Molar pregnancy: A fifteen - year experience of a single tertiary institution.

By

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Declaration by candidate

I, Sedick Ahmed Camroodien, hereby declare that the research work **"Molar pregnancy: A fifteen - year experience of a single tertiary institution",** submitted to the University of Cape Town is an original work done by me. The results of this thesis have not been submitted to any other University for award of any degree.

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Plagiarism declaration

I, Sedick Ahmed Camroodien, know plagiarism is wrong. Plagiarism is to use another's work and pretend it is one's own.

I have used the Vancouver style for citation and referencing. Each contribution to, and quotation in this research **"Molar pregnancy: A fifteen - year experience of a single tertiary institution",** from the work of other people has been attributed and has been cited and referenced.

This research is my own work. I have not allowed and will not allow anyone to copy my work with the intention of passing it off as his or her own work.

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List of abbreviations

ARDS	Acute respiratory distress syndrome
CHM	Complete hydatidiform mole
COC	Combined oral contraceptive
ETT	Epithelioid trophoblastic tumour
FIGO	International Federation of Gynaecology and Obstetrics
GSH	Groote Schuur Hospital
GTD	Gestational trophoblastic disease
GTN	Gestational trophoblastic neoplasia
Hb	Haemoglobin
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HM	Hydatidiform mole
IUCD	Intra-uterine contraceptive device
LH	Luteinizing hormone
PET	Pre-eclamptic toxaemia
PHM	Partial hydatidiform mole
PSTT	Placental site trophoblastic tumour
PTD	Persistent trophoblastic disease
RFLP	Restriction fragment length polymorphism
SD	Standard deviation
UHM	Unclassified hydatidiform mole

Abstract

Background:

Gestational trophoblastic disease (GTD) is a group of uncommon conditions associated with pregnancy that arise from abnormal placental trophoblastic tissue following abnormal fertilization (1). Despite its rarity, it is of clinical and epidemiological importance because it affects women in the reproductive age group and is associated with morbidities and may sometimes be fatal (2). Molar pregnancy represents as two entities, complete or partial mole, which are mostly benign and can be distinguished by gross morphology, histopathology and genetic analysis (3). The incidence and etiologic factors contributing to the development of GTD have been difficult to characterize. Problems in accumulating reliable epidemiologic data can be attributed to inconsistencies in case definitions, inability to adequately characterize the population at risk, no centralized databases, lack of well-chosen control groups against which to compare possible risk factors, and rarity of the diseases (4). Several potential risk factors for molar pregnancies have been suggested. These include paternal age, vitamin deficiencies, maternal genetic translocations and environmental toxins. The only clear data relate to the impact of maternal age and the previous occurrence of a prior molar pregnancy (3,5,6). With minimal data from African countries about GTD, there remains a greater need for early recognition, timely referral and prompt and proper treatment of this condition (7).

Aim:

The aim of this descriptive study was to provide a detailed analysis of all patients diagnosed with molar pregnancy at Groote Schuur hospital (GSH) for the period January 2004 – December 2019.

Methodology:

This was a retrospective descriptive study of all women who were referred and followed up at the molar clinic at GSH with a confirmed histological diagnosis of molar pregnancy during the period 2004 – 2019. Subjects were identified from the molar clinic register at GSH, and folders retrieved for those meeting the inclusion criteria. Analysis was by simple frequencies and rates using SSPS statistical software. Subgroup analyses was performed by chi squared and t-tests.

Results:

There were 554 057 deliveries and 235 cases of molar pregnancies during that period, with an incidence of 0.42/1000 deliveries. Women aged 20 – 40 years and multiparous women constituted 78.7% and 59.8% of patients. Most (51.3%) patients were diagnosed in their second trimester. The most common presenting complaint was vaginal bleeding (37.4%), and the commonest complication was hyperthyroidism (16.6%). Twenty-six (11.2%) patients required a blood transfusion. Ten patients (4.2%) required a second evacuation with only 4 patients (1.7%) requiring a hysterectomy due to excessive haemorrhage. Patients with molar pregnancy normalized their HCG at 12 weeks post evacuation. There were 47 cases of persistent disease, of which 42 cases were referred for chemotherapy. The remaining 5 cases did not require chemotherapy as they achieved spontaneous regression after the second evacuation. Suction evacuation was performed in 97.4%. With regards to follow up, 44.3% of patients defaulted post evacuation surveillance and care.

Conclusion:

As the incidence of molar pregnancy in our centre continues to decline, it is important that we take the necessary steps to improve the follow-up protocols for patients with this condition. Doing so will avoid experiencing loss to follow-up.

Chapter one: Introduction and literature review

1.1 Background

Gestational trophoblastic disease (GTD) is a group of uncommon conditions associated with pregnancy that arise from placental trophoblastic tissue following abnormal fertilization (1,8). The spectrum includes molar pregnancy, persistent trophoblastic disease, chorio-carcinoma and the very rare placental site trophoblastic tumour. Despite its rarity, it is of clinical and epidemiological importance because it affects women in the reproductive age group and is associated with morbidities and may sometimes be fatal (2). Most patients with GTD follow the benign course, presenting with either a complete mole or a partial mole which regresses spontaneously after evacuation of the uterus. Only a few patients develop persistent molar pregnancy, which often requires additional treatment. The diagnosis can be made on gross morphology, histopathology and genetic analysis (3). The incidence and etiologic factors contributing to the development of GTD have been difficult to characterize (4). Problems in accumulating reliable epidemiologic data can be attributed to inconsistencies in case definitions, inability to adequately characterize the population at risk, no centralized databases, lack of well-chosen control groups against which to compare possible risk factors, and rarity of the diseases (4).

While a constellation of symptoms and signs has historically been associated with molar pregnancy, such events are less common due to routine ultrasonography in early pregnancy and the resulting early diagnosis of molar pregnancy (1). A number of potential risk factors for molar

pregnancies have been suggested, including paternal age, vitamin deficiencies, maternal genetic translocations and environmental toxins but the only clear data relate to the impact of maternal age and the previous occurrence of a prior molar pregnancy (3,5,6). With minimal data from African countries about GTD, there remains a greater need for early recognition, timely referral and prompt and proper treatment of this condition (7).

A complete mole results from monospermic or di-spermic fertilization of an empty oocyte, and is characterized by absence of fetal tissue, diffuse swelling of the chorionic villi, and diffuse trophoblastic hyperplasia (3). The genetic material is solely derived from the father, making them androgenic, with the maternal genetic component lost either late in oocyte development or at the time of conception (5). Partial mole results from di-spermic fertilization of a normal ovum and is characterized by focal trophoblastic hyperplasia and villous swelling, as well as presence of identifiable fetal tissue (3). The conception is tri-ploidy with two sets of chromosomes from the father and one from the mother (5). GTN can arise after any type of pregnancy and comprises of invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT), and epithelioid trophoblastic tumour (ETT) (1,8). GTD produce the pregnancy hormone – human chorionic gonadotropin (hCG), which serves as an excellent biomarker of disease progression, response to treatment, and can be used as subsequent post treatment surveillance (8). Thus, a plateaued or rising hCG level enables the early detection of progression of CHM and PHM to GTN that occurs in 15% - 20%, and 0.5% - 5% of cases respectively (8). The use of this biomarker together with the development of highly effective therapies has transformed survival outcomes, so that today nearly all women affected by GTN can expect to be cured if managed properly (8)

1.2 Incidence:

The incidence and etiologic factors contributing to the development of GTD have been difficult to characterize (4). The problems in accumulating reliable epidemiologic data can be attributed to factors, such as inconsistencies in case definitions, inability to adequately characterize the population at risk, no centralized databases, lack of well-chosen control groups against which to compare possible risk factors, and rarity of the diseases (4).

Data from Europe, North America, and Oceania showed intermediate ratios of GTD ranging from 66 per 100 000 pregnancies in Italy to 121 per 100 000 in the United States (6). Remarkably high ratio was found in Alaska (389 per 100 000 deliveries); Hawaii (460 per 100 000 live births); Brazil 465 per 100 000 and the Middle East (320 – 580 per 100 000 pregnancies) but Hawaii, Brazil and the Middle East have rates higher than Alaska (6). One study from Paraguay reported the lowest ratio found in any region for GTD (23 per 100 000 pregnancies). Data from Asian countries were heterogeneous, ranging between 81 per 100 000 pregnancies in China to 1754 for 100 000 deliveries in Indonesia (6). A South African review from a single referral institution estimated the incidence of 1.2/1 000 deliveries for molar pregnancy and 0.5/1 000 deliveries for GTN (9).

Worldwide, there is marked temporal, regional and ethnic variation in the prevalence of CHM (12). Estimates range from 0.6–1.1/1000 in Europe, Australia, New Zealand and North America to 0.8–5.8/1000 in South America, Southeast Asia, Japan and the Middle East (4,10). The rate in East Asia is approaching 1 in 120 pregnancies (1). In Uganda the prevalence is 3.4 per 1000 deliveries (11), with Nigeria reporting a figure of 1 in 379 deliveries (2). The incidence of partial mole is about 3 per 1000 pregnancies (8).

The geographical pattern for choriocarcinoma is similar to the overall distribution of GTD (6). Europe, North America, Australia, some areas of Latin America, and the Middle East showed low ratios that generally ranged between 2 and 7 per 100 000 pregnancies (6). The highest ratio was found in Greenland (19 per 100 000 live births) (6). China, India, Indonesia, and Thailand showed ratios ranging from 63 to 202 per 100 000 pregnancies (6). Whilst Japan, Singapore, and the Philippines reported ratios below 23 per 100 000(8). Nigeria reported notably high ratios of 99 per 100 000 pregnancies and 335 per 100 000 deliveries (6).

1.3 Risk factors:

A number of potential risk factors for molar pregnancies have been suggested, including paternal age, vitamin deficiencies, maternal genetic translocations and environmental toxins but the only clear data relate to the impact of maternal age and the previous occurrence of a prior molar pregnancy (5).

1.3.1 Age

The overall risk for a molar pregnancy is shown to be slightly increased at the extremes of age, with a risk of 1:450 in teenagers under 16; relatively unchanged at (< 1:500) for women in the reproductive age group and then increases significantly for those aged > 40, with a risk of 1:101 at age 45 and 1:8 for women aged > 50 (5). The risk of CHM, but not PHM is strongly associated with maternal age (5).

1.3.2 Previous molar pregnancy

A previous HM is the second-best established risk factor (6), increasing the risk to 10 times that for sporadic moles (8). The risk seems to increase to about 25% in women who have had more than one previous HM (6). A higher risk of HM exists after a CHM (about 10%) than after a PHM (about 2%) (6). A previous HM has been associated with a 1000–2000 times increased risk of choriocarcinoma (6).

1.3.3 Dietary factors:

Dietary deficiency of beta – carotene and animal fat are considered to be etiological factor for complete mole, but not for partial mole (8).

1.3.4 Race:

Race/ethnicity is a risk factor for both complete and partial molar pregnancy, which was most significant for Asian women (3). Asians, Hispanic and black women were less likely than whites to develop partial moles (3). The effects of race on gestational trophoblastic disease are acknowledged in the literature (3). However, the exact reason behind this observation is not

known. There are also little data from African countries that could provide a better understanding of the possible environmental or genetic factors that can affect the development of this condition.

1.3.5 Blood group

Women with group A or AB blood and male partner with group 0 or A seemed to have a higher risk of HM compared with women with group B or 0 blood (6).

1.3.6 Oral contraceptive pills

The use of oral contraceptives after a molar evacuation has been reported to increase the risk of invasive mole and choriocarcinoma by almost three times (6). However, two small studies, including a randomised trial showed that oral contraceptive use did not increase the risk of subsequent GTD (6,12,13).

1.3.7 Other:

A previous history of spontaneous abortion gives women a 2- to 3-fold increased risk of a molar pregnancy compared to women without a history of miscarriage (4).

1.4 Presentation:

The classic features of molar pregnancy are irregular vaginal bleeding, hyperemesis, excessive uterine enlargement and early failed pregnancy (14). Other common presenting complaints include amenorrhoea and lower abdominal pain (2). Rarer presentations include hyperthyroidism, early onset pre-eclampsia or abdominal distension due to theca lutein cysts (1). Very rarely, women can present with acute respiratory failure or neurological symptoms such as seizures; these are likely to be due to metastatic disease (14).

If there is vaginal passage of the gestational product, vesicles may be seen (8). The typical honeycomb appearance of a complete mole on ultrasound is rarely seen, especially in the first trimester (8). Typically, there is absence of fetal parts, cystic appearance of the placenta, and a deformed gestational sac that may appear like a spontaneous abortion (8). Hence, some molar pregnancies are only diagnosed on histologic examination after evacuation for a spontaneous

abortion (8), which could result in molar pregnancies being frequently misdiagnosed as incomplete miscarriages (9).

Features associated with high-risk molar pregnancy are hCG levels > 100 000, uterus exceeding 20 weeks, large theca lutein cysts, maternal age greater than 40 years, prior molar pregnancy, hyperthyroidism and pre-eclampsia (11).

Median gestational age at diagnosis of complete molar pregnancy is 11 – 12 weeks (15). There is a global trend towards decline in median gestational age at diagnosis of complete molar pregnancy over the past years with the widespread use of ultrasound and hCG measurement (15). While earlier diagnosis of CHM has been reported to be associated with a decrease in classical presenting symptoms such as bleeding, anaemia, and excessive uterine size, it has not been associated with any decrease in the development of post molar GTN (15).

Patients with PHM usually do not exhibit the dramatic clinical features of complete moles (16). More than 90% of patients present in the late first trimester or early second trimester with a presumed diagnosis of a missed or incomplete abortion (16). The volume of tissue is generally not excessive and clinical features like theca lutein cysts, hyperthyroidism or respiratory insufficiency are seldom present (16). Pre-evacuation hCG levels are usually in the low to normal range and the diagnosis is often made after histological review of curettage specimens (16).

1.5 Assessment:

Evaluation should include history, physical examination, serum hCG, serum haemoglobin and directed imaging (typically, pelvic ultrasound and chest X-ray) (1). A chest CT may be ordered if the chest X-ray suggests lung metastasis, but only lesions visible on chest X-ray should be scored (1). An MRI of the brain should be obtained if a patient is found to have metastatic disease in the lung (1).

Once the diagnosis of molar pregnancy is suspected the patient should be evaluated for the presence of medical complications (anaemia, preeclampsia, hyperthyroidism) by way of vital signs and laboratory tests.

The preoperative evaluation should also include blood type and crossmatch, serum hCG level, and electrocardiogram if appropriate (4). After the diagnosis is confirmed and the patient is determined to be hemodynamically stable, the most appropriate method of molar evacuation

should be decided upon (4).

Suction evacuation and curettage, ideally performed under ultrasound guidance, is the preferred method of evacuation of a molar pregnancy, independent of uterine size, if maintenance of fertility is desired (8). This procedure is usually performed to remove all of the molar tissue and avoid uterine perforation, which can occur during this procedure with a 1% chance of mortality. After anaesthesia has been obtained, the cervix is then dilated to allow a wide-bore tube to pass through (4).

It is recommended that an intravenous oxytocin infusion is started at the onset of suction curettage and continued for several hours postoperatively to enhance uterine contractility (8). Because of the increased risk of bleeding, blood for transfusion should be made available when the uterus is over 16 weeks old (8). If the uterus is >16weeks' size, there is a risk of pulmonary embolization of molar tissue, and care in a referral centre is warranted (1). Transient pulmonary insufficiency associated with pulmonary embolization, or a systemic inflammatory response syndrome (SIRS) generally only lasts for one to two hours and responds to appropriate supportive measures (1) Acute cardiopulmonary distress has been observed after the evacuation of molar pregnancy in 27% of the cases, more so in patients with uterine size of 16 weeks or greater (17). Symptoms usually develop within 4-12 hours after evacuation of the uterus and are marked with cough, tachycardia, tachypnoea, hypoxemia, diffuse rales and bilateral pulmonary infiltrates on a chest radiograph (17) Attention to blood and crystalloid replacement decreases pulmonary complications, such as pulmonary oedema and ARDS (4). Rh immune globulin should be given to Rh- negative women at the time of molar evacuation as RhD factor is expressed on the trophoblast (8). Judicious use of appropriate evacuation equipment and techniques, access to blood products, careful intraoperative monitoring, and early recognition and correction of complications results in improved outcomes. A hysterectomy is an alternative to suction curettage if childbearing is complete (8). In addition to evacuating the molar pregnancy, hysterectomy provides permanent sterilization and decreases the need for subsequent chemotherapy by eliminating the risk of local myometrial invasion as a cause of persistent disease (8). Because of the potential for metastatic disease even after hysterectomy, the risk of post molar GTN still remains at 3-5%, thereby requiring continued hCG follow-up (4). Medical induction of labour and hysterotomy are not recommended for molar evacuation, since these procedures increase maternal morbidity such as blood loss, incomplete evacuation requiring dilation and curettage, as well as a need for caesarean delivery in subsequent pregnancies, following a hysterotomy (4,8). The two methods also increase trophoblastic dissemination and the development of post molar GTN requiring chemotherapy (4,8).

1.6 Diagnosis:

Pathologic diagnosis of molar pregnancy is made by examination of curettage specimens (4).Tissue is often obtained early in gestation, and the diagnosis of molar pregnancies based on histology alone can be problematic (1). Cytogenetic techniques, such as chromosomal banding and restriction fragment length polymorphism (RFLP) analysis of DNA, have allowed unique chromosomal patterns of complete and partial molar pregnancies to be identified and differentiated (1). Negative immunostaining for P57KIP2, an imprinted gene expressed by the maternal allele, is diagnostic of a complete mole, as the placenta of all other gestations demonstrate nuclear staining of cytotrophoblast and villous mesenchyme (1). Ploidy analysis can help differentiate partial (triploid) from complete (diploid) mole but cannot distinguish between GTD and other aetiologies of triploidy (1). Selective molecular genotyping enables the comparison of alleles by evaluating molecular characteristics such as microsatellite instability (1). This allows for definitive diagnosis when histologic review is equivocal, but the cost of such testing may prohibit widespread adoption of this technique (1). There are no significant features to predict cases that subsequently develop persistent trophoblastic disease (18). Flow cytometry can distinguish diploid complete from triploid partial moles (4).

1.7 Ultrasound:

Ultrasound imaging has been utilized for decades in the diagnosis of GTD (1). The classic "snowstorm" appearance due to hydropic villi is less commonly appreciated in current practice since the diagnosis of GTD is typically made early in the first trimester (1). Ultrasonography plays a critical role in the diagnosis of both complete and partial mole, and it has virtually replaced all other means of preoperative diagnosis (4).

The chorionic villi of complete moles exhibit diffuse hydropic swelling, hence a characteristic vesicular ultrasonographic pattern can be observed, consisting of multiples echoes (holes) within the placental mass and usually no fetus (4). The majority of histologically proven complete moles are associated with an ultrasound diagnosis of missed miscarriage or anembryonic pregnancy (14). The accuracy of pre-evacuation diagnosis of molar pregnancy increased with increasing gestational age (14).

Ultrasound can be of value in predicting a high likelihood of partial mole with the ratio of the transverse to the antero-posterior dimension of the gestational sac being greater than 1.5, presence of cystic changes as well as an irregularity, or increased echogenicity in the decidual myometrium interface (16).

1.8 Quantitative hCG:

hCG is a disease-specific tumour marker produced by hydatidiform moles and gestational trophoblastic neoplasms. It is easily measured in both urine and blood, and hCG levels have been shown to correlate with the burden of disease. It is a placental glycoprotein composed of an α subunit resembling that of the pituitary glycoprotein hormones and a β subunit that is unique to placental production. Hydatidiform moles are commonly associated with markedly elevated hCG levels above those of normal pregnancy. Fifty percent of patients with complete mole have pre-evacuation hCG levels > 100 000 mIU/mL (4). Partial moles are not distinguished by such elevated hCG levels.

1.9 Post molar evacuation follow up:

After primary surgical treatment, weekly serum β-hCG assays should be obtained until 3 consecutive weekly assays are normal. Normalization usually occurs within 8 weeks, but 20% of patients will have elevated levels for 14 to 16 weeks' post-evacuation (1). Post molar GTN rarely occurs after the spontaneous return of hCG levels to normal (8,19). The risk of subsequent GTN is between 0.5 and 1% in patients with partial moles, and once the hCG normalizes the risk of developing GTN falls to 1:3000 (1).
Hence, a single additional confirmatory normal hCG measurement 1 month after first hCG normalization is recommended for a PHM and monthly hCG measurements should be obtained for only 6 months after hCG normalization for a CHM (8). Most centres now follow up women with partial hydatidiform moles with serial hCG samples until two normal values have been obtained (1).

While earlier guidelines suggested the use of contraception to avoid pregnancy for 12 months after normalization of hCG, recent data have demonstrated no increased risk of recurrent molar pregnancy 6 months subsequent to improvement. The current recommendation is now 6 months of contraception (1).

1.10 Contraception:

Intrauterine device insertion is not recommended at the time of evacuation because of the potential for uterine perforation (1). Luteinizing hormone (LH) may interfere with the detection of low levels of hCG (1,12,13). Oral contraceptives are safe, and do not prolong HCG regression and may be useful for contraception and to suppress endogenous LH during the period of surveillance.

1.11 Complications:

Haemorrhage is one of the commonest complications of hydatidiform mole and is reported in about 20% of cases (2,7). A comprehensive pre-treatment hormonal evaluation should be conducted in molar pregnancy cases to prevent serious complications such as thyroid storm that could arise in these patients. Hyperthyroidism occurring in patients with molar pregnancies is usually subclinical, and most patients remain asymptomatic (7).

1.12 Risk factors for GTN:

The likelihood of persistent disease developing after evacuation of a complete mole increases with evidence of marked trophoblastic growth, such as a pre-evacuation hCG level > 100,000 mIU/ mL, excessive uterine growth (>20- week size), and theca lutein cysts > 6cm in diameter (4). Patients with > 1 of these signs have approximately a 40% incidence of post molar GTN compared to 4% for those without any of these signs (4). Patients with an age >40 years, a repeat molar pregnancy, an aneuploid mole, and medical complications of molar pregnancy, such as toxaemia, hyperthyroidism, and massive trophoblastic embolization, are also at increased risk for post- molar GTN (4).

1.13 Post molar GTN:

Post molar GTN is usually diagnosed by hCG surveillance without symptoms (8). Other evidence of persistent GTD include persistent amenorrhoea, persistent vaginal bleeding or theca lutein cysts, development of massive trophoblast immobilization several weeks after abortion or evacuation, and evidence of extra-pelvic disease, at least 2 months after abortion or uterine evacuation (11). Therefore, patients on follow-up should have serial chest X-rays, clinical evaluation and assay of serum hCG levels (11).

Presently, there are at least two sets of criteria for the diagnosis of GTN and the consequent initiation of chemotherapy. One is advised by the International Federation of Gynaecology and Obstetrics (FIGO): A plateaued (four or more values of hCG within the same 10% range for at least three weeks) or increasing (two consecutive increases in hCG concentration of 10% or more for at least two weeks) hCG concentration after evacuation, histologic evidence of choriocarcinoma and an elevated hCG concentration six months after evacuation, even when still decreasing (20). The other is by the Charing Cross Trophoblastic Disease Centre, which, as well as the FIGO criteria, also uses a serum hCG concentration of more than 20 000 MIU/ML four weeks or more after uterine evacuation; heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage; evidence of metastases in brain, liver, or gastrointestinal tract, or radiologic opacities >2 cm on chest radiograph. In practice, the most frequent indicators of post-molar GTN and the need for chemotherapy are plateaued or increased serum hCG concentrations (20).

Chapter two: Methodology

2.1 Rationale of the study:

GTD is rare (2). Most countries do not have GTD registry and data are being compiled mainly from hospital reports and case series, which makes it difficult to determine the incidence denominators (9). To date, there are very few studies conducted on GTD in Africa, Southern and South Africa. The purpose of this descriptive study is to provide a detailed analysis of all patients diagnosed with molar pregnancy at Groote Schuur hospital for the period January 2004 – December 2019.

2.2 Study aim

The aim of the study was to provide an analysis of the experience of molar pregnancy over a 15-year period at a single tertiary institution.

2.3 Study design

This was a retrospective descriptive study of all women referred with molar pregnancy from the referring hospitals in the Metro West to the molar clinic at GSH for the period 2004 – 2019.

2.4 Study setting

The Molar Clinic is a tertiary level gynaecological oncology out- patient clinic based at a public hospital, namely Groote Schuur, situated in Cape Town. This clinic serves all patients with a confirmed diagnosis of molar pregnancy within the Metro West district. The facility is managed by the gynaecological oncology unit. The population is predominantly from a low socio-economic background.

2.5 Study subjects and identification

The subjects included all women referred to GSH with a diagnosis of molar pregnancy from January 2004 – December 2019. All cases had been documented in the Molar clinic register. Only patients registered and followed up at the molar clinic at GSH, with a confirmed diagnosis of molar gestation on histology were included. Folders without histological confirmation of molar pregnancy, missing patient notes and non – molar histology were excluded from the study.

2.6 Sample size

Data was collected from 292 females based on the above inclusion and exclusion criteria. At the molar clinic there were estimated to be about 15 referrals per year of GTD. Thus, in 15 years, it was anticipated that there would be more than 200 subjects.

2.7 Data collection

Folders of patients were retrieved, and data collected onto a purpose- designed data collection sheet. Basic demographic data were collected.

2.8 Study objectives

The outcomes of interest for the study included the following:
1. The incidence of molar pregnancy and persistent disease. We used delivery stats from all the hospitals and Midwife Obstetric Units (MOUs) within the Metro West that referred to GSH as a denominator.
2. Socio-demographic factors amongst patients diagnosed with molar pregnancy and persistent disease.
3. The clinical presentations of molar pregnancy and persistent disease.
4. The percentage of spontaneous regression; and percentage of persistent trophoblastic disease.
5. To predict possible risk factors of disease persistence amongst women initially diagnosed with molar pregnancy, who later required chemotherapy.

2.9 Statistical analysis

Stata version 17 (Stata Corp, College Station, TX, USA) software and WINPEPI. (www.brixtonhealth.com/pepi4windows.html) were used for data analysis. Continuous variables were summarised using mean (standard deviation) or median (interquartile range). Categorical variables were summarised using count (percent). T-test or Wilcoxon rank-sum test were used to compare means between two groups. Associations between categorical variables were tested using Pearson chi-squared test or Fisher's exact test. Estimates were reported with the corresponding 95% confidence intervals. The significance level was set at $p<0.05$.

2.10 Data management

Data on the category of molar pregnancy was collected from the molar clinic register, and the patient files were retrieved from records using the hospital number. The data extraction form was piloted on a few patient files as part of validation. Any shortcomings were then addressed before data collection commenced. All this data was captured onto a data collection sheet. All the data was entered anonymously using the assigned patient numbers.

2.11 Ethical issues

Since the study was a retrospective analysis, there was no requirement for consent. The data was kept and archived in a secure environment. The study subjects were not contacted, and the information was retrieved from their records automatically. All the subjects' data was stored in secure subject folders, and only the clinicians were authorized to access them. The data was anonymized to comply with the requirements of the Helsinki declaration. All electronic data was password-protected, and only the researchers and the supervisors were allowed to access it.

2.12 Research approval

Ethical approval for the study was requested from the University of Cape Town's Human Research Committee [HREC REF: 067/2021]. Permission to collect data from patient folders was obtained from the relevant authorities at GSH. The study only commenced after approval had been granted, see Appendix 2.

Chapter three: Results

3.1 Gestational trophoblastic disease

Table 1 Average frequency and incidence of individual entities of GTD, 2004 - 2019

GTD diagnosis	Number	Percentage	[a]Incidence (95% CI)
Molar pregnancy	235	88	0.42 (0.37 to 0.48)
Complete hydatidiform mole	151	56	0.27 (0.23 to 0.32)
Partial hydatidiform mole	84	31	0.15 (0.12 to 0.19)
Unspecified mole	32	12	0.06 (0.04 to 0.08)
Choriocarcinoma	1	0.4	0.02[b]
Persistent trophoblastic disease	47	17	0.03 (0.05 to 0.10)

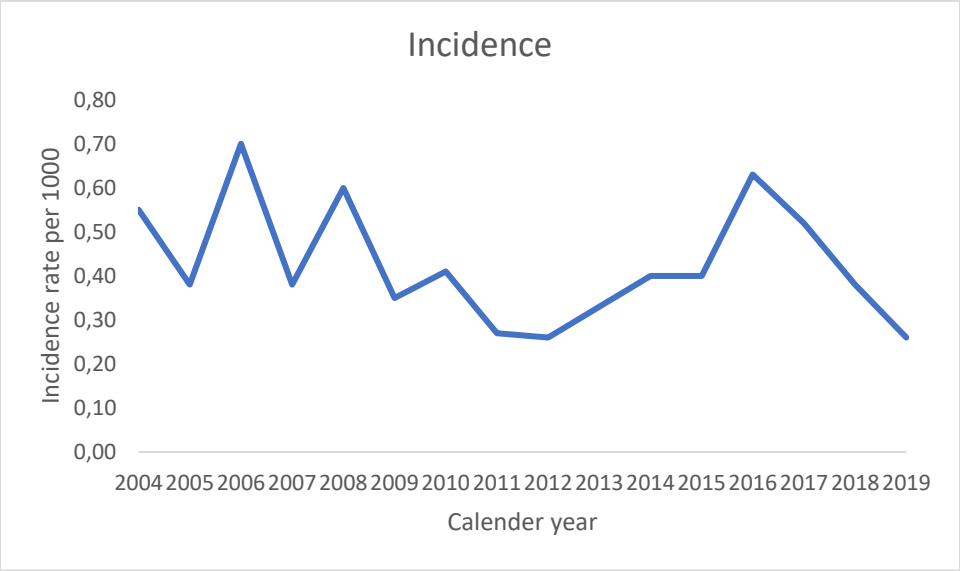
[a] Incidence per 1000 deliveries

[b] Incidence per 10 000 deliveries

A total of 292 folders were identified in the Molar clinic register and the folders were retrieved. Fifty-seven folders were excluded, of which 32 were unspecified moles, 18 had no histological diagnosis of molar pregnancy, 6 folders had missing clinical notes and one had a histological diagnosis of choriocarcinoma. Thus, two hundred and thirty-five files of patients with the diagnosis of molar pregnancy met the study inclusion criteria for analysis.

To evaluate potential trends in the annual incidence rates, Fig. 1 shows the annual incidence rates in the Metro West region of Cape Town between 2004 – 2019. An initial slight increase is seen over the first three years, followed by persistent drop in the incidence rates from 2007 to 2015. There was a sudden increase during 2016, which was still lower than the highest incidence experienced in 2006. This was followed by a persistent drop in the incidence rate from 2017 – to 2019.

Figure 1 Incidence rate per 1000 deliveries for molar pregnancy patients at GSH between 2004 – 2019.



An overview of the frequency and incidence per year between 2004 – 2019 of molar pregnancy appears in Table 2.

Table 2 Incidence rate per 1000 deliveries for molar pregnancy patients at GSH between 2004 - 2019

YEAR	Number	Incidence (95% CI)
2004	16	0.55 (0.32 to 0.90)
2005	12	0.38 (0.20 to 0.67)
2006	23	0.70 (0.45 to 1.06)
2007	13	0.38 (0.20 to 0.65)
2008	22	0.60 (0.37 to 0.90)
2009	13	0.35 (0.19 to 0.60)
2010	15	0.41 (0.23 to 0.68)
2011	10	0.28 (0.13 to 0.51)
2012	9	0.26 (0.12 to 0.50)

2013	11	0.33 (0.16 to 0.59)
2014	14	0.40 (0.22 to 0.68)
2015	14	0.40 (0.22 to 0.67)
2016	21	0.63 (0.39 to 0.96)
2017	18	0.52 (0.31 to 0.82)
2018	14	0.38 (0.21 to 0.64)
2019	10	0.26 (0.13 to 0.49)
TOTAL	235	0.42 (0.37 to 0.48)

3.1.1 Demographic characteristics of subjects with molar pregnancy

Table 3 Demographic distribution of patients with molar pregnancy.

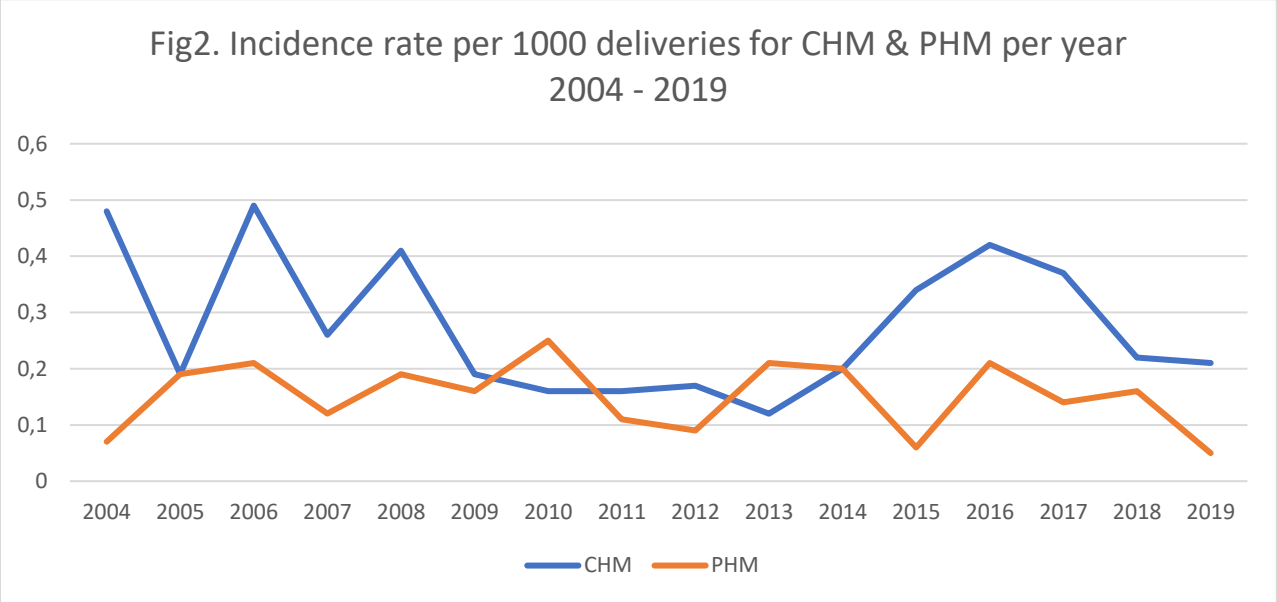
Variable	CHM		PHM		All MOLAR PREGNANCY	
	n	%	n	%	n	%
Age						
<20 years	23	15	7	8	30	13
20-40 years	112	74	73	87	185	79
>40 years	16	11	4	5	20	8
n	151		84		235	
Antecedent pregnancy						
Live birth	74	90	45	90	119	90
Miscarriage	6	7	5	10	11	8
Molar	2	2	0	0	2	1
n	82		50		132	
Interval between antecedent pregnancy and diagnosis of molar pregnancy (months)						
Median (IQR)	48	24-72	48	30 – 96	-	
7 - 12 MONTHS	4	10	3	12	7	11
> 12 MONTHS	34	89	22	88	56	89
n	38		25		63	
Parity						
Nulliparous	61	40	30	36	91	39

Multiparous	88	58	52	63	140	60
Grand multiparous	2	1	1	1	3	1
n	151		83		234	
Gestational age at admission (weeks)						
<13 Weeks	28	44	25	53	53	48
13 - 26 Weeks	36	56	21	45	57	51
> 27 Weeks	0	0	1	2	1	1
n	64		47		111	
Smoking						
Yes	25	30	14	30	39	30
No	59	70	33	70	92	70
n	84		47		131	
HIV						
Positive	16	19	8	16	24	18
Negative	70	81	41	84	111	82
n	86		49		135	
BLOODGROUP						
A	33	32	15	26	48	30
B	21	20	10	17	31	19
AB	4	4	5	9	9	6
O	46	44	27	47	73	45
n	104		57		161	

IQR = interquartile range

CHM and PHM represented 56.3% (incidence 0.27 per 1000 deliveries) and 31.3% (incidence 0.15 incidence per 1000 deliveries) of all molar pregnancy cases, respectively. Fig 2. A gradual reduction in CHM was seen between 2004 – 2013, with incidence rates decreasing from 0.48 per 1000 deliveries in 2004 to 0.12 per 1000 deliveries in 2013. This is followed by a slight increase in incidence from 2014 – 2016 before showing a decrease again in incidence to 0.21 per 1000 deliveries. PHM has remained relatively constant over the study period with an incidence ranging between 0.05 – 0.21 per 1000 deliveries.

Figure 2 Incidence rate per 1000 deliveries for CHM & PHM per year 2004 - 2019



The mean (standard deviation) age for CHM was 28.28 (8.67) and PHM was 27.76 (7.04). The distribution of CHM and PHM per age group are shown in Table. 3 with over presentation of CHM, PHM in the 20 – 40-year age group. Subjects with CHM were more frequently younger than 20 years or older than 40 years than those with PHM, but this was not found to be significant (p-value = 0.07).

With most, the antecedent pregnancies were live births with 90% in CHM, CHM. Two patients had a molar pregnancy in the past, and both were diagnosed with complete mole.

The median time between antecedent pregnancy and the diagnosis of molar pregnancy was 48 months in both CHM and PHM with a range of 24 – 72 months and 30 – 96 months, respectively. Nearly 60% of patients were Multiparous.

About 51% of molar pregnancy patients were detected during the-second trimester of their pregnancies. For CHM the bulk of patients (56.2%) were diagnosed in the second trimester of pregnancy, but a majority of PHM (53.2%) were diagnosed within the first trimester (p-value=0.28). A greater number (70%) did not smoke. South Africa has the highest prevalence of HIV, affecting mostly the young. Twenty four out of the 135 patients were HIV – positive, which is like the prevalence of this age group in this country. Similar trends were seen for CHM and PHM patients, (p–value = 0.74).

The most common blood group was blood group O, followed by blood group A and blood group B. The least common blood group was AB, with a rate of 5%. The trends were similar for PHM and CHM.

3.1.2. The clinical manifestation of molar pregnancy patients

Table 4 Clinical manifestations of patients with molar pregnancy

Clinical Manifestations	CHM		PHM		All molar pregnancies	
	n	%	n	%	n	%
Vaginal bleeding	58	38	30	36	88	37
Hyperemesis	7	5	1	1	8	3
Abdominal pain	17	11	10	12	27	11
Anaemia	7	5	4	5	11	5
Unknown	70	46	36	43	106	45
Amenorrhoea	11	7	10	12	21	9
Asymptomatic	3	2	4	5	7	3
n	173		95		268	

The information regarding clinical manifestations of molar pregnancy patients is shown in Table 4. The frequent presenting symptoms were abnormal vaginal bleeding (37.4%), lower abdominal pain (11.5%) and amenorrhea (8.9%). Only 8 patients presented with hyperemesis gravidarum with 7 of these patients found within the CHM group. No patients were found to have a uterus larger than their gestational age within this study. This finding might have been influenced by the manner in which notes were incompletely recorded in the individual patient files. Only 11(4.7%) patients presented with anaemia (Hb <8g/dl). Of note, 45.1% patients' clinical presentation was not known due to inconsistency in note keeping within the files.

3.1.3. Complication of molar pregnancy

Table 5 Complications observed in patients with molar pregnancy.

Complication	CHM		PHM		All molar pregnancy	
	n	%	n	%	n	%
Hyperthyroidism	28	18	11	13	39	17
Pre - eclampsia	0	0	1	1	1	0,5
Pulmonary embolus	0	0	1	1	1	0,5
Hypovolaemic shock	3	2	0	0	3	1
No complication	120	79	70	83	190	81
N	151		84		235	

Many of the cases (n=190) experienced no complications. The commonest complication observed was hyperthyroidism, found in 39 (16.6%) cases, which was commoner amongst CHM (18.5 vs 13%). Twenty-six (11.2%) cases required blood transfusion. Nineteen (12.6%) of these cases were found in CHM and 7 (8.5%) cases were in PHM. Three patients went into hypovolaemic shock. One case developed pre-eclamptic toxaemia (PET) and another had a confirmed pulmonary embolism. All occurred in PHM patients.

3.1.4. Management outcomes in patients with molar pregnancy

Table 6 Management outcomes in patients with molar pregnancy.

Management	CHM		PHM		All molar pregnancy	
	n	%	n	%	n	%
Metastasis on CXR	2	1	0	0	2	1
Blood transfusion	19	13	7	9	26	11
Second evacuation	6	4	3	3.6	10	4
Hysterectomy	3	2	1	1	4	2

There were only 2(0.9%) cases which showed metastasis on CXR. Both these cases were found in CHM patients.

Ten (4.2%) cases required a second evacuation, see table 7. Four patients (1.7%) required a hysterectomy, 3 (1.9%) cases were CHM, and 1 (1.2%) case was PHM. The indications for the hysterectomies were (1) Massive haemorrhage at initial evacuation, (2) Invasive molar pregnancy and (3 & 4) rising HCG with family complete and the patients opted for a hysterectomy instead of chemotherapy.

Table 7 Reasons for repeat evacuations in post molar GTN patients

Case	Initial BHCG	Post evacuation BHCG	BHCG at 2nd Evacuation	Interval between evacuations (days)	MOLAR	CHEMOTHERAPY	REMISSION WITHOUT CHEMOTHERAPY	BHCG > 1500 mIU/ML AT SECOND EVACUATION
1 (988)	151182	20062	12524	30	CHM	YES	NO	YES
2 (077)	5767000	723600	9085	62	CHM	YES	NO	YES
3 (813)	477941	107707	616	62	CHM	NO	YES	NO
4 (482)	175533	61550	48024	36	PHM	NO	YES	YES
5 (151)	475339	80635	2307	49	CHM	NO	YES	YES
6 (824)	508682	95242	43956	46	CHORIOCARCINOMA	YES	NO	YES
7 (271)	922050	31222	99520	45	PHM	YES	NO	YES
8 (343)	100000	32392	32392	36	CHM	YES	NO	YES
9 (558)	4432	4023	4242	52	PHM	NO	YES	YES
10 (749)	149766	47813	20837	41	CHM	NO	YES	YES

3.1.5 Contraception choice in patients with molar pregnancy

Table 8 Outcome variables in patients with molar pregnancy

Almost all (80.8%) patients agreed to use a form of a contraceptive method after their suction evacuation. The injectable contraception was the most common contraceptive method used. Only 3 (1.3%) patients declined any form of contraception. The reasons for declining contraception were not documented in the clinical notes.

Outcome variables in patients with molar pregnancy	CHM		PHM		All molar pregnancies	
Variables	n	%	n	%	n	%
Median initial HCG	210131		60880			
Median post evacuation HCG	18498		3081			
Persistent trophoblastic disease	26	18%	9	11%	35	15%
Loss to follow up	66	45%	36	43%	102	44%
Progressed to PTD	26	17%	9	11%	35	15%

3.1.6. Outcome variables in patient with molar pregnancy

A total of 229 (97.5%) cases had an evacuation as the primary treatment of choice. The median (IQR) initial HCG was 210131 (88452 - 545240) in CHM and 60880 (13772 - 267485) in PHM, p – value <0.001. The post evacuation median (IQR) HCG was 18498 (1132 - 77610) in CHM and significantly lower 3081 (538.5 - 34530.5) in PHM, p-value = 0.006. There was a post evacuation drop of 90% and 94% in the CHM and PHM respectively.

Thirty – one (20.5%) CHM and eleven (13.1%) PHM cases advanced to post molar GTN. Those patients with post molar GTN spent on average of 8 weeks after evacuation at the molar clinic before being referred for chemotherapy. Their last median (IQR) HCG on referral were 5751 (1715-25316) for CHM and 6360 (2811-17272) for PHM. Ninety-three (40.3%) patients completed their post treatment follow up. A greater proportion of PHM (45.8%) completed their follow up within the molar clinic than CHM (37.4%). The average weeks spent in the molar clinic within this group was 36 (CHM) and 35 weeks (PHM). Not all patients in this study adhered to follow-up rules, as 44.3% were lost to follow-up and never returned. On average the CHM group spent 10 weeks at the clinic before defaulting and the PHM spent 15 weeks before defaulting follow up. However, the average last HCG in the CHM group was 10 and 1 for PHM before they defaulted care.

3.2. PERSISTENT TROPHOBLASTIC DISEASE

A total of 554057 deliveries were recorded from 1st January 2004 – 31st December 2019 with 47 Post molar GTN cases diagnosed within the same period. The incidence of Post molar GTN within the institution was 0.08 per 1000 deliveries. Out of these, 31 cases (66%) were CHM, and 11 cases (23%) were PHM and remaining 5 cases (11%) were from UHM. The Post molar GTN incidence rate per 1000 deliveries per year is shown in Table 10. On average, the institution saw 3 cases of PTD per year during the study period.

Table 9 Incidence rate per 1000 deliveries for PTD patients at GSH between 2004 - 2019

YEAR	Number	Incidence (95% CI)
2004	5	0.17 (0.06 to 0.40)
2005	3	0.06 (0.01 to 0.23)
2006	0	0.0 (0.00 to 0.11)
2007	1	0.03 (0.00 to 0.16)
2008	4	0.05 (0.01 to 0.20)
2009	1	0.03 (0.00 to 0.15)
2010	6	0.14 (0.04 to 0.32)
2011	2	0.06 (0.01 to 0.20)
2012	1	0.03 (0.00 to 0.16)
2013	3	0.09 (0.02 to 0.26)
2014	2	0.06 (0.01 to 0.21)
2015	2	0.06 (0.01 to 0.21)
2016	5	0.15 (0.05 to 0.35)
2017	3	0.06 (0.01 to 0.21)
2018	6	0.14 (0.04 to 0.32)
2019	2	0.05 (0.01 to 0.19)
Total	47	0.07 (0.05 to 0.10)

3.2.1 Demographic characteristics of PTD

Table 10 Demographic distribution of patients with PTD.

Characteristic	CHM		PHM		PTD	
	n	%	n	%	n	%
Age						
<20 years	1	4	0	0	1	3
20-40 years	19	73	6	67	25	71
>40 years	6	23	3	33	9	26
n	26		9		35	
Antecedent pregnancy						
Live birth	-		-		20	87
Miscarriage	-		-		2	9
Molar	-		-		1	4
n					23	100
Interval between antecedent pregnancy and diagnosis of PTD (months)						
Median (IQR).	84	72 - 120	102	48 - 228	96	72 - 144
Parity						
Nulliparous	10	38	0	0	12	30
Multiparous	16	61	8	89	27	67
Grand multiparous	0	0	1	11	1	2
n	26	100	9	100	40	100.0
Smoking						
Yes	2	14	1	14	3	14
No	12	86	6	86	18	86
n	14	100	7	100	21	100
HIV						
Positive	6	29	1	12	7	24
Negative	15	71	7	87	22	76
n	21	100	8	100	29	100
BLOODGROUP						
A	7	39	0	0	9	37
B	5	28	0	0	6	25
AB	0	0	0	0	0	0
O	6	33	3	100	9	37
n	18	100	3	100	24	100

The demographic parameters of patients with PTD are summarized in Table 10. The mean age of the patients was 32.6 years. The mean age in the CHM group who developed PTD was 31.7 years and 37.1 years in the PHM group (p = 0.07). Majority of patients (71.4%) were in the 20 – 40 years age group. There was only 1 patient who was diagnosed with a CHM that was <20 years and she progressed to PTD. Thirty three percent of PHM patients were found to be > 40 years who progressed to PTD compared to 23.1% of CHM(p=0.72).

Regarding the antecedent pregnancy, live births were the overwhelming majority. Previous molar pregnancy was only found in 1 (4.3%) case of PTD.

The median (IQR) time between antecedent pregnancy and the diagnosis of PTD was 96 (72 to 144) months, 84 (72 to 120) months in CHM and 102 (48 to 228) months in PHM.

3.2.2 Clinical manifestation of PTD

Table 11 Clinical manifestations of PTD patients.

Clinical Manifestation	CHM		PHM		PTD	
	n	%	n	%	n	%
Vaginal bleeding	13	50	2	22	16	40
Hyperemesis	1	4	0	0	1	2
Lower abdominal pains	3	11	0	0	3	7
Anaemia	3	11	3	33	6	15
Unknown	11	42	5	56	19	47
Amenorrhoea	1	4	1	11	2	5
Asymptomatic	1	4	0	0	1	2
n	33		11		48	

The clinical manifestation of patients with PTD are illustrated in Table 11. Vaginal bleeding was the commonest presenting complaint (40%) followed by Anaemia (15%) and lower abdominal pains (7.5%). In a significant proportion (47.5%) of patients, the presenting complaint was not documented upon referral to the molar clinic.

3.2.3 Complications of PTD

Table 12 Complications of PTD patients.

Complication	CHM		PHM		PTD	
	n	%	n	%	n	%
Hyperthyroidism	6	23	3	33	9	22
Hypovolaemic shock	1	4	0	0	1	2
No complication	19	73	6	67	29	72
n	26	100	9	100	40	100

Table 12 shows the complications observed in patients who developed PTD. Majority of PTD patients never developed any complications. Hyperthyroidism was the commonest (22.5%) complication followed by hypovolaemic shock (2.5%).

3.2.4 Management outcomes in PTD

Table 13 Management outcomes in PTD patients.

Management	CHM		PHM		All PTD	
	n	%	n	%	n	%
Metastasis on CXR	1	4	0	0	1	2.6
Blood transfusion	5	19	3	37	8	20
Second Evacuation	6	19	3	27	9	19
Hysterectomy	2	8	1	11	4	10

Table 13 shows the summary of management outcomes amongst patients with PTD. Only 1 (2.6%) case showed metastasis on CXR. Eight (20%) cases required a blood transfusion, 9 (19%) required a second evacuation, which was statistically significant in PHM (p=0.02) and 4 (10%) required a hysterectomy.

3.2.5 Outcomes variables in PTD

Table 14 Outcome variables in PTD patients.

Variables	CHM Median	PHM Median	PTD Median
INITIAL HCG	428247.5	396000	428247
POST EVAC HCG	42247	31222	42247
WEEKS ATTENDED MOLAR CLINIC	8	8	8
MONTHLY HCG (weeks)			
4	5880	3904	6308
8	4079	6360	4650
12	3034	3300	2909
16	44.5	912.5	104
20	2	3	5
24	1	1	1
PTD LAST HCG	5751	6360	7047

The median initial HCG in the PTD group was 428 247 and the post evacuation HCG value was 42 247. These patients spent an average of 8.2 weeks within the molar clinic before being referred to LE33 for chemotherapy. During this time the HCG levels were being monitored to ascertain whether the patient has developed PTD. The median HCG values are shown in Table 14, with emphasis on the HCG values at weeks 4 and 8 respectively, after which chemotherapy was commenced.

3.3 Hyperthyroidism

During this study, hyperthyroidism was the commonest complication amongst patients with molar pregnancy 39 (16.6%) cases and PTD 9 (22.5%) respectively. From the patients' records, none of the patients required ICU admission for complications related to hyperthyroidism. Due to lack of clinical data from the respective clinical records, one could not comment further on whether the hyperthyroidism was of a clinical or biochemical nature and whether specific treatments were administered to treat this complication.

Chapter four: Discussion and conclusions

4.1 Incidence

Our retrospective study involved 235 patients with molar pregnancy. The incidence of molar pregnancy in this study was 0.42 per 1000 deliveries (1:2358) and that for CHM, and PHM were 0.27 (1:3669) and 0,15 (1:6596) per 1000 deliveries respectively, which was much lower than a local study that documented a molar pregnancy incidence of 1.2 per 1000 deliveries and choriocarcinoma of 0.5 per 1000 deliveries (9,21). Compared to other African countries, our incidence for CHM is extremely low and more in keeping with incidence ranges in Europe, Australia, New Zealand, and North America (2,10,11). Our study (87.7%) is in keeping with the most current evaluations which confirm that the majority (80%) of GTD are hydatidiform moles and 15% are persistent disease (1). We also clearly observed a decline in the incidence of both hydatidiform mole and choriocarcinoma as is evident internationally over the past 30 years (4,16).

4.2 Demographic and clinical characteristics:

The mean age of patients with molar pregnancy was 28 years (SD8.7) within our study. Maternal age is associated with risk of hydatidiform mole with higher incidence among women under the age of 20 years and rising after the age of 40 years (22). This is not supported by findings in this study as 78.7% of the patients were in the 20 – 40-year age group and only 12.8% and 8.5% were in the under 20 year and over 40-year age group respectively. The study findings are replicated in another local audit, conducted in the eastern regions of South Africa. The study did however show a higher proportion of CHM at the extremes of age with 15.2% < 20 years and 10.6% > 40

years of age in comparison to PHM but was not statistically significant (p=0.07). This finding agrees with a study by A. Melamed et al, which showed that subjects with CHM were more frequently younger than 20 years or older than 40 years than those with PHM ($p < 0.001$) (3).

The obstetric history of the patients revealed that about 59.8% were multigravida, with 38.9% being nulliparous. This is disheartening to note because these young nulliparous women were just beginning their reproductive life and this experience could negatively impact their mental health and contribute further to the great burden of disease that mental health issues places on our health care system in South Africa. Our study also found that multiparity were highest among patients with PHM (62.6%) compared to CHM (58.3%) but like A. Melamed et al, the distribution of parity did not differ among the groups ($p = 0.80$).

Approximately 51.3% of the patients were in their second trimester of pregnancies when molar pregnancies were diagnosed. This data is different to studies from India and other documentations in the literature where most patients were diagnosed during the first trimester (7,23). This is because dating scans are underutilized in the Metro West, especially among patients who are not aware of their last menstrual period, (LMP). Early ultrasound examination is also needed in all pregnant women, especially in our setting, where patients may be unaware of their diagnosis.

Several potential risk factors for molar pregnancies have been suggested but the only clear data relate to the impact of maternal age and the previous occurrence of a prior molar pregnancy (5). A previous HM is the second-best established risk factor (6), increasing the risk to 10 times that for sporadic moles (8). In this study only 2 (1.5%) women had the antecedent pregnancy as molar, with the vast majority having a live birth (90.1%) as their antecedent pregnancy.

Race and ethnicity are a risk factor for both complete and partial molar pregnancy, which was most significant for Asian women (3). Asians, Hispanic and black women were less likely than whites to develop partial moles (3). A protective effect of black race for GTD is quoted in the literature, and the reason is unknown and there is little data from African countries which might help explain whether genetic or environmental factors underlie this observation. The incidence of molar pregnancy was found to be very low, 0.42 per 1000 deliveries during the period of 2004 – 2019. Unfortunately, we never received ethics approval to include race as a variable within our data collection to prove the above contention. Since majority of patients presenting to the molar clinic at GSH are of African descent, one could certainly deduce that there may be a protective advantage. Our study agrees with a study by I. Maesta et al who found that patients of African

descent are significantly younger and of higher parity than other races (24). This can be partly explained by differences in patterns of childbearing.

Blood group O+ is the commonest blood type in South Africa. Women with blood Group A or AB have a higher risk of HM compared with group B or O (6). The dominant blood group for molar pregnancy in this study was O (45.3%) followed by A (29.8%) and then B (19.2%). Blood group AB only represented a small percentage (19.2%) of cases. However, in the PTD group, both blood group 0 and A were the commonest (37.5%) followed by B (25%). Of significance is the fact that Blood group A was the most dominant (38.9%) in those patients with CHM who progressed onto PTD, but this was not statistically significant (p=0.09).

4.3 Clinical manifestation:

This study revealed that the most common clinical manifestation of molar pregnancy is abnormal vaginal bleeding. This occurred in 37.5% of cases. Unfortunately, 45.1% of the patients never had their presenting complaint documented in their notes. The second commonest presentation was lower abdominal pain (11.5%) followed by Amenorrhea (8.9%). This agrees with the documentation in the literature where the commonest presenting complaint is abnormal vaginal bleeding (22).

4.4 Complications

Clinical hyperthyroidism was the commonest complication. A total of 39 (16.6%) cases were diagnosed. This result was much higher than those previously reported by other investigators, but very similar to a study by Sinawat et al and Pundir et al, conducted in Thailand and India respectively (7,23). This difference may be attributed to the fact that thyroid function assessment is performed routinely, probably explaining the high incidence of biochemical hyperthyroidism detected in our study suggested that a comprehensive pre-treatment hormonal evaluation is warranted in molar pregnancy cases to prevent serious complications such as thyroid storm that could arise in these patients (23).

Judicious use of appropriate evacuation equipment and techniques, access to blood products, careful intraoperative monitoring and early recognition and correction of complications results in improved outcomes (8). There were no complications in 80.8% of patients who were managed at a tertiary level hospital. Only 1.3% of patients suffered from hypovolaemic shock, and 1 patient developed a pulmonary embolus. These findings differ from other African countries, where acute

haemorrhage was the commonest complication and why almost all their patients receive blood transfusion (7). In this study only 11.2% of patients required a blood transfusion. The very low complication rate in this study can be attributed to the fact that the management of molar pregnancy policy in the Metro West is a well-designed and written policy which states that all cases of suspected molar pregnancy, diagnosed at a primary level of care must be referred urgently to tertiary care for further assessment and management. Secondary level hospitals within the Metro West can proceed to manage the molar pregnancy provided the uterus is less than 16 weeks gestation. Every patient is assessed by an anaesthetist, and the evacuation is performed by a qualified gynaecology resident, with the support of a consultant. The evacuation is always only carried out until 22h00 after which the procedure is scheduled for the following morning when all senior personnel are on duty to manage any complications which may arise during the procedure.

4.5 Management:

Suction evacuation and curettage, ideally performed under ultrasound guidance, is the preferred method of evacuation of a molar pregnancy independent of uterine size if maintenance of fertility is desired (8). It is the method which will achieve removal of all molar tissue and avoid uterine perforation, a procedure with <1% chance of mortality (1). In this study 97.5% of women had an evacuation under ultrasound guidance as the primary treatment of choice. Surgical evacuation also allowed for a confirmed histological diagnosis to be made in 87.7% of cases as it provides a specimen to be sent for histological assessment.

Ten (4.2%) patients required a second evacuation. The second evacuation was performed on average 46 days after the initial evacuation. The median hCG at the time of the second evacuation was 30764 mIU/mL. The indications for repeat evacuation were ongoing vaginal bleeding (41%), incomplete initial evacuation with retained products evident on ultrasound (35%) and rising hCG (24%). Five patients who required a second evacuation failed to achieve spontaneous regression of their HCG level and required chemotherapy. Majority of the patients had an initial diagnosis of CHM. The UK and US guidelines advises against repeat evacuation due to the low level of benefits and the risks of perforation and haemorrhage (25). Van Trommel et al advises to consider a second evacuation if all of the following factors are present: ultrasound demonstration of residual disease within the uterine cavity, an hCG plateau or rise, absolute hCG value of < 20 000 mIU/ml and no other indications for immediate chemotherapy (26). In general, repeat evacuations performed when the hCG is above 5000 appear to have only low rates of benefit (25). In our study 50% of patients had a sustained drop in HCG levels after a second

evacuation and entered into spontaneous remission after the second procedure. This finding is better compared to a study conducted by Schlaerth et al who noted only 20% of patients achieved similar success (27). Interesting is the fact that our 50% spontaneous remission rate after a second evacuation is in keeping with an observational study performed by Pezesgki et al who published a 10-year study of 544 patients. In their study they achieved a 68% successful remission rate. However, they documented a HCG level greater than 1500 iu/ml at the time of the second evacuation was associated with a need for postoperative chemotherapy (27). In our study this never held true as 90% of our patients had a HCG level greater than 1500 iu/ml. Our study clearly shows a higher rate of benefit of repeat evacuation despite a higher hCG at the time of repeat evacuation. Given these discrepant findings, a further prospective study within our institution should be conducted to adequately assess the risk and benefit of a repeat evacuation within our population and to ultimately assist within future guidelines regarding this management option within the low-risk patients with post molar GTN. However, the number of second evacuations remains small within our institution.

4.6 Contraception:

The injectable contraceptive was by far the most popular choice (75%) as there is a greater preference for the injectable contraceptive in our reproductive age population within the Metro West. Only 13.5% of patients chose the combined oral contraceptive. Barrier contraception, was less popular, compared to studies from India where almost 47% patients opted for barrier contraception. These findings differ to those presented in other studies (7,23).

4.7 Outcomes:

Molar pregnancy is commonly associated with markedly elevated hCG levels above those of normal pregnancies (4). Fifty percent of patients with CHM have pre-evacuation hCG levels > 100 000 mIU/ml (4). PHM are not distinguished by such elevated levels (4). The initial hCG for CHM and PHM in this study was 210 131mIU/ml and 60 880 mIU/ml respectively.

After primary surgical treatment, weekly serum hCG assays should be obtained until 3 consecutive weekly assays are normal (1). This usually occurs within 8 weeks, but 20% of patients have elevated levels for 14 – 16 weeks post evacuation (1). In this study the median HCG was 13.5 units (1-253 units) for CHM and 3(1-78.5) for PHM at 8 weeks respectively.

However, at 12 weeks both CHM (1[1-22]) and PHM (1[1-10.5]) patients had normalized their HCG assays.

Of the 235 patients registered at the molar clinic only 40.4% completed post evacuation follow up. A total of 44.3% of patients were lost to follow within this study. These findings are comparable to findings found in studies conducted in Nigeria, where the follow rate was as low as 32 – 38.2% in different parts of Nigeria (22).

4.8 PTD

Post molar GTN is usually diagnosed by HCG surveillance without symptoms (8). Other evidence of PTD include persistent amenorrhea, persistent vaginal bleeding or theca lutein cysts, development of massive trophoblastic immobilization several weeks after abortion or evacuation, and evidence of extra-pelvic disease, at least 2 months after abortion or evacuation (2). Therefore, patients on follow up should have serial chest x-rays, clinical evaluation, and assay of serum HCG levels (11). Forty-seven (17.5%) cases had Post molar GTN, of which 13.2% of CHM and 4.7% of PHM progressed to Post molar GTN. The diagnosis of Post molar GTN was mainly derived from HCG follow up. The CHM and PHM incidence is consistent with the literature in that about 15 – 20 % of CHM and 0.5 – 5% of PHM resulted in Post molar GTN (8).

A total of 42 (15.7%) patients received post evacuation chemotherapy. This finding is much lower than a local study (21). Our institution-initiated chemotherapy based on an HCG that plateaued or increased, which is in practice, the most frequent indicator of post molar GTN (20). Patients with PTD displayed a median HCG of 6308 and 4650 at 4 and 8 weeks respectively. The same held true for CHM which displayed HCG of 5880 and 4079 and for PHM which showed HCG of 3904 and 6360 for the same period respectively. This HCG at 4 and 8 weeks is significantly higher compared to that found in molar pregnancy which was 105 and 13.5 for CHM and 27 and 3 for PHM at 4 and 8 weeks respectively. Hence this study indicates that if your HCG at 4 and 8 weeks is more or equal to 6000 and 4000 respectively then your chances of developing PTD is higher. This finding agrees with the literature in which it is stated that another indication for prophylactic chemotherapy in molar pregnancy include failure of HCG becoming normal by the stipulated time of 10 – 12 weeks, rising of HCG post evacuation, and evidence of metastases irrespective of the level of HCG (7). The above findings are also in agreement with a study which based its diagnosis of PTD on persistently elevated serum BCHG levels with or without chemotherapy, at least 2 months after abortion or uterine evacuation (11).
Only 1 case (2.6%) presented with metastases on CXR which was in a patient with CHM who progressed to PTD. This is not in agreement with the literature which states that patients should

be followed up with serial chest x-rays together with clinical evaluation and assay of serum HCG levels (11).

Of the patients with PTD, 20.5% required a blood transfusion and 19.1% required a second evacuation. More patients with PHM who progressed to Post molar GTN required a second evacuation compared to CHM (p=0.02). Ten percent of patients required a hysterectomy. This finding was higher than what was found in Abuja, Nigeria, where 5.9% required a subtotal hysterectomy for uncontrollable bleeding (20). Hyperthyroidism is a feature associated with high-risk molar pregnancy (11). A high proportion of our Post molar GTN patients developed hyperthyroidism in this study as well (22.5%). This could be explained by the fact that their initial HCG on average was higher (428247.5 MIU/ML) compared to molar pregnancy patients (210131 MIU/ML). This could arise from stimulation of thyrotropin receptors by HCG (7). Our study again emphasizes the importance of comprehensive pre-treatment hormonal evaluation to prevent serious complications such as thyroid storm that could arise in these patients (7).

Another important finding in the Post molar GTN group, the post evacuation HCG was twice as high (42247 MIU/ML) compared to molar pregnancy (18498 MIU/ML) patients in this study. This could possibly serve as a marker to indicate to the clinician that the patient might be at an increased risk of Post molar GTN, especially in low resource setting where serial HCG measurements are not always possible and more importantly for patients on the African continent where follow up in patients with molar pregnancy is very poor. A post evacuation cut off value of > 42 000 MIU/ML for CHM and > 31 000 MIU/ML for PHM might indicate persistent disease. However further prospective studies need to be performed to confirm this.

4.9 Hyperthyroidism

The hyperthyroidism group of patients presented with a higher initial and post evacuation HCG value (746266.5 MIU/ML) in comparison to euthyroid molar pregnancy patients. However interesting to note is the fact that this group still managed to normalize their HCG at 12 weeks as was the case seen in the euthyroid molar pregnancy group.

4.10 Follow up

The poor follow up rate among Metro West patients who were treated at the GSH molar clinic is believed to be due to them not being able to afford the transportation cost to attend the clinic. On average, those who were lost to follow up only attended the clinic for 10 to 15 weeks.
The last comprehensive check-up that they had at the molar clinic was 10mmol/L and 1mmol/L for CHM and PHM, respectively. Those who followed up with a follow-up visit within the clinic typically spent about 36 and 45 weeks before they were discharged.
Post molar GTN rarely occurs after spontaneous return of HCG levels to normal (9). The HCG data in this study agrees with the literature in that the HCG remained normal for the subsequent 3 months in both CHM and PHM. There could be a case for discharging these patients to a primary centre for further reviews. Considerations should be taken for shorter surveillance once normal levels are achieved.

The literature concludes that after HCG values fall spontaneously within the normal range, patients can safely be discharged from follow up (16). Bagshawe et al also found that none of the patients with HCG levels falling to the normal range within 2 months after evacuation developed sequelae requiring treatment (16). When HCG levels fell to normal after 2 months after evacuation, the risk of recurrence was one in 96 (16). Within our study CHM and PHM showed a spontaneous normalization of their HCG levels by 3 months and 2 months respectively. No patient developed any further sequelae requiring treatment once they showed normalization of their HCG in both CHM and PHM respectively during the study period. Despite strong efforts, many patients did not complete the recommended HCG follow up program. Only 40.4% of all uncomplicated patients monitored by HCG measurements completed the follow up program.

A recommendation that patients are followed up until normal HCG levels are achieved would have resulted in 83% of patients being discharged from follow up within 3 months. We further recommend that once a normal HCG level is achieved, telemedicine is employed to further follow uncomplicated molar pregnancy patients for a further 3 months. We believe this approach seems a safe and reasonable compromise as this study proves the fact that malignant sequelae are very low and that the follow up program in these patients are resource intensive and places an undue economic, social, and emotional burden on them.

The follow up program seems to be associated with an increase rate of loss to follow up. Clinicians need to adjust and draft more flexible protocols to accommodate patients with complex socioeconomic backgrounds. And this seems to be the case for other African countries as well.

4.11 Study limitations

The retrospective nature of this study makes it susceptible to bias. The sample size was small, which impacts on statistical significance analysis. In addition, as with any retrospective study, we were limited in getting certain necessary detailed information due to not having a structured referral template. The other limitation is that the incidence of subsequent pregnancies after complete treatment of molar pregnancy was not studied. A prospective study is recommended in the future.

4.12 Study strengths

This study was the first analysis of molar pregnancy in our institution and highlighted gaps in care to allow improvement in our treatment protocols and surveillance tools. Our sample size was comparable and often larger than many other previous studies investigating outcomes in patients with molar pregnancy both locally and internationally. Secondly the study was conducted over an extended time span. Other strengths include a central pathology review and the use of a single well characterized HCG assay. It will also contribute to local literature and may be relevant to other low – income settings.

4.13 Conflict of interest:

There is no conflict of interest for this study

4.14 Recommendations:

- Health care workers must exclude GTD in all postpartum and post miscarriage patients who present with persistent vaginal bleeding.
- Better outcome is possible with good patient counselling for improved follow up.
- All confirmed molar pregnancies should have a full pre-treatment assessment and evaluation.

- All pregnant patients must have a first trimester dating scan to aid with an early diagnosis of GTD and ultimately prevent increased risk of morbidity associated with the disease.
- A GTD database should be started at GSH to aid in contributing to GTD literature worldwide and for the African continent.
- A standardized referral template must be designed to aid in future research within this field.
- Patients should be followed up at the molar clinic until normal HCG levels are achieved. Thereafter telemedicine should be employed, and patients can be monitored telephonically in which patients report to their local clinics for serial HCG measurements until 3 additional normal HCG measurements are achieved in CHM and 1 additional normal HCG value is achieved for PHM.
- A new HCG tracking chart must be designed in line with findings of this study data upon which further research can be conducted in the future.

4.15 Conclusion

This is the first study at GSH evaluating an extensive experience of molar pregnancy over an expanded time frame within our institution. Our findings confirm that the incidence of molar pregnancy is low and on a declining trend as is witnessed globally. Vaginal bleeding continues to be the most common presenting symptom of molar pregnancy. Age, prior molar pregnancy, smoking has not been found to be a significant risk factor for molar pregnancy within our study population. Early diagnosis of molar pregnancy can change the clinical presentation, diagnosis, and treatment of the disease. Majority of our patients have uncomplicated molar pregnancy with hyperthyroidism being the commonest complications. There remains a need for early recognition, timely referral, prompt, and proper treatment of this condition. Adequate follow up of these patients with emphasis on the need for contraception should be reinforced. Black Africans population may have a protective effect against the disease. This study shows that CHM

normalizes at 12 weeks and PHM at 8 weeks, after which the risk of post molar GTN remains relatively low. Given the poor follow rate within our population we recommend the use telemedicine / early down referral once HCG normalizes. Further surveillance should include 3 further normal HCG values for CHM and 1 further HCG value for PHM.

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APPENDIX 1:DATA SHEET

Study number:

Demographics:

Measure	Result
Age in years	
Smoking – [Y/N]	1= Yes 2=No 3=unknown
Gravidity	
Parity	
Antecedent pregnancy [Term (T); Miscarriage (A), Ectopic (E), Molar (M)]	1=Term 2= Miscarriage 3=Ectopic 4=Molar 5=TOP 6=unknown
HIV status – [P/N]	1=Positive 2=Negative 3=Unknown
Blood group & Rhesus factor	1=A 2=B 3=AB 4=O 5=Unknown
Interval from last pregnancy [In months]	3=Unknown

Clinical Presentation:

Measure	Result
Vaginal bleeding [1]	
Hyperemesis [2]	
Uterine size larger than gestational age [3]	
Lower abdominal pain [4]	

Anaemia [5]: (Hb < 8g/dL)	
• Pre op Hb	
• Post op Hb	
Unknown [6]	
Amenorrhoea [7]	
Asymptomatic [8]	
Expected gestational age [In weeks]	3=Unknown

Maternal Complications

Hyperthyroidism – [1]	
If hyperthyroidism: Specify TSH	
Specify T4	
Pre – eclampsia [2]	
Acute respiratory failure [3]	
Seizures [4]	
Hypovolaemic shock – [5]	
ICU admission [6]	
Uterine perforation [7]	
Other [8]	
None [9]	
Pulmonary embolus [10]	

Diagnosis:

Measure	Result
Complete [1]	
Partial [2]	
Choriocarcinoma [3]	
PSTT [4]	
ETT [5]	
Blighted ovum [6]	

Miscarriage [7]	
Unknown [8]	
Hydatidiform mole undifferentiated [9]	
Ectopic [10]	

Initial evaluation:

Measure	Result
Initial HCG [mIU/mL]	
Day 1 post evacuation HCG [mIU/mL]	
CXR – Metastasis [Y/N]	1=Yes 2=No 3=Unknown
CT performed – [Y/N]:	1=Yes 2=No 3=Unknown
• If yes, indication for CT	1=Persistent trophoblastic disease

Management:

Measure	Result
Evacuation under ultrasound guidance [Y/N]	1=Yes 2=No 3=Unknown
Blood transfusion administered [Y/N]	1=Yes 2=No 3=Unknown
2nd evacuation required [Y/N]	1=Yes 2=No 3=Unknown
Need for hysterectomy [Y/N]	1=Yes 2=No 3=Unknown
• Indication for	

hysterectomy	
Contraception administered None [1], injectable [2], IUCD [3], Implanon [4], COC [5] and Other [6]	1= None 2=Injectable 3=IUCD 4=Implanon 5=Combined oral contraceptive pill 6=Condoms 7=Unknown 8=Patch

Maternal outcomes:

Measure	Result
Complete regression at four months [Y/N]	1=Yes 2=No 3=Unknown
Rise / plateau of HCG [Y/N]	1=Yes 2=No 3=Unknown
HCG at 4 weeks post evacuation	1= Negative 2= Positive 3=Unknown
HCG at 6 months post evacuation	1= Negative 2= Positive 3=Unknown
Chemotherapy [Y/N]	1= Yes 2= No 3=Unknown

Ultrasound findings:

Measure	Result
Agreement between initial ultrasound diagnosis with histological diagnosis – [Y/N]:	1= Yes 2= No 3=Unknown
• Complete mole [1]	

• Partial mole [2]	
• Unknown [3]	
• Not applicable [4]	
• Choriocarcinoma [5]	
Outcome	LTF=Loss to follow up DC= Discharge PTD= Persistent trophoblastic disease Transferred Recurrence Choriocarcinoma

APPENDIX 2: UCT HREC APPROVAL

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submisisons@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

11 March 2021

HREC REF: 067/2021

Dr N Mbatani
Department of Obstetrics & Gynaecology
H-Floor OMB
Email: nomonde.mbatani@uct.ac.za
Student: Drcam84@gmail.com

Dear Dr Mbatani

PROJECT TITLE: GESTATIONAL TROPHOBLASTIC DISEASE: A FIFTEEN - YEAR EXPERIENCE OF A SINGLE TERTIARY INSTITUTION-MMED CANDIDATE-Sedick Ahmed Camroodien

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 March 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Sedick A Camroodien will also be involved in this study.

Please quote the HREC REF 067/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

TBurgess

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

APPENDIX 3: UCT INSTITUTIONAL APPROVAL LETTER

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: GSHReserach.Request@westerncape.gov.za

Dr Nomonde Mbatani
OBSTETRIC & GYNAECOLOGY

E-mail: Nomonde.mbatani@uct.ac.za / drcam84@gmail.com

Dear Dr Mbatani,

RESEARCH PROJECT: Gestational Trophoblastic Disease: A Fifteen-Year Experience Of A Single Tertiary Institution (MMed. Dr Sedick Ahmed Camroodien)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 March 2022.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) Confidentiality must always be maintained.
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) Kindly submit a copy of the publication or report to this office on completion of the research.
n) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.
o) Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.

I would like to wish you every success with the project.

Yours sincerely

***p.p.* DR BERNADETTE EICK**
CHIEF OPERATIONAL OFFICER
Date: 30 April 2021

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APPENDIX 4: TURNITIN DECLARATION FORM D19

FORM D19

Plagiarism Declaration

"This thesis/dissertation has been submitted to the Turnitin module (or equivalent similarity and originality checking software) and I confirm that my supervisor has seen my report and any concerns revealed by such have been resolved with my supervisor."

Name: SEDICK AHMED CAMROODIEN

Student number: CMRSED001

Signature: 

Date: 13th July 2022