level Inkosi Albert Luthuli Central Hospital is a referral unit that caters for the entire province of KwaZulu Natal. The unit is visited by approximately 100 new couples every year and is the only dedicated public sector infertility unit in the province commissioned for this purpose. The infrastructure for ART in the form of dedicated reproductive medicine and feto-maternal subspecialists, genetic counsellors, ultrasonographers, psychologists, social workers, dieticians and urologists as well as a specifically designed laboratory and theatre facilities are present. However due to local government health policies and financial considerations, ART is currently unavailable in the province. Furthermore second and third line ovulation induction agents are also not offered.

This retrospective audit of the infertility unit was therefore undertaken to determine the patient profile and causes of infertility and evaluate the success rate of currently available medical and surgical treatment and in so doing emphasise the need for ART and second / third line pharmaceutical agents in the provincial sector whilst highlighting any possible preventative measures.

Ethical approval was granted by the University of KwaZulu Natal Biomedical Research Ethics Committee. Two hundred and eighty one newly referred couples that visited the infertility unit between January 2004 and December 2006 were included in the study. Information was recorded on a structured proforma (See Appendix) and focussed on couple demographics, risk factors for infertility, gynaecological and obstetric history, previous fertility treatment, specific investigations, infertility management and treatment outcomes. Those

patients in whom the pregnancy outcomes were unknown were contacted telephonically. Those that were still undergoing treatment but had not visited the clinic in over 18 months were deemed to have defaulted.

Analysis was done in conjunction with the statistician using SPSS software version 15.0 with Chi square tests and p-values as tests of significance, and odds ratio as a determinant of exposure effect. The success rate of fertility treatment was determined by the pregnancy rate and live birth rate. Term delivery rates, miscarriage rates, pre-term delivery rates, multiple gestation rates and ectopic pregnancy rates were also calculated.

CHAPTER 4

Results

Table 1 – Demographic Data (n = 281)

	Mean Range	Number (%)
Age (years)	31.1 (19 – 42)	
< 25		35 (12.5%)
25 – 35		169 (60.1%)
> 35		77 (27.4%)
Race		
African		146 (52.0%)
Indian		116 (41.3%)
Coloured		15 (5.3%)
White		4 (1.4%)
Primary Infertility		152 (54.0%)
Secondary Infertility		129 (46.0%)
Parity	0.27 (0 – 3)	
1		44 (15.7%)
2		15 (5.3%)
3		11 (3.9%)
Previous Miscarriages		59 (21.0%)
Duration of infertility (years)	6.1 (1 – 20)	
1		18 (6.4%)
2		35 (12.5%)
3		40 (14.2%)
4		29 (10.3%)
>5		159 (56.6%)
Body mass index (kg/m²)	32.1 (19 – 43)	
< 25		26 (9.3%)
25 – 30		71 (25.3%)
> 30		184 (65.4%)
Cigarette Smoking		36 (12.8%)
Alcohol Use		5 (1.8%)
Medical disorders		
Hypertension		11 (3.9%)
Diabetes		6 (2.1%)
Asthma		3 (1.1%)
Hypothyroidism		3 (1.1%)
Hyperthyroidism		1 (0.4%)
Cushing's disease		1 (0.4%)
Epilepsy		1 (0.4%)
Previous PID / STI		76 (27%)
Previous Ectopic Pregnancies		18 (6.4%)
Menstrual Abnormalities		
Oligo-amenorrhea		101 (35.9%)
Meno-metrorrhagia		17 (6.0%)
Previous infertility Treatment		76 (27.0%)

A total of 281 new couples attended the infertility clinic over the 3 year period. The female demographic data is presented in Table 1. The mean age of participants was 31.1 years with 1 in 4 patients being under the age of 25 years and 1 in 8 with infertility already over the age of 35 years. The majority were from the African (52%) and Indian (41.3%) race groups. Fifty four percent had primary infertility with 25% of patients having had at least one viable pregnancy and 21% a previous miscarriage. The mean duration of infertility was 6.1 years with only 27% having had prior infertility treatment. Sixty five percent of patients had a body mass index (BMI) greater than 30 kg/m². Thirty six patients (12.8%) were cigarette smokers. Ninety four patients had other risk factors for tubal infertility including previous STI / PID (27%) and prior surgery for ectopic pregnancies (6.4%). Patients with PID (OR = 4.13, 95% CI 1.92 – 8.89; P = 0.01) and previous ectopic pregnancies (OR = 4.77, 95% CI 0.19 – 0.62; P= 0.02) were significantly more likely to have tubal factor infertility as compared to the other causes.

Table 2 – Causes of infertility in different race groups

	Overall (n = 281)	African (n = 146)	Indian (n = 116)	Coloured (n = 15)	White (n = 4)
Anovulation	92 (32.7%)	44 (30.1%)	42 (36.2%)	4 (26.7%)	2 (50.0%)
Tubal Factors	85 (30.3%)	54 (37.0%)	27 (23.3%)	3 (20.0%)	1 (25.0%)
Male factors	33 (11.7%)	19 (13.0%)	13 (11.2%)	1 (6.7%)	0
Endometriosis	22 (7.8%)	4 (2.7%)	16 (13.8%)	1 (6.7%)	1 (25.0%)
Unexplained	20 (7.1%)	8 (5.5%)	10 (8.6%)	2 (13.3%)	0
Both male and female factors	17 (6.1%)	10 (6.8%)	5 (4.3%)	2 (13.3%)	0
Uterine factors	12 (4.3%)	7 (4.9%)	3 (2.6%)	2(13.3%)	0

The causes of infertility, as shown in Table 2, were determined to be anovulation (32.7%), tubal factor (30.3%), male factor (11.7%), endometriosis (7.8%), uterine factor (4.3%) and unexplained in 7.1% of cases. Couples with both male and female factors contributed to 6.1% of infertility. In African women, tubal factors (37.0%) was the commonest cause of infertility while in Indian women, anovulation (36.2%) was the commonest cause. African women were significantly more likely than Indian women to have tubal factor infertility (OR = 1.93 95% CI 1.12 – 3.34; P = 0.02). Endometriosis was found in more Indian women than African women (13.8% vs 2.7%) and African patients were significantly less likely to have endometriosis than Indian patients (OR = 0.18 95% CI 0.06 – 0.54; P = 0.01). Amongst those with anovulation, the causes were PCOS (70.6%), obesity (10.9%), hyperprolactinaemia (3.3%), thyroid dysfunction (6.5%) and premature ovarian failure (2.2%)

Table 3 compares the causes of infertility to specific demographic factors. In all age groups anovulation and tubal causes were the main causes of infertility. The leading cause of primary infertility was anovulation (42.7%) and for secondary infertility the commonest cause was tubal factors (46.5%). Apart from patients with endometriosis (BMI 28.1 kg/m^2), patients with other causes had a BMI greater than 30 kg/m^2. Previous PID (55.3%), STI (29%) and ectopic pregnancies (72.2%) were commonest amongst those with tubal infertility. Oligoamenorrhea was a frequent symptom amongst those with anovulation (82.1%) while 41% with menometrorrhagia had uterine factor infertility (leiomyomata).

Table 3 – Causative factors and Demographics (n = 281)

	Anovulation (n = 92)	Tubal Factors (n = 85)	Male factors (n = 33)	Endometriosis (n = 22)	Unexplained (n = 20)	Both male & female factors (n=17)	Uterine factors (n = 12)
Age							
< 25 (n = 35)	9 (25.7%)	11 (31.4%)	2 (5.7%)	7 (20.0%)	2 (5.7%)	4 (11.4%)	0
25 – 35 (n = 169)	65 (38.5%)	49 (29.0%)	15 (8.8%)	13 (7.7%)	11 (6.5%)	11 (6.5%)	5 (3.0%)
> 35 (n = 77)	18 (23.3%)	25 (32.5%)	16 (20.8%)	2 (2.6%)	7 (9.1%)	2 (2.6%)	7 (9.1%)
Race							
African (n = 146)	44 (30.1%)	54 (37.0%)	19 (13.0%)	4 (2.7%)	8 (5.5%)	10 (6.8%)	7 (4.9%)
Indian (n = 116)	42 (36.2%)	27 (23.3%)	13 (11.2%)	16 (13.8%)	10 (8.6%)	5 (4.3%)	3 (2.6%)
Coloured (n = 15)	4 (26.9%)	3 (20.0%)	1 (6.6%)	1 (6.6%)	2 (13.3%)	2 (13.3%)	2(13.3%)
White (n = 4)	2 (50.0%)	1 (25.0%)	0	1 (25.0%)	0	0	0
Primary Infertility (n= 152)	65 (42.7%)	25 (16.4%)	20 (13.2%)	16 (10.5%)	12 (7.9%)	10 (6.6%)	4 (2.6%)
Secondary Infertility (n = 129)	27 (17.8%)	60 (46.5%)	13 (10.0%)	6 (4.7%)	8 (6.2%)	7 (5.4 %)	8 (6.2%)
Average BMI kg/m²	35.5	31.8	31.6	26.5	33.6	32.2	33.5
Previous PID (n=38)	3 (7.9%)	21 (55.3%)	5 (13.2%)	1 (2.6%)	2 (5.3%)	5 (13.2%)	1 (2.6%)
Previous STI (n=38)	6 (15.8%)	11(29.0%)	6 (15.8%)	3 (7.9%)	5 (13.2%)	4 (10.5%)	3 (7.9%)
Previous ectopic pregnancy (n = 18)	1 (5.6%)	13 (72.2%)	0	0	0	4 (22.2%)	0
Oligo-amenorhea (n=101)	83 (82.1%)	2 (2.0%)	2 (2.0%)	3 (3.0%)	4 (4.0%)	7 (6.9%)	0
Menometrorrhagia (n = 17)	1 (5.9%)	2(11.8%)	2 (11.8%)	6 (35.3%)	0	0	7(41.2%)

Table 4 – Female Investigations (n = 281)

Investigation	Number
HIV Positive	14 (5%)
RPR Reactive	6 (2.1%)
Pap Smear	
ASCUS	13 (4.6%)
Premalignant	3 (1%)
Trans-vaginal Ultrasound	
Normal	102 (36.3%)
Polycystic Ovary	83 (29.5%)
Hydrosalpinx	50 (17.8%)
Multifibroid uterus	32 (11.4%)
Endometrioma	14 (5.0%)
Magnetic Resonance Imaging (n = 14)	
Normal	6 (42.9%)
Pituitary Microadenoma	7 (50.0%)
Pituitary Macroadenoma	1 (7.1%)
Hysterosalpingogram (n = 71)	
Normal	29 (40.8%)
Distal block	13 (18.3%)
Cornual block	8 (11.3%)
Bilateral blockage	9 (12.7%)
Hydrosalpinx	10 (14.0%)
Failed (Cervical Stenosis)	2 (2.8%)

Apart from specific fertility tests all patients had routine screening tests including human immunodeficiency virus (HIV), rapid plasma reagin (RPR) and pap smears were performed (Table 4). Fourteen patients (5%) were found to be HIV positive and 2.1% tested positive for syphilis. No patients were on highly active anti-retroviral therapy (HAART) and 1 was found to have a CD4 count less than 200 cells/mm³. The majority (91.8%) of pap smears were benign. Atypical squamous cells of undetermined significance (ASCUS) accounted for 4.6% and 3 patients (1.1%) had premalignant lesions; 2 patients had low-grade squamous intra-epithelial lesions (LGSIL) and 1 had a high-grade squamous intra-epithelial lesion (HGSIL). Over one-third (36.3%) had a normal trans-vaginal ultrasound scan (TVS). Polycystic ovaries (29.5%) and hydrosalpinx (17.8%) were the commonest abnormal ultrasound findings. Fourteen patients (5.0%) had hyperprolactinaemia. These patients had a magnetic resonance imaging (MRI) performed identifying 8 (57.1%) with prolactinomas. A hysterosalpingogram (HSG) was peformed on 71 patients. Forty two patients (59.1%) had evidence of tubal blockage.

Table 5 depicts the routine male investigations. Only 10 patients (3.5%) were HIV positive and 3 (1.1%) had a reactive RPR test. Male factors were found to contribute to infertility in 17.9% (50 patients). Of these, female factors also played a role in 32.1% (17 patients). Using the WHO guidelines, oligozoospermia was the commonest aberration, being found in 48% of patients. Nine patients (18%) had azoospermia. Of the patients with male factor anomalies, a previous history of cryptorchidism and subsequent surgical correction was found in two patients (4%), childhood viral infection in one patient (2%) and one patient had a history of previous varicocele repair (2%).

Table 5 – Male Investigations (n = 281)

Investigation	Number
HIV Positive	10 (3.5%)
RPR Reactive	3 (1.1%)
Semen Analysis Abnormal - Oligozoospermia - Asthenozoospermia - Teratozoospermia - Oligoasthenozoospermia - Oligoteratozoospermia - Asthenozoospermia - Azoospermia	 50 (17.7%) - 24 (10.4%) - 3 (1.3%) - 5 (2.1%) - 4 (1.7%) - 2 (0.9%) - 3 (1.3%) - 9 (3.9%)

Table 6 describes the specific endocrine and metabolic derangements that were found in women with PCOS which was the commonest cause of anovulation affecting 65 patients (70.7%). An inverse FSH to LH ratio was found in 1 in 2 patients (47.7%). Fifteen patients (23%) with raised testosterone levels, 26 patients (40%) with increased levels of androstenedione and 21 patients with elevated dehydroepiandrosterone sulphate (DHEAS) had evidence of hyperandrogenaemia. Elevated fasting insulin was found in over half of PCOS patients (53.8%). Eight patients (12.3%) had impaired glucose tolerance and 2 (3.1%) had overt diabetes mellitus. Abnormal lipid profiles were found in 12 patients (18.5%).

Table 6 – Endocrine and Metabolic parameters in PCOS (n = 65)

Investigation	Number
LH > FSH	31 (47.7%)
Elevated Testosterone	15 (23.1%)
Elevated Androstenedione	26 (40%)
Elevated dehydroepiandrosterone sulphate (DHEAS)	21 (32%)
Hyperinsulinaemia	35 (53.8%)
Impaired glucose tolerance	8 (12.3%)
Diabetes Mellitus	2 (3.1%)
Hypercholesterolemia	7 (10.8%)
Hypertriglyceridemia	5 (7.7%)

Table 7 summarises the pregnancy rate (PR) and outcomes after the various modalities of treatment. Sixty three patients (22.4%) with severe male factor and / or tubal factor infertility requiring ART as primary management were unable to be treated. Overall, the pregnancy rate of those treated was 20.6% (45 conceptions) with a live birth rate of 18.3%. The miscarriage rate was 1.8% (4 patients), all occurring in the first trimester. One patient undergoing ovulation induction conceived twins (0.9% multiple pregnancy rate). There were no preterm deliveries or ectopic pregnancies. The mean duration from onset of treatment to conception was 16.4 months.

Table 7 – Pregnancy Rates and Outcomes

	Pregnancy Rate	Live Birth Rate	Miscarriage Rate	Multiple Gestation Rate	Maternal Complications
Medical Treatment(107)	26 (24.3%)	23 (21.5%)	2 (1.9%)	1 (0.9%)	6 (5.6%)
Surgical Treatment (84)	12 (14.3%)	11 (13.1%)	1 (1.2%)	0	0
Combined Medical & Surgical (27)	7 (25.9%)	6 (22.2%)	1 (3.7%)	0	0
Overall (218) *	45 (20.6%)	40 (18.3%)	4 (1.8%)	1 (0.5%)	6 (2.8%)

* 63 patients not treated; Required ART as primary management

The medical management of infertility was limited to the treatment of anovulation. A total of 107 patients underwent medical therapy. An ovulation rate of 76.6% (82 patients) and 26 pregnancies were achieved (PR = 22.4%). Twenty-four (8.5%) patients had follicular tracking and timed intercourse with 8 patients (33.3%) falling pregnant after an average of 4.5 cycles. Seven pregnancies out of 45 (15.5%) were achieved on CC and timed intercourse after an average of 5.2 cycles; 5 patients on the 50mg dose, and 1 each on the 100mg and 150mg doses respectively. With the addition of metformin to CC for those PCOS patients with insulin resistance (n=29), 10 pregnancies (34.5%) were achieved; 6 patients whilst on the 50mg dosage, 3 patients whilst on the 100mg dose and 1 on the 150mg dose at an average of 8.2 cycles. Nine patients with PCOS, had at least one intrauterine insemination (IUI) performed using laboratory services from the private sector whilst also on CC and/or metformin. One patient conceived (11.1%) in this group whilst on 100mg of CC.

Twenty patients (7.1%) in the series were found to have unexplained infertility after diagnostic tests revealed no cause of infertility. All patients were offered induction of ovulation with clomiphene citrate. None of these patients conceived within the study period.

Surgical management was offered to patients with tubal factor infertility, uterine factor infertility and those with endometriosis. The overall pregnancy rate after surgical treatment was 14.3%. Tubal factor infertility affected 85 patients (30.2%) including 11 patients (3.9%) requesting reversal of tubal ligation. Twenty one patients had laparoscopy and adhesiolysis after which 3 patients spontaneously conceived (PR = 14.3%). Six salpingolyses were performed with 1 pregnancy (PR = 16.7%) and 9 neosalpingostomies were performed with one pregnancy (PR = 11.1%). The live birth rate for tubal surgery alone was 13.9% after an average of 8.5 months.

Eleven patients (3.9%) in this series representing 12.9% of patients with tubal factor infertility requested tubal ligation reversal. Two patients were turned away because of age related factors, both being 43 years old and perimenopausal. The most commonly quoted reason for reversal was a change in partner (45.5%) either due to divorce or death of a spouse. Other reasons included the death of a child/children and regret at premature decision for sterilisation. Over half of these patients (54.5%) were under 30 years of age when the tubal ligation was performed. Nine reversals were performed by laparotomy and micro-surgical technique using the loupes. Six patients (66.6%) had undergone sterlisation using the Modified Pomeroy technique and 3 patients (33.3%) had undergone Filshie clip insertion. Three successful pregnancies were achieved (PR = 33.3%) after an average of 13.2 months. There were no ectopic pregnancies after tubal surgery.

In this audit endometriosis was found in 22 patients (7.8%). Sixteen patients had diathermy/excision of the endometrial deposits. One uncomplicated term pregnancy was achieved (6.3%). Apart from diathermy/excision, 8 patients also had endometriomas removed with 1 pregnancy (PR = 12.5%) achieved during the study period. The average time from surgery to conception was 6.6 months.

In this study, leiomyoma were present on routine ultrasound scan in 32 patients (11.4%) and were deemed causative in only 12 patients (4.3%). Five uncomplicated open myomectomies were performed with one term delivery by caesarean section (PR = 20%) after 10 months.

Twenty seven patients (9.6%) had combined medical and surgical treatment with a 25.9% pregnancy rate. Fourteen patients underwent ovarian drilling after failure to ovulate on CC and metformin with a 25% pregnancy rate. Thirteen patients had tubal surgery and CC. One conception was achieved, 16 months after initiation of treatment.

The maternal complication rate was 2.8% (6 patients) all of whom had PCOS and had undergone ovulation induction with clomiphene citrate. Three patients (50%) developed gestational diabetes and 3 (50%) developed preeclampsia. There was no other associated maternal or fetal morbidity in this group, with all patients delivering live infants at term.

Both male and female factors affected 17 patients (6.1%) in this audit. The majority of females had ovulatory (47.1%) and tubal dysfunction (29.1%) while oligozoospermia was the commonest sperm abnormality (58.8%). The majority of these patients (86.7%) and those with severe male factor infertility could not receive any further treatment due to the unavailability of ART and form part of the 22.4% that could not be offered any treatment. The overall pregnancy rate was determined to be 16% with 84% of participants still requiring further treatment.

CHAPTER 5

Discussion

This audit has identified anovulation and tubal factor as the primary causes of infertility. An overall pregnancy rate of 16% was achieved with the currently available medical and surgical treatment. Eighty four percent of couples did not conceive. Twenty two percent of couples with severe male factor and tubal damage could not be offered treatment due to the unavailability of ART. This audit has demonstrated the need for such a service in KwaZulu Natal.

The majority of patients in this audit were from the African (52%) and Indian (41.3%) community. According to the 2006 mid-year population statistics, there were 9.4 million people in KZN, representing 21% of the South African population.[74] Eight million were African (85%), 0.8 million were Indians (8%) with 0.5 million Whites (5%) and 0.2 million Coloureds (2%). Of these the majority of Indians (665 000) live within the Ethekweni district in which IALCH is situated.[74]

The correlation between advancing age and decline in fertility is well established.[15,16,17] In this audit, the average age of the participants was 31.1 years (range 19 to 42). In a similar audit at King Edward VIII Hospital (KEH), Durban the average age was also 31 years (range 20 to 45). [7] Similarly, the age of participants in a Cape Town study also averaged 30.3 years (range 21 to 41). [75] These figures are more in keeping with international figures where there is a trend toward deferment of marriage and childbearing due largely to changing socio-cultural and economic factors and the necessary role of women in the workplace. Although this reasoning may apply to a more affluent sector of the study population, lack of patient

awareness and availability of infertility services in the province may also play a role in this regard.

The duration of infertility averaged 6.1 years as compared to the King Edward study that averaged 7.7 years [7] and a Cape Town study that averaged 4.8 years.[75] These statistics seem to be in keeping with norms in developing countries where couples seek therapy after at least 2.5 years of trying to conceive spontaneously [76] as compared to developed countries where 50% of couples seek therapy after less than two years.[9] This long duration of infertility is possibly a reflection of ineffective care, lack of accessibility to treatment or patients knowledge of available resources.

Lifestyle factors including cigarette smoking, alcohol use, recreational drug use and obesity have been shown to impact negatively on reproductive function [8] and of these, obesity is a most common especially in patients with PCOS. The average BMI was 32.1kg/m² with 65.4% of patients having a BMI greater than 30 kg/m². Of note is that 66% of African patients and 45% of Indian patients in the study had a BMI greater than 30kg/m². Although anovulatory infertility was common amongst obese patients, it failed to reach statistical significance because the majority of patients were obese. This is in keeping with the national South African statistics where 58.5% of African women and 48.9% of Indian women were found to be either overweight or obese. [77] There is a worrying trend toward obesity in developing countries and is thought to be as a result of changes in dietary habits, urbanisation and physical activity. [78]

The main cause of infertility among couples in this series was anovulation (32.7%) and this was also the leading cause found in those with primary infertility (42.7%). Worldwide

ovulatory disorders account for 20 to 25% of infertile women.[6] In the Chigumadzi study (1998) in African infertile women, 18% were deemed to have anovulation which was the fourth most common cause of infertility. In this audit, 40% of Africans had anovulatory infertility.[7] That study did not report on BMI and it is possible that this difference in the incidence of ovulatory disorders is because the majority of patients in this study were obese with an average BMI of 32.1kg/m². Apart from PCOS, obesity is a major cause of anovulation.[8] Furthermore, South African women are now more obese compared to 12 years ago.[77]

Tubal factor was found in 30% of patients; this being the most common cause in African participants (37%). African patients were significantly more likely to have tubal factor infertility (OR = 1.93 95% CI 1.12 – 3.34; P = 0.02). Tubal factor was also the leading cause of infertility (77%) in this race group in the Chigumadzi study (1998).[7] A possible explanation for the apparent decrease in incidence of tubal factor infertility in this study is the increased proportion of cases of anovulation. In the United Kingdom, tubal factors contributed to 14% of causes of infertility.[49] The majority of those with tubal infertility had typical risk factors including PID (55.3%), STI (29%) and previous ectopic pregnancy (72.2%). One in five patients with tubal infertility also smoked cigarettes. The commonest cause of secondary infertility was also tubal factors (46.5%). Amongst this group 64% had conceived at a young age (19.6 years) and probably developed tubal disease after subsequent sexual exposures.

Overall, male factors were found to contribute to infertility in 17.9% (50 spouses) in this series. Of these, female factors also played a role in 32.1% (17 patients). Male factor infertility alone was found in 11.7% (33 patients) of the study population, affecting both African and Indian race groups in equal proportion – approximately 1 in 10 patients. Worldwide male factor infertility accounts for up to 30% of infertility [6] and may play a

contributory role in 40% of couples.[14] Chigumadzi et al (1998) found a 21% male factor infertility rate. In cases of male infertility, 20% will be successful after artificial insemination by the husband.[7] The majority (80%), however, require some form of assisted reproduction including IVF and ICSI.[55] Both are currently unavailable at IALCH. The most common feature in those with male infertility was oligozoospermia in 48% and azoospermia in 18%. Although the negative correlation between infertility and lifestyle factors such as age, obesity, cigarette smoking and alcohol consumption are well known,[6] this information was not efficiently recorded in the majority of patient's files and is a shortcoming in this audit. A detailed questionnaire for couples at initial evaluation at the clinic would aid this problem in the future.

Endometriosis was found in more Indian women than African women (13.8% vs 2.7%) and African patients were significantly less likely to have endometriosis than Indian patients (OR = 0.18 95% CI 0.06 – 0.54; P = 0.01). In the Chigumadzi study (1998) no patients were found to have endometriosis. A possible reason for this increase in occurrence is that the large majority of the participants in that study were African and the opportunities for diagnostic laparoscopies in 1998 in the public sector were limited. This audit revealed a lower number of cases of endometriosis (7.8%) compared to the 25% to 50% found in infertile women worldwide.[13]

Although evaluated in a relatively resource poor setting, twenty patients (7.1%) in the series were found to have unexplained infertility after diagnostic tests revealed patent tubes, normal sperm parameters and evidence of ovulation. Worldwide unexplained infertility occurs in 15 to 30% of couples.[68] The diagnosis of unexplained infertility, however, remains contentious with many experts suggesting that it is too subjective and dependant largely on the particular centre's resources and on what tests are performed and at what quality level.[79] Tubal infertility, premature ovarian failure and endometriosis are frequently misdiagnosed as

unexplained infertility.[79] Similarly, the test for antisperm antibodies is expensive and their presence also does not alter management i.e ovulation induction and IUI followed by IVF or ICSI.[14]

Leiomyomas were found in 11.4% of patients. In the absence of other causes, twelve patients (4.3%) were thought to have uterine factor infertility in the form of leiomyoma, correlating to internationally quoted figures. Worldwide, leiomyomas are associated with infertility in 5 to 10%, and responsible in only 2 to 3%.[71] Uterine factors were the second most common cause of infertility (21%) in the Chigumadzi study (1998).[7]

No patients presented with congenital abnormalities of the uterus. The reason for this apparent absence of patients with congenital abnormalities is probably due to a referral bias. Patients with congenital uterine abnormalities usually present with primary amenorrhea or recurrent miscarriages. After primary investigation at the peripheral hospitals, these patients are either referred to the gynaecological endocrine clinic or to the recurrent miscarriage clinic and not directly to the infertility clinic.

The KZN official government health site quotes a 14.2% prevalence of HIV amongst males and a 16.4% amongst females in the province.[74] The correlation between tubal infertility and sexually transmitted infection is well documented.[2] In this study, 14 female patients (5%) and 10 spouses (3.6%) were found to be HIV positive with 6 couples found to be sero-concordant. The likely reason for the low prevalence in the study population is that many patients are still turned away at the secondary and tertiary institutions prior to referral and that there are no modalities of treatment available at IALCH to assist safe conception in HIV positive couples. For concordant couples sperm washing and timed artificial insemination is

the current recommendation.[80] For serodiscordant couples in which the female is HIV positive, insemination of the partner's sperm is advised at time of ovulation.[80] In serodiscordant couples in which the male is infected, the treatment options include donor insemination, sperm washing and IUI, and sperm washing and IVF in cases of tubal blockage and failed IUI.[80] None of these modalities are currently available at IALCH.

The presence of HIV is also related to the occurrence of other STIs (syphilis and human papilloma virus), and to the incidence of infective and pre-malignant lesions of the cervix. Six female (2.1%) and 3 male patients (1.1%) had reactive RPR tests. The WHO estimates the prevalence of sexually transmitted infections at 119 per 1000 population in sub-Saharan Africa as compared to 19 per 1000 in North America and Western Europe.[9] Given that STIs are prevalent in our study population (27%), one would expect a high incidence of pre-malignant lesions. However, this audit found a 1.1% (3 patients) prevalence and Chigumadzi et al (1998) found a 2% prevalence of pre-malignant lesions.[7] The probable cause is appropriate referral for colposcopy prior to attendance at the infertility clinic.

All patients had trans-vaginal ultrasound scans performed. Over one third (36.3%) of scans were normal. Polycystic ovaries were the most common abnormal finding in 83 patients (29.5%). Sixty-five patients (32.1%) were ultimately diagnosed with PCOS using the Rotterdam criteria. Hydrosalpinx was the next most common abnormality found in 17.8% of patients. Leiomyoma were found in 32 patients (11.4%) but were deemed causative in only 12 patients (4.3%). Fifty seven percent of cases diagnosed as endometriomas on ultrasound were confirmed at histology and the remaining 43% were haemorrhagic corpus luteum cysts.

In the assessment of tubal factor infertility, patients either had HSG or laparoscopy and dye. HSG was preferred as a first line investigation in asymptomatic women while laparoscopy was performed in those with a suggestive history and symptoms of disease, usually chronic pelvic pain and dyspareunia. This was done so that further surgical management (adhesiolysis, salpingolysis, cystectomy) could be performed at the same time. HSG was avoided in symptomatic women so as to not precipitate pelvic infection. Being a referral centre, patients were also referred to the unit with HSG or laparoscopy and dye results. Of the 71 patients that had HSG, 42 patients (59.1%) demonstrated tubal blockage. Blocked tubes were confirmed on 31 of 36 (86.1%) of these patients that had subsequent laparoscopy, whilst the remaining 5 patients (13.9%) were presumed to have had tubal spasm at time of HSG.

In this audit PCOS was deemed causative in approximately 70% (65 patients) of women with ovulatory factor infertility. Worldwide, PCOS is also the commonest reason for anovulation, being found in 80% of anovulatory women.[21] Uncontrolled steroidogenesis is thought to be integral to the pathogenesis of PCOS with 60 to 80% of women having high testosterone levels and 25% having high concentrations of DHEAS. [20] In this series just 23% (15 patients) had raised testosterone levels and 32% (21 patients) had increased DHEAS with 40% (26 patients) having high levels of androstenedione. Although serum analysis may fail to measure biochemical hyperandrogenism in as many as 20% to 40% of patients, in the presence of clinical signs, the diagnosis of PCOS cannot be deferred.[20]

PCOS causes an abnormal pulsatility of gonadotrophins with increased LH and either normal or decreased levels of FSH occur in approximately 40% of women. [81] In this audit, 58.5% (38 patients) had elevated LH levels with approximately 48% (31 patients) having inverse FSH to LH ratios. This inverse proportion was mostly present in those with a BMI

greater than 30 kg/m² (74%) in contrast to figures quoted by Norman et al (2007) in which the majority of such patients had a normal BMI. This is most probably due to the majority of patients in this audit being either overweight or obese with only 9.3% having a BMI less than 25kg/m².[23]

Insulin resistance is central to the pathogenesis of PCOS. [82] Hyperinsulinemia was present in 53.8% (35 patients) of our PCOS population with 12% (8 patients) displaying impaired glucose tolerance and 3% (2 patients) overt diabetes mellitus (DM) on random blood glucose levels. Women with PCOS have a 35 to 40% decrease in insulin mediated glucose uptake with 40% of obese women having impaired glucose tolerance.[20] The South African Indian population has a high prevalence of PCOS and insulin resistance [83] but despite this, the rate of impaired glucose tolerance and DM was found to be relatively low in this study. This may be due to the cohort of PCOS patients being relatively young with an average age of 29.2 years. These women may become diabetic a few decades later as a long term consequence of PCOS.

At IALCH, those with insulin resistance and BMI above 30 kg /m^2 were started on metformin. Tang et al (2010) in a Cochrane metanalysis recently concluded that its use either alone or with clomiphene citrate had no effect on live birth rate, although ovulation rates with CC or alone did increase.[35] Metformin is also used in those with overt diabetes mellitus as evidenced by an oral glucose tolerance test. In these patients, once pregnant, metformin is continued throughout pregnancy. De Leo et al (2011) described significant decreases in miscarriage rates, gestational diabetes with improved neonatal outcomes in PCOS patients with hyperinsulinaemia that continued metformin compared to normal controls.[84]

The overall pregnancy rate with the available medical and surgical treatment was 16%. Anovulation and PCOS in particular is managed by lifestyle modification and induction of ovulation. The pregnancy rate after the various modalities of medical treatment was 24.3%. Twenty four obese (average BMI 30.3 kg/m²) PCOS patients underwent dietary modification, follicular tracking and timed intercourse in spontaneous unstimulated cycles. A pregnancy rate of 33.3% (8 pregnancies) was achieved after weight loss alone. A 5% decrease in weight improves the hormonal milieu such that ovulation can occur. [20]

At IALCH those women with anovulatory infertility, unexplained infertility and those who failed to conceive after surgical treatment , are started on clomiphene citrate at a dose of 50mg daily from day 2 to day 6 of the menstrual cycle. Those that do not ovulate are stepped up to 100mg and then to 150mg if ovulation does not occur for a further 3 cycles. Those that do not ovulate are considered clomiphene citrate resistant and second line intervention is needed. If ovulation does occur, that particular dose is maintained until pregnancy is achieved. Forty five patients were treated with CC and timed intercourse. A 77% ovulation rate was achieved with a pregnancy rate of 15.6% (7 pregnancies) achieved at an average of 4.5 cycles. The ovulation rate is comparable to quoted figures where approximately 75% to 90% of anovulatory women will ovulate and 35% to 40% will conceive.[27]

At IALCH, those with insulin resistance and BMI above 30 kg /m^2 were started on metformin. With the addition of metformin to CC for those PCOS patients with insulin resistance (n = 29), an ovulation rate 67.7% and pregnancy rate of 34.5% was achieved after an average of 5.1 cycles. Although the addition of metformin remains controversial, these results are comparable to those found in larger studies which concluded that for ovulation induction, the combination of CC and metformin was found to be 2 to 4 fold more effective than CC alone

and also more effective in those with CC resistance. Ovulation was achieved in 76% compared to 42% on CC alone.[36,37] However, these results were challenged by Legro et al (2007) who found no significant differences in rate of ovulation (64% vs. 72%) and ongoing pregnancy rate (40% vs. 46%) when comparing CC plus a placebo to CC plus metformin. [38] At IALCH, the use of metformin is now limited to those with overt diabetes mellitus as evidenced by an oral glucose tolerance test. Once pregnant, metformin is continued throughout pregnancy. De Leo et al (2011) described significant decreases in miscarriage rates, gestational diabetes with improved neonatal outcomes in PCOS patients with hyperinsulinaemia that continued metformin compared to normal controls.[84]

Although associated with increased rates of multiple gestation and risks of OHSS, gonadotrophins are successfully used worldwide and recommended as an alternate second line management for patients with CC resistant PCOS (ESHRE/ASRM PCOS Consensus Workshop Group). Gonadotrophins are unavailable in the public sector in KwaZulu Natal. In the absence of gonadotrophins, 10 patients had laporoscopic ovarian drilling (LOD) whilst also on CC with a 10% pregnancy rate. Only 3 patients (30%) failed to ovulate after LOD. After LOD 66% of patients will ovulate spontaneously.[13] No patients developed premature ovarian failure. The third-line management of PCOS is IVF and no patients in this study were able to benefit from this procedure.

Tubal surgery included laparoscopy and adhesiolysis, salpingolysis and neosalpingostomy. The cumulative live birth rate for tubal surgery in this series (excluding tubal ligation reversal) was 13.9%. Singhal et al (1991) described a 30% birth rate after tubal surgery.[85] The comparatively low success rate can possibly be attributed to the fact that there are no treatment alternatives available. In the absence of IVF, patients with tubal infertility, irrespective of the severity of tubal damage, can only have tuboplasty at IALCH.

Unfortunately the grades of severity of tubal damage were not differentiated according to the Hull and Rutherford classification which would have enable the unit to accurately prognosticate and to counsel the patient regarding the chances of ectopic pregnancy, pregnancy and live births.[86]

Eleven patients (3.9%) requested tubal ligation reversal and 9 laparotomies were performed achieving a pregnancy rate of 33.3%; 2 patients from the Filscie clip group and one from the Pomeroy group. The pregnancy rate after tubal re-anastamosis after reversal is quoted at 80%.[87] The reason for the discrepancy in success rate is possibly due to the majority of patients having undergone sterilisation at caesarean section using the modified Pomeroy technique which utilizes a large portion of fallopian tube. Pregnancy rates are best if at least 4 cm of viable tube remains after the reversal.[87] Other than micro-surgical reversal, IVF is the other option. Surgery restores tubal function whereas IVF replaces it. Surgery also allows for the possibility of subsequent pregnancies.

While the use of medical management either alone, or in combination with surgery, was found to be of little benefit in terms of fertility, pregnancy rates are increased after surgical management of endometriosis.[65] In this study, the pregnancy rate after surgery for stage I/II endometriosis was 8.3%. Marcoux et al (1997) demonstrated a 29% live birth rate after endometriosis ablation and adhesiolysis.[66] After surgery for mild disease, if ovulation induction and IUI fails, or in the presence of severe disease with tubo-ovarian distortion, IVF is recommended.[67] Both these treatment modalities are currently unavailable.

Although the diagnosis of unexplained infertility remains controversial, all patients were started on CC. Randomised controlled trials support the use of short term CC,

gonadotrophins, IUI and ART. [68] The only treatment option available at IALCH is CC. No conceptions were achieved.

After 5 open myomectomies, a term pregnancy rate of 20% was achieved. Term pregnancy rates after myomectomy usually range from 40% to 50% with a decrease in miscarriage rates from 41% to 19% after surgery. [72] The possible explanation for the low pregnancy rate is the late presentation of patients with larger multifibroid uteri and the associated decrease in pregnancy rate after myomectomy. In this audit, myomas were not found to be causative in any patients with recurrent miscarriage.

This audit has shown that with a relatively low pregnancy rate of 16%, there is a need for assisted reproductive services in the province. Second and third line therapies for the medical management of the commonest cause of infertility, anovulation, are also a necessity. Furthermore, ART is required as primary management for 22% of patients with severe male factor and tubal damage and for those with other causes of infertility who fail to conceive after surgical treatment.

CHAPTER 6

Conclusion and Recommendations

In South Africa, and worldwide, the availability of infertility services is determined by political, economic and socio-cultural concerns that dictate national health policies regarding the allocation of finances, personnel and equipment. In developed countries, infertility is regarded as a viable medical concern with treatment being incorporated into national health schemes.[9] However, because developing countries are burdened with other major primary health care concerns and often considered in need of population control, infertility is not acknowledged as a serious public health problem. Infertility treatment is not incorporated into programs of family planning leaving many with the stigmatisation of involuntary childlessness. Most infertility treatment occurs outside government health centres that provide services to the minority who can afford to pay for ART and private care. This audit has demonstrated that with approximately 100 new couples visiting the infertility unit at IALCH every year, there is a need for further infertility services in the province. Inkosi Albert Luthuli Central Hospital is in a fortunate position of having much of this infrastructure already in place.

Primary health care initiatives, (e.g. sexual health, HIV/AIDS campaigns) will indirectly aid in preventing infection and subsequent tubal factor infertility. Young women should also be made aware of increased the risk of secondary infertility following the acquisition of pelvic infections. A grading system such as the Hull and Rutherford Classification should be used to prognosticate the success of conception in those undergoing tuboplasty. More public awareness of the dangers of obesity will not only make women aware of the associated risk of ovulatory infertility but also warn them against the long term consequences of the metabolic syndrome. Semen quality is also adversely affected by obesity. Other lifestyle

factors affecting fertility such as cigarette smoking and alcohol and recreational drug use should also be publically highlighted. With the history taking of infertile couples being of utmost importance, the unit itself can improve by using a detailed structured proforma at first assessment to accurately evaluate both partners. The long delay prior to seeking assistance also indicates that the general public is either unaware of fertility services in the province or that there are insufficient services available.

However, most of the other causes of infertility are largely non-preventable. In patients with anovulation and unexplained infertility only first line therapy is currently offered. Gonadotrophins as a second option, and ART as subsequent treatment in those that fail to conceive, are currently unavailable. For those with male factor infertility and for those other causes with failed surgical management, ART is the only other alternative. Furthermore with the high prevalence of HIV/AIDS in the province, many also afflicted with infertility are unable to conceive safely once treatment has been initiated. Infertility health care initiatives in certain provinces in the country, as well as in Africa and abroad, have established links with the pharmaceutical and non-governmental sectors in order to reduce the cost of ART which enables the patient to finance a portion of the amount for a fixed number of cycles. Such collaboration would also be of benefit in KZN.

With the comparatively limited successes of the currently available medical and surgical management, local government health initiatives aimed directly at infertility management in a fully fledged infertility unit with ART needs to be made available in the province.

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APPENDIX

Data Sheet

Case Nr A**.** Demographics

1. Age		
2. Race		
3. Gravidity / Parity	Grav	Para
4. Type of Infertility	a. Primary	b. Secondary
5. Duration of Infertility		

B. Female Risk Factors

1. BMI (weight / height)			
2. Cigarette Smoking	a. Yes	b. No	
3. Alcohol	a. Yes	b. No	
4. Other drugs	a. Yes	b. No	c. Type
5. Medical co-morbidities	a. DM	b. HPT	c. Other

C. Menstrual History

1. Normal			
2. Abnormal	a. Oligo / amenorrhea	b. Menorrhagia	c. Metrorrhagia

D. Male Risk Factors

1. BMI (weight / height)					
2. Cigarette Smoking	a. Yes		b. No		
3. Alcohol	a. Yes		b. No		
4. Other drugs	a. Yes		b. No		c. Type
5. Medical co-morbidities	a. DM		b. HPT		c. Other
6. Age					
7. Previous STI	a. Ulcerative		b. Non ulcerative		
8. Previous HIV test	a. Pos	b. Neg	c.Unknown	d. CD4	e. On Arvs

E. Female Factors

1. Previous PID		a. Inpatient Rx		b. Outpatient Rx	
2. Previous STD		a. Ulcerative		b. Non ulcerative	
3. Endocrine disorder		a. PCOS	b. Thyroid	c.HyperPRL	Other
4. Congenital Uterine Abnormality		a. Yes	b. No	c. Type	
5. Previous HIV test	a. Pos	b. Neg	c.Unknown	d. CD4	e. On Arvs

F. Previous Obstetric History

1. Delivery of term baby	a. 0	b. 1	c. 2	d. 3	e. Still alive?
2.Delivery of Preterm baby	a. 0	b. 1	c. 2	d. 3	e. Still alive?
3. Miscarriage	a. Yes		b. No	c. Spont	c. Induced
4. Ectopic	a. Yes		b. No		c. Mx
5.Post abortal / puerpal sepsis	a. Yes		b. No		c. Mx
6. Same Consort	a. Yes		b. No		

G. Contraceptive History

1. Pill	a. Yes	b. No
2. Injectable	a. Yes	b. No
3. IUCD	a. Yes	b. No
4. Condom	a. Yes	b. No
5. No contraception	a. Yes	b. No

H. Previous Interventions

1. Previous medical	a. Yes	b. No	c. Type of Rx	
2. Previous Surgical	a. Yes	b. No	c. Type of Rx	
3.Healthcare Practitioner	a. GP	b. Specialist	c. Traditional	d. Other

I. Female Investigations

I(i) Routine Investigations

1. HIV	a. Not done		b. Positive		c. Negative	
2. RPR	a. Not done		b. Positive		c. Negative	
3. Pap	a. N/D	b. Infl	c. NAD	d. ASC	e. LG	f. HG
4. TVS	a. NAD	b. PCOS	c. Endo	d. MFU	e. TOM	

I(ii) PCOS / Anovulation Investigations

5. Day 21 Progesterone	a. Not done	b.Normal	c. High	d. Low	e. Value
6. Oestradiol	a. Not done	b.Normal	c. High	d. Low	e. Value
7. FSH	a. Not done	b.Normal	c. High	d. Low	e. Value
8. LH	a. Not done	b.Normal	c. High	d. Low	e. Value
9. Testosterone	a. Not done	b.Normal	c. High	d. Low	e. Value
10. DHEAS	a. Not done	b.Normal	c. High	d. Low	e. Value
11. Glucose	a. Not done	b.Normal	c. High	d. Low	e. Value
12. Insulin	a. Not done	b.Normal	c. High	d. Low	e. Value
13. 17-OH Progesterone	a. Not done	b.Normal	c. High	d. Low	e. Value
14. Androstenedione	a. Not done	b.Normal	c. High	d. Low	e. Value
15. HDL	a. Not done	b.Normal	c. High	d. Low	e. Value
16. LDL	a. Not done	b.Normal	c. High	d. Low	e. Value
17. Cholesterol	a. Not done	b.Normal	c. High	d. Low	e. Value
18. Triglyceride	a. Not done	b.Normal	c. High	d. Low	e. Value

I(iii) Investigations of medical disorders

19. TSH	a. Not done	b.Normal	c. High	d. Low	e. Value
20. Prolactin	a. Not done	b.Normal	c. High	d. Low	e. Value
21. ANF	a. Not done	b. Positive	c. Negative		
22. ACA	a. Not done	b. Positive	c. Negative		
23. Cortisol	a. Not done	b.Normal	c. High	d. Low	e. Value
24. MRI	a. Not done	b. Normal	c. Abnormal	d. Defect	

I(iv) Surgical Diagnostic Investigations

25. HSG	a. Not done	b. Normal	c. Abnormal	d. Defect	e. Complication
26. Hysteroscopy	a. Not done	b. Normal	c. Abnormal	d. Defect	e. Complication
27. Lap and dye	a. Not done	b. Normal	c. Abnormal	d. Defect	e. Complication

I(v) Other Investigations

28. Male Karyotype	a. Not done	b. Normal	c. Abnormal	d. Defect
29. Female Karyotype	a. Not done	b. Normal	c. Abnormal	d. Defect

J. Male Investigations

1. HIV	a. Positive			b. Negative		
2. RPR	a. Positive			b. Negative		
3. Semen Analysis	a. Normal			b. Abnormal		
4. Spp defect	a. Count	b.Viability	c.Morph	d.Motility	e. Blood	f. Pus

K. Induction of Ovulation

1. Clomiphene Citrate	a. Indicated	b. Not indic	c. Success	d.No success
2. Metformin & CC	a. Indicated	b. Not indic	c. Success	d.No success

L. Medical Treatment

1. FT & TI	a. Indicated	b. Not indic	c.Conception	d.No Conception	e. Complications	f. Nr of cycles
2. CC & TI	a. Indicated	b. Not indic	c.Conception	d.No Conception	e. Complications	f. Nr of cycles
3.CC,met& TI	a. Indicated	b. Not indic	c.Conception	d.No Conception	e. Complications	f. Nr of Cycles
4. CC & IUI	a. Indicated	b. Not indic	c.Conception	d.No Conception	e. Complications	f. Nr of cycles
5.CC,met, IUI	a. Indicated	b. Not indic	c.Conception	d.No Conception	e. Complications	f. Nr of cycles

M. Surgical Treatment

1. Laparoscopy & dye	a. Yes	b. No	c. Complication	d. No Complication
2. Laparoscopy, surgery and dye	a. Yes	b. No	c. Complication	d. No Complication
3. Tubal ligation reversal	a. Yes	b. No	c. Complication	d. No Complication
4. Salpingolysis	a. Yes	b. No	c. Complication	d. No Complication
5. Neosalpingostomy	a. Yes	b. No	c. Complication	d. No Complication
6. Excision / Diathermy	a. Yes	b. No	c. Complication	d. No Complication
7. Cystectomy – endometrioma	a. Yes	b. No	c. Complication	d. No Complication
8. Myomectomy	a. Yes	b. No	c. Complication	d. No Complication
9. Ovarian Drilling	a. Yes	b. No	c. Complication	d. No Complication

N. Conception with Medical Treatment

1. Conception	a. Yes	b. No	c. Ectopic	d. Multiple gest

O. Conception with Surgical Treatment

1. Conception	a. Yes	b. No	c. Ectopic	d. Multiple gest

P. Pregnancy Outcome with Medical Treatment

1. Outcome with Medical Rx	a. Term
	b. Preterm
	c. Miscarriage
	d. Complications

Q. Pregnancy Outcome with Surgical Treatment

1. Outcome with Surgical Rx	a. Term
	b. Preterm
	c. Miscarriage
	d. Complications

R. Duration of time between medical treatment and conception

1. FT & TI	a. 0 – 6 months	b. 6 - 12 months	c. 12 - 24 months	d. >24 months
2. CC & TI	a. 0 – 6 months	b. 6 - 12 months	c. 12 - 24 months	d. >24 months
3.CC,met & TI	a. 0 – 6 months	b. 6 - 12 months	c. 12 - 24 months	d. >24 months
4. CC & IUI	a. 0 – 6 months	b. 6 - 12 months	c. 12 - 24 months	d. >24 months
5.CC,met, IUI	a. 0 – 6 months	b. 6 - 12 months	c. 12 - 24 months	d. >24 months

S. Duration of time between surgical treatment and conception

1. Laparoscopy & dye	a. 0 – 6 months	b. 6 - 12 months	c.12-24 months	d. >24 months
2. Laparoscopy, surgery and dye	a. 0 – 6 months	b. 6 - 12 months	c. 12-24 months	d. >24 months
3. Tubal ligation reversal	a. 0 – 6 months	b. 6 - 12 months	c. 12-24 months	d. >24 months
4. Salpingolysis	a. 0 – 6 months	b. 6 - 12 months	c. 12-24 months	d. >24 months
5. Neosalpingostomy	a. 0 – 6 months	b. 6 - 12 months	c. 12-24 months	d. >24 months
6. Excision / Diathermy	a. 0 – 6 months	b. 6 - 12 months	c. 12-24 months	d. >24 months
7.Cystectomy– endometrioma	a. 0 – 6 months	b. 6 - 12 months	c. 12-24 months	d. >24 months
8. Myomectomy	a. 0 – 6 months	b. 6 - 12 months	c. 12-24 months	d. >24 months
9. Ovarian Drilling	a. 0 – 6 months	b. 6 - 12 months	c. 12-24 months	d. >24 months