PROFILE OF MORTALITY AMONGST WOMEN WITH GESTATIONAL TROPHOBLASTIC DISEASE (GTD) INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS (HIV) IN RELATION TO HIV NON-INFECTED WOMEN

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This dissertation is submitted to the University of KwaZulu Natal, Nelson R Mandela School Of Medicine, in part fulfilment of the requirements for the degree of Masters of Medicine in the Department of Obstetrics and Gynaecology.

DECLARATION

I, Samantha Budhram, hereby declare that the work on which this dissertation is based is original and is my own unaided work carried out by me under the supervision of Dr M. Moodley. This work has not been submitted previously to this or any other university.

SIGNED: .....

DATE: 14/10/2008

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ABSTRACT

OBJECTIVES:

To determine if women with Human Immunodeficiency Virus infection with severe degrees of immunosuppression are more predisposed to mortality from Gestational Trophoblastic Disease compared with HIV-infected women with less severe degrees of immunosuppression and Human Immunodefiency Virus (HIV) non-infected women.

DESIGN:

Retrospective review of case records.

METHOD:

A retrospective review was performed on all patients with Gestational Trophoblastic from 2003 to July 2007. A chart review was conducted and information captured on a data sheet. This retrospective audit was performed at the combined gynaecology oncology clinic of Inkosi Albert Luthuli Central Hospital. All information was kept confidential and was strictly for the purposes of the audit.

STATISTICS:

Factors associated with mortality were tested using Fisher's exact test. Odds ratios were reported as a measure of the strength of association. Breslow-Day's test for homogeneity in odds ratios was used to compare mortality in HIV-infected and HIV non-infected women. The analysis was done using Stata 9.

RESULTS:

A total of 78 patients with Gestational Trophoblastic Disease were reviewed. There were 53 patients with invasive molar pregnancy and 25 patients with choriocarcinoma. The HIV sero-prevalence was 31%. There were 15 deaths (19%). There were 8 HIV-infected (33%) and 7 HIV non-infected (13%) women who demised. Of the 8 patients with CD4 counts less than 200 cells/ μL, 7 patients demised. There were no mortalities amongst patients with CD4 counts more than 200 cells/μL. Of the 15 deaths, 5 HIV-infected patients and 5 HIV non-infected patients received chemotherapy. There were 5 patients admitted in very poor general condition precluding the administration of chemotherapy. Amongst the 10 patients who received chemotherapy and demised, the causes of death included widespread disease, multiorgan failure and toxicity due to chemotherapy.

CONCLUSION:

The overall survival of all patients managed with Gestational Trophoblastic Disease was 82% in keeping with the expected high survival reported elsewhere. The majority of patients who demised were admitted in poor general condition and had abnormal blood profiles. Despite resuscitation, these patients failed to improve precluding the administration of chemotherapy which is the mainstay of treatment. Although the numbers are small, there is clear evidence that if patients are HIV-infected with CD4 counts $\leq$ 200 cells/μL, the mortality is high (75%). In contrast, the outcome is excellent if the CD4 counts are > 200 cells/μL despite transient grade 2 myelotoxicity.

CHAPTER 1

INTRODUCTION

Gestational Trophoblastic Disease (GTD) encompasses a spectrum of abnormal proliferations of the trophoblast, ranging from benign to malignant forms of the disease. Conditions included under the term GTD include partial and complete hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumours and epitheloid trophoblastic tumours. Gestational Trophoblastic Tumour (GTT) refers to persistent GTD whilst Gestational Trophoblastic Neoplasia (GTN) refers to all GTD. Gestational Trophoblastic Disease is characterized by distinct clinical presentations, biochemistry and radiological features. In fact, GTD is one condition for which the diagnosis is based on clinical, biochemical and radiological investigations. Histology is usually not necessary and attempts to obtain histological confirmation may lead to torrential haemorrhage.

Over the last few decades there have been differences in the management of GTD across the world. This situation had arisen mainly because the disease did not require histological confirmation and differences in staging systems and chemotherapeutic regimens utilized. Difficulties therefore arose in comparisons of treatment outcomes. With the advent of high resolution ultrasound and accurate tests for measuring serum β-human chorionic gonadotrophin (β-HCG), there has been a trend to diagnose GTD earlier. The formation of the International Society for the Study of Gestational Trophoblastic Diseases (ISSGTD) led to consensus amongst world authorities in GTD.

This resulted in a uniform scoring system, agreement on the International Federation of Obstetrics and Gynaecology (FIGO) staging system and chemotherapeutic regimens (Kohorn, 2001). These guidelines have been shown to be feasible in clinical practice (Ngan, 2004). Early diagnosis, prompt referral to a tertiary centre and appropriate therapy produce the most optimal outcomes.

Although the primary therapy for GTD is chemotherapy and monitoring, surgery has an important secondary role especially for complications of the disease and residual resistant disease. However, the decision to perform surgery should be judicious and executed with the advice of senior colleagues. Close monitoring during therapy is necessary as there is a tendency for complications to arise following institution of chemotherapy necessitating admission to a high-care or intensive care facility. Consideration of such an admission should be made prior to institution of chemotherapy.

There is a tendency for GTD to occur more commonly in developing parts of the world which are plagued by epidemic proportions of human immunodeficiency virus infections. This has complicated the management of GTD especially because of co-morbid HIV-related illnesses at the time of presentation as well as poor immunity reflected by low CD4 counts. Often, many developing parts of the world do not have access to anti-retroviral therapy making treatment difficult.

CHAPTER 2

THE EPIDEMIOLOGY OF GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic disease is a rare entity making up only 1 % of all gynaecological malignancies. There is variation in the incidence of GTD due to many centres which have reported values based on hospital admissions rather than using the population as a denominator. Gestational trophoblastic disease occurs more commonly amongst the Asian belt. In Japan the incidence of hydatidiform mole is 1-2/1000 pregnancies and is thought to be approximately three times higher than the incidence in Europe or North America (0.6 – 1.1/1000 pregnancies) (Takeichi, 1987; Schorage *et al*, 2000). Incidence rates for choriocarcinoma are more limited due to the methods of diagnosis and definitions of disease. The incidence rate for choriocarcinoma in India is 19/1000 pregnancies compared to 0.2 - 0.7/1000 pregnancies in North America and Europe. Recent publications have shown a decline of GTD in Korea, where the rate has fallen from 4.4/1000 pregnancies in the 1960s to 1.6/1000 pregnancies in the 1990s. Gestational Trophoblastic Disease affects predominantly young women and is one of the few gynaecological malignancies with high cure rates. In Africa and other parts of the world, the incidence of GTD is not reported. After one molar pregnancy, the risk of a repeated molar pregnancy is about 1% (Rice *et al*, 1989). Although this risk is low, patients are advised to have an ultrasound in the late first trimester to confirm the presence of a normal gestation (Berkowitz *et al*, 1998).

RISK FACTORS FOR GESTATIONAL TROPHOBLASTIC DISEASE

Although several factors have been postulated to be associated with GTD, the aetiology remains unclear. A "J" shaped curve has been described with regards the age incidence in that young adults and women older than 40 years tend to have higher rates. Hydatidiform mole occurs in 0.6% of pregnancies if there is a past history of a molar gestation. Caucasian women tend to have lower incidences of GTD compared with Asian women. Women with blood group B tend to have higher incidences of molar pregnancies. Genetic factors may play a role as there is a higher risk of molar pregnancy if sisters have had molar gestations.

Dietary factors are often linked to socioeconomic background. Previous reports from Taiwan implicated nutritional deficiencies such as albumin. Other reports noted that a high carotene intake is associated with a lower risk of molar pregnancies. The relative risk for smokers has been reported to be 2.6 if women smoke more than 15 cigarettes per day, compared with 2.2 for women who smoke less than 15 cigarettes per day. The relative risk of GTD in association with prior use of oral contraception was 1.9 (95% CI: 1.2 – 3.0). It is thought that oral contraceptives slow the rate of HCG regression post treatment. Despite these findings it is not recommended that contraceptive prescribing patterns should change and the benefits of a repeat gestation, notably a molar gestation is still less with the use of the oral contraceptive.

CHAPTER 3

THE PATHOLOGY OF GESTATIONAL TROPHOBLASTIC DISEASE

HYDATIDIFORM MOLE

Hydatidiform mole exists as a partial or complete mole. Complete moles are devoid of foetal tissue, membranes or umbilical cord structures. Macroscopically a common finding is the appearance of "grape-like" vesicles which correspond to grossly oedematous chorionic villi. Microscopically, there is abnormal trophoblastic proliferation and oedematous villi with absence of foetal vessels. Partial moles have few oedematous villi and the amount of molar tissue is usually less than that seen with complete moles. When a foetus is present, it has gross chromosomal and congenital abnormalities. Microscopically there are focal central cisterns and stromal fibrosis as well as abnormal trophoblastic proliferation. In situations when it is difficult to distinguish partial from complete moles, ploidy status may be useful since most partial moles are triploid. In addition to the aforementioned, trophoblastic tissue may invade the myometrium and/or adnexae. Such invasive patterns can be distinguished on imaging, including simple ultrasound, in combination with Doppler studies. The presence of villi distinguishes such molar proliferations from choriocarcinoma.

Choriocarcinoma may be confined to the pelvis or may be metastatic in nature. Macroscopically, the tissue is grossly haemorrhagic, well circumscribed masses of tissue which may occur singly or in clusters.

The molar tissue generally penetrates into the myometrium and/or adnexae. Distant metastases are common to sites such as the brain, liver and lungs. About 50% of choriocarcinomas follow on molar gestations, 25% following abortions, 22.5% following a normal gestation and 2.5% following an ectopic gestation. Placental-site trophoblastic tumour is a rare entity with just over 100 cases described in the literature. These tumours arise from the intermediate trophoblast and secrete human placental lactogen (HPL) and small amounts of HCG (Kurman *et al*, 1984). Microscopically, these tumours contain mononuclear cells with large amounts of cytoplasm. The cells generally infiltrate between the muscle fibres of the uterus. Deep myometrial invasion is uncommon. However, widespread metastases and high mortality is well recognised. The current World Health Organisation (WHO) pathological classification of GTD is reflected in Table I.

CHAPTER 4

STAGING FOR GESTATIONAL TROPHOBLASTIC DISEASE

The diagnosis of gestational trophoblastic tumour is based on clinical, radiological and biochemical findings. In order to determine prognosis and apply appropriate treatment regimens, many systems based on clinical, anatomical and prognostic systems have been utilised worldwide. The formation of the ISSGTD led to the incorporation of the FIGO and World Health Organisation (WHO) classifications. This resulted in a new staging/classification system to be utilised worldwide. This system has been approved by the council of FIGO (FIGO Oncology Committee Report, 2002). Previous classification systems such as the National University Singapore system (Tham & Ratnam, 1998) have been incorporated into the current FIGO staging/scoring system. Blood group has been omitted from the FIGO scoring system as its prognostic value is of doubtful significance. Independent predictors of mortality include: antecedent term pregnancy, liver or brain metastases and long interval between previous pregnancy state and current presentation (Bower *et al*, 1997).

Changes in the current accepted staging system as described by Kohorn (2001), reflect a change in the risk score for liver metastases from a score of 2 to 4. Metastatic lung disease may be detected by chest X-ray rather than computerised axial tomography scanning (CAT). If lung lesions are present, then the best imaging for brain and abdominal disease is magnetic resonance imaging (MRI).

However, CAT scanning is commonly utilised for this purpose. This staging system has been shown to produce a better outcome than the modified WHO prognostic index score and is practical in the clinical setting (Ngan, 2004). The current nomenclature for staging is to state the FIGO stage followed by the risk score e.g., FIGO III: 7. The FIGO stages and WHO risk-scoring are reflected in Tables II and III respectively. A score of ≤ 6 represents low-risk disease and ≥ 7 reflects high-risk disease. Low-risk disease is treated with single agent methotrexate, whilst high-risk disease is best treated with multi-agent chemotherapy (Etoposide, Methotrexate, Actinomycin, Cyclophosphamide and Oncovin).

A retrospective analysis by Hancock *et al* (2000), reviewed the outcomes of patients managed according to this revised classification system. It was found that the risk scoring system correlated far better with outcome than the modified WHO prognostic index score. Thus, the new classification/scoring system will result in uniform management throughout the world and form the basis for the comparison of treatment results.

CHAPTER 5

THE DIAGNOSIS OF GESTATIONAL TROPHOBLASTIC DISEASE

The diagnosis of molar pregnancy is based on the findings of a triad of: clinical, biochemical and radiological studies. The clinical presentation includes a period of amenorrhoea, vaginal bleeding, sometimes with the passage of vesicles or bunch of "grape-like" structures per vagina, uterine enlargement larger than the period of amenorrhoea, hyperthyroidism, hyperemesis gravidarum and pre-eclampsia. With the advent of high resolution ultrasound, molar pregnancy can be detected in the first trimester. For complete moles, the mean gestational age at diagnosis with ultrasound is 12.4 weeks compared with 14.3 weeks at which partial moles are diagnosed (Lindholm and Flam, 1999).

The classic ultrasound feature of a molar gestation is the description of an enlarged uterus containing an echogenic mass with cystic spaces (Benson *et al*, 2000). Further ultrasound evaluation including Doppler is able to detect the presence of invasive molar pregnancy. About 15% to 25% of patients with complete molar gestations have theca lutein cysts and ovarian enlargement of more than 6cm detected with the use of ultrasound (Montz *et al*, 1988). Due to trophoblastic proliferation elevated serum quantitative β-HCG levels in conjunction with the clinical and radiological findings are the cornerstone for the diagnosis of GTD. Serum β HCG levels correlate with the volume of trophoblastic

tumour and findings of > 92 000 U/L in association with an absent foetal heart are indicative of complete molar gestations (Romero *et al*, 1985).

Choriocarcinoma may develop after any type of gestation, but commonly follows a previous molar gestation in about 50% of patients. Postpartum choriocarcinoma is well described and often the diagnosis is missed, resulting in late presentation with fatal consequences (Nugent *et al*, 2006). Clinical features include vaginal bleeding, anaemia, hyperthyroidism and in some cases, features of metastatic disease such as haemoptysis. The commonest metastatic sites include the lungs (80%), liver (10%), brain (10%) and vagina (30%), although a rare site in the hand has been described (Afshar *et al*, 2007). Lung involvement may be asymptomatic or patients may present with mild respiratory discomfort. Occasionally, the chest X-ray may be negative and CT scanning may reveal multiple lung lesions (Moodley *et al*, 2004). Torrential vaginal bleeding due to vaginal lesions may result in haemorrhagic shock. Prompt resuscitation, vaginal packing, pelvic angiography and arterial embolisation are highly effective in salvaging such patients (Moodley *et al*, 2003a).

Persistent molar pregnancy includes molar tissue evident after suction curettage, invasive moles and choriocarcinomas. The majority of post-molar GTD are invasive moles or persistent moles (70% to 90%) (Lurain *et al*, 1983). It was previously thought that partial moles do not transform into choriocarcinomas. However, both partial and complete moles are at risk of progressing to malignant disease (Seckl *et al*, 2000). The risk is 5% for

partial moles and 20% for complete moles. The diagnosis of post molar GTD as accepted by FIGO include:

1. The presence of histological choriocarcinoma
2. Persistent HCG values 6 months post evacuation of the uterus
3. Rise of HCG of 10% or greater for 3 values or more over at least 2 weeks on days 1, 7 and 14.
4. Four HCG values or more demonstrating a plateau (± 10%) over a 3 week period; days 1, 7, 14 and 21.

Placental site trophoblastic tumour is a rare form of GTD (1-2% of all GTD) (Ajithkumar *et al*, 2003), often diagnosed incidentally by histopathology of a uterine or endometrial curetting specimen. A high index of suspicion needs to be maintained especially if the HCG values are unusually low. The characteristic features of placental site trophoblastic tumours are low levels of serum HCG, secretion of human placental lactogen (HPL), resistance to chemotherapy and unpredictable behaviour with the risk of metastatic spread. Fisher *et al* (1992), demonstrated that placental site trophoblastic tumour may arise following a normal term gestation or hydatidiform mole or previous molar gestations (12%) (Moore-Maxwell & Robboy, 2004; Moodley, 2007). Although most patients are in the reproductive age group, placental site trophoblastic tumour can present in menopausal women (Colleen *et al*, 1998).

The common clinical manifestation is vaginal bleeding following a period of amenorrhoea. Of interest is that most such gestations occur after a female gestation and can be associated with nephritic syndrome (Lathrop *et al*, 1988; Hui *et al*, 2000 & Feltmate *et al*, 2001). Although in most instances the disease is confined to the uterus, distant metastases have been documented. Papadopoulos *et al* (2002), reported that distant metastases were found in 30% of their patients managed at the Charing Cross Hospital in the United Kingdom. Radiological findings include a heterogenous, hyperechoic mass with multiple cystic spaces within the myometrium (Allen *et al*, 2006). These features may resemble the radiological features of other types of GTD. The clinical outcome of patients with placental site trophoblastic disease depends on many factors including, interval since last pregnancy and whether the disease is localised or metastatic. Mortality is highest if there are brain metastases (Lathrop *et al*, 1988). Surgery in the form of hysterectomy is indicated followed by adjuvant chemotherapy for metastatic disease.

CHAPTER 6

THE GENETICS AND COMPLICATIONS ASSOCIATED WITH GESTATIONAL TROPHOBLASTIC DISEASE

Most complete molar gestations have 46 XX karyotype. It is thought that both chromosome pairs are derived from paternal chromosomes. Fertilisation of an empty ovum by a haploid set of chromosomes followed by duplication of the chromosomes is thought to be the genetic basis (Androgenesis) (Wake *et al*, 1978). Dispermy accounts for 46 XY moles which occur in about 4% of cases (Ohama *et al*, 1981). Dispermic triploidy forms the genetic basis of partial moles and result from the fertilisation of an ovum by two spermatozoa. The occasional tetraploid karyotype in partial moles has also been described (Vejerslev *et al*, 1987). The possible karyotypic patterns seen with partial moles include: 69 XXY (70%), 69 XXX (27%) and 69 XYY (3%) (Lawler *et al*, 1982).

The risk of a complete mole progressing to invasive malignancy is in the order of 20%. However, based on genetic analysis of choriocarcinomas, it has been difficult to trace back an origin to complete moles (Chaganti *et al*, 1990). Arima *et al* (1995), using polymerase chain reaction analysis of nine post-molar tumours, demonstrated that choriocarcinomas developed from a full term gestation preceding a complete molar pregnancy. Placental site trophoblastic tumours genetically, may arise from molar gestations or from previous normal term gestations.

The cytogenetics of placental site trophoblastic tumours is essentially diploid in origin (Lathrop *et al*, 1988). Ichikawa *et al* (1998), demonstrated *p53* expression in placental site trophoblastic tumour cells. Chromosomal gains and losses have been described with choriocarcinoma including deletion at 8p and amplification at 7q (Ahmed *et al*, 2000).

There are many complications related to molar gestations such as pre-eclampsia, hyperthyroidism, hyperemesis gravidarum, torsion or rupture of theca lutein cysts, acute respiratory distress, uterine sepsis, perforation and haemorrhage into viscera. Hyperthyroidism is often biochemical and is clinically diagnosed in about 10% of molar gestations. Clinical hyperthyroidism is managed with the use of anti-thyroid drugs and beta-blockers. Hyperthyroidism should be corrected prior to surgery to prevent thyroid crises. Uterine perforations usually occur during suction evacuation of a soft, enlarged uterus. Bleeding from trophoblastic tissue can be spontaneous or following chemotherapy or attempts to excise or biopsy tissue. This type of bleeding can be torrential and life-threatening.

CHAPTER 7

MANAGEMENT OF NON-INVASIVE MOLAR PREGNANCY

Non-invasive molar pregnancy is characterised by the absence of molar tissue penetrating the myometrium and or adnexae as detected by ultrasound and colour flow Doppler. Such patients require basic investigations, resuscitation, preparation of the cervix with Lamicel hygroscopic dilator and suction curettage in theatre (Moodley, 2007). Basic investigations include:

1. Blood tests
    a. Full blood count, coagulation profile (INR/PTT), renal function (Urea and Electrolytes), Rhesus blood group
    b. Thyroid function test
    c. Quantitative β–HCG
    d. HIV ELISA antibody test & CD4 count

2. Radiological tests
    a. Ultrasound examination of the pelvis and abdomen
    b. Chest X-ray
    c. Doppler flow of the uterus to exclude invasion
    d. CT/MRI of the brain and abdomen only if the chest X-ray demonstrates lung metastases

The cervix should be softened with Lamicel hygroscopic dilator and agents which stimulate uterine contractions such as prostaglandins, should be avoided to prevent embolisation of trophoblastic tissue to the lungs and malignant complications (Schlaerth *et al*, 1988; Tidy *et al*, 2000). Suction curettage is performed under oxytocic infusion to prevent uterine perforation. Careful observation of the patient post evacuation is necessary, sometimes in a high-care facility especially if biochemical abnormalities such as hyperthyroidism are present prior to suction curettage. Contraception should be prescribed and weekly serial β-HCG levels measured. These levels should become negative within a 6 month period, failing which, chemotherapy is advocated.

THE ROLE OF PROPHYLACTIC CHEMOTHERAPY

Most patients who require suction evacuation of uterus will have full resolution of the disease as judged by negative β-HCG values within 6 months post evacuation. A minority of patients will require chemotherapy based on the diagnosis of persistent molar gestations. As a result the issue of prophylactic chemotherapy is controversial. In this situation single agent methotrexate has been administered for several hours during evacuation of molar contents or hysterectomy (Sivanesaratnam & Ng, 1977). The disadvantages include toxicity in the background of a large number of patients who will not require chemotherapy and trophoblastic neoplasia, which takes many years to manifest, is then usually resistant to chemotherapy (Curry *et al*, 1975).

Kim *et al* (1986), demonstrated that in high-risk patients prophylactic chemotherapy is associated with a reduction of post-molar GTD from 47% to 14%. It therefore appears that the risks of chemotherapy outweigh the benefits and should no longer be current practice.

MANAGEMENT OF GESTATIONAL TROPHOBLASTIC NEOPLASIA

Invasive molar pregnancy, choriocarcinoma and persistent molar pregnancy are regarded as gestational trophoblastic neoplasia. These patients should be referred to a tertiary level centre for expert care. The criteria for diagnosis have been described. These patients should be staged according to the FIGO 2000 staging and risk scoring performed according to the recommendations of the International Society for the Study of Gestational Trophoblastic Diseases (ISSGTD) (Appendix) (Soper *et al*, 2004). Low-risk patients with a score of ≤ 6 are managed with single agent chemotherapy e.g., methotrexate, on a weekly basis. High- risk patients with a score of ≥ 7 are managed with multi-agent chemotherapy in the form of EMA CO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide and Oncovin). The EMA CO regimen is well tolerated and Newlands *et al* (1998), documented the cumulative 5 year survival of 86.2% (95%CI: 81.9 – 90.5%). Kim *et al* (2007), also documented beneficial outcomes with early treatment of patients with high-risk molar pregnancy. Recently El-Lamie *et al* (2006), described the omission of the CO part of this regime to reduce toxicity, using EMA EP (Etoposide, Cisplatinum) for resistant cases and incorporation of paclitaxel in the third-line management. With these protocols, 81.4% of patients with high-risk

metastatic gestational trophoblastic tumours could be cured. Chemotherapy response is monitored by serial β-HCG estimations after each cycle of chemotherapy. Empirically, two and three more cycles are given to low and high-risk patients, respectively, once the HCG levels have become negative. Haemorrhage from an invasive molar pregnancy may occur if evacuation of the uterus is attempted and therefore primary chemotherapy is recommended (Soper *et al*, 2004).

Placental site trophoblastic disease is not staged according to the FIGO system and the primary therapy is hysterectomy. These tumours are inherently resistant to chemotherapy. Metastatic placental site trophoblastic disease is treated with hysterectomy followed by adjuvant chemotherapy. Chemotherapy regimens in this situation include EMA CO or EMA EP combinations (Randall *et al*, 2000; Behtash *et al*, 2008).

ROLE OF SURGERY IN GESTATIONAL TROPHOBLASTIC DISEASE

Whilst chemotherapy is the primary form of treatment, surgery has an important secondary role especially for complications. However, surgery in this setting carries with it risks and should only be performed by experienced personnel. It is judicious to have intensive care unit facilities as backup to support the surgical interventions. A wide range of surgical interventions have been described including laparotomy for uterine sepsis or perforation, torsion of theca lutein cysts, thoracotomy and craniotomy for resection of isolated residual resistant nodules, surgery to control internal haemorrhage and conservative techniques such as angiography and embolisation of feeding vessels such as

the internal iliac arteries. Lurain *et al* (2006), reported that surgery was necessary in 48% of 50 patients with high-risk GTD, of which 87.5% were cured. Soper *et al* (2007), recently described a multimodality approach to central nervous system metastases using chemotherapy, craniotomy and stereotactic surgery with successful outcomes. Hysterectomy is indicated for uterine complications and is an acceptable procedure for the primary treatment of an older patient with molar pregnancy who does not desire future fertility (Soper *et al*, 2004). Otherwise resection of an isolated residual resistant nodule within the uterus is feasible for the younger patient who desires future fertility. Ligation of feeding arteries such as the uterine or internal iliac artery is feasible but should only be performed if angiographic embolisation has failed. This is due to the high success rate of embolisation techniques (Tse *et al*, 2007).

While gestational trophoblastic disease can be cured, 10-25% of patients with metastatic disease die of this disease. Mortality from this disease, although rare, can be linked to certain parameters that confer a poor prognosis. The prognostic factors as set out by the International Federation of Obstetrics and Gynaecology (FIGO) (FIGO Oncology Committee, 2002) include age, antecedent pregnancy (mole/abortion/term), interval between antecedent pregnancy and start of chemotherapy, pre-treatment β-Human Chorionic Gonadotrophin (HCG) levels, largest tumour size, site of metastases, number of metastases and previous failed chemotherapy. A modified World Health Organization (WHO) scoring system has been combined with the FIGO staging. In 2000, FIGO accepted this WHO scoring system based on these prognostic factors.

Gestational trophoblastic disease has an excellent response rate to chemotherapy with cure rates of almost 100% for low-risk disease and 70% for high-risk GTD treated with chemotherapy. Although the mortality from high-risk metastatic GTD was about 90% with chemotherapy, this has been converted to a cure rate of 92% or greater (Kohorn *et al,* 2000).

OUTCOMES OF PATIENTS WITH GESTATIONAL TROPHOBLASTIC DISEASE

The response to chemotherapy is excellent. The risk of a patient presenting with a second mole after a partial or complete molar pregnancy is in the order of 1-2% (Berkowitz *et al*, 1998). Patients are advised not to conceive for 12 months post treatment. There is no evidence that the oral contraceptive pill increases the risk of malignant sequelae or regression of the HCG levels (Morrow *et al,* 1985). Non-metastatic disease has a cure rate of almost 100% (Roberts & Lurain, 1996). Up to 13% of patients with high-risk disease will develop recurrence (Mutch *et al*, 1990). Most patients have normal subsequent pregnancies. Generally there are no reports of increased chromosomal or congenital abnormalities in subsequent pregnancies. However, Matsiu *et al* (2003), reported that there was a 40% greater chance of abnormal pregnancy outcomes (abortions, stillbirths, repeat molar gestation) in patients who conceived within 6 months of completing chemotherapy compared with patients who waited for more than 12 months after completing chemotherapy (10%). An ultrasound scan in the first trimester following previous GTD is recommended.

CHAPTER 8

THE IMPACT OF THE HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION ON GTD

The literature describing the association and impact of the HIV infection amongst women with GTD is limited to case reports. Ojwang *et al* (1992), recommended that the Human Immunodeficiency Virus (HIV) infection be included in the list of WHO prognostic factors for choriocarcinoma. In the three cases described by Ojwang *et al* (1992), (all HIV infected, CD4 counts not documented) one had a prolonged course of chemotherapy without remission, a second responded only after hysterectomy was combined with chemotherapy and the third had extensive metastases with tumour in unusual sites (nasal metastases) despite low risk factors. Since the clinical manifestations of all three were severe, HIV infection was proposed as a poor prognostic factor for choriocarcinoma. Moodley *et al* (2003b), described the successful use of cytotoxic chemotherapy for gestational trophoblastic disease in an HIV infected patient and also demonstrated successful outcomes in HIV-infected patients with reasonable levels of immunity. Failure to treat such women would have resulted in their demise much earlier than from the HIV infection itself. Ashley, in a case presentation and literature review in 2002, postulated that it is possible that in AIDS (Acquired Immune Deficiency Syndrome) patients, failure of an immune response to destroy tumour cells (trophoblastic emboli which are shed into maternal serum are usually destroyed by maternal immune response) leads to metastatic lesions, thus predisposing such patients to the development of choriocarcinoma.

The role of HIV infection in patients with Gestational Trophoblastic Disease is of importance to much of Africa and needs to be defined as in a large part of Sub-Saharan Africa, HIV infection is epidemic and there exists an increased chance of finding patients with concurrent gynaecological malignancies and HIV infection. Chemotherapy is one of the widely used treatment modalities in cancer with its known toxic side-effects that may further compromise immunity which may lead to increased morbidity and mortality unrelated to the malignancy itself. The use of these cytotoxic agents in patients with HIV infection poses many management and ethical problems. The benefits and risks associated with administering chemotherapy, leading to further immunosuppression in HIV-infected patients, needs to be carefully analysed and may require dosage adjustments, co-administration of granulocyte colony stimulating factors (GCSF) to support bone marrow function and/or the concurrent use of anti-retroviral therapy. The successful use of cytotoxic chemotherapy in combination with anti-retroviral therapy has been described by Moodley *et al* (2003b).

There are case reports and retrospective studies (Moodley *et al,* 2003b; Ashley, 2002; Moodley *et al*, 2001; Tangtrakul, 1998; Moodley *et al*, 2003c) describing concurrent HIV infection and gestational trophoblastic disease in patients, but no randomized controlled studies or guidelines exist outlining management. In addition there is no literature documenting the causes of mortality amongst women with gestational trophoblastic disease in relation to HIV serostatus. We performed a retrospective analysis of causes of mortality in patients with gestational trophoblastic disease and HIV infection with varying degrees of immuno-suppression and compared their profiles with the causes of

mortality in HIV non-infected patients with Gestational Trophoblastic Disease. After institutional ethical approval was granted, the audit was performed for all patients with trophoblastic disease managed at Inkosi Albert Luthuli Central Hospital, which is a large tertiary hospital serving the indigent population of KwaZulu Natal, South Africa. The study period included patients treated from 2003 to 2007.

CHAPTER 9

STUDY: PROFILE OF MORTALITY AMONGST WOMEN WITH GESTATIONAL TROPHOBLASTIC DISEASE INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS (HIV) IN RELATION TO HIV NON-INFECTED WOMEN

AIM:

1. To establish causes of mortality in women with GTD in association with HIV infection in relation to HIV non-infected women.
2. To determine if changes in management are necessary

PATIENTS AND METHODS

After institutional ethical approval was obtained, all patients with Gestational Trophoblastic Disease managed in the combined gynaecology oncology clinic at Inkosi Albert Luthuli Central Hospital were recruited for the study. This hospital is a large tertiary referral hospital for the province of Kwa-Zulu Natal serving mainly the indigent population. The study period included a review of records of patients treated from 2003 to July 2007. All data was recorded on a questionnaire and submitted for statistical analysis.

STATISTICAL METHODS

Factors associated with mortality were tested using Fisher's exact test. Odds ratios were reported as a measure of the strength of association. Breslow-Day's test for homogeneity in Odds Ratios was used to compare mortality in HIV infected and HIV non-infected women. The analysis was done using Stata 9.

CHAPTER 10

RESULTS

There were a total of 78 patients with trophoblastic disease managed over the study period. The mean age of all patients was 31 years (16 – 50 years). Of all patients, 68 were under 40 years of age. There were 53 patients with a diagnosis of invasive molar pregnancy and 25 patients with choriocarcinoma. Table IV (Appendix) illustrates the general parameters for the 78 patients including the International Federation of Obstetrics and Gynaecology (FIGO) staging, site of metastases, chemotherapy, side effects of chemotherapy and Intensive Care Unit (ICU) monitoring. In terms of race, there were 69 African patients, 2 Coloured and 7 Indian patients with GTD. There were 24 patients who were HIV-infected. The HIV seroprevalence amongst patients with GTD was therefore 31%. There was one HIV-infected patient admitted in a critically ill condition and whose CD4 count was not determined. Of the 23 HIV-infected patients with known CD4 counts, 8 patients had CD4 counts less than 200 cells/μL (36%). In total there were 15 deaths (19%). All 15 mortalities occurred amongst African patients. There were 11 deaths amongst patients younger than 40 years of age (16%). There were 8 (33%) HIV-infected patients and 7 HIV non-infected (13%) who demised, (OR: 2.7 CI: 0.8-9.0, p= 0.1). Majority of patients who demised were managed as choriocarcinoma (87%). Mortality was significantly related to CD4 counts. Of the 8 patients with CD4 counts less than 200 cells/μL, 7 patients demised.

There were no mortalities amongst HIV-infected patients whose CD4 counts was more than 200 cells/μL, compared with 7 deaths amongst 8 patients (88%) whose CD4 counts was less than 200 cells/μL ($p = 0.001$).

Twelve patients (50%) managed as FIGO stage III/IV demised compared to 3 (6%) patients with Stage I/II disease ($p < 0.001$). Of the 15 patients who demised there were 3 patients with brain metastases, 8 patients with lung metastases, 2 with liver metastases, 1 with gastrointestinal metastases and 1 with metastases to the scalp. Of the 13 patients who required arterial embolisation for uncontrollable haemorrhage, 9 were successful. Of the remaining 4 patients in which embolisation was unsuccessful, one required bronchial artery embolisation and died due to pulmonary haemorrhage, one died from hypovolaemic shock despite arterial embolisation for intrabdominal bleeding. Of the remaining two patients, one required a total abdominal hysterectomy and the other internal iliac artery ligation for persistent bleeding following embolisation. Both these patients survived. There were 5 patients admitted in very poor general condition precluding administration of chemotherapy. The reasons for their poor general conditions are reflected Table V. Majority of these patients were HIV-infected. The numbers of patients with abnormal blood profiles on admission were: anaemia (n=33) and hyperthyroidism (n=27). Mortality was significantly higher in patients with abnormal blood profiles (n=12; 27%), compared with patients who had normal blood profiles (n=2; 6%), ($p = 0.03$). Of the 15 patients who demised and who had abnormal blood profiles, 1 patient had renal failure; 8 patients had hyperthyroidism; 10 patients had anaemia and 6 patients had both anaemia and hyperthyroidism.

In total, 73 out of 78 patients received chemotherapy (94%). Of the patients who received chemotherapy and demised, 6 received single agent chemotherapy in the form of methotrexate whilst 4 patients received multi-agent chemotherapy (etoposide, methotrexate, actinomycin, cyclophosphamide, and oncovin). Of the 15 patients who demised, 5 patients did not receive chemotherapy and demised of their disease. All 63 patients who survived received some form of chemotherapy ($p < 0.001$). Amongst the 10 patients who received chemotherapy and demised, the causes of death were: widespread disease (n=5); multiorgan failure, septicaemia and neutropaenia (n=2); widespread disease, multi-organ failure, septicaemia and neutropaenia (n=2); and cause unrelated to the primary disease or chemotherapy (rheumatic cardiac disease) (n=1). One patient demised due to a combination of hypertension, hyperthyroidism, and cardiac failure in the background of Rheumatic heart disease.

Of the 15 deaths, 5 HIV-infected patients and 5 HIV non-infected patients received chemotherapy. Of the 6 patients requiring intensive care-unit management for severe respiratory distress, 5 demised (83%), due to the extent of their disease. Two of these patients were HIV-infected. Only 13% of patients not requiring intensive care died ($p = 0.001$). In total, there were 4 patients whose demise was related to side effects of chemotherapy. Of these 4 women, one commenced chemotherapy with a CD4 count of 62 cells/μL in conjunction with anti-retroviral therapy and subsequently developed neutropaenia, septicaemia, and multiorgan failure. Of the remaining 3 HIV non-infected patients, the cause of mortality was related to neutropaenia, septicaemia, multiorgan

failure and atrial fibrillation. Of all patients who developed myelotoxicity, the majority (over 90%) developed grade 2-3 myelotoxicity.

Of the 24 HIV-infected patients, 21 (88%) patients received chemotherapy. Of these, 16 were successfully treated (76%) whereas 5 demised. The outcomes of the 8 patients with CD4 counts ≤200 cells/μL are illustrated in Table VI. The profile of mortality amongst HIV non- infected patients is reflected in Table VII.

The majority (75%) of HIV- infected patients with CD4 counts ≤200 cells /μL presented with advanced FIGO stages (III/ IV), compared to 80% of HIV-infected patients with CD4 count >200 cells /μL who presented with early FIGO stages (I/ II) (p=0.02). Further, only 26% of HIV non-infected patients presented with advanced FIGO stages (III/IV) (p=0.02) (Figure 1), compared to 75% of HIV-infected patients with CD4 counts ≤200 cells /μL (p=0.01).

CHAPTER 11

DISCUSSION

Gestational trophoblastic disease encompasses a spectrum of proliferative disorders of the trophoblast with hydatidiform mole, choriocarcinoma and placental site trophoblastic tumour (PSTT) being the important clinical entities. The incidence of molar pregnancy varies geographically with the highest rates in Eastern countries. The incidence rate of molar pregnancy in South-East Asia ranges from 1-2/1000 pregnancies in Japan and China (Takeichi, 1987; Schorage *et al*, 2000) to 12/1000 in Indonesia (Farid *et al,* 1984). Many factors are associated with the incidence of molar pregnancy, such as maternal age, diet, gravidity, past pregnancy history, genetics and ethnicity (Teoh *et al,* 1972). The incidence rate of choriocarcinoma also varies geographically and may be under-reported since histological confirmation is not obtained in some centres in the world.

Gestational trophoblastic disease is associated with an excellent prognosis due to the inherent sensitivity of tumour tissue to chemotherapy. Since GTD is a relatively uncommon condition, a high index of suspicion is always necessary by the practising clinician. Any women in the reproductive age group with the presentation of metastatic disease should be suspected of having trophoblastic disease. The diagnosis of GTD is usually based on clinical, biochemical and imaging parameters. As such, choriocarcinoma does not require a tissue diagnosis with its attendant morbidity.

Whilst non-invasive hydatidiform mole is treated with suction curettage as the definitive procedure, invasive molar pregnancy and choriocarcinoma are best treated primarily with chemotherapy. The recommended management of PSTT is surgery in the form of hysterectomy, with chemotherapy being reserved for advanced stage disease.

The implementation of the FIGO oncology committee recommendations have standardised the treatment of GTD worldwide and now allows appropriate comparisons of results internationally (FIGO Oncology Committee, 2002). Based on this scoring system, patients with a score of ≤ 6 should receive single agent methotrexate or actinomycin D, whilst patients with a score of ≥ 7 should be treated with multi-agent chemotherapy. Newlands *et al* (1991), demonstrated excellent responses of over 80% with the EMA CO regime, which has now become the first-line chemotherapy for high-risk disease. It appears from the literature that there are mixed results of outcomes of patients with GTD and co-existing HIV infection. However, it would also appear that the management of HIV-infected patients with reasonable levels of CD4 counts and GTD is successful with chemotherapy and in the short term patients would otherwise demise from GTD rather than HIV infection itself (Moodley *et al*, 2003c). The management of GTD should preferably be centralised to accumulate expertise and provide a specialised service to such patients. This is especially true now with the HIV epidemic and the co-existence of GTD in patients with HIV infection.

Although the outcomes of patients with GTD are largely positive, mortalities have been described. A retrospective review of 2033 gynaecological admissions at a referral centre

in Nigeria, showed that choriocarcinoma is one of the leading causes of mortality of the 79 deaths documented (Anya *et al*, 2006). El-Lamie *et al* (2006), in a retrospective report of 261 patients treated for GTD, over an 11 year period documented a 20% mortality rate. The causes of mortality included acute respiratory distress syndrome prior to treatment as well as treatment complications. Further, the presence of brain and/or liver metastases correlated with poor survival, followed by chemotherapy resistance and the type of antecedent pregnancy.

Papadapoulos *et al* (2002), reported a mortality rate of 21% amongst 34 patients with PSTT. All deaths (n=7) were disease-related with lung involvement and antecedent pregnancy of 4 years and more being high-risk factors for mortality. The WHO scoring system for GTD is not utilised in the management of PSTT and has not been shown to correlate with outcome (Papadapoulos *et al,* 2002). Song *et al* (1998), reported a reduction in mortality from >90% to <20% when chemotherapy was introduced in the management of choriocarcinoma. Ebeling *et al* (1995), reported a mortality rate of 8.6% due to the disease and noted that outcomes where significantly better for patients who were treated mainly at specialised centres. Postpartum choriocarcinoma usually has a worse prognosis due to delay in diagnosis. Nugent *et al* (2006), documented a mortality rate of 6% (2/35) and a mean survival of 7.8 years (1/21years) amongst patients with postpartum choriocarcinoma.

Choriocarcinoma after a non-molar pregnancy, usually presents five to six months post delivery. Tidy et al (1995), documented a mortality of 21% after a live birth compared to

6% after a molar abortion. Maternal mortality in patients with hydatidiform mole is mainly due to the primary disease-related complications such as severe haemorrhage and coagulopathy (Tsakok *et al,* 1983).

Cisse *et al* (2002), have recommended prophylactic hysterectomy after molar pregnancy to prevent the occurrence of choriocarcinoma. They reported a mortality rate of 49.2% and an average survival of 48 months amongst 61 patients with choriocarcinoma treated in Senegal. Our results demonstrate that the majority of deaths occurred in patients with advanced (FIGO) stage disease. The high mortality amongst patients with brain and lung metastases (Table IV) is in keeping with the findings of El-Lamie *et al* (2006). Of note is that of the 8 patients with lung metastases and HIV-infection, 7 patients demised. These patients were noted to be in poor general condition, developed respiratory distress and succumbed despite attempts to resuscitate and provide Intensive Care Unit (ICU) ventilation for some of them.

The occurrence of mortalities amongst only African patients reflects the demography of the province of KwaZulu Natal, South Africa. The background HIV-seroprevalence in the province of KwaZulu Natal for years 2003, 2004 and 2005 were 37.5%, 40.7% and 39.1%, respectively, as reported from the antenatal clinic attendees. Over the period from 2003 to 2007, there were 24 HIV-infected patients with GTD resulting in a HIV seroprevalence of 31%. This high figure is also reflective of the high background prevalence of HIV in the province of KwaZulu Natal as compared to the rest of South Africa.

A significantly larger percentage (29% vs. 13%) of mortalities occurred amongst HIV-infected women. A statistically significant increase in mortality was noted amongst HIV-infected patients with CD4 counts less than 200 cells/μL compared with HIV-infected patients with CD4 counts greater than 200 cells/μL ($p < 0.001$). An evaluation of these mortalities demonstrates that these patients had widespread metastases, co-morbid conditions such as pneumonia, renal failure, jaundice and biochemical abnormalities. In contrast, one of the 7 HIV-infected patients who demised was admitted in good general condition, but developed side effects and multiorgan failure secondary to chemotherapy. Review of the 17 HIV-infected patients who were treated and survived, demonstrate that they were admitted in good general condition with no co-morbidities and 15/16 patients had CD4 counts greater than 200 cells/μL. Two patients with CD4 counts less than 200 cells /μL were commenced on chemotherapy in spite of respiratory involvement to treat and improve lung function. It is appreciated that the administration of chemotherapy to women with CD4 counts $\leq$ 200 cells/μl is problematic. However, in the absence of literature, experience demonstrates that it is not feasible to administer chemotherapy in these scenarios

Only one HIV non-infected patient admitted with co-morbidity i.e., pneumonia, demised without receiving chemotherapy. The other mortalities amongst the HIV non-infected patients were mainly due to treatment-related side-effects. Likewise, all HIV non-infected survivors had no co-morbidities on admission. In view of the rarity of GTD in association with HIV infection, literature is based mainly on case series. The findings from this study corroborates our previous analysis (Moodley *et al*, 2003b) of outcomes of treatment in

relation to HIV serostatus providing evidence of good outcomes if HIV-infected patients have CD4 counts greater than 200 cells /μL. However, our current study provides evidence of mortality and reasons thereof, if the CD4 counts are less than 200 cells /μL, especially if co-morbid conditions are present on admission. Although HIV clinics are available in our environment and provide anti-retroviral therapy, the process of acquiring anti-retroviral therapy is a lengthy one.

Ojwang *et al* (1992), described unusual presentations and treatment related problems with HIV-infected patients in their series. Based on their limited numbers, a recommendation was made to include HIV infection as a prognostic factor in the WHO scoring system. Although our numbers are small, the occurrence of mortalities amongst patients with CD4 counts less than 200 cells /μL provides evidence of poor outcomes. The findings of our study do not confirm that HIV infection itself is a poor prognostic factor, unless the CD4 count is less than 200 cells /μL, especially in the background of co-morbid illnesses. Such patients with CD4 counts $\leq$ 200 cells/μl are noted to present with more advanced stage disease, compromising prognosis. Since the number of patients within the subgroups stratified for HIV status is small, it is not possible to advocate management guidelines.

The findings in this study (Figure 1) lends support to the theory postulated by Ashley (2002), that patients with AIDS are predisposed to choriocarcinoma possibly due to failure of an immune response to destroy tumour cells leading to metastatic lesions.

To date there is no literature providing similar findings described in this study. There is therefore a need for centres managing GTD to document outcomes of patients in relation to HIV serostatus and strong consideration should be given for the inclusion of HIV infection with low CD4 counts as a poor prognostic factor in the scoring system.

CHAPTER 12

CONCLUSION/ RECOMMENDATION

Clinicians should have a high index of suspicion for the diagnosis of Gestational Trophoblastic Disease (GTD). With the advent of ultrasound and sensitive HCG assays, early diagnosis of GTD is possible. The primary modality of therapy for GTD is chemotherapy which ensures high success rates. Patients with HIV infections and GTD present with varying degrees of immunosuppression. The performance status, CD4 count and the other parameters need to be determined on admission.

Improvement of general conditions and chemotherapy is indicated for women with CD4 counts more than 200 cells/μL. For patients with CD4 counts below 200 cells/μL, an individualized approach seems most appropriate. In these patients improvement of their general conditions, administration of anti-retroviral therapy, determination of FIGO stage and review of their condition is most appropriate. Amongst these women, cytotoxic chemotherapy may be indicated if the patients overall condition improves and it is judged safe to administer chemotherapy. Careful monitoring of all patients is necessary. Future studies should be directed towards multi-center trials to determine the best management of HIV-infected patients with GTD.

APPENDIX

TABLE I: WHO CLASSIFICATION GTD

Hydatidiform mole (HM) (Benign)

- Complete
- Partial

Invasive mole (IM) (Malignant)

Choriocarcinoma (Malignant)

Placental site trophoblastic tumour (PSTT)

Epitheloid trophoblastic lesions

Miscellaneous trophoblastic lesions

- Exaggerated placental site
- Placental site nodule or plaque

Unclassified trophoblastic lesions

TABLE II: FIGO STAGING (2000)

STAGE	CRITERIA
I	Disease confined to the uterus
II	Disease outside of uterus, but limited to the genital structures
III	Disease extends to the lungs with or without known genital tract involvement
IV	All other metastatic sites

TABLE III: WHO SCORING SYSTEM IN GESTATIONAL TROPHOBLASTIC DISEASE BASED UPON PROGNOSTIC FACTORS

FIGO Score	0	1	2	4
Age (years)	<40	≥40	-	-
Antecedent pregnancy	Hydatiform mole	Abortion	Term pregnancy	-
Interval from index Pregnancy (months)	<4	4-6	7-12	>13
Pretreatment hCG (mIU/ml)	<1000	1000-<10,000	10,000-<100,000	≥100,000
Largest tumor size including Uterus (cm)	-	3-4	≥5	-
Site of metastases	Lung	Spleen / kidney	Gastrointestinal	Brain / Liver
Number of metastases identified	-	1-4	5-8	>8
Previous failed chemotherapy	-	-	Single drug	Two or more drugs

TABLE IV: GENERAL PARAMETERS FOR 78 PATIENTS WITH GTD

	(n)	HIV-infected	Deaths	(% Deaths)
FIGO Stage				
I	50	11	-	-
II	4	3	3	75
III	14	5	5	36
IV	10	5	7	70
Metastases				
1. Brain	5	2	3	60
2. Lung	19	8	8	42
3. Liver	3	3	2	67
4. Gastro intestinal	2	0	1	50
5. Urinary Bladder	1	0	0	0
6. Scalp	1	1	1	100
Chemotherapy				
Single	24	6	6	25
Multiple	49	15	4	8
None	5	3	5	100
Side Effects of Chemotherapy				
1. Neutropaenia	41	14	5	12
2. Thrombocytopenia	9	4	4	44
3. Renal Failure	5	1	3	60
ICU Care	6	2	5	83

TABLE V: REASONS FOR POOR GENERAL CONDITION

Case	HIV status	Reason
1	Negative	Widespread metastases
2	Negative	Pulmonary tuberculosis, pulmonary haemorrhage, widespread disease
3	Positive	Pneumonia, pulmonary oedema, widespread metastases
4	Positive	Pneumonia, cardiac failure, lung metastases
5	Positive	Jaundice, renal failure

TABLE VI: OUTCOMES FOR 8 PATIENTS WITH CD4 COUNTS ≤ 200 cells/μL

FIGO Stage: Score	CD4 (cells/ μL)	Chemotherapy	Number of cycles	Outcome	Anti-retroviral Therapy
Patient 1 IV:18	104	No	Nil	Demised - Widespread metastases; poor general condition – Pneumonia.	No
Patient 2 IV:20	43	Yes	1 (MTX)	Demised - Condition deteriorated, PTB	Yes (< 2months)
Patient 3 IV:17	62	Yes	9 (MTX)	Demised - Septicaemia; neutropaenia, multiorgan failure	Yes (< 2 months)
Patient 4 III:18	200	Yes	1 (EMACO)	Demised - Hyperthyroidism; hypertension; Pneumonia	No
Patient 5 III/14	158	Yes	1 (MTX)	Demised - Widespread disease; condition deteriorated, Pneumonia	Yes (< 2 months)
Patient 6 II:18	32	No	Nil	Demised - Jaundice, renal failure, widespread disease, condition deteriorated precluding administration of chemotherapy	No
Patient 7 I:10	189	Yes	7 (EMACO)	Survived	Yes (> 2months)
Patient 8 IV: 13	133	Yes	16 (EMACO	Demised,- initially cured with 12 cycles, recurred, received 4 cycles, defaulted and demised	Yes (> 1 year)

KEY:

MTX: Methotrexate

EMACO: Etoposide, Methotrexate, Actinomycin, Cyclophosphamide, Oncovin

TABLE VII: PROFILE OF MORTALITY AMONGST HIV NON-INFECTED PATIENTS

Patient	Condition on Admission	Chemotherapy (n=cycles)	Side effects leading to death	Cause of death
1	Well Hyperthyroid Brain Metastases	EMA CO x 3	NIL	Brain Metastases
2	Hyperthyroid Rheumatic heart Disease hypertension	MTX x 1	Renal impairment	Cardiac Failure
3	Well	MTX x 3	Renal Impairment TCP Neutropaenia	Septicaemia Multi-organ failure
4	GIT Metastases	MTX x 1	Renal Impairment TCP Neutropaenia	Renal Failure Atrial Fibrillation Septicaemia
5	Lung Metastases	NIL	NIL	Pulmonary haemorrhage
6	Poor Brain/lung Metastases Hyperthyroid	NIL	NIL	Widespread Metastases
7	Lung Metastases	EMA CO x 4	Neutropaenia	Septicaemia Metastases Lungs widespread

KEY:

MTX: Methotrexate

EMACO: Etoposide, Methotrexate, Actinomycin, Cyclophosphamide, Oncovin

TCP: Thrombocytopaenia

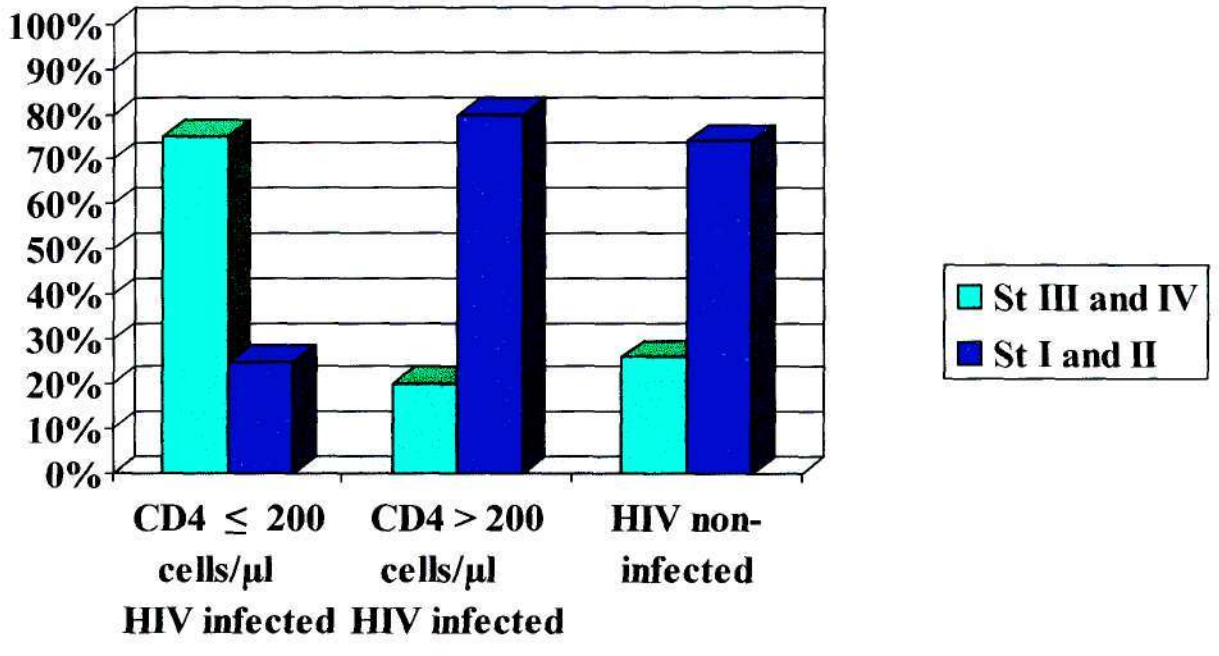

Figure 1

Comparison of FIGO Stages for HIV infected and HIV non-infected patients

12-Feb-2008

Dear Dr. Manivasan Moodley,

Re: IJGC-2007-00760+.R1-PROFILE OF MORTALITY AMONGST WOMEN WITH GESTATIONAL TROPHOBLASTIC DISEASE INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS (HIV): ARGUMENT FOR A NEW POOR PROGNOSTIC FACTOR.

I am pleased to confirm that your paper has been accepted for publication in the International Journal of Gynecological Cancer. You will be receiving the proofs via e-mail prior to publication. The proofs must be returned on schedule or the paper will be delayed in printing.

The Editors thank you very much for your cooperation in the review process. We look forward to more papers from you and your colleagues.

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Sincerely yours,
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