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M.B.B.S. (BENIN)

MAY 2015

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A DISSERTATION SUBMITTED TO THE NATIONAL POSTGRADUATE MEDICAL COLLEGE OF NIGERIA IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE FELLOWSHIP OF THE NATIONAL POSTGRADUATE MEDICAL COLLEGE OF NIGERIA, FACULTY OF PATHOLOGY (FMCPath)

MAY 2015
DECLARATION

I hereby declare that this dissertation is an original work done by me, DR OBAHIAGBON IKPONMWOSA, of the Department of Morbid Anatomy, University of Benin Teaching Hospital, and that it has neither been previously submitted to any other college or body for consideration, nor has it been sent to any journal for publication.

SIGN..............................................................

DATE............................................................
ATTESTATION

This is to certify that we supervised DR OBAHIAGBON, IKPONMWOSA of the Department of Morbid Anatomy, University of Benin Teaching Hospital, in the conduct of this study entitled:


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DEDICATION

To my better half and backbone, Anita, and to my sweet little angels, Nicole and Abigail

To my parents, Dr and Mrs F I Obahiagbon; my siblings, Uwa, Osarobo and Oyemwen, and to Chief Douglas Uso… you all lovingly played your part in making me.
ACKNOWLEDGEMENT

My deepest appreciation goes to God Almighty, my eternal benefactor, the giver of life and normal physiology. Words would fail me in appreciating his manifold blessings and mercies.

My sincere gratitude also goes to my able supervisors, Drs V J Ekanem and E E Ugiagbe, for their unwavering commitment to the progress of this work at every stage of its evolution. Much of its success is very much due to their guidance, constructive criticism and scrutiny, as well as close and prompt supervision.

I also wish to thank all the other Consultants in my department, Prof. J U Aligbe, Dr D E Obaseki, my very fatherly and supportive Head of Department, Dr (Mrs) A N Olu-Eddo, Dr W O Akhiwu, Dr G D Forae and Dr (Mrs) M O Udoh, for all their support and input in my training. I will not forget my fellow residents who have provided good company through this journey. The contribution of members of staff of our Histopathology Laboratory, especially Dr (Mrs) E E Adeyemi and Miss Precious, is also hereby acknowledged.

I sincerely appreciate the efforts of my assessors and members of staff of the Faculty of Pathology of the National Postgraduate Medical College of Nigeria for the prompt attention given to my proposal, which helped me save valuable time.

Finally, I must not fail to express my profound gratitude to Prof M O Ibadin, the Chief Medical Director of this hospital, for the opportunity given me to train here.
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ABSTRACT

**Background:** Gestational trophoblastic disease (GTD) is a spectrum of proliferative disorders of the placental trophoblast with a range of histological appearances and clinical behaviours. It is reported to be commoner in the developing countries. Although its aetiopathogenesis is as yet incompletely understood, it is well established that early detection and prompt treatment lead to the preservation of normal health and fertility.

**Aim and Objectives:** This study sought to determine the morphological pattern as well as the age and site distribution of the various forms of GTD histologically diagnosed in the University of Benin Teaching Hospital, Benin City, between January 2003 and December 2012. It is a hospital based, retrospective review utilizing materials from the archives of the Department of Morbid Anatomy, University of Benin Teaching Hospital. The parameters studied include the specific histological diagnoses, and the age and site distribution.

**Results:** A total of 103 cases of GTD were encountered over the ten year period. The age range was 18 – 62 years, and the mean age was 32 years. GTD was found here to be less common at the extremes of reproductive age, with the peak prevalence being in the third and fourth decades. Partial mole was commonest (52.4%), followed by choriocarcinoma (23.3%) and complete mole (22.3%). The ratio of partial to complete mole was 2.3:1, while the benign / malignant ratio was 3.3:1. The uterus was the site of GTD in 82.5% of cases, while 17.5% of cases were distributed among ectopic sites. There was failure to clinically or grossly identify molar vesicles in 75.9% of cases of hydatidiform mole; this highlights the relevance of histopathological examination of all products of both intrauterine and ectopic gestation.
**Conclusion:** The prevalence of GTD appears to have been rising in this environment in the recent years, though the pattern is largely unchanged for now. Malignant GTD (choriocarcinoma) however seems to be fairly common, as is ectopic GTD.

**Keywords:** Gestational trophoblastic disease, morphological pattern, Benin City.
CHAPTER 1

1.1 INTRODUCTION

Gestational trophoblastic disease (GTD) refers to a spectrum of proliferative disorders of the placental trophoblast, with a wide range of histological appearances and clinical behaviours.\(^1\) The World Health Organization (WHO) classification of gestational trophoblastic diseases\(^2,3\) includes hydatidiform mole (partial, complete, and invasive), tumours (gestational choriocarcinoma, placental site trophoblastic tumour and epithelioid trophoblastic tumour), tumour-like conditions, including exaggerated placental site, placental site nodule or plaque, and mixed or unclassified trophoblastic lesions.\(^4,5\)

The aetiology and pathogenesis are not well understood; however, GTD has been associated with ethnicity, extremes of reproductive age, prior molar pregnancy, lower socioeconomic class, and diet. Studying GTD should be of great interest because of its excellent prognosis if diagnosed early and treated promptly, especially as there is great potential for the preservation of both a healthy life and normal fertility.\(^6,7\)

GTD is reported to have the highest incidence in Africa and Asia and the lowest incidence in Western Europe and North America,\(^8\) and so it appears to be a problem of the less developed areas of the world. Results of studies done in Nigeria show that GTD is fairly common among Nigerian women of reproductive age, and the following figures quickly reveal the magnitude of the problem and provide statistical evidence as to why GTD should be so studied: 1 in 172 deliveries in Ibadan, 1 in 184 in Lagos, 1 in 357 in Jos,\(^9\) 1 in 166 in Gombe\(^10\) and 1 in 252 from a study carried out a few decades ago in Benin.\(^11\) Moreover, many of the studies were on hydatidiform mole rather than on the entire spectrum of GTD, raising the possibility that
although other forms of GTD may be less common, these reported incidences could have been even higher than reported had choriocarcinoma and the less common forms of GTD been included in the calculations.

Many of the earlier studies were done before there was as much awareness of the condition as there is today. As such, previous studies in these centres were done when the utilization of histopathology services was low, and many cases were missed in clinical services. This ten year review of the morphological pattern of GTD in the University of Benin Teaching Hospital was deemed necessary to demonstrate how increased utilization of histopathology services for confirmation of cases of suspected GTD, among other factors, may have impacted on the pattern of GTD in more recent years.

**Rationale for the Study**

Gestational trophoblastic disease (GTD) constitutes an important cause of maternal morbidity and raises the potential for increased maternal mortality. This study is of relevance to clinical practice in that early and proper clinicopathological diagnosis, appropriate histological classification, and prompt treatment and follow-up will offer great potential for cure and for the preservation of normal health and fertility.

With the increasing availability of histopathological services in recent times, clinicians seek histopathological confirmation for clinical suspicion of GTD more than in previous decades. This study was to highlight the impact (if any) that these and other factors might have had on the frequency and morphological pattern of GTD in our environment, and more so by comparing its findings with those of earlier studies in our environment.
1.2 AIM AND OBJECTIVES

1.2.1 Aim

This study sought to determine the morphological pattern of the various forms of gestational trophoblastic disease histologically diagnosed of specimens from endometrial curettage, hysterectomies and laparotomies, in the University of Benin Teaching Hospital, Benin City, between January 2003 and December 2012.

1.2.2 Objectives

1. To isolate cases of histologically diagnosed gestational trophoblastic lesions and classify them using the WHO histological classification of gestational trophoblastic disease.

2. To determine the age and site distribution of gestational trophoblastic disease in the University of Benin Teaching Hospital.

3. To compare and contrast the findings of this study with those of previous and related studies from elsewhere in Nigeria and other nations.

4. To highlight the impact that increased availability and utilization of histopathological services might have had on the frequency and morphological pattern of GTD in UBTH.
CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

Gestational trophoblastic disease (GTD) encompasses a heterogeneous group of lesions with unclear aetiopathogenesis, overlapping clinical features and fairly distinctive morphological characteristics. The World Health Organization classification of GTD includes complete and partial hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT), epithelioid trophoblastic tumour, exaggerated placental site, and placental site nodule. Some of these lesions are true neoplasms, whereas others represent abnormally formed placentas with a predisposition for neoplastic transformation of the trophoblast. Invasion is one of the distinct features of malignant disease, but healthy trophoblast can be detected by polymerase chain reaction in the maternal circulation.²,¹²

2.2 MORPHOLOGY OF NORMAL TROPHOBLASTIC CELLS

In normal placentation, the trophoblast associated with chorionic villi is called the villous trophoblast, whereas the trophoblast elsewhere is the extravillous trophoblast. Three distinct types of trophoblastic cells have been recognized: cytotrophoblast, syncytiotrophoblast, and intermediate trophoblast. Villous trophoblast is composed, for the most part, of cytotrophoblast and syncytiotrophoblast with small amounts of intermediate trophoblast. In contrast, extravillous trophoblast that infiltrates the decidua, myometrium, and spiral arteries of the placental site is composed of intermediate trophoblast.¹²,¹³
The functional unit of the placenta is made up of the trophoblastic villi that arise from the trophoectoderm following formation of the blastocyst. During the first trimester, they are composed of an outer syncytiotrophoblastic layer and an inner cytotrophoblastic layer, which surround a central mesenchymal core containing primitive fibroblasts, blood vessels and scattered macrophages (Hofbauer cells).13

The syncytiotrophoblast is the differentiated component of the trophoblast and is composed of multinucleated giant cells with abundant acidophilic or amphophilic, often vacuolated cytoplasm. Their nuclei may appear darkly staining and pyknotic and do not show mitotic activity. The cells are strongly immunoreactive for human chorionic gonadotropin (hCG), keratin, human placental lactogen (hPL; variably, and depending on the gestational age), placental-like alkaline phosphatase (PLAP), pregnancy-specific β1-glycoprotein (SP1), and inhibin.12,13 They are negative for epithelial membrane antigen (EMA), HNK1 (CD57), and CD146 (Mel-CAM).14

The cytotrophoblast (Langhans cells) is the germinative component of the trophoblast and normal cytotrophoblastic cells show mitotic activity. It is the progenitor of the syncytiotrophoblast, and is made up of uniform, smaller (compared to syncytiotrophoblastic cells), polygonal to oval mononuclear epithelial cells, with clear or granular cytoplasm and a well-defined cell membrane, which are negative for all of the above markers except keratin. In the term placenta, the cytotrophoblast is inconspicuous, and the syncytiotrophoblast is clumped in the form of ‘syncytial knots’.12,13

The intermediate trophoblast, also known as interstitial extravillous trophoblast or X cells is present in the villi and in the membranes but is particularly numerous in the extravillous region that forms the deepest structural component of the implantation site.13 It has morphological and
functional features including hormone secretion, that are “intermediate” between cytotrophoblast and syncytiotrophoblast. The most distinctive immunohistochemical property of these cells is a strong reactivity for hPL. They are also positive for keratin, CD66a (CEACAM1), CD146 (Mel-CAM, a marker for implantation site intermediate trophoblast), HNK1/CD57 (only in the villi), EMA (only in the chorion), and HLA-G (a non-classic major histocompatibility complex class I antigen).\textsuperscript{15} It has been proposed that there are three subpopulations of intermediate trophoblastic cells with distinctive morphologic and immunohistochemical features: implantation site type, chorionic type, and villous type.\textsuperscript{13} Villous trophoblasts show membranous pattern of E-cadherin staining and a mixed membranous and granular pattern of β-catenin distribution.\textsuperscript{16}

The villous vessels become apparent at 6 weeks. At about 8 weeks they contain only nucleated red blood cells, but by weeks 10–12 the percentage of nucleated cells drops to 10%, and after week 12 they are virtually absent.\textsuperscript{13}

\subsection*{2.3 EPIDEMIOLOGY OF GESTATIONAL TROPHOBLASTIC DISEASE}

There is indeed very great variation in the worldwide incidence of hydatidiform mole and choriocarcinoma, with higher incidence reported in the less developed regions of the world (Africa, Asia and Latin America) than in the developed world (North America, Western Europe and Australia). This wide disparity is partly accounted for by the variation in the methodology employed by the researchers and also by the fact that many of them have used hospital based rather than population based data, and so there may have been overreporting of cases. The consequence of these is that the incidence rates from different parts of the world become difficult to compare. There are hardly any epidemiologic data on incidence or geographic distribution.
reported for the more recently described placental site trophoblastic tumour and epithelioid trophoblastic tumour as most of the data in the literature are with regard to hydatidiform mole and choriocarcinoma. Despite the different incidence rates reported from various parts of the world, the overall incidence of gestational trophoblastic disease has been reported to have been on the decrease in recent years, especially in places from which higher incidence rates had previously been reported.\textsuperscript{17}

The frequency of hydatidiform mole in North America and Europe is approximately 100 per 100,000 pregnancies. The frequency is higher in many areas of Asia and the Middle East, with incidence rates ranging from 100 to 1,000 per 100,000 pregnancies.\textsuperscript{18} In Erbil city, North of Iraq, Kurdistan region, the incidence of GTDs was 1/318 pregnancies\textsuperscript{19} and 28 per 1000 live births in Hyderabad, Pakistan.\textsuperscript{20} In Singapore, the incidence of molar pregnancy was found to range between 1 in 1,601 and 1 in 721 deliveries.\textsuperscript{21} The national prevalence rate of hydatidiform mole in the Philippines was 2.4/1,000,\textsuperscript{22} while in Kuala Lumpur, Malaysia, the incidence rate of hydatidiform moles was estimated to be 1 in 384 pregnancies.\textsuperscript{23} In North Africa the reported incidence rates include 1 in 793 in Tunisia\textsuperscript{24} and about 4 in 1000 pregnancies in Morocco.\textsuperscript{25}

The frequency of hydatidiform mole in Nigeria also shows some variation according to reports from various parts of the country. In a study on pathomorphology of molar gestation in Zaria, the frequency of hydatidiform mole was 1 in 612 deliveries,\textsuperscript{26} a finding much at variance with a frequency of 1 in 166 deliveries reported from Gombe by Mayun.\textsuperscript{10} Elsewhere in northwestern Nigeria, Audu et al conducted a retrospective study on 71 patients who were managed for hydatidiform mole at the University of Maiduguri Teaching Hospital, (UMTH) Maiduguri over a 10-year period, and the institutional incidence of molar pregnancy was found to be 3.8/1,000
deliveries. In a retrospective review of all the cases of hydatidiform mole seen at the Jos University Teaching Hospital (JUTH), Jos, north central Nigeria, over a 5-year period, the incidence was observed to be 1 in 357 deliveries.

A ten-year retrospective review by Aligbe et al in Benin, south southern Nigeria, revealed an incidence of 1 in 252 deliveries compared to 1 in 623 deliveries reported from Calabar in the same geo-political zone. The incidence in south eastern Nigeria is notably lower than in other regions according to observations made in Enugu by Egwuatu and Ozumba in retrospectively analyzing cases of molar pregnancies over a ten year period and finding the incidence of hydatidiform mole to be 0.82 per 1000 pregnancies.

A ten year review of hydatidiform mole in Ile-Ife, western Nigeria, revealed an incidence of 2.4 per thousand deliveries, which was less than 4.9 per thousand reported previously for that environment. In a review of 208 cases of hydatidiform mole managed at the University College Hospital Ibadan, western Nigeria, between January 1966 and December 1996, the institutional frequency for partial mole was 1 per 667 deliveries, while that of complete mole was 1 per 655 deliveries.

Ocheke et al have suggested that the reason for this geographical variation is the fact that these are hospital-based studies in tertiary referral centres in environments with varying degrees of hospital utilization.

Choriocarcinoma occurs with a frequency of 1 in 20,000 to 1 in 40,000 pregnancies in the United States and Europe. Estimates for the incidence in Asia, Africa, and Latin America generally are higher with incidence rates of 1 in 500 to 1,000 pregnancies reported. As with molar disease,
there are marked regional variations in incidence rates. Results from a study in an institution in Nigeria revealed that choriocarcinoma was the third most common malignant tumour in women, ranking behind breast and cervical carcinoma. Thus, methodological problems notwithstanding, choriocarcinoma appears to occur significantly more frequently in developing countries than in Europe and North America. As with hydatidiform mole, the overall incidence of choriocarcinoma has dramatically decreased in recent years as socioeconomic conditions improve. These observations suggest that low socioeconomic conditions or dietary factors may contribute to the development of GTD. Asbestos exposure has recently been reported to be associated with the development of GTD.

Gestational trophoblastic lesions are nearly always disorders of the reproductive years, although in rare cases, GTD can develop in a postmenopausal woman with a long interval between the diagnosis of GTD and the antecedent pregnancy. Women who are sexually active are at risk for developing GTD, but the incidence is substantially higher in women before 20 and after 40 years. The absolute number of cases of mole or choriocarcinoma in women over 40 years is smaller owing to their lower fertility. In contrast, maternal age has no effect on the risk of partial mole. Neither paternal age nor race seems to affect the risk of developing a hydatidiform mole. Malignant sequelae for hydatidiform mole occur more frequently in older patients. While hydatidiform mole, choriocarcinoma, exaggerated placental site, and placental site nodule are nearly always confined to reproductive age women, placental site trophoblastic tumour and epithelioid trophoblastic tumour occur infrequently in postmenopausal women.

Aligbe et al reported the incidence of GTD in Benin to be higher in the second and third decades of life, a finding comparable to that of Mayun, who observed that molar gestation was a
common gynaecological problem in Gombe affecting women mainly in their third decade of life. These support the fact that GTD is essentially a problem of the reproductive age group.

Extremes of reproductive age appear to raise the risk of molar gestation. Egwuatu and Ozumba reported that the incidence of molar pregnancy in Enugu was lowest among teenage women and increased markedly with advancing age over 35 years; but studies in Uganda and Pakistan revealed that ages less than 20 years, just as well as more than 35 years were associated with an elevated risk of complete hydatidiform mole. This latter finding can be corroborated by the findings from a study in Morocco in which the relative risk of complete mole observed, was much increased among women under 20 years old (×6.8) and those over 40 years old (×15). Furthermore, in a study in Iran, there were 28 (18.9%) patients over the age of 40, of which 18 (15.90%) of these had a complete hydatidiform mole. Within this group, 9 (6.8%) changed to a persistent mole. There was a significant relationship between age over 40 and complete mole (p<0.02).

Reports from Abu Dhabi, The United Arab Emirates (UAE), revealed that the age specific incidence of complete mole was minimal between the ages of 30 and 34 years (relative risk 1), showed a minor peak in teenagers (relative risk 3.1, 95% confidence interval 6.5-1.4), and a major peak in those of 35 years and over. Between 35 and 39 years the relative risk was 2.5 (95% CI 6.2-1.0) and at 40 years or more the relative risk was 9.8 (95% CI 28.9-3.3). No age group showed a significantly increased risk of partial mole.

Several studies reveal that a history of prior spontaneous abortions is more common in patients with hydatidiform mole and choriocarcinoma than with a normal pregnancy. In a study in
western Nigeria, as much as 26.1% of the cases studied had had a previous spontaneous abortion. Furthermore, women who have had one hydatidiform mole are at increased risk of having another, with the risk appearing to be higher for those who had had more molar pregnancies. In a Ugandan study of 94 cases, 10(10.7%) women had the antecedent pregnancy as molar, while 16(17.0%) and 4(4.3%) had at least 1 and 2 molar pregnancies respectively, and 19 (20.2%) had unspecified spontaneous abortions prior, some of which could have been molar. In a study in Pakistan, the antecedent pregnancy was hydatidiform mole in 63.3% patients, abortion in 30% and full term pregnancy in 6.6% patients.

Term pregnancy and live births seem to have a protective effect, with GTD reported in many studies as being less common in patients who are parous. The protective effect appears to increase with an increased number of live births. In a study in Tunisia, molar pregnancies were found to be more frequent in pauciparous patients; however, studies in Calabar and Hyderabad, Pakistan, associated multiparity and grandmultiparity respectively with an increased risk of GTD.

Socio-demographic factors as socio-economic status, ethnicity or race are also reported to influence the risk and incidence of GTD. Egwuatu and Ozumba observed that molar pregnancy and postmolar malignant trophoblastic disease occurred much less frequently among the Igbo women of Enugu than the Yorubas of western Nigeria. In a retrospective study on the incidence and time trends of gestational trophoblastic disease over an eleven year period in Riyadh, Saudi Arabia, the temporal trends exhibited significant reduction in the incidence of GTD during the study period. This study concluded that the
incidence of GTD had declined with the rapid socio-medical development of the Kingdom of Saudi Arabia, and is now comparable to that of Europe.\textsuperscript{39}

A hospital based study of benign gestational trophoblastic disease was undertaken in eight hospitals in Karachi, Pakistan. The frequency of the disease was found to be 3.89/1000 pregnancies and was found to be higher - 1 in 237 deliveries - in the economically deprived women admitted to a free government hospital, compared to only 1 in 471 deliveries in a private, fee-for-service hospital.\textsuperscript{34}

A study in the Philippines associates GTD with indigence.\textsuperscript{22} In a retrospective histopathological study of hydatidiform molar pregnancy among Malaysian women in Kuala Lumpur, Malaysia, it appeared that hydatidiform molar pregnancy had the highest prevalence among the Indians, a finding similar to an earlier Singapore study.\textsuperscript{23}

Some studies have suggested certain blood groups as additional risk factors for gestational trophoblastic disease. Blood group A has been suggested as a significant risk factor for GTD.\textsuperscript{34} In a ten year retrospective cross-sectional study conducted at Imam Khomeini Hospital in Ahvaz, Iran, the percentage of patients with blood groups A and O was the same (37.9\%), and there was a significant relationship between blood groups (O\textsuperscript{+} and A\textsuperscript{+}) and complete mole (p<0.05).\textsuperscript{35} A study in the United Kingdom revealed an increased risk of molar pregnancy in women with blood group B.\textsuperscript{40}

Oral contraceptives have also been implicated as a risk factor for GTD. Prolonged oral contraceptive use has been associated with an increased risk of gestational choriocarcinoma in a study conducted in the western United States. The findings from that study raise the hypothesis that long-term oral contraceptive use, or a correlate of use such as exposure to sexually transmitted infections, increases the risk of one or more of the manifestations of gestational
Large studies in the United States and China suggest that a long duration of oral contraceptive use before conception does, indeed, increase the risk of gestational trophoblastic tumours.42

2.4 CYTOGENETICS

The commonest genetic constitution in a complete mole is diploid 46XX, resulting from fertilization of an anucleate ovum by a single 23X sperm which subsequently duplicates (homozygous). Occasionally fertilization occurs with two spermatozoa and an anucleate ovum, resulting in the 46XY configuration (heterozygous). Partial moles are most commonly triploid, with two paternal and one maternal set of chromosomes (diandric triploidy). This results from fertilization of an apparently normal ovum by two spermatozoa. The maternal genetic contribution, in contrast to a complete mole, is not lost and is retained, karyotype is 69 XXY.43

Most well documented partial moles are (diandric) triploids, but not all triploid conceptuses are associated with partial moles, as it is believed that digynic triploids generally do not present as molar pregnancy.12

Genetic analyses of choriocarcinomas reveal them to be mostly diploid, with aneuploidy being a poor prognostic factor. The cases preceded by complete mole have been demonstrated to be of diandric (androgenetic) origin.44

The cytogenetics of GTD other than hydatidiform mole and choriocarcinoma, such as placental site trophoblastic tumour and epithelioid trophoblastic tumour, has not been as well studied because of their relative rarity. However, new techniques such as fluorescence in situ hybridization (FISH), interphase cytogenetics, and polymorphism of oligonucleotide repeat sequences (microsatellites) can be performed on formalin fixed, paraffin embedded (FFPE)
tissue. Although the majority of GTD are diagnosable based on morphology alone, the application of these newer techniques may become more and more important in diagnosis and management of GTD. Microsatellite markers that differ in maternal or paternal origins have been used to confirm a complete mole. Both FISH using chromosome-specific markers and polymerase chain reaction using polymorphic markers have been employed to assist in differentiating a hydropic abortus from a partial mole, and a partial mole from a complete mole.\textsuperscript{12}

To assess the accuracy of histological diagnosis by correlating with the genetic composition, researchers at the University of Hong Kong performed fluorescent microsatellite genotyping to detect the presence or absence of maternal genome in a hydatidiform mole and carried out chromosome \textit{in situ} hybridization to analyze the ploidy. For genotyping analysis, paraffin sections of 36 complete and nine partial moles, diagnosed according to histological criteria, were microdissected and DNA was separately extracted from the decidua and molar villi. Six pairs of primers that flank polymorphic microsatellite repeat sequences on five different chromosomes were used. The genotyping results correlated with histological evaluation in 88\% (37/45) of hydatidiform mole and correlated with chromosome \textit{in situ} hybridization findings in all the cases. Compared with genetic diagnosis, histological evaluation was more reliable for the diagnosis of a complete mole (91\%, 31/34) than that of a partial mole (55\%, 6/11) \((P=0.0033)\). Genotyping and chromosome \textit{in situ} hybridization can provide reliable adjunct to histology for the classification of a hydatidiform mole, especially in cases with difficult histological evaluation and early gestational age.\textsuperscript{45}

To assess the degree of difficulty in diagnosing partial mole among a group of Australian histopathologists by analyzing intraobserver and interobserver agreement for these diagnoses,
fifty mixed cases of partial mole, complete mole, and non-molar pregnancy were submitted to seven histopathologists, two of whom were expert gynaecological pathologists; the other five were district general hospital consultants. Each firmly diagnosed the slides as partial mole, complete mole, or non-molar pregnancy. After a year, the slides were submitted for a second diagnostic round to assess intraobserver as well as interobserver agreement. Kappa statistics showed that complete mole could be reliably distinguished from non-molar pregnancy, but neither non-molar pregnancy nor complete mole could be easily differentiated from partial mole. In only 35 out of 50 cases was there agreement between five or more of the seven participants. Agreement between the expert gynaecological pathologists was no better than for others in the group. Interestingly, the intraobserver agreement for each pathologist was good to excellent.46 These results implied that the reported histological criteria were either not being applied consistently or that they were lacking in practical use. An atypical growth pattern of trophoblast, rather than the polar accentuation seen in normal first trimester pregnancies, seems to be the important diagnostic histological feature for partial mole.46 Quantitatively imprecise morphologic criteria contribute to the inaccuracy in the reporting of partial mole; analysis of ploidy is useful in the evaluation of problem cases.47 Diagnosis of hydatidiform mole by histology and ploidy analysis is limited by overlap of criteria for nonmolar hydropic abortion, complete mole, and partial mole. With early presentation, diagnosis is difficult due to limited tissue and lack of clinical features. Accurate diagnosis of these entities is important for both prognosis and patient management. A study in Pennsylvania, United States of America, assessing a polymerase chain reaction (PCR) assay for polymorphic short tandem repeats (STR) for discrimination between nonmolar hydropic abortion, complete
mole, and partial mole based on the genetic composition of molar pregnancies, concluded that molecular genetic testing of products of conception from paraffin-embedded tissue accurately distinguishes complete mole, partial mole, and nonmolar hydropic abortion. Identification of triploidy by flow cytometry can confirm a histological impression of partial mole. Histological and ploidy analysis alone of products of conception results in underdiagnosis of complete moles.\textsuperscript{48}

One American study demonstrates that even with morphologic assessment by gynaecologic pathologists and p57 immunohistochemistry, 20\% to 30\% of cases will be misclassified, and, in particular, distinction of PHMs and nonmolar gestations will remain problematic.\textsuperscript{49}

Although p57 immunostaining alone can identify CHMs, which lack p57 expression because of the lack of maternal DNA, this analysis cannot distinguish PHMs from nonmolar specimens as both express p57 because of the presence of maternal DNA. Short tandem repeat genotyping, which can determine the parental source of polymorphic alleles, can distinguish among all of these entities by discerning androgenetic diploidy, diandric triploidy, and biparental diploidy to rigorously diagnose CHMs, PHMs, and nonmolar specimens, respectively. An algorithmic approach using these techniques to refine morphologic diagnosis has been developed for routine practice.\textsuperscript{50}

A study in Vienna, Austria, aimed to evaluate the hypothesis that the presence of c-erbB-2 oncogene amplification and expression, in combination with parameters such as DNA-content and karyotype of the sex chromosomes, confer an increased risk of developing persistent GTD. From the findings of the study, it was concluded that c-erbB-2 amplification and/or protein expression in combination with DNA-content show a significant correlation with the
proliferative and aggressive potential of GTD. Therefore, their combined use as a possible marker for persistent GTD\textsuperscript{51} has been suggested.

2.5 PATHOGENESIS OF GESTATIONAL TROPHOBLASTIC DISEASE

The pathogenesis of GTD is largely unclear.\textsuperscript{52} The most well-studied gestational trophoblastic lesion is hydatidiform mole and, to a lesser extent, choriocarcinoma.\textsuperscript{53} Development of a hydatidiform mole appears to be associated with an excess of paternal haploid set of chromosomes. The higher the ratio of paternal/maternal chromosomes, the greater the molar change. Complete moles show a 2:0 paternal/maternal ratio, whereas partial moles show a 2:1 ratio.

There are at least three distinctive types of gestational trophoblastic neoplasia (GTN) including the most common type, choriocarcinoma, and the less common ones, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour. Molecular analysis on GTN is largely based on the identification and characterization of trophoblastic markers in various types of GTN, and the reference of their unique gene expression patterns to different trophoblastic subpopulations in normal early placentas.\textsuperscript{53}

Upon neoplastic transformation of trophoblastic stem cells (presumably the cytotrophoblast), specific differentiation programmes determine which trophoblastic tumour develops. GTN differentiates along patterns that recapitulate the stages of normal early development of the placenta. For example, choriocarcinoma is composed of variable amounts of neoplastic cytotrophoblast, syncytiotrophoblast, and intermediate (extravillous) trophoblast, and resembles the previllous blastocyst (recall that chorionic villi are not found in choriocarcinomas, or any of the GTN), which comprises a similar mixture of trophoblastic subpopulations. On the other hand,
the neoplastic cytotrophoblast in PSTT differentiates mainly into intermediate (extravillous) trophoblastic cells in an implantation site, whereas the neoplastic cytotrophoblast in epithelioid trophoblastic tumour differentiates into chorionic-type intermediate (extravillous) trophoblastic cells in chorion laeve. According to this model therefore, choriocarcinoma becomes the most primitive trophoblastic tumour, whereas PSTT and epithelioid trophoblastic tumour are relatively more differentiated. In addition, it explains the histologic mixture of choriocarcinoma and PSTT and/or epithelioid trophoblastic tumour in some GTNs.12

2.6 HYDATIDIFORM MOLE

A hydatidiform mole is an abnormal placenta characterized by enlarged, oedematous, and vesicular chorionic villi accompanied by villous trophoblastic hyperplasia. It is subdivided into complete hydatidiform mole and partial hydatidiform mole based on morphologic, cytogenetic and clinicopathological features, with morphologic features alone being sufficient for such subdivision as far as typical cases are concerned. However, the classical features of complete and partial moles that in the past were based on histological examination of specimens obtained in the second trimester are not as apparent nowadays, making the histopathologic diagnosis more difficult, because the routine use of ultrasound in pregnancy has led to the clinical diagnosis and evacuation of moles much earlier in gestation, often in the first trimester.44 In addition, a variety of other genetic abnormalities such as trisomy and monosomy may be associated with abnormal placentas that display minor degrees of hydropic change and trophoblastic proliferation but are not moles.

Recently proposed expanded criteria for the histologic diagnosis of hydatidiform mole are rather subtle and not easily reproducible and consequently, the histologic diagnosis of hydatidiform
mole remains somewhat subjective, with much tendency for interobserver and even intraobserver variability. Ancillary diagnostic techniques such as genetic analysis are expensive and not readily available in most histopathology laboratories.\textsuperscript{54,55}

The ratio of complete to partial mole varies among studies,\textsuperscript{8,10,11,27} but most researchers have found complete mole to be commoner than partial mole. Although there are clinicopathologic and cytogenetic differences between both forms, any molar gestation carries some risk of progression to malignant GTD, though the risk is higher for complete than partial mole.\textsuperscript{12,54,55}

\subsection*{2.6.1 COMPLETE HYDATIDIFORM MOLE}

Complete hydatidiform mole is characterized by hydropic swelling of the majority of villi, and a variable degree of trophoblastic proliferation and atypia. Most complete hydatidiform moles have a 46XX karyotype. Early complete moles may not show hydropic swelling but trophoblastic proliferation and atypia are present.\textsuperscript{44} In typical complete moles, massively enlarged, oedematous villi confer the characteristic grape-like, vesicular appearance to the placenta. Owing to earlier gestational age at sonographic diagnosis nowadays, the specimen volume of contemporary complete moles is much less than previously. In advanced mole, which is now rarely encountered, swollen villi may range from a few millimeters to as large as 3.0 cm in diameter but usually average about 1.5 cm. Rarely, foetal development may occur in complete mole. Following suction curettage, molar villi may collapse and a large amount of haemorrhagic tissue may mask the oedematous villi, especially if a mole is extracted early in pregnancy, before villous enlargement becomes evident. As such, there may be no gross evidence of molar enlargement.\textsuperscript{12}
Some of the hydropic villi of complete mole are surrounded by an attenuated layer of degenerating trophoblast. In others, the trophoblast forms large hyperplastic sheets of cells. The distended core of the villus is traversed by widely separated, broken strands of fibrillar material (‘cistern’ formation). Blood vessels seem absent or very scanty in haematoxylin-eosin-stained sections, but do not seem much diminished in number in CD34-stained preparations. The stromal changes of molar villi, including stromal mucin and stromal nuclear debris (apoptosis), appear very early and represent a diagnostic clue. The trophoblastic hyperplasia characteristically has a circumferential but haphazard arrangement around the individual villi, in contrast to the polar proliferation seen in normal first-trimester villi. The plexiform pattern of intermixed syncytiotrophoblast and cytotrophoblast seen in choriocarcinoma does not occur.\textsuperscript{13}

The histologic features of an early complete mole are: (1) redundant or polypoid bulbous terminal villi; (2) hypercellular villous stroma with primitive stellate cells; (3) a labyrinthine network of villous stromal canaliculi; (4) focal hyperplasia of cytotrophoblast and syncytiotrophoblast on both villi and the undersurface of the chorionic plate; (5) atypical trophoblast lining the villi and in the implantation site;\textsuperscript{56} and (6) increased villous stromal apoptosis.\textsuperscript{57}

The implantation sites associated with a complete hydatidiform mole very often show a morphological feature akin to that of an exaggerated placental site. As with the trophoblastic hyperplasia on the villous surface, the cells are more abundant and atypical than what is encountered with an abortus and even an exaggerated placental site. Compared to normal placentas, complete moles show a higher level of apoptosis in cytotrophoblast, thus suggesting a complex but delicate regulation of the cell population in complete moles.\textsuperscript{12}
2.6.2 PARTIAL HYDATIDIFORM MOLE

Approximately 15–35% of all moles are of the partial type. In contrast to complete mole, the condition is often associated with the presence of an embryo or foetus (with congenital anomalies) or its amnion.\textsuperscript{12} The volume of placental tissue is relatively normal, and the grossly vesicular villi are mixed with normal-appearing ones. The former often show focal oedema leading to central ‘cistern’ formation and stromal inclusions of trophoblast. More villi than in the complete mole have an irregular, scalloped outline and contain blood vessels with foetal (nucleated) red blood cells. Fibrosis of the villous stroma is common. Trophoblastic proliferation is present, although generally to a lesser degree than in complete mole, and cytoplasmic vacuolization of the syncytiotrophoblast is prominent.\textsuperscript{13}

A partial mole is optimally diagnosed when the following four microscopic features are present: (1) two populations of villi (one hydropic and one small and fibrotic), (2) enlarged villi with central cavitation,(3) irregular villi with geographic, scalloped borders with trophoblast inclusions, and (4) minimal trophoblast hyperplasia(usually focal and involving syncytiotrophoblast).\textsuperscript{58}

2.6.3 DIFFERENTIAL DIAGNOSIS OF HYDATIDIFORM MOLE

Diagnosis of hydatidiform moles by histology can be complicated by overlap of morphological criteria for complete mole, partial mole, and a nonmolar hydropic abortus. Complete mole is often readily distinguishable morphologically from partial mole, but diagnostic challenges may arise with early complete mole. Evidence of a foetus or embryo including villous erythrocytes strongly favours the diagnosis of partial mole,\textsuperscript{12,13} bearing in mind the rare possibility of a twin
gestation with one conceptus being a complete mole. It may be difficult to morphologically distinguish a hydatidiform mole from an abortus with abnormal villous morphology, and there is a considerable degree of interobserver variability in making this distinction. The villous trophoblast in spontaneous abortions either is attenuated or, if proliferating, has a polar distribution. Furthermore, trophoblastic atypia is absent or minimal.\textsuperscript{13}

Placentas with genetic abnormalities other than triploidy such as trisomy, can display morphologic changes suggestive of partial mole and can be misinterpreted as such by morphologic diagnosis alone. Helpful clues will include that spontaneous abortions often are associated with failure of development or early demise of the embryo, the so-called blighted ovum or hydropic abortus. These specimens show some villous oedema with hydropic swelling, just like molar placentas. The hydropic abortus usually is a smaller specimen, however. The villi in a hydropic abortus are enlarged only slightly and do not assume the large dimensions found in complete or partial moles. Cisterns can be seen in nonmolar abortions but they are focally distributed. Hyperplasia of villous trophoblast is absent in these cases.\textsuperscript{59}

The trophoblast proliferating from the villous surface of an abortus shows polar distribution characterized by proliferation of trophoblast at the distal end of the villus that implants into the basal plate. Similarly, villi with trophoblastic islands can be regarded as polarized villi that are also associated with a nonmolar abortus. This directional orientation contrasts with the irregular or circumferential proliferation of molar trophoblast. Irregular trophoblastic hyperplasia from the villous surface is an especially critical feature for diagnosing molar pregnancy.\textsuperscript{12}

Chorionic villi associated with chromosomal abnormalities that are not triploid, such as trisomy,
may display hydropic change and abnormal villous morphology that mimic a partial mole. These abnormal placentas associated with hydropic abortus are not associated with an increased risk of GTD and therefore the differential diagnosis is clinically important. A logistic approach in differential diagnosis of specimens with abnormal villous morphology has been proposed. In that study, it is recommended that morphologically abnormal villi should be assessed for p57 immunostaining, which serves as a triage assay for the diagnosis of complete hydatidiform moles. When the diagnosis by routine morphology is equivocal, morphologic features together with a negative p57 result indicate a complete hydatidiform mole with a rare exception that the complete hydatidiform mole retains the maternal allele of chromosome 11 in which the p57 gene resides. Molecular genotyping is then applied to validate a diagnosis of complete hydatidiform mole by demonstrating androgenetic diploidy and to resolve p57-positive cases into diandric triploid partial hydatidiform mole, biparental diploid nonmolar specimens, and the rare complete hydatidiform mole with aberrant p57 expression.

Since complete and partial mole are characterized by distinctive molecular genetic features, ploidy analysis has proven valuable in distinguishing a diploid complete mole from a triploid partial mole and diploid hydropic abortus from a triploid partial mole. Flow cytometry and digital imaging systems are frequently employed to analyze ploidy; however, ploidy assays cannot be used to diagnose hydatidiform moles per se or to distinguish a diploid complete mole from a diploid hydropic abortus. Recently, the multiplex short tandem repeats (microsatellite markers) DNA analysis has gained wide acceptance in genotyping products of conception with abnormal villous morphology.

When histologic sections reveal large aggregates of atypical or proliferating trophoblast without any villi, then malignant GTD such as choriocarcinoma or placental site trophoblastic tumour
ought to be suspected. The pathologist must ensure that sampling is adequate because villi in the specimen may have been sparse and fragmented. Even complete mole can have limited villi in the sections if much of the tissue has been spontaneously aborted or if dealing with repeated curettage following primary evacuation; in such situations therefore, the entire specimen should be processed. Limited examination of a uterine, vaginal, or pulmonary lesion may show only trophoblast, but deeper sectioning may reveal molar villi.\textsuperscript{12}

### 2.7 INVASIVE AND METASTATIC MOLE

Also called chorioadenoma destruens, the term invasive mole refers to a hydatidiform mole (nearly always of the complete type but occasionally of the partial type) in which villi penetrate deeply the myometrium and/or its blood vessels.\textsuperscript{63} It occurs in 16\% of all complete moles, and represents an exaggerated expression of the capacity of normal trophoblast for invasion, a necessary property for implantation. The myometrial permeation in invasive mole may be extensive and may lead to persistent haemorrhage, but the serosa is usually intact. However, uterine perforation may occur. The vascular invasion may result in trophoblastic nodules in sites outside the uterus, such as the vagina, lung, brain and spinal cord (metastatic mole). Invasive/metastatic mole is distinguished from the usual mole by invasiveness and from choriocarcinoma by the presence of villi, which are also present in the ‘metastatic’ foci. The degree of trophoblastic proliferation in invasive mole does not differ significantly from that of its ordinary counterpart.\textsuperscript{13}

### 2.8 CHORIOCARCINOMA

Choriocarcinoma is highly malignant and is the most aggressive form of GTD. Most cases occur following a complete hydatidiform mole, making it more common in high prevalence areas for
hydatidiform mole. It has been estimated that 1–2% of complete moles are followed by choriocarcinoma. It could also occur following a partial mole (this is very rare), ectopic pregnancy, nonmolar intrauterine abortion, or term pregnancy. In the latter instance, which is exceptionally rare, the tumour may appear as one or more masses in an otherwise normal placenta or develop following the delivery. In addition, cases of ‘in-situ’ choriocarcinoma arising from the trophoblast of stem villi in the first trimester of pregnancy have been described.

Choriocarcinoma has gross features that characteristically include being soft, dark red, haemorrhagic, round and nodular tumour masses. Histologically, the tumour comprises clusters of cytotrophoblast separated by streaming masses of syncytiotrophoblast, imparting a characteristic dimorphic plexiform or biphasic pattern. Haemorrhage and necrosis, though usually present, are of no real diagnostic significance, being also commonly found in spontaneous abortions. The absence of villi is also characteristic and their presence is said to rule out the diagnosis of choriocarcinoma regardless of the degree of atypia of the trophoblastic cells. The rationale for this criterion would seem difficult to explain: since choriocarcinoma arises from complete mole, there should be a point in time at which both molar and choriocarcinomatous tissue is simultaneously present. Yet, there is no question that it represents a useful parameter at the practical level.

Immunohistochemically, choriocarcinoma cells are positive for hCG and keratin. There may also be reactivity for hPL, SP1, and CEA. There can be a minor component of intermediate trophoblastic cells immunoreactive for hPL, CD146 (Mel-CAM), HLA-G, and inhibin.

The natural history of untreated choriocarcinoma is characterized by the development of early haematogenous metastases, the most common sites being the lung, brain, liver, kidney, and
They can be clinically solitary, may occur in the most unusual places, and often present with massive haemorrhage. Interestingly, the foetus is rarely involved, even in cases of widespread metastatic disease. Residual tumour in the uterus of patients dying of disseminated choriocarcinoma may be inconspicuous or altogether absent.

Many of the morphologic changes seen in other organs in patients with choriocarcinoma can be accounted for by the increased secretion of hCG and other hormones by the tumour cells. These include hyperplasia of endocervical glands, decidual reaction (both endometrial and ectopic), Arias-Stella phenomenon, bilateral enlargement of the ovaries by theca-lutein cysts (‘hyperreactio luteinalis’), and hyperplasia of mammary lobules. The detection of ovarian theca-lutein cysts long after a case of choriocarcinoma has been treated is usually a sign of persistent disease. In the endometrial decidual reaction of patients with choriocarcinoma, the spiral arterioles fail to develop as they do in the normal cycle, the appearance of the mucosa being similar to that seen after the administration of progestogens.

2.9 PLACENTAL SITE TROPHOBLASTIC TUMOUR

A rare form of GTD that used to be called atypical choriocarcinoma and trophoblastic pseudotumour. Around 75% of cases are preceded by a normal pregnancy, and only 5% by a molar pregnancy. It seems to stem from the trophoectoderm of the female conceptum as a paternally derived X chromosome and the absence of a Y chromosome appear necessary for its formation.

Grossly, PSTT is either a well localized or an ill-defined myometrial mass. Compared to invasive mole or choriocarcinoma, haemorrhage is not as conspicuous. It may result in deep myometrial penetration, spontaneous uterine perforation or perforation following curettage. Microscopically,
large trophoblastic cells with abundant eosinophilic cytoplasm and nuclear pleomorphism are seen invading the myometrium and vessel lumina. The cells have morphologic, ultrastructural and immunohistochemical features which match those of implantation site intermediate trophoblast, the subtype of intermediate trophoblastic cells that invade the endometrium and myometrium of the placental site in early pregnancy.\textsuperscript{12}

There is strong and diffuse immunoreactivity for hPL, whereas that for hCG tends to be focal.\textsuperscript{73} There is also positivity for keratin, CD66a (CEACAM1), CD146 (Mel-CAM), pregnancy-associated major basic protein, HLA-G and inhibin.\textsuperscript{74} The DNA pattern, by flow cytometry, is usually diploid,\textsuperscript{75} both in its benign and rare malignant forms. The MIB-1 (Ki-67) labeling index is higher than in exaggerated placental site reaction but lower than in choriocarcinoma.\textsuperscript{76}

The differential diagnosis of placental site trophoblastic tumour includes other gestational trophoblastic diseases, as well as non-neoplastic placental proliferations of intermediate trophoblast. PSTT differs from choriocarcinoma for lack of a dimorphic population of cytotrophoblast and syncytiotrophoblast (although scattered multinucleated cells may be present), lack or paucity of haemorrhage, and the presence of an interdigitating pattern of muscle invasion.\textsuperscript{13}

\textbf{2.10 EPITHELIOID TROPHOBLASTIC TUMOUR}

This relatively recently described form of GTD was originally described as a peculiar change in the metastatic foci of choriocarcinoma surgically excised following chemotherapy,\textsuperscript{77} but is now known to also occur \textit{de novo}. The primary tumour usually occurs in the endomyometrium, but can occasionally be located in the uterine cervix,\textsuperscript{78} develop outside the uterus in places such as
the broad ligament, or even present as a primary lung tumour, simulating microscopically squamous and pleomorphic carcinomas of this organ. hCG levels are usually elevated.

Grossly, it is solid and cystic, discrete, and haemorrhagic. Microscopically, it comprises of a relatively uniform population of intermediate trophoblastic cells disposed in nests and solid aggregates. There is extensive necrosis and a hyaline matrix with a geographic configuration. The overall microscopic picture is reminiscent of a carcinoma. Immunohistochemically, there is diffuse reactivity for keratin, α-inhibin, EMA, p63, HLA-G, and E-cadherin, but only focal reactivity for hPL, hCG, PLAP, and CD146 (Mel-CAM). Shih et al believe that the tumour is composed of chorion laeve-type intermediate trophoblast. It behaves as a malignant tumour, with metastases to the lungs and other sites.

2.11 EXAGGERATED PLACENTAL SITE REACTION

Was formerly misnamed syncytial endometritis, but this lesion is not primarily inflammatory and is devoid of syncytiotrophoblast but is rather believed to be the result of excessive but otherwise normal infiltration of the implantation site by intermediate trophoblast. Owing to shared cytologic and immunohistochemical features with placental site trophoblastic tumour, both might be difficult to differentiate. Exaggerated placental site reaction is the likelier diagnosis when the lesion is microscopic in size, lacks mitotic activity, contains a hyaline material between the trophoblastic cells, and is admixed with decidua and villi.

2.12 PLACENTAL SITE NODULE AND PLAQUE

These appear as single or multiple, mostly well-circumscribed, variably cellular round or flat lesions (nodules and plaques, respectively) that tend to be extensively hyalinized. Most of the individual cells have abundant amphophilic or acidophilic cytoplasm, irregularly shaped nuclei,
and very scanty mitotic activity, but the others have a glycogen-rich clear cytoplasm. Mallory bodies (representing abnormal cytoplasmic aggregates of keratin filaments) may be present. Placental site nodules and plaques, can also occur in the cervix, fallopian tube, and other sites, and can be differentiated from placental site trophoblastic tumour by their smaller size, better circumscription, extensive hyalinization, degenerative appearance, and paucity of mitotic activity. Shih and Kurman et al have pointed out that placental site nodules and plaques closely resemble the intermediate trophoblast of the chorion laeve rather than that at the implantation site, hence they are diffusely positive for PLAP but only focally positive or negative for hPL and CD146 (Mel-CAM).\textsuperscript{5}
CHAPTER 3

MATERIALS AND METHODS

Data regarding specimens diagnosed as GTD following endometrial curettage for incomplete abortion, as well as records of any invasive, extrauterine or metastatic GTD diagnosed in the Morbid Anatomy Department of the University of Benin Teaching Hospital (UBTH), between January 2003 and December 2012, were the materials for this study.

These were specimens received from the Department of Obstetrics and Gynaecology, UBTH, other hospitals within the Benin City metropolis and within Edo State, as well as from neighbouring states. The tissues were fixed in 10% formal saline and representative blocks were taken for processing, staining and slide production.

Data including age, nature of specimen, and preoperative diagnosis were retrieved from the departmental surgical day books for the years under review. Slides were retrieved from the archives and the paraffin blocks corresponding to the recorded histology numbers were retrieved for fresh slide preparation where necessary. All slides were stained with haematoxylin and eosin (H&E).

Study Design

This was a descriptive cross-sectional study.

Study Area

The study was done in the Department of Morbid Anatomy, UBTH. This hospital is the major tertiary care hospital and referral centre in the Benin metropolis, having well established obstetric, gynaecological and histopathology departments, and serving as catchment centre to neighbouring states.
**Diagnosis and Classification**

Diagnosis and classification was according to the 2008 World Health Organization (WHO) recommendation.²

**Data Analysis**

The data was analyzed using the statistical package for social sciences (SPSS, V.16.0), with representative tables.

**Exclusion Criteria**

(1) Cases of missing records, slides and paraffin blocks

(2) Cases that did not fulfill the diagnostic criteria for GTD upon review

**Challenges and Limitations**

This study would have been enhanced by the inclusion of advanced investigative techniques such as fluorescent *in situ* hybridization (FISH), chromogenic *in situ* hybridization (CISH), flow cytometry and ploidy analysis in the diagnosis and classification of the entities under GTD. However, there were limitations posed by the fact that facilities for these modalities are not available in our environment. There were also the constraints of time, cost and distance if these services were to be sourced from another center. The desire to include these in the nearest future however remains uppermost in the mind of the author.

**Ethical Clearance**

Ethical clearance was obtained and evidence of approval attached herewith.
CHAPTER 4
RESULTS

4.1 GENERAL FINDINGS

During the ten-year period spanning from 2003 – 2012, a total of 24,274 surgical specimens were received and diagnosed in the Department of Histopathology, University of Benin Teaching Hospital. Of these, 103 (0.42%) cases diagnosed as entities under gestational trophoblastic disease (GTD) were included in the study. Cases of both benign and malignant forms of GTD were observed, but there were a few entities not reflected in the study because no such cases were found during the period under review.

4.2 AGE DISTRIBUTION

The ages of the patients ranged from 18 – 62 years. The mean age was 32 years, the median age was 31 years and the modal age was 28 years. As shown in table I, the peak age of GTD was found to be the 20 – 29 year age group, with 44 cases accounting for 42.72%, very closely followed by the 30 – 39 year age group with 43 cases (41.75%). As also depicted in table I, two of the three major diagnostic entities of GTD in this study, namely, complete mole and choriocarcinoma, had their peak ages at 20 – 29 years, closely followed by 30 – 39 years. Partial mole however had its peak in the 30 – 39 year age group, followed by the 20 – 29 year age group. The extremes of reproductive age had much fewer cases: the 15 – 19, 50 – 59 and 60 – 69 year age groups had only one (0.97%), two (1.94%) and one (0.97%) case respectively.
4.3 SPECIMENS RECEIVED

As depicted in table II, majority of the specimens were sent and received as products of conception (56 cases; 54.4%) and endometrial tissue (16 cases; 15.5%). Hysterectomy specimens accounted for 12.6% of cases. The remainder of the specimens received were mainly from the fallopian tubes. A point to note is the fact that of the 79 cases of hydatidiform mole diagnosed, molar vesicles were detected by ultrasonography or clinical observation of the endometrial tissue or products of conception in only 19 cases (24.1%).

4.4 SITE DISTRIBUTION

The uterus was the major site for GTD as evidenced by 85 cases (82.5%), followed distantly by the fallopian tubes with 15 cases (14.6%). The right fallopian tube was more commonly affected than the left, with 11 (10.7%) and four (3.9%) cases respectively. Occasional cases were found elsewhere, that is, in the right ovary, cervix and vagina, each of which had one case. These findings are displayed in table III.

4.5 DIAGNOSES

BENIGN GTD

4.5.1 HYDATIDIFORM MOLE

Partial mole was the commonest form of GTD encountered, accounting for 54 cases (52.4%), followed by complete mole (23 cases; 22.3%), as shown in table I. The ratio of partial to complete mole was 2.3:1. Two cases (1.9%) of invasive mole were found.
4.5.1.1 Partial Mole

There were 54 cases of partial mole. The ages of the patients ranged from 23 – 62 years. The mean age was 32.4 years, the median age was 32 years and modal age was 34 years. As shown in table I, the peak age of partial mole was found to be the 30 – 39 year age group, with 27 cases (50.0%), closely followed by the 20 – 29 year age group, with 21 cases (38.9%). Partial mole was found much less frequently at the extremes of reproductive age.

The site distribution for partial mole (table III) was such that 41 (75.9%) of the 54 cases occurred in the uterus, while 13 (24.1%) occurred in ectopic sites, namely the fallopian tubes. The right and left fallopian tubes had nine (16.7%) and three (5.6%) cases respectively.

4.5.1.2 Complete Mole

There were 23 cases of complete mole. The ages of the patients ranged from 20 – 47 years. The mean age was 32.4 years, the median age was 32 years and the modal age was 24 years. As demonstrated in table I, the peak age of complete mole was found to be the 20 – 29 year age group with 10 cases (43.5%), closely followed by the 30 – 39 year age group with eight cases (34.8%). The 40 – 49 year age group had five cases (21.7%). Of note is the fact that no cases occurred before 20 years or after 47 years of age.

As can be seen clearly from table III, the uterus was the site for 22 (95.7%) out of the 23 cases of complete mole. Only one case occurred at an ectopic site (right fallopian tube).

4.5.1.3 Invasive Mole

Two cases of invasive mole were found, both of them in women aged 28 years. One of them was an invasive complete mole of the uterus while the other was an invasive partial mole of the right fallopian tube (depicted in Fig. 4).
MALIGNANT GTD

Most cases of GTD were of the benign variety, as outlined in table I, and all the cases of benign GTD were hydatidiform moles, with partial, complete and invasive mole together making up 79 cases (76.7% of GTD). The remaining 24 cases (23.3%) were malignant (choriocarcinoma). The ratio of benign to malignant GTD was 3.3:1.

4.5.2 CHORIOCARCINOMA

There were 24 cases of choriocarcinoma. The ages of the patients ranged from 18 – 56 years. The mean age was 33.1 years, the median age was 32 years and the modal age was 28 years. As shown in table I, the peak age of choriocarcinoma was in the 20 – 29 year age group with 11 cases (45.8%), followed by the 30 – 39 year age group with eight cases (33.3%). Three cases were found in the 40 – 49 year age group, and only one case each was found before the age of 20 and after the age of 49 years.

Table III shows the site distribution for choriocarcinoma. One of the 24 cases was first diagnosed in the cervix and another one in the vagina. There was a single case of an ectopic (left tubal) gestational choriocarcinoma.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>0-19</th>
<th>20-29</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>Total (%)</th>
</tr>
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<tr>
<td><strong>Benign: n = 79 (76.7%)</strong></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Partial mole</td>
<td>0</td>
<td>21</td>
<td>27</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>54 (52.4)</td>
</tr>
<tr>
<td>Complete mole</td>
<td>0</td>
<td>10</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>23 (22.3)</td>
</tr>
<tr>
<td>Invasive mole</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td><strong>Malignant: n = 24 (23.3%)</strong></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>1</td>
<td>11</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>24 (23.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1</td>
<td>44</td>
<td>43</td>
<td>12</td>
<td>2</td>
<td>1</td>
<td>103 (100.0)</td>
</tr>
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</table>
Table II: Frequency distribution of the various types of specimens received

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<tr>
<th></th>
<th>Frequency</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products of conception</td>
<td>56</td>
<td>54.4</td>
</tr>
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<td>Uterus</td>
<td>13</td>
<td>12.6</td>
</tr>
<tr>
<td>Left fallopian tube</td>
<td>4</td>
<td>3.9</td>
</tr>
<tr>
<td>Right fallopian tube</td>
<td>10</td>
<td>9.7</td>
</tr>
<tr>
<td>Endometrial tissue</td>
<td>16</td>
<td>15.5</td>
</tr>
<tr>
<td>Unspecified</td>
<td>4</td>
<td>3.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>103</strong></td>
<td><strong>100.0</strong></td>
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</tbody>
</table>
### Table III: Site distribution of GTD

<table>
<thead>
<tr>
<th>Site</th>
<th>Partial Mole</th>
<th>Complete Mole</th>
<th>Invasive mole</th>
<th>Chorio Mole</th>
<th>Frequency</th>
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</thead>
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<tr>
<td>Uterus</td>
<td>41</td>
<td>22</td>
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<td>21</td>
<td>85</td>
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<td>Cervix</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vagina</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Right fallopian tube</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Left fallopian tube</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Right ovary</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>54</strong></td>
<td><strong>23</strong></td>
<td><strong>2</strong></td>
<td><strong>24</strong></td>
<td><strong>103</strong></td>
</tr>
</tbody>
</table>

**Key to abbreviations:**

**GTD** – Gestational Trophoblastic Disease

**Chorio** – Choriocarcinoma
Fig. 1: Partial mole showing hydropic distention of some chorionic villi. Also present are smaller, fibrotic villi (*H & E X 40*).
Fig. 2: Complete mole showing moderate oedematous distention of nearly all the chorionic villi. There is obvious circumferential trophoblastic proliferation as indicated by the arrows (H & E X 40).
Fig. 3: Complete mole showing marked hydropic distention of chorionic villi. The stroma of the villi show marked cistern formation (H & E X 40).
Fig. 4: Invasive mole of the fallopian tube. There is a mass of molar chorionic villi and proliferating trophoblastic cells deep within the wall of the tube. The endosalpinx is shown on the left (H & E X 40).
Fig. 5: Choriocarcinoma, a biphasic malignant neoplasm composed of proliferating atypical trophoblastic cells, namely, cytotrophoblasts (thin arrow) and syncytiotrophoblasts (thick arrow), on a background of extensive haemorrhagic necrosis. No chorionic villi were seen (H & E X 100).
CHAPTER 5
DISCUSSION

5.1 GENERAL

Globally, there is variation in the pattern of GTD from one geographical region to another,\textsuperscript{37} and even within the same region, race or ethnic group. The overall incidence of gestational trophoblastic disease has been reported to have been on the decrease in recent years, especially in places from which higher incidence rates had previously been reported.\textsuperscript{17} The same however cannot be said about many developing areas of the world, such as our study area, where the increased utilization of histopathology services in recent years might have created the impression of a rising incidence. Furthermore, the plurality of tertiary care hospital based studies rather than population based studies is another factor to consider in this regard.

This review included 103 cases of GTD over a ten-year period. An earlier ten-year study here in Benin\textsuperscript{11} had revealed 48 cases of GTD. It becomes obvious therefore from the foregoing that although GTD still contributes less than 0.5\% of the total histological diagnoses of specimens received in this centre, its incidence appears to have been on the increase in recent years. This finding may be attributable to increasing awareness and utilization of histopathology services in this region rather than an actual rise in the incidence of GTD. One indicator of increased utilization of histopathological services in the more recent years is the steady rise in the number of specimens received in the UBTH Histopathology Laboratory from 862 in 1993, to 1236 in 2003, and to 3625 in 2012.
5.2 AGE DISTRIBUTION

It is well known that gestational trophoblastic lesions are nearly always a disorder of the reproductive years, although in rare cases, GTD can develop in a postmenopausal woman with a long interval between the diagnosis of GTD and the antecedent pregnancy. Women who are sexually active are at risk of developing GTD. While hydatidiform mole, choriocarcinoma, exaggerated placental site, and placental site nodule are nearly always confined to reproductive age women, placental site trophoblastic tumour and epithelioid trophoblastic tumour occur infrequently in postmenopausal women. Not surprisingly therefore, most of the cases of GTD are clustered in the reproductive age group as evidenced by the age distribution in this study. The age range observed for this study was 18 – 62 years. The age range reported in Nnewi, southeastern Nigeria seems somewhat narrower at 15 – 46 years as does 16 – 51 years reported in the Kurdistan region of Iraq. There is not much difference however in the age range observed in this study, especially with the observation that only three out of the 103 cases occurred after the age of 49 years. Taking these away, the age range for GTD in this study would be narrowed to 18 – 49 years.

The age range for hydatidiform mole in this study was 20 – 62 years; slightly narrower than this are 18 – 52 years and 15 – 49 years reported by Eniola et al and Mayun et al respectively. The age range for complete mole here was 20 – 47 years, comparable to 14 – 52 years observed by Kaye et al in a Ugandan study, and 16 – 55 years by Boufettal et al in Morocco. The age range for partial mole in this review was 23 – 62 years, a range broader than 17 – 43 years reported by Chong et al in Singapore.

The mean age for GTD in this study was 32 years, close to a mean of 31 years reported by Mbamara et al, but higher than 28.5 and 27.97 years reported by Moodley et al and Al Alaf et
The mean ages for partial and complete mole were similar, being 32.4 and 32.4 years respectively. This figure is similar to 31.8 years reported as the mean age for hydatidiform mole in Ile-ife,\textsuperscript{8} somewhat higher than 28 years reported in Ibadan\textsuperscript{30} and Jos,\textsuperscript{9} but much higher than 25.7 and 25 years reported in Zaria\textsuperscript{26} and Morocco\textsuperscript{25} respectively. The mean age of 32.4 years observed for complete mole in this study is higher than 29.6 years reported in Uganda\textsuperscript{33} and much higher than 26 years reported in Syria.\textsuperscript{43} These variations among age ranges and mean ages might probably be accounted for by geographical, environmental and racial factors. For instance, it has been reported in studies from the United States and China that prolonged oral contraceptive use raises the risk of GTD.\textsuperscript{41,42} Other studies that report GTD to be more common with pauciparity lend credence to this.\textsuperscript{31,37} Furthermore, the frequency of hydatidiform mole is higher in many areas of Asia and the Middle East than in Europe and North America,\textsuperscript{18} and among the female residents of a multiracial society like Kuala Lumpur, Malaysia, it is commonest in the Indians.\textsuperscript{23}

Some studies in various parts of the world have revealed GTD to be commoner at the extremes of reproductive age; for example, studies in Ile-ife,\textsuperscript{8} Uganda,\textsuperscript{33} Pakistan,\textsuperscript{20} and Hawaii,\textsuperscript{38} Egwuatu and Ozumba\textsuperscript{29} reported that the incidence of molar pregnancy in Enugu was lowest among teenage women and increased markedly with advancing age over 35 years; but studies in Uganda and Pakistan revealed that ages less than 20 years, just as well as more than 35 years were associated with an elevated risk of complete hydatidiform mole.\textsuperscript{33,34} This latter finding can be corroborated by the findings from a study in Morocco in which the relative risk of complete mole observed, was much increased among women under 20 years old (×6.8) and those over 40 years old (×15).\textsuperscript{25} Al Alaf\textsuperscript{19} reported the incidence of GTD to be substantially higher before 20 years and after 40 years, while an American study revealed that malignant sequelae of hydatidiform
mole tend to occur more frequently in older women. Nevertheless, the results of this study suggest that GTD in all its common forms is commonest at the peak of reproductive life: the peak age of GTD was found to be the 20 – 29 year age group, with 44 cases accounting for 42.72%, very closely followed by the 30 – 39 year age group with 43 cases (41.75%), meaning that GTD was found to be commonest in the third and fourth decades of life, with 84.47% of the cases occurring between ages 20 and 39, and only 15.53% of the cases occurring at the extremes of reproductive age. This is corroborated by the findings from an Iraqi study in which 62% of the cases were in the age group 20 – 39 years, and those of a South African study that found only 20% of sufferers of GTD to be over 35 years.

5.3 SPECIMENS RECEIVED

Majority of the specimens received in the laboratory were labeled products of conception (54.4%), endometrial tissue/curettage (15.5%), and uterus (12.6%), and these proportions vary widely with 30%, 8.9% and 3.6% respectively, reported in a study in Zaria. The variation with the study in Zaria is probably due to non-inclusion of choriocarcinoma. That same study on hydatidiform mole reveals that there was failure to clinically or grossly identify molar vesicles in 45% of cases of histologically diagnosed hydatidiform mole; the corresponding figure in this study was much higher at 75.9%, while an earlier study in Benin had reported 64.4%. Despite these variations, it is clear that histopathological examination of products of conception is a necessity, otherwise, many cases of GTD will be missed or have delayed diagnoses.

5.4 SITE DISTRIBUTION

GTD can arise primarily from any possible site of conception or implantation, although the uterus is quite understandably the commonest site of occurrence. In this review, although the uterus was expectedly by far the commonest site of occurrence for all forms of GTD, accounting
for 85 (82.5%) of the total of 103 cases, the frequency of ectopic GTD is noteworthy: there were 15 cases (14.6%) of GTD occurring in the fallopian tubes. Eleven (10.7%) and four (3.9%) cases of GTD were found in the right and left fallopian tubes respectively. Adding these to the other less common sites of ectopic GTD, the total number of cases of ectopic GTD was 18 (17.5%). It would however appear from the existing literature that GTD arising from ectopic sites is rather uncommon, much less common than the current study suggests: for example, a study in Gombe\textsuperscript{10} revealed no case of ectopic mole, while another in Zaria\textsuperscript{26} revealed just one case of an ectopic mole. Most of the literature reviewed is silent as to the question of ectopic GTD.

### 5.5 Diagnoses

In general, the overall management of GTD is interdisciplinary, with the pathologist playing a crucial and sensitive role. In most cases, exact histopathological diagnosis of the trophoblastic lesion remains the gold standard for guiding clinical therapy. Although there are now advanced ancillary diagnostic techniques (mostly in developed areas of the globe) to serve as adjuncts to refine the traditional morphology–based diagnoses, currently, there are no reliable immunohistochemical, genetic or molecular biologic markers for predicting aggressive behavior for hydatidiform mole.\textsuperscript{85}

With the dearth of advanced ancillary diagnostic techniques in resource-poor areas, it is imperative that pathologists practicing in such centres continue to keep abreast of the morphological diagnostic criteria for the various forms of GTD. In this study, the diagnosis and classification of GTD was done according to the current World Health Organization (2008) classification (see appendix). Partial mole was the commonest manifestation of GTD in this review, accounting for 52.4% of all cases. This compares favourably with the findings of a study by Aligbe et al.,\textsuperscript{11} in which partial mole was the commonest lesion, contributing 47.9% of all
cases of GTD. A study in Damascus, Syria, even revealed partial mole to constitute 60% of GTD, the significance of this being that partial mole is less likely to progress to choriocarcinoma than complete mole. On the contrary, Al Alaf et al reported complete mole to be the commonest form of GTD, accounting for as high as 82.5%, while partial mole made up only 10%. Also, Horn and Bilek reported complete mole as the commonest manifestation of GTD with 69.6%. These variations may be contributed to by non-uniformity in the morphologic diagnostic criteria for partial and complete mole, especially as advanced ancillary diagnostic modalities for fine-tuning the morphologic diagnoses, such as genetic analysis, are expensive and not readily available in most histopathology laboratories.

Choriocarcinoma constituted 24 cases (23.3%) of GTD in this study, and was the second commonest form. A German study found 32 cases of choriocarcinoma accounting for 20.25% (second commonest form of GTD). Curiously however, a study in Nnewi reported choriocarcinoma to be the most prevalent form of GTD, accounting for as high as 66.7% of cases, and hydatidiform mole 33.3%. Furthermore, a study in Zaria revealed choriocarcinoma to be the commonest form of GTD, making up 37% of the 99 cases seen. Possible reasons for such may be late presentation at a time when benign GTD had already evolved into malignant neoplasia, although choriocarcinoma does also arise sequel to antecedent normal pregnancy, in which case genetic, ethnic, and geographical, as well as other yet poorly understood risk factors may be more important.

The least common forms of GTD seem to be the rare malignant lesions like the placental site trophoblastic tumour and epithelioid trophoblastic tumour, the benign placental site nodule and exaggerated placental site reaction, and the invasive mole. In this review, two cases (1.9%) of invasive mole were identified. In favourable comparison, studies in Zaria and Malaysia found
two cases (2.0%) and one case (2.6%) of invasive mole respectively; but in contrast, a study in Pakistan\textsuperscript{20} found seven cases (23.3%) out of 30 cases of GTD studied, while another in Germany\textsuperscript{85} revealed 13 (8.2%) out of 158 cases of GTD. Studies on hydatidiform mole in Gombe\textsuperscript{10} and Maiduguri\textsuperscript{27} report no cases of invasive mole. Studies on both benign and malignant GTD by Mbamara\textsuperscript{7} et al and Nizam\textsuperscript{20} et al reveal no cases of placental site trophoblastic tumour, but Horn and Bilek report in a German\textsuperscript{85} study one case (0.6%) of placental site trophoblastic tumour, and two cases (1.3%) of placental site nodule (none found in this study).

As to whether or not partial mole occurs more commonly than complete mole, there are a number of studies on either side of the divide, and some others seemingly on the fence. The finding of 54 cases of partial mole and 23 cases of complete mole in this study puts the ratio of partial to complete mole at about 2.3:1. Similar ratios of 2.2:1 and 2:1 are reported in Hawaii\textsuperscript{38} and Tunis\textsuperscript{37} respectively, and less comparable ratios of 2.8:1, 1.5:1 and 1.5:1 are reported in Ireland\textsuperscript{47}, Syria\textsuperscript{43} and Calabar\textsuperscript{28} respectively. Unlike in this and other studies where there are a lot more partial than complete moles, still other studies reveal, to varying degrees, more complete than partial moles. The complete to partial mole ratio is reported as 4.1:1 in Ile-ife,\textsuperscript{8} 1.7:1 in Zaria\textsuperscript{26} and 10.3:1 in Hong Kong.\textsuperscript{45} Two Nigerian studies in Ibadan\textsuperscript{30} and Gombe\textsuperscript{10} reveal almost equal numbers of complete and partial moles, with ratios close to 1:1.

Most cases in this review were benign, giving a benign / malignant ratio of 3.3:1. This ratio is quite comparable to 3.8:1 reported in Germany,\textsuperscript{85} but is higher in comparison to 2:1 in Zaria,\textsuperscript{26} and 2.3:1 in South Africa,\textsuperscript{84} and is much higher than 1:2 reported in Nnewi,\textsuperscript{7} where most of the lesions were malignant. The ratio of benign to malignant GTD is as high as 12:1 and 14:1 in Northern Iraq\textsuperscript{19} and Pakistan\textsuperscript{20} respectively, where relatively few cases of malignant GTD were reported.
In conclusion, GTD continues to be an important spectrum of diseases affecting women of mainly the reproductive age, especially in developing countries like Nigeria, with a significant propensity to develop from benign to malignant disease, as reflected in the number of instances of malignant disease (choriocarcinoma was the second commonest form of GTD in this study). Although GTD is reported to have become less of a health problem in recent years in advanced countries, the same cannot be said of developing areas like our environment, where the prevalence appears to have been rising in recent years, though the overall pattern is largely unchanged for now. The rising prevalence may be partly attributable to the relatively increased availability and utilization of histopathological services in recent years in this environment. A point to note however is that cases of GTD arising in ectopic primary sites seem to be appearing with increasing frequency.

5.6 RECOMMENDATIONS

(1) Histological examination of all products of both intrauterine and ectopic gestation continues to be essential for confirmation of diagnosis. Further studies to refine the morphologic diagnoses can be carried out using ancillary investigations, including immunohistochemistry, cytogenetic analysis and molecular studies. These will help to further improve the quality of patient care.

(2) There is also the need for population based studies on GTD with a view to determining the correct incidence and prevalence.
REFERENCES


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86. Lurain JR. Gestational trophoblastic disease II: classification and management of gestational trophoblastic neoplasia. AJOG. 2011; 204: 11-18.
APPENDIX I

WORLD HEALTH ORGANISATION (WHO) 2008 CLASSIFICATION OF GESTATIONAL TROPHOBLASTIC DISEASE²

Complete hydatidiform mole (CHM)
Partial hydatidiform mole (PHM)
Invasive hydatidiform mole (IHM)
Gestational choriocarcinoma (CC)
Placental site trophoblastic nodule (PSN)
Exaggerated placental site (EPS)
Placental-site trophoblastic tumour (PSTT)
Epithelioid trophoblastic tumour (ETT)
Mixed or unclassified trophoblastic lesions
APPENDIX II

INTERNATIONAL FEDERATION OF GYNAECOLOGY AND OBSTETRICS (FIGO)
COMBINED ANATOMIC STAGING AND MODIFIED WHO RISK-FACTOR
SCORING SYSTEM FOR GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN)86

STAGING FOR GTN

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<th>Stage</th>
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<tbody>
<tr>
<td>I</td>
<td>Disease confined to uterus</td>
</tr>
<tr>
<td>II</td>
<td>Disease extends outside uterus but limited to genital structures (adnexa,</td>
</tr>
<tr>
<td></td>
<td>vagina, broad ligament)</td>
</tr>
<tr>
<td>III</td>
<td>Disease extends to lungs with or without genital tract involvement</td>
</tr>
<tr>
<td>IV</td>
<td>Disease involves other metastatic sites</td>
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SCORING SYSTEM FOR GTN

<table>
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<tr>
<td>Antecedent pregnancy</td>
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<tr>
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<tr>
<td>Pretreatment hCG, mIU/mL</td>
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<tr>
<td>Largest tumor mass, including uterus, cm</td>
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</tr>
<tr>
<td>Site of metastases</td>
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</tr>
<tr>
<td>No. of metastases</td>
<td>–</td>
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<tr>
<td>Previous failed chemotherapy</td>
<td>–</td>
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</tbody>
</table>

KEY: GI, gastrointestinal; hCG, human chorionic gonadotropin. **Total score for patient is obtained by adding individual scores for each prognostic factor: low risk <7; high risk ≥7.**