University of Khartoum
Graduate College
Medical & Health Studies Board

Gestational Trophoblastic Disease in Sudanese Women
A clinicopathologic Study

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MBBS Elzaem Elazhari University 2002

A thesis submitted in partial fulfillment for the requirements of the Degree of
Clinical MD in Pathology

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2012
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MD Pathology
DECLARATION

Hereby I declare that this thesis entitled (GESTATIONAL TROPHOBLASTIC DISEASE ACLINICO PATHOLOGICAL STUDY) is carried out by me and under supervision of Dr. Nadia EL-Dawi, for partial fulfillment of the requirement for MD in clinical pathology from Khartoum University. This thesis is not being submitted elsewhere.
DEDICATION:

TO

MY PARENTS,

MY WIFE,

MY CHILDREN AND

MY BROTHER TARIG
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ACKNOWLEDGEMENT

I sincerely thank Dr. Nadia El Dawi for her valuable advices, continuous support and knowledge during this study.

I am highly grateful to Dr. Mohammed Mohammed Osman for his advices and guidance and knowledge imparted to me during this work.

Lastly I thank all my colleagues for their help and unconditional support during this study.
**LIST OF ABBREVIATION**

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<td>1.</td>
<td>AJCC</td>
<td>American join committee of cancer</td>
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<td>2.</td>
<td>CD</td>
<td>Cluster of differentiation</td>
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<td>3.</td>
<td>EMA</td>
<td>Epithelial membrane antigen</td>
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<td>4.</td>
<td>CHM</td>
<td>Complete hydatidiform mole</td>
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<td>FIGO</td>
<td>The federation of gynecology and obstetrics</td>
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<td>GTD</td>
<td>Gestational trophoblastic diseases</td>
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<td>GTN</td>
<td>Gestational trophoblastic neoplasia</td>
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<td>8.</td>
<td>GTT</td>
<td>Gestational trophoblastic tumor</td>
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<td>HCG</td>
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<td>HFM</td>
<td>Hydatidiform mole</td>
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<td>11.</td>
<td>HPL</td>
<td>Human placental lactogen</td>
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<td>12.</td>
<td>MEL-CAM(CD 146)</td>
<td>Melanoma cell adhesion molecule</td>
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<td>13.</td>
<td>NIH</td>
<td>National institute of health</td>
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<td>14.</td>
<td>PLAP</td>
<td>Placental acid phosphatase</td>
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<td>15.</td>
<td>PSTT</td>
<td>Placental site trophoblastic tumor</td>
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<td>WHO</td>
<td>World health organization</td>
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Abstracts

**Background:** Gestational trophoblastic diseases are characterized by an abnormal trophoblasts proliferation.

Epidemiologically, trophoblastic diseases occur with much greatest frequency in the Far East and other parts of the third world than in the Western Hemisphere. The diseases are seen in the teenage and premenopausal age groups.

The objective of this study was to report on cases of gestational trophoblastic diseases received in the department of histopathology at National Health Lab in Khartoum state, its pattern, mode of presentation and histopathological features.

**Methods:** This is a descriptive retrospective study. The slides were retrieved from archives and reviewed by the researcher with the supervisor. The slides were prepared from tissues fixed in 10% formalin and handled according to histological protocol. A hundred and nine cases were included after exclusion of cases with deficient records or missed histopathology slides and blocks. Clinical information was gathered from the records including the age, parity, type of specimen. The data were analyzed using computer program (SPSS).

**Results:** The mean age of patients was 31.5 years, 38% of cases occurred in the age group (20-29 years) followed by 31% in the age group (30-39 years). Twenty percent of cases occurred in ladies above 40 years and 11% below 20 years. Multiparous were the most affected group (52%) followed by grand multipara (31%) .Primigravidae were the least affected (17%). Pure vaginal
bleeding was the main presentation in 51% and in 5% of cases it was associated with passage of vesicles and in 1% with abdominal pain. In 10% of cases the diagnosis was made during routine U/S follow up. In 32% of cases there was a previous history of abortion.

Microscopically partial mole was the dominant lesion (65%), followed by complete mole 28%, choriocarcinoma 4% and invasive mole 3%. Cases of placental site trophoblastic tumors, placental site nodules, epithelioid trophoblastic tumors were not encountered in this study.

**Conclusion:** Gestational trophoblastic disease mostly affects multipara in the second and third decades of life. Microscopy partial mole was the most common lesion (65%). Vaginal bleeding was the main presentation and abortion was a risk factor.
المستخلص

الخلفية:
مرض الأرومة الغذائية هو مجموعة من الأمراض تنشأ نتيجة للنمو والتتكاثر غير الطبيعي لخلايا التروفوبلاست.

تعتبر أمراض الأرومة الغذائية كثيرة الانتشار في الشرق الأقصى وأجزاء من العالم الثالث مقارنة بأوروبا والدول الغربية كما تعتبر أكثر شيوعا في النساء دون العشرين وفترة ما قبل سن اليأس.

الهدف الرئيسي من هذا البحث هو دراسة حالات أمراض الأرومة الغذائية بالعمل القومي في ولاية الخرطوم، انواعه، كيفية حدوثه وانواعه المجهرية

الوسائل:
هذا البحث هو دراسة توصيفيه لحالات سابقة وقد تم إجراؤها في شعبة الأنسجة المريضة بالعمل القومي على الشرائح المتواجدة والتي تم جمعها من الأرشيف ومراجعة الباحث لها مع المشرف. تم تحضير هذه الشرائح بعد حفظها في مادة الفورمالين بتركيز 10%. تم جمع منة وتسعة شريحة بعد استبعاد العينات غير مكتملة المعلومات أو غير متوفرة الشرائح. تم جمع المعلومات الطبية من السجلات التي يحتوي على العمر، عدد مرات الحمل السابق، نوعية العينة والفحص المجهرى.

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النتائج:

في هذه الدراسة وجدنا أن متوسط الأعمار التي يحدث فيها مرض الأرومة الغاذية هو 31.5 سنة كما وجد أن 38% من الحالات في الفئة العمرية مابين (20-29 سنة).

يبلغ 31% في الفئة العمرية بين (30-39 سنة) أيداً أثبتت الدراسة أن 20% في الفئة العمرية أعلى من 40 سنة وان 11% في مادون 20 سنة. في هذا البحث كذلك وجدنا أن أمراض الأرومة الغازية اكتر انتشاراً في النساء متدفقات الولادات 52% يليهم كثرة الولادة جداً 31% ثم يليهم البكريات 17% وقد كانت معظم الحالات مصحوبة بنزيف مهلي فقط 51%. في 5% من الحالات كان مصحوباً بخروج حوضي، في 1% كان مصحوباً بالام في الولادة 10% من الحالات تم تشخيصها عن طريق الموجات الصوتية أثناء المتابعة الدورية. في 32% من الحالات كانت مصحوبة بأمراض.

وأظهرت الدراسة المجهريه في هذا البحث شيوخ الحمل الوربي الجنين 65% يليه الحمل الوربي المكتمل 28% ثم التحولات السرطانية 4% ثم أخيراً الحمل الوربي المنتشر 3%.

الخلاصه: مرض الأرومة الغاذية مرض كثير الانتشار في النساء متددات الولادات وكذلك في العقد الثاني من العمر. يعتبر الإجهاض عامل خطره. نسبة شيوخ هذا المرض لايمكن تحديها اعتماً على هذه الدراسة نسبة لإجرائها في معهد واحد.
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INTRODUCTION & LITERATURE REVIEW

1-1-INTRODUCTION:

Gestational trophoblastic diseases are a group of lesions ranging from benign to frankly malignant. All of them are derived from trophoblasts\(^1\), which are cells forming the outer layer of a blastocyst.\(^2\) They provide nutrients to the embryo and develop into a large part of the placenta.

Historically these lesions were known since 400 BC when Hippocrates described the first lesion and called it dropsy of the uterus. While in AD 600 Aetius of Armida described a uterus “filled with bladderlike objects,” which probably also represented this process. In 1827 Velpeau and Boivin first recognized hydatids as cystic dilations of chorionic villi. Sanger, in 1889, coined the term sarcoma uteri deciduocellulare as a malignant tumor derived from the decidua of pregnancy.
In 1895, Marchand demonstrated these tumors to be the sequelae of pregnancy, abortion, or hydatidiform mole and described the proliferation of the syncytium and cytotrophoblast. In 1903, Teacher confirmed Marchand's work and negated Sanger's theory of sarcomatous degeneration of the decidua.\(^{(3)}\)

In 1927 a breakthrough in the understanding of GTD happened by the recognition of human chorionic gonadotropin, which is highly elevated in these conditions and is produced by cytotrophoblasts\(^{(4)}\), and it was used later in follow up of patients, monitoring of treatment and detection of relapse. Nowadays ultrasonography has an important role in the diagnosis of GTD. These lesions are extremely sensitive to chemotherapy\(^{(5)}\) and folic acid antagonists.

**1-2- DEVELOPMENT OF TROPHOBLASTICS**

Normally trophoblastic cells exist in two sites, either in association with chorionic villi and, this is villous trophoblast, or outside the villi and, this is extra villous trophoblast.
1-2-1-Development of villous trophoblastic cells:
Embryologically villous trophoblastic cells developed in 3 stages:
Prelacunar, lacunar and early villous stages
1-Prelacunar stage:
It is defined as the period from conception to day 8. After fertilization of the ovum the zygote develops into a blastocyst which is a flattened vesicle made up of about $10^7$-256 cells. The cells of the outer wall which surround the blastocystic cavity are the trophoblast while the inner cell mass on the inner surface is a small group of large cells forming the embryoblast.

The first step in implantation of the blastocyst is called apposition, in which the blastocyst is oriented, and the embryonic pole attaches to the endometrium and thus forms the implantation pole. This step occurs on day 6-7.

In the following days, the trophoblastic cells proliferate forming double layers that progressively invade the endometrial epithelium. The inner layer of the trophoblast is composed of cytotrophoblast
and the outer layer which faces the maternal tissue is transformed to syncytiotrophoblast by fusion of neighboring cytотrophoblastic cells. At the implantation pole the syncytial mass forms branching finger like extensions that deeply invade, and interdigitate with the endometrium. This is the trophoblastic shell\(^\text{(6)}\). (Figure-1a&amp;b)

2-Lacunar stage:
This stage starts by the appearance of small vacuoles in the syncytiotrophoblastic mass on day 8. These vacuoles grow forming a system of lacunae which are separated from each other by bands of syncytiotrphoblast called trabeculae. By day 12 the blastocyst is deeply implanted and the uterine epithelium closes over the implantation site\(^\text{(6)}\).

The cytотrophoblastic cells extend into the trabeculae, and by day 13 reach the trophoblastic shell. At this point the trophoblast covering the blastocyst is divided into three layers\(^\text{(6)}\):

(A) -the primary chorionic plate, facing the blastocystic cavity.
(B)-the lacunar system, including the trabeculae
(C)-the trophoblastic shell, facing the endometrium.

(A) The primary chorionic plate:
The primary chorionic plate is composed of cytотrophoblast covered by syncytiotrophoblast on the maternal side. On day 14, it is transformed into the triple layered chorionic plate by spreading of embryonic mesenchyme around the inner surface of the cavity and the cytотrophoblast layer. At this time the first villous outgrowths from the trabeculae start. The trabeculae are henceforth called the villous stems, which later become the stem villi.
The lacunar system is transformed into the intervillous space. So the chorionic plate serves as a base from which the villous trees are suspended⁶.
(B)-Lacunar system:
It lies below the primary chorionic plate. At the luminal surface of the lacunae the syncytiotrophoblast is present with underlying cytotrophoblast. Below the cytotrophoblast and facing the endometrial connective tissue is an additional discontinuous layer of syncytiotrophoblastic elements\(^{(6)}\).

(C)-Trophoblastic shell:
As the cytotrophoblast expands into the trabeculae, the distal ends of the trabeculae join together and form the outermost layer of the trophoblastic shell. Initially this is a syncytiotrophoblastic structure but as the cytotrophoblast reaches the shell on day 15 the shell becomes more heterogeneous. From day 22 onward the term trophoblastic shell is usually replaced by basal plate, a term that includes the base of intervillous space together with all placental and maternal tissues that adhere to it after parturition\(^{(6)}\). (Figure-1c&d)
3-The early villous stage: from day 13-28

Is marked by the presence of the primary villi which are composed only of an outer syncytiotrophoblast layer and a core of cytotrophoblast. They develop as the cytotrophoblast invades the trabeculae and the trophoblastic sprouts grow into the lacunae. Primitive villous trees are formed by proliferation and branching of the primitive villi. The stems of these trees are derived from the trabeculae. The villi that keep their contact to the trophoblastic shell are known as anchoring villi. (Figure-1c&d)

The secondary villi are formed as the mesenchymal layer of the secondary chorionic plate invade the primary villi. They consist of an outer layer of syncytiotrophoblast, an inner layer of cytotrophoblast and core of connective tissue. Within few days the mesenchyma reaches the tip of the villi(6). (Figure-1e&f)

Tertiary villi are marked by the appearance of capillaries in the villous stroma. These capillaries appear on day 18-20 and are derived from the
hemangioblastic progenitor cells, which locally differentiate from the mesenchyme. Complete fetoplacental circulation is established, at the beginning of the fifth week, by fusion of capillary segments forming a capillary bed. Fetal and maternal blood comes in contact with each other as soon as fetoplacental circulation is established but the two blood streams are separated from each other by a placental barrier which is composed of syncytiotrophoblast, cytotrophoblast, basal lamina, connective tissue and fetal endothelium\(^6\).

From the second month and beyond, the mean villous diameter decreases, and the capillaries are more numerous and closer to the villous surface\(^6\).

1-2-2-Development of Extra Villous Trophoblast and Phenotypes

Extra villous trophoblast is a general term for a group of trophoblastic cells formed from the remainder of the trophoblasts in the prelacunar stage, not used in villi formation and
residing outside the villi. They are the basic material for the development of all non-villous parts of the placenta: chorionic leave, marginal zone, chorionic plate, basal plate, cell columns, septa and cell islands.

The extra villous trophoblasts are subdivided according to location and differentiation into:

1-extra villous syncytio trophoblast: are syncytial remainders, mostly at the inter villous surfaces of all non villous parts

2-multinucleated trophoblastic giant cells: deeply invasive multinucleated elements, probably derived from syncytial fusion of invasive extra villous cytotrophoblasts

3-extra villous cytotrophoblast: all mononuclear cytotrophoblast outside the villi

4-proliferative phenotype of extra villous trophoblast: proliferating stem cells resting on or near the basal lamina facing the villous or chorionic stroma
5- interstitial trophoblast: all trophoblast cells which do not invade the uteroplacental vessels
6- endovascular trophoblast: trophoblastic cells that invade the walls and lumina of uteroplacental vessels
7-intra mural trophoblast: invasive trophoblastic cells infiltrating the walls of uteroplacental vessels
8-intra arterial trophoblast : invasive trophoblast cells replacing endothelium and forming intraluminal plugs in uteroplacental vessels\(^{(7-8)}\).

1-3-Histology of trophoblastic cells:
Syncytiotrophoblast cells:
On light microscopy, the syncytiotrophoblast cells are large multinucleated cells with less distinct cell borders and dense eosinophilic cytoplasm. Mitotic figures are not identified. In early pregnancy they appear as one layer surrounding the cytotrophoblast while in late pregnancy they have variable thickness. It may be focally thinned out to almost invisible forming what is known as the vasculosyncytial membrane. In some areas it may
appear as a single cell layer, while in other areas the nuclei may be piled up forming syncytial knots\(^9\).

Ultrastructurally they are highly complex featuring irregular nuclear outlines and contain desmosomes, thick bundles of tonofilaments and abundant microvilli on the cell surface\(^9\).

Immunohistochemistry reveals high reactivity for HCG and Human Placental Lactogen\(^{10}\).

Cytotrophoblastic cells (the Langhans’ cells):
In early pregnancy they form a continuous layer beneath the syncytiotrophoblastic cells. In late pregnancy as the villi surface expands, the cytotrophoblastic cells become widely separate and they form a discontinuous layer.

At all stages of pregnancy, the cytotrophoblastic cells have the following features on the light microscope:
They are uniformly oval to polygonal containing single nuclei with dispersed chromatin and scanty clear cytoplasm. The cells have distinct cell borders\(^9\). Mitoses may be seen.
Ultra structurally, the cells have smooth nuclear outlines and contain less numerous desmosome and they neither contain intermediate filaments nor microvilli on the cell surface\(^9\). Immunohistochemically the cells are not reactive to HCG and HPL\(^{10}\).

Extra villous trophoblast:
Formerly was known as intermediate trophoblast. These cells are variably shaped round, polyhedral and spindle. They are generally mononucleated but occasionally may be multinucleated. The cell border is less distinct. They contain abundant amphophilic cytoplasm\(^{11}\). Mitoses may be seen. Ultra-structurally they have intermediate complexity, intermediate nuclear outline, less numerous desmosomes, less abundant microvilli on the cell surface and para nuclear intermediate filaments. Immunohistochemically the cells are strongly positive for HPL and variably reactive with HCG\(^{10}\).
1-4-Functions of trophoblast:
Trophoblasts are specialised cells that play an important role in embryo implantation and interaction with the decidualised maternal endometrium.
The syncytiotrophoblast is involved in maternofetal transfer mechanisms which include:
1- catabolism and synthesis of proteins and lipids.
2- synthesis of hormones such as:
a- Human chorionic gonadotropin.
b- Human chorionic somatotropin.
c- Human placental lactogen.
d- Human growth hormones.
3- diffusional transfer of gases and water.
4- active transfer of amino acids and electrolytes.
The cytotrophoblast is considered to be the trophoblastic stem cell.

1-5- Trophoblastic Diseases
It is an umbrella term for a group of histologically distinct disorders that arise from trophoblastic tissue. They are also referred to as gestational
trophoblastic tumors (GTTs) and gestational trophoblastic neoplasia (GTNs); they may be benign or malignant diseases

All are characterized by:
1- production of (HCG)
2- sensitivity to chemotherapy

**1-6-Classifications of GTD:**
GTD are primarily classified into: molar and nonmolar. Molar lesions include complete hydatidiform mole, partial hydatidiform mole and invasive mole. Non molar diseases includes choriocarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumor and placental site nodule\(^{(12)}\).

**1-6-1-Clinical classification:**
According to the National Institute of Health (NIH)\(^{(13)}\), GTD are divided into:
1- Gestational trophoblastic disease (benign GTD)
   a- Complete hydatidiform mole.
   b- Partial hydatidiform mole.
2-Gestational trophoblastic tumor (Malignant GTD)
-Non metastatic
-Metastatic.

1-6-2-Modified WHO classification-(2003)

Hydatidiform mole
  Complete mole
  Partial mole
Invasive mole
Metastatic mole

Trophoblastic neoplasms
  Choriocarcinoma
  Placental site trophoblastic tumor
  Epithelioid trophoblastic tumor

Non- neoplastic, non molar trophoblastic lesions
  Placental site nodule
  Exaggerated placental site\(^{(14)}\).

1-7- EPIDEMIOLOGY

The incidence rates of GTD are difficult to adjust because of the limitations in the methodology of these studies. Some studies of incidence rates have used hospital based rather than population based data, which may result in over reporting.
The overall reported incidence of hydatidiform mole and choriocarcinoma varies widely throughout the world, being highest in developing countries (Asia, Africa and Latin America) and low in developed countries (North America, Europe and Australia).

In Asia, the incidence rate of hydatidiform mole can be as high as 1 in 500 pregnancies. In USA and Europe it varies between 1 in 1000 to 1 in 2000 pregnancies.

Based on recent studies the world wide incidence rate of complete and partial mole is 1 per 1500-2000 pregnancies and 1 per 700 pregnancies, respectively.

In choriocarcinoma, as molar disease, there is marked regional variation in incidence rates. In Nigeria it is the third most common malignant tumor, at one institution, rankling behind breast and cervical carcinoma. In USA and Europe the frequency is 1 in 20000 to 1 in 40000\(^{(15)}\).
Risk factors:

1- Age: GTD is a disease of reproductive age being higher in teenagers and women above 40 years. There is a 10-fold rate among women above 40 years age\(^{(16)}\). Maternal age has no effect on partial molar pregnancy. Neither paternal age nor race seems to affect the risk of developing hydatidiform mole. Placental site trophoblastic tumor and epithelioid trophoblastic tumors occur infrequently in postmenopausal women\(^{(17)}\).

2- Race: GTD has a higher incidence in Africans and Asians.

3- Parity: GTD is decreased in women who are parous with multiple term pregnancies and live births. A case control study demonstrated that the risk factors for partial molar pregnancy include irregular cycles, only male infants among prior live births and oral contraceptive pills use for more than 4 years.
4- Blood group: Women with recurrent molar pregnancies have blood group B. In Japan, patients with lower incidence of GTD are Rh⁻ve blood type compared to normal population.
5- Reports are inconclusive, older reports describing a lower incidence of GTD among women with high carotene intake\(^{(16)}\).
6- Smoking: is associated with an increased risk of GTD.
7- Previous abortion: History of prior spontaneous abortions is more common in patients with complete molar pregnancy and choriocarcinoma than normal pregnancies.\(^{(17)}\)
8- Past molar pregnancy: Women who have had one hydatidiform mole are at increased risk of having another.

1-8-**Clinical Features:**
Clinically, patients presented with a history of amenorrhea followed by:
- Vaginal bleeding which may be significant and prolonged, leading to significant anemia. The
patient may occasionally experience the passage of pathognomic grape-like vesicles.
- Uterine size larger than gestational age
- Toxemia is classically associated with hypertension, proteinurea, and hyper-reflexia. When it happens in early pregnancy, GTD should be ruled out
- Hyperemesis is more likely to happen in patients with markedly elevated levels of HCG.
- Hyperthyroidism may be associated with classical signs of tachycardia, tremors, and warm skin.
- Theca lutein ovarian cysts are related to high levels of HCG\(^{(18)}\). They resolve spontaneously after successful treatment of GTD.

**1-9-Pathology:**

Trophoblastic diseases are either derived from villous trophoblast, as in molar pregnancy or choriocarcinoma or from extra villous trophoblasts as in placental site trophoblastic tumor, exaggerated placental site, and placental site nodule.
Hydatidiform molar pregnancy:

Traditionally, it is subdivided into complete and partial molar pregnancies. They differ in both gross and microscopic appearance as well as in molecular level. Grossly complete hydatidiform mole shows, uniformly large grape like, transparent vesicles (Figure 2 & 3), and no fetus or gestational sac in most cases, while partial hydatidiform mole shows large hydropic vesicles admixed with nonmolar placental tissue, and a fetus with developmental abnormalities, may be present (19). Microscopic findings:
The microscopic findings of complete mole shows enlarged villi with generalized hydropic changes and central cisterns. Marked hyperplasia of both villous cytотrophoblast and syncytiotrophoblasts is seen. Hyperplasia of intervillous and implantation trophoblasts as well as striking cytological atypia are seen. There are no fetal parts (19) (Figure 4). On the other hand examination of partial molar pregnancy may show enlarged villi admixed with small and normal sized ones or enlarged villi with scalloped border and trophoblast inclusions. Less frequent or prominent
cavitations than in CHM are seen. Mild or focal syncytiotrophoblastic hyperplasia with lacy or moth eaten appearance. Evidence of fetal development including nucleated RBCs in villous capillaries, chorionic plate, amnion, cords, or fetal tissues\(^{(19)}\) (Figure 5)

On molecular basis cytogenetic studies show that complete mole has a normal diploid DNA content derived from the paternal genome. Most complete moles are 46 XX.

Complete molar pregnancy results from either:

1- Fertilization of an empty ovum (lost its nucleus) by a single sperm, then due to subsequent duplication of the haploid spermatozoal component, diploid genotype result. or

2- Fertilization of an empty ovum by two sperms. Fusion of the two male pronuclei results in 46 XY genotype which is rare and constitutes about 15% of complete molar pregnancies.

Moles with 46YY are not found and it is assumed to be a lethal condition. Triploid and tetraploid are very rare in complete mole.
The partial mole is usually triploid with two sets of chromosomes of paternal origin and a haploid maternal set\(^{(20)}\). Partial mole is a result of fertilization of an ovum by two sperms resulting in triploid karyotype 69XXX. 69XXY or rarely 69XYY\(^{(21)}\).

![Figure 2: Gross appearance of intrauterine molar pregnancy](image)

![Figure 3: Gross appearance of the grape like chorionic villi](image)
Figure 4: Microscopic appearance of complete molar pregnancy (H&E)

Figure 5: Microscopy of partial molar pregnancy (H&E)
Invasive Mole:

Grossly appears as small area of haemorrhage or multiple vesicles in the myometrium, or in florid cases as hemorrhagic cavities deeply and extensively invading the myometrial wall\(^22\). Diagnoses can only be made in a hysterectomy specimen. Microscopically, characterized by invasion of the myometrium or its vascular spaces by molar villi with proliferating cyto- and sncytio- trophoblasts without intervening decidua (Figure 6&7).

Figure 6: gross appearance of uterus with invasive mole
Figure 7: Microscopy of invasive mole showing villi within the myometrium

**Choriocarcinoma:**

Grossly, dark red, hemorrhagic masses, friable on cut surface with variable necrosis.

Microscopically, the tumor has a biphasic growth pattern with syncytiotrophoblast cells surrounding groups of cytotrophoblast cells\(^{(23)}\). The
syncytiotrophoblastic cells have abundant basophilic cytoplasm and multiple large irregular hyperchromatic nuclei. The cytrophoblastic cells have clear cytoplasm and large atypical and vesicular nuclei with clumped chromatin and prominent nucleoli. Frequent mitoses are seen in these cells. Minor components of intermediate trophoblasts are seen. The tumor shows prominent vascular invasion with hemorrhagic lakes and extensive necrosis. No chorionic villi\(^{(23)}\) are seen in gestational choriocarcinoma (Figure 8&9).

Figure 8: Uterus; gross appearance of choriocarcinoma
**Placental site trophoblastic tumor:**

It is a neoplasm of non villous trophoblast derived from placental site representing the malignant counterpart of the exaggerated placental site.

Grossly it is well circumscribed with ill defined borders. The cut surface is soft, yellow tan with focal hemorrhage or necrosis\(^{(24)}\).

Microscopically, the tumor is characterized by:

Sheets, and at the periphery, tumor cells infiltrate between muscle fibers in sheets, nests, cords, or singly. Invasion and replacement of vascular walls by intermediate trophoblast admixed with fibrinoid material is seen. These cells are mononucleated or less frequently
binucleated or multinucleated. The cytoplasm is amphophilic or eosinophilic but less frequently may be clear. The nuclei are small to large irregular hyperchromatic with variable degree of pleomorphisms\(^{(24)}\). Rare syncytiotrophoblast cells. Average mitotic figures 2-5/10 HPF are seen (figure10).

Figure 10: Microscopic appearance of placental site trophoblastic tumor

**Placental site nodule:**

None neoplastic lesion of intermediate trophoblast derived from chorion leave(fetal membrane)

**Gross Findings:**

1-small up to 1 cm
2-if visible, yellow, tan or hemorrhagic on cut section.

Microscopic findings:

1- Well circumscribed lobulated border.
2- Nests, cords or single cells embedded in abundant dense eosinophilic extra cellular matrix.
3- Small round extensions with pseudo infiltrative growth sometimes present at the periphery.
4- Abundant eosinophilic or vacuolated cytoplasm, small and vesicular, or large and irregular nuclei with degenerative chromatin pattern. (25)
5- No mitotic activity. (figure 11)

Figure 11: Microscopic appearance of placental site nodule
Epithelioid trophoblastic tumor:
It is a neoplasm of intermediate trophoblast derived from the chorion leave (fetal membrane) thought to represent the malignant counterpart of placental site nodule.
Grossly, it is a discrete expansile nodule measuring up to 5 cm. On cut section is solid, tan to brown often with areas of hemorrhage and necrosis.
Microscopy:
1-well circumscribed expansile margin
2-The tumor cells form sheets, nests, islands or nodules with blood vessels present in the center.
3-Extensive geographic necrosis in between nests, islands, and nodules.
4-Intimate association of cells with eosinophilic, hyaline like material and necrotic material.
5-Mononucleated cells with uniform nuclei and eosinophilic and clear cytoplasm. (Figure 12 & 13)
6-Average mitotic index 2/10 HPF (range 0-9) \(^{(13)}\).
Figure 12: Gross appearance of epithelioid trophoblastic tumor

Figure 13: Microscopy of epithelioid trophoblastic tumor
1-10-Diagnosis:

Usually straightforward in clinically suspected cases. Ultrasound has an important role in diagnosis but definitive diagnosis depends on histopathology.

1- Clinical history.
2- Laboratory investigations:

   - HCG, it is a placental glycoprotein composed of two dissimilar subunits alpha and beta. Several forms exist, including at least six major variants of HCG detected in serum: hyperglycosylated, nicked, HCG missing the B-subunit C terminal segment, free B subunit, nicked free subunit, and free alpha subunit. In urine these samples plus urine B-core fragments exist\(^{(27)}\).

So HCG can be measured as:

A- Serum HCG: markedly elevated in complete molar pregnancy with levels more than 100000 m IU/ml. However patients with partial mole are less likely to present with very high levels of HCG. Patients with placental site trophoblastic disease can present with normal levels of HCG.

B- Urine HCG: It is of limited uses because of high false positive results\(^{(28)}\).
-HPL, is present in tumor cells on immunohistochemical staining, but cannot be used as a tumor marker.

3-Radiological diagnosis:
- Ultrasound: very sensitive, especially transvaginal. Complete mole appear as a complex echogenic, intrauterine mass containing many small cystic spaces, forming what is known as snow storm pattern. The partial mole shows two characteristic features:
  A- The ratio of transverse to anterio posterior dimension of gestational sac is greater than 1.5.
  B- Irregular appearance with cystic changes in the tissues surrounding the gestational sac show storm appearance.

4-Investigations of metastasis:
Chest X ray, CT scan of the chest, Abdomen, Pelvis and CT scan, MRI of the brain. Some theories suggest that measurement of HCG in the CSF is of value in detection of brain metastasis.

5-Immunohistochemical studies:
   Have value in non molar conditions especially in its differentiating from non trophoplasttic conditions
<table>
<thead>
<tr>
<th></th>
<th>Choriocarcinoma</th>
<th>PST T</th>
<th>Epithelioid trophoblastic tumor</th>
<th>Nontrophoblastic uterine tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCG</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Inhibina</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>-</td>
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<tr>
<td>Hpl</td>
<td>+</td>
<td>++</td>
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<td>p63</td>
<td>+</td>
<td>-</td>
<td>+++</td>
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</tbody>
</table>

Table (1)
Immunohistochemical studies in non molar and trophoblastic conditions\(^{(29)}\)
In molar pregnancy it is of limited value because of immunohistochemical phenotype similarity to placental tissue. Cytotrophoblasts are typically positive for cytokeratins and CD 10 but negative for HCG, inhibin and HPL, while syncytiotrophoblast are strongly positive for HCG. PLAP, inhibin and CD10 and weakly positive for HPL\(^{(30)}\). 6-Cytogenetic studies are usually done in research to differentiate between complete mole which is diploid and partial moles which is triploid\(^{(31)}\).

1-11-STAGING:

There many systems have been used for the staging of GTD, include:

- The National Institute of Health (NIH) System.
- The World Health Organization (WHO) scoring System.
- The Federation of Gynecology and Obstetrics (FIGO) staging system.
- The (TNM) staging system.\(^{(32)}\)
111-1 The National Institute of Health (NIH) System:

This system was introduced in 1970 on the basis of an analysis of patients treated for GTD. Patients are divided into:

**Group I:** Non metastatic disease, no evidence of disease outside the uterus.

**Group II:** Metastatic, any disease outside the uterus. This group is further divided into good prognoses metastatic disease and poor prognoses metastatic disease on the basis of factors that correlated with poor response to initial single agent chemotherapy.

**A-** Good prognosis metastatic disease

1- Duration of disease (last pregnancy) < 4 months
2- Low pretreatment HCG titers < 100000IU/24h in urine or < 40000 mlU/ML in serum
3- No metastases to brain or liver.
4- No significant prior chemotherapy

**B-** Poor prognosis metastatic disease

1- Duration of disease (last pregnancy) >4 months.
2- High pretreatment HCG titer > 100000IU/24h in urine or >40000 mlU/ML in serum
3-Brain or liver metastases.
4-Significant prior chemotherapy.
5-Term pregnancy.

1-11-2 The World Health Organization (WHO) scoring System:

This system is helpful in identifying which patients would benefit from single agent or multiple agent chemotherapy and also is more predictive of the clinical outcome. Patients with a score of 8 or greater are considered to be at high risk and more likely to require combination chemotherapy to achieve complete remission. Patients with score less than 8 are considered to be at low risk and would benefit from single agent chemotherapy.

**WHO Scoring System:**

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Less than 39 years</td>
<td>0</td>
</tr>
<tr>
<td>Greater than 39 years</td>
<td>1</td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Hydatidiform mole</td>
<td>0</td>
</tr>
<tr>
<td>Abortion</td>
<td>1</td>
</tr>
</tbody>
</table>

| Interval between end of antecedent pregnancy and start of chemotherapy. |
|-----------------------------|-----|
| <4 months                   | 0   |
| 4-6 months                  | 1   |
| 7-12 months                 | 2   |
| > 12 months                 | 4   |

<table>
<thead>
<tr>
<th>HCG (IU/ml)</th>
<th></th>
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<tbody>
<tr>
<td>&lt; 1000</td>
<td>0</td>
</tr>
<tr>
<td>1000-10,000</td>
<td>1</td>
</tr>
<tr>
<td>10,000-1,00,000</td>
<td>2</td>
</tr>
<tr>
<td>&gt;1,00,000</td>
<td>4</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO Groups (female x male)</td>
<td></td>
</tr>
<tr>
<td>Ox A or AxO</td>
<td>1</td>
</tr>
</tbody>
</table>
1-11-3- FIGO staging system:

Is an anatomic staging system:

Stage I: Limited to uterine corpus.
Stage II: Extended to the adnexia, outside the uterus but limited to the genital structures.
Stage III: Extends to the lung with or without genital tract involvement
Stage IV: All other metastatic sites.

1-11-4-The TNM staging system:

This system was introduced by AJCC

TNM definitions:
- Primary tumor (T)
  - TX: Primary tumor cannot be assessed.
  - T0: No evidence of primary tumor.
-T1: Disease limited to uterus.
-T2: Disease outside the uterus but limited to genital structures (Ovary, tube, vagina, broad ligaments)
-M0: No clinical metastasis
-M1a: Lung metastasis
-M1b: All other distant metastasis

AJCC stage groupings:
Stage IA: T1, M0, no risk factors.
Stage IB: T1 M0 one risk factors.
Stage IC: T1 M0 two risk factors
Stage IIA: T2 M0 no risk factors.
Stage IIB: T2 M0 one risk factor.
Stage IIC: T2 M0 two risk factors
Stage IIIA: Any T, M1a no risk factors.
Stage IIIB: Any T, M1a one risk factor.
Stage IIIC: Any T, M1a two risk factors.
Stage IVA: Any T, M1b no risk factors.
Stage IVB: Any T M1b one risk factor.
Stage IVC: Any T, M1b two risk factors \(^{(34)}\).
1-12-Treatment:

1-Initial Management:

The primary treatment of patients with molar pregnancy is evacuation of the uterus. Suction curettage is the method of choice in complete molar pregnancy. Medical termination of complete molar pregnancy should be avoided when possible due to risk of trophoblastic tissue embolization. In partial mole suction and curettage may be limited by the presence of fetal parts and therefore medical termination may be necessary.

2-Initial assessment:

Patients are followed-up for six months. This follow up involves periodic assays of urine and serum HCG initially weekly reduced to monthly depending on the rate of HCG fall. If the level of HCG has fallen to normal within 8 weeks of uterine evacuation then marker follow up can safely be reduced to 6 month in total. However, if HCG levels remain elevated beyond 8 weeks follow up is continued until the HCG level is normal and for 6 months thereafter.
3- Treatment of persistent GTD:

-Second uterine evacuation may be performed provided that:

  A- HCG elevation is low.

  B- There is significant amount of abnormal intrauterine tissue on repeat U/S

-Chemotherapy:

Is required in 20% of complete mole and 0.5% of partial molar pregnancies. Indication for chemotherapy are:

- Serum HCG >20000 IU/L after one or two uterine evacuations.

- Static or rising HCG levels after one or two uterine evacuations.

- Persistent HCG elevations 6 months postuterine evacuations.

- Persistent uterine bleeding with raised HCG levels.

- Pulmonary metastasis with static or rising HCG.

- Metastasis in liver, brain or GIT.
-Histological diagnoses of choriocarcinoma.\(^{(35)}\)

Based on the WHO scoring system, patients with a score of \(<6\) are treated by single agent chemotherapy, while patients with a score \(>7\) are treated by a combination of chemotherapeutic agents. It is unusual to use radiotherapy, with exception to brain and liver metastases where it is used in combination with chemotherapy.

4-Hysterectomy:

It continues to play an important role in the management of persistent GTD especially in those countries where there are problems with patients surveillance and provision of chemotherapy.\(^{(30)}\)

Indications for hysterectomy are:

- Where intractable hemorrhage is present.
- In the presence of residual uterine or pelvic tumor mass following adequate chemotherapy
- In cases of placental site trophoblastic tumor.\(^{(35)}\)
- Hysterectomy for disease confined to uterus in women who have completed child-bearing
-Resection of chemotherapy resistant nodules\(^{36}\).

1-13-PROGNOSIS and FOLLOW UP:

-During treatment:
Prior to each cycle HCG, full blood count, renal and liver function tests are checked.

-Following completion of treatment:
Once treatment is concluded serum HCG is measured:
A-Weekly for the first 6 weeks
B-Monthly for the subsequent 6 months
C-If values remain normal; follow up with periodic urine HCG for life.

-Conception:
All patients are advised to avoid the use of estrogen containing oral contraceptive pills whilst HCG levels are elevated as there is a theoretical risk of inducing metastatic or drug resistance disease. All patients are advised to avoid using intrauterine contraceptive devices until normal menstrual cycles are re-established.
-Pregnancy:
Patients are advised not to conceive for at least 12 months from the conclusion of their treatment. There is a risk of teratogenicity resulting from cytotoxic chemotherapy and secondly the risk of recurrent GTD is greatest during this time. (37)

1-14-OBJECTIVES

1-14-1- General objective:

To study cases of GTD received in the Department of Histopathology at NHL Khartoum state.

1-14-2-Specific objectives:

1. To study the pattern of occurrence of GTD in relation to age, mode of presentation and parity

2. To study the histopathological features of GTD.

3. To study the percentage incidence of each histological type in relation to the total number
MATERIALS & METHODS

2.1. Study design:

The study is a descriptive retrospective recorded data – based study.

2.2. Study area:

The study was conducted at the Department of Histopathology NHL, which provides nationwide diagnostic services as well as training and research services.

2.3. Study population:

Cases diagnosed at the department between January 2007- December 2010.

2.4. Inclusion criteria:

Case with complete records and available histological slides or paraffin wax embedded blocks.

2.5. Exclusion criteria:

Case with deficient record (missed request form) or missed histopathology slides and blocks.
2.6. Data collection:

Clinical data was collected from patients request forms in questionnaire containing the age, parity, type of specimen & microscopic features.

The slides were retrieved from the archives and revised under supervision to confirm the diagnosis of gestational trophoblastic lesions and determine the histological type. The slides were prepared from tissue fixed in 10% formalin and handled according to histological protocol.

2.7. Data analysis:

The data was analyzed electronically using computer program (SPSS). Chi squire test was calculated to compare the association.
3- RESULTS AND ANALYSIS
4- 1-DISCUSSION

In this study 109 cases were reviewed and showed that the age of the patients ranged between 14-55 years, and the mean age was 31.5 years this coincides with a study done in Nigeria by SU Marma and his colleague (38) in which the mean age was 31 years, but it varies from other studies as in south Africa, where Moodley M and his colleagues (39) found the mean age of patients to be 28.5 years. In the study of Razieh Mohammed and her colleagues the mean age in Iran was 27.6 years (40). In this study most cases (38%), occurred in the 2\textsuperscript{nd} decade (20-29 years) followed by the 3\textsuperscript{rd} decade of life (30-39 years) and this coincides with studies of Dr. Sajjanshetty Shalini (41) from India and Aligbe J.u. and colleagues (41) from Nigeria. Thirty one percent of cases occurred in the extremities of reproductive age and are distributed as follow (20%) in ladies above 40 years and (11%) below 20 years. The cases occurred in upper limit of the age in this study group was higher than the study of Razieh Mohammed and colleagues in Iran (40) (18.9%) and
lower than the result of Tariq Kashoggi study in KSA\(^{(43)}\) where he found that 30% of all cases present above 40 years. Locally it generally coincides with the only study done in Sudan by Sana Bakery Mustafa\(^{(44)}\) (Figure No.14).

Relation to gravidity (28 cases were excluded from the study due to incomplete information in records and they represent 25.6% of cases) revealed that the gravidity ranged from primigravida to gravida 13. The majority of cases occurred in gravida between 2-4 which represent (52%), followed by grand multipara (31%), especially in gravidity between 5-8, in which (17%) of cases occur. Primigravida were the least group of patients associated with GTD, where (17%) of cases occur (Figure 15).

There are two studies mentioned by Sajjanshetty Shalini\(^{(41)}\) from India and Tariq Kashoggi\(^{(43)}\) from KSA which coincide with our study in which GTD commonly occurred in the 2-4\(^{th}\) pregnancies (42%&52% respectively). On the other hand, this study differs from the aforementioned studies and another study by Razieh Mohammed\(^{(40)}\) and her colleagues in Iran, who
found that PG was the second most common affected group (36%). In contrast we found it in grand multipra (31%). The study also showed that in (68%) of cases there was no history of previous abortion, while in the rest of the cases (32%) there was a previous history of abortion and the number of abortions ranged from 1-4 (Figure No 16). This coincides with Moodley M & his colleagues (39) study in South Africa (33%), and is slightly higher than the local study of Sana (44)& the study of Razieh Mohammed (40) in Iran (28% for each)

Clinically most cases presented by vaginal bleeding (51%), in (5%) the vaginal bleeding was associated with passage of vesicles and in (1%) the vaginal bleeding was associated with abdominal pain. In our study (10%) of cases were diagnosed by U/S during routine follow up. One case was previously diagnosed as molar pregnancy and presented by rising HCG. Thirty two percent of cases were mentioned just as molar pregnancies in request forms. Due to deficient clinical information in the records, three cases (2.5%) were excluded from the analysis.
These results of presentation coincide with the local study of Sana\textsuperscript{44}, where vaginal bleeding was the major presenting feature (78%); on the other hand passage of vesicles occurs in 5% of cases, which is slightly higher from the same study (3%). Studies by BM, IU Takai and their colleagues\textsuperscript{45} from Nigeria & Sajjanshetty Shalini\textsuperscript{41} from India showed abnormal vaginal bleeding in (100%), but SU Marma and her colleagues\textsuperscript{39} in South Africa showed that abnormal vaginal bleeding occurs in (73.3%), Sajjanshetty Shalini\textsuperscript{41} in India also mentioned that in 64% of the reviewed patients, in addition to vaginal bleeding had abdominal pain, compared to 1% in our study. Ninety one percent of his patients had amenorrhea (Figure No.17). In this study there is under estimation of results which may be due to undetermined clinical presentation, mentioned as molar pregnancy and equivalent to (32%).

Histological examination showed that molar pregnancy was the dominant diagnosis (96%) and choriocarcinoma forms 4% (Figure N0.18). Locally, this result typically coincides with the study of Sana Mustafa\textsuperscript{44}, in which molar pregnancy forms 96% and
choriocarcinoma 4%. Outside the country this study has the same pattern of studies done by Moodley M and his colleagues\(^{39}\) in South Africa, Razieh Mohammed and her colleagues\(^{40}\) in Iran, Dr. Sajjanshetty Shalini\(^{41}\) in India and Aligbe J.u. and colleagues\(^{42}\) from Nigeria which showed prevalence of molar pregnancy but with little variations in percentages. Exceptionally this study differs from a study done in Nigeria by Maram and her colleagues\(^{38}\), which showed prevalence of choriocarcinoma (66.7%) followed by molar pregnancy (33.3%).

Detailed analysis of this study showed that partial molar pregnancy was the commonest diagnosis (65%) followed by complete molar pregnancy (28%), this coincides with two studies done in Nigeria by BM, IU Takai and their colleagues\(^{45}\) (71%) and the other by Aligbe J.u. and colleagues\(^{42}\) (47%) and also with a study done in Netherland by Charlotte Lylool and his colleagues\(^{46}\) (44%). On the other hand all these studies, including our study, differ from other studies done by Mourali M & his colleagues in Tunisia\(^{47}\), Razieh Mohammed and her colleagues\(^{40}\) in Iran and
Sajjanshetty Shalini\(^{(41)}\) in India, who found that, complete molar pregnancy was the commonest diagnoses (68.15%, 81% and 55.2% respectively). Choriocarcinoma, which comprises 4% & represents the third common pathology in this study; this coincides with Hornlc, Bilek K study in Germany\(^{(48)}\), Harma M & colleagues\(^{(49)}\) in Turkey and Aligbe J.u Ekanem & colleagues\(^{(42)}\) in Nigeria. But it differs from Nizam K & his colleagues’ study\(^{(50)}\) in Pakistan in which choriocarcinoma was the least common pathology and SU Marama and her colleagues\(^{(38)}\) in Nigeria in which choriocarcinoma was the prevalent lesion. Vaginal bleeding was the classical leading complain which was typically similar to all studies. In contrast to Grimes DA\(^{(51)}\) study in Nigeria, abortion was not a risk factor for choriocarcinoma. In this study choriocarcinoma exclusively occurred in multipara, so it increases with increased parity and this coincides with the study of Agboola A study in Nigeria\(^{(52)}\) (Table No.2). Invasive molar pregnancy was the least common pathology in this study and so in the studies of: Harma M & colleagues\(^{(49)}\) from Turkey,
Martaadisoebrata D from Indonesia\textsuperscript{(53)}, Aligbe J.u Ekanem & his colleagues\textsuperscript{(42)} from Nigeria and Hornlc, Bilek K\textsuperscript{(48)} in Germany. Invasive mole was not encountered in the studies done in Nigeria by BM, IU & their colleagues\textsuperscript{(44)} and SU Marma & her colleagues\textsuperscript{(38)}. In this study, the peak incidence of invasive mole is in 3\textsuperscript{rd} decade grand multiparous mothers, which typically coincides with, Martaadisoebratas’ study\textsuperscript{(53)} in Indonesia. Analysis of complete molar pregnancy showed that the peak incidence also occurred in the 2\textsuperscript{nd} and third decade and the majority of cases occurred in the 2\textsuperscript{nd} decade. This coincides with a study done in Uganda\textsuperscript{(54)} by Dan K Kaye, and with Thapak & colleagues’ study in Katmandu\textsuperscript{(55)} and also with the study done by Boufettal H & his colleague\textsuperscript{(56)}. Patients in reproductive age extremities (over 40 and less than 20 years) comprise 44% (22% for each), which means increased risk with age extremities, and this is similar to the last study by Boufettal H & his colleague (Table No.3). Table 4 in this study showed that CHM was common in multiparous women (15 out of 26) followed by grand multipara 6 patients, especially in gravia between 9-13
where 4 cases occur, and then PG by 5 cases. In contrast to this findings Boufettal & his colleague(56) found to be common in para 1 and PG while in Nepal Thapak & colleague(55) said it is common in PG. Hysterectomy specimens were submitted in 13% of cases of CHM (Figure No.19). This is relatively high if compared with Thapak & colleagues study in which hysterectomy specimens form 1.2 %. This variation may be due to the increased frequency of the disease above 40 years and the lack of expert radiologists. In partial mole hysterectomy was performed in 6% of patients (Figure No.20). This is also high if compared with Mourali M & his colleagues(46).

Cases of placental site trophoblastic tumors, placental site nodules, epithelioid trophoblastic tumors were not encountered in this study. This is similar to studies done by of Razieh Mohammed and her colleagues in Iran(40), Aligbe J.u. and colleagues(41) from Nigeria, Tariq Kashoggi in KSA(43)& BM, IU Takai and their colleagues(45) from Nigeria. This result differs from studies done in south Africa by Moodley M and his colleagues(39) who found that 2% of cases were
placental site trophoblastic tumors. Mourali M & his colleagues done in Tunisia & Charlotte Lyool and his colleagues\(^{(46)}\) in Netherland both described less than 1% of placental site trophoblastic tumors. Sajjanshetty Shalini\(^{(41)}\) from India described 1.8% of cases as placental site trophoblastic tumors & 8% as placental site trophoblastic nodules.
4-2-CONCLUSION

• This study is a single institute study so accurate incidence cannot be estimated. But based on this study we can say that GTD is not an uncommon disease.
  • In this study the GTD was higher in the 2\textsuperscript{nd} & 3\textsuperscript{rd} decades (69\%) compared to (11\%) in PG & (20\%) in above 40 age group, so reproductive age extremities are not risk factors for GTD as in the literature.
• The study showed that one third of cases were associated with abortion, so it can be considered as a risk factor.
  • Because more than half of cases (52\%) occur in multipara, 31\% in grand multipara & 17\% in PG, so increased parity can increase the risk of GTD especially if there is a previous history of abortion.
  • As more than one third of cases (38\%) occur in the second decade, GTD should be suspected in any multiparous lady in her second decade of life, with a previous history of abortion presenting with hyperemesis gravidarum in her current pregnancy.
4-3- RECOMMENDATIONS

It is recommended that:

1- Establishment of many specialized centers or units for GTD, for management and follow up of patients.

2- Strict criteria for follow up should be established by specialists.

3- The histopathologic reports should include the advice of follow up of the patients by HCG.

4- Chest X ray should be done for patient with choriocarcinoma.

5- Records should be complete. Including maternal history of previous abortion especially molar pregnancy and ultrasound reports which is essential for proper histopathological evaluations.

6- Cytogenetic analysis is a promising tool in this field and it should be included in researches.

7- During preparation of this study we noticed that most patients had no u/s reports, so we recommend that any patient with vaginal bleeding must be followed by u/s.
4-4-REFERENCES


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4-5-APPENDICES

KHARTOYM UNIVERSITY-FACULTY OF
MEDICINE
DEPARTMENT OF PATHOLGY

QUESTIONARE OF GTD

No:
Age:
Parity:
Clinical Remarks:
Type of specimen:
Microscopic examination:
- Presence of villi within the uterine cavity or deeply within the myometrium.
- Size of villi:
  A- Enlarged villi of equal in size.
  B- Enlarged villi admixed with small and normal size villi.
- Scalloped borders with trophoblastic inclusions.
- Presence of generalized hydropic changes in villi with central cistern.
- Presence of prominent cavitation.
- Morphology of trophoblastic cells:
  
  A- Marked hyperplasia of both cyto & syncytio
trophoblastic cells.
  B- Mild and focal syncytiotrophoblastic cells
  hyperplasia with lacy and moth eaten appearance.
  C- Striking cytological a typia.
  D- Highly pleomorphic with a typical mitoses.
  E- Presence of syncytiotrophoblasts
  surrounding cytotrophoblasts.
  F- Presence of extensive hemorrhage ad
necroses.

- Evidence of Fetal development:
  A- Presence of nucleated RBCs in villous capillaries.
  B- Fetal tissue.

Histological Diagnosis.
CHAPTER 1
INTRODUCTION & LITERATURE REVIEW
CHAPTER 2
MATERIALS & METHODS
CHAPTER 3 RESULTS AND ANALYSIS
CHAPTER 4

DISCUSSION
Results and analysis

Age distribution in study population

diagnosed as GTD (n=103)
Relationship of GTD with gravidity
in study group (n=81)

- Multi Parous (2-4): 52%
- Grand Multi parous (5-8): 17%
- Grand Multi parous (9-13): 14%
- Pg: 17%

Figure No. 15
Relationship of GTD with abortion in study group (n = 81)

Figure No. 16
Clinical presentation of GTD in study group (n=106)

- Vaginal bleeding: 51%
- Vaginal bleeding + passage of vesicles: 5%
- Molar pregnancy: 32%
- Previous history of molar pregnancy: 1%
- Diagnosed by u/s: 10%
- Vaginal bleeding + abdominal pain: 1%

Figure No. 17
Types of gestational trophoblastic diseases in study group (n=109)

- Partial molar pregnancy: 65%
- Complete molar pregnancy: 28%
- Invasive mole: 3%
- Choriocarcinoma: 4%

Figure No. 18
Relation of complete mole with age in study group (n = 31)

<table>
<thead>
<tr>
<th>more than 40</th>
<th>(30-39)</th>
<th>(20-29)</th>
<th>less than 20</th>
<th>total</th>
<th>Excluded Cases</th>
<th>Excluded Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>8</td>
<td>9</td>
<td>7</td>
<td>31</td>
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<td>0%</td>
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</tbody>
</table>

Table No (2)
Relationship of complete mole with gravidity in study group (n=36)

<table>
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<th>grand multi parous (9-13)</th>
<th>grand Multi prous (5-8)</th>
<th>Multi Parous (2-4)</th>
<th>Pg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
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<td>4</td>
<td>2</td>
<td>15</td>
<td>5</td>
<td>26</td>
</tr>
</tbody>
</table>

Table No. (3)
## Relationship of choriocarcinoma with gravidity in study group (n=3)

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<th>pg</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>grand multi parous (9-13)</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
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</tbody>
</table>

Table No (4)
Relationship of complete mole with Types of specimen in study group (n=30)

Figure No.19
Relationship of partial mole with Types of specimen in study group (n=71)
Partial mole: variably size chorionic villi with cisterna and irregular margins (× 40)

H&E
Partial mole: chorionic villi with inclusion and cytotrophoblastic hyperplasia (×200) H&E
Complete molar pregnancy: enlarged villi with central and regular borders (× 40) H&E
Complete molar pregnancy: syncytio and cyto trophoblastic cells hyperplasia (100) H&E
Figure (25)

Invasive molar pregnancy: villous within the myometrium (x40) H&E
Figure (26)

Chrocarcinoma: extensive haemorrhage and necrosis (×40) H&E
Figure (27)

Chrocarcinoma: syncytial trophoblastic cells surrounding cyto trophoblastic cells (×200) H&E
Figure (28)

Chrocacinoma: highly pleomorphic cells (×300) H&E
Figure (29)

Chrocacinoma: pleo morphism with atypical miltores (x 400) H&E