Gestational Trophoblastic Diseases

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INTRODUCTION

Gestational trophoblastic disease (GTD) comprises of a series of tumours or tumour-like conditions which are of placental origin. It is the third commonest cancer affecting women after the cancers of the breast and cervix respectively. They arise from the trophoblast- the layer of cells that surrounds the tiny embryo. They are unique in that they can be diagnosed and treated without histology since they have a distinct biochemical marker. They secrete beta- human chorionic gonadotropin (ß-HCG) and it has become possible by monitoring the circulating levels of ß -HCG to determine the early development of trophoblastic disease and also monitor response to treatment. For example, finding ß -HCG more than 20 days after delivery is indicative of secretion by trophoblastic tissues.

Uteri Hydropil, Aetius of Amida as far back as 483-565BC[1] observed that when the menses have been suppressed for sometimes and the patient has not become pregnant, the uterus becomes filled with tumour and small bladder-like objects are developed in the fluid. The knowledge of the disease has thus tremendously increased to what is presently known in terms of the pathogenesis, natural history, management and prognosis.

EPIDEMIOLOGY

For unexplained reasons, the incidence of GTD is commoner in Asia and Africa than in western countries. For instance, the incidence of hydatidiform mole is 1 of 2,000 pregnancies in the united states[2] while that of Japan is 2 cases per 1000 pregnancies. In the Far East, some sources estimate the rate as high as 1 per 120 pregnancies[3]. Hydatidiform mole is about 10 in 1,000 in Indonesia[4]. However, it is believed not to have any racial or ethnic predilection because Asian women living in the United States do not appear to have a different rate of molar pregnancy than other ethnic groups, thus suggesting environmental influences. Prior GTD has been implicated as a risk factor as women who have hydatidiform mole or choriocarcinoma are at increased risk of having another. Also, for unexplained reasons, women with blood group B or AB have a slightly higher risk of GTD than those with A or O. GTD obviously occur in women of reproductive age, however, women older than 35 years have a 2-fold increase in risk and women older than 40 years have a 7-fold increased risk[2, 3]. There is some evidence, although weak that indicates that women whose diets are low in B-carotene, Vitamin A, protein and folic acid have a slightly higher risk of developing GTD[3, 5]. In Ibadan, molar pregnancy was found to be commoner in the low socio economic class[6]. The risk of hydatidiform mole is highest for women who become pregnant before age 17 or in their later 30s or even later. Paternal age greater than 45 years also increases the risk of developing hadatidiform mole[7].

CLASSIFICATION

The gestational trophoblastic diseases consists of

1.) Hydatidiform Mole
2.) Invasive Mole
3.) Placental Site Trophoblastic Tumour
4.) Choriocarcinoma

HISTOPATHOLOGICAL ENTITIES

Hydatidiform mole (mola hydatidiforma)

A hydatidiform mole is an overgrowth of tissue from the placenta. Most often, a hydatidiform mole is an abnormal fertilized egg. The abnormal egg develops into a hydatidiform mole rather than a fetus. A hydatidiform mole can develop from cells that remain in the uterus after a miscarriage or a full term pregnancy. Rarely, a hydatidiform mole develops when the fetus is normal[2]. It is a disease of trophoblastic proliferation. It can mimic pregnancy, causing high hCG levels and therefore gives false positive

readings of pregnancy tests.

A mole is characterized by cystic swelling of chorionic villi accompanied by variable trophoblastic proliferation. The mole can be complete or partial.

Complete moles are diploid in nature and are purely paternal in origin. An enucleate egg is fertilized by a haploid sperm which then duplicates its chromosomes or the egg is fertilized by 2 sperms. This process is called androgenesis. Cytogenetic studies of these mole show that more than 90% have a 46XX pattern and the remaining 10% are 46XY.
The complete moles have no fetal parts. It carries 2% risk of malignancy to choriocarcinoma[3]. The anatomical appearance is like a bunch of grapes ("honeycombed uterus" or "cluster of grapes"). All or most of the villi are edematous and there is diffuse trophoblastic hyperplasia. Histologically, complete moles show over expression of several growth factors including *C-myc,* epidermal growth factor and *C-erb B-2* compared to normal placenta. A rare form of recurrent complete mole is bi-parental in origin and results from misexpression of imprinted genes. This type of mole occurs when maternal imprints in the ovum are lost. Although, the resulting conceptus has genes from both parents, loss of maternal imprints gives the functional equivalent of two paternal genomes. Recurrent molar pregnancies of this type are familial and appear to be inherited as an autosomal recessive trait. A candidate origin of chromosome 19q13.4 has been identified[2].

Partial moles are triploid in nature. It is an abnormal conceptus with an embryo -fetus- that tends to die early with a placenta that has focal swellings. There is a mixture of both normal and abnormal fetal parts. They result from fertilization of an egg by one diploid or two haploid sperms, thus the following combinations are possible; 69XXY 70%, 69XXX 27%, 69XYY 3%.
Women with hydatidiform mole usually have a clinical diagnosis of spontaneous abortion or missed abortion. In digynic triploid conceptions, which have two maternal contributions to the nuclear genome, the trophoblastic hyperplasia associated with molar pregnancies does not generally develop and the fetus is better preserved[8].
For the partial mole, some fetal parts are seen, since it is derived from both maternal and paternal genetic constituents. The villous edema involves only a proportion of villi and the trophoblastic proliferation is focal and slight usually involving the syncitiotrophoblast. In contrast to complete moles, partial moles are rarely followed by choriocarcinoma.

Invasive mole
This is a tumour like process with invasion of the myometriium. There is trophoblastic hyperplasia of both the syncitiotrophoblast and cytotrophoblast with persistence of placental villous structures. It could have arisen from a complete hydatidiform mole. It however does not often progress to choriocarcinoma. It may regress spontaneously and does not show features of true cancer. If untreated, it invades the uterine wall, resulting in perforation and hemorrhage.

Choriocarcinoma
This is an epithelial malignant neoplasm of trophoblastic cells that arise from any form of previously normal or abnormal pregnancy. Most gestational choriocarcinoma arise in the uterus. Ectopic pregnancy may provide extra uterine site of origin. Choriocarcinoma is the highly malignant variant of the GTD spectrum. Gestational choriocarcinoma are highly invasive but respond well to chemotherapy. The antecedent pregnancy could be a live birth, still birth, abortion at any stage, ectopic pregnancy or hydatidiform mole. 50% arise in HM, 25% in previous abortions and approximately 22% in normal pregnancies. It is estimated that 1:40 HM may be expected to give rise to a choriocarcinoma, in contrast to 1in approximately 150,000 normal pregnancies. Thus, complete HM is the commonest antecedent of choriocarcinoma[7]. In Ile-Ife, Nigeria, most of the patients who were managed had had repeated uterine evacuation for supposed incomplete abortion.

Choriocarcinoma is a soft, fleshy, yellow-white tumour with a marked tendency to form a large pale area of ischeamic necrosis, foci of cystic softening and extensive hemorrhage. There is a villous architecture in a hemorrhagic background of necrosis. The histology reveals purely epithelial chorionic villi which grow by the abnormal proliferation of cytotrophoblast and syncitiotrophoblast. In its rapid growth, it is subject to hemorrhage, ischaemic necrosis and secondary inflammation. It may metastasize to lungs, vagina, brain, bone marrow, liver and other organs.

Placental Site Trophoblastic Tumours
This arises from the trophoblast of the placental bed. It is composed mainly of cytotrophoblastic cells. It may be of a high or low-grade malignancy. This entity is however important because of its resistance to standard chemotherapy when compared with other GTDs.

CLINICAL FEATURES

Hydatidiform mole

The commonest symptom is vaginal bleeding in pregnancy during the first trimester. There may be passage of vesicles (grape-like materials). There may also be recurrent altered bloody discharge also known as the red currant discharge. Nausea and vomiting severe enough to require hospitalization has been reported in about 10% of cases. This hyperemesis is due to the extremely elevated ß -HCG. There could also be symptoms similar to pre-eclampsia. This occurs usually in the first trimester or partly in the second trimester. This is nearly diagnostic of hydatidiform mole because pre-eclampsia is extremely rare this early in normal pregnancies. There is high blood pressure, proteinuria and there may be swelling in feet, ankles and legs. Symptoms of hyperthyroidism are seen which include tachycardia, restlessness, nervousness, heat intolerance, unexplained weight loss, loose stools, trembling hands, warm and moist skin. This is due to human chorionic thyrotropin. Patients may be anaemic due to loss of blood. The pregnancy size is usually inconsistent with expected gestation. A uterine enlargement greater than expected is a classic sign of complete mole[2]. The enlargement is caused by excessive trophoblastic growth and retained blood. Some patients may however present with size appropriate for age or even smaller.

It is important to know that patients with partial mole do not usually have the same clinical features as those with complete mole. These patients usually present with signs and symptoms consistent with an incomplete or missed abortion.

Invasive mole

They usually present like hydatidiform mole but may metastasize to the vagina resulting in vaginal bleeding and the lungs may be involved later. Patient may present with features of shock if there is uterine perforation resulting in intraperitoneal hemorrhage. It is also a cause of slow resolution or persistently high hCG levels after uterine evacuation.

Choriocarcinoma

Uterine choriocarcinoma do not classically produce a large uterine bulky mass. It becomes manifest only by irregular spotting of a bloody, brown, sometimes foul smelling fluid. The discharge may appear in the course of an apparently normal pregnancy, after a miscarriage or after curettage. The presentation may be varied depending on the site of metastasis. Common sites are lungs, vagina, brain, liver and GIT. Cases involving the spleen, gingival and the jaw have been reported[8]. The common features however include vaginal bleeding, haemoptysis, haematuria, hemiplegia and gastrointestinal bleeding.

Placental Site Trophoblastic Tumour

The exact clinical spectrum is yet to be defined. It may be difficult to differentiate it from ectopic hCG-producing carcinomas.

ENDOCRINOLOGY OF GESTATIONAL TROPHOBLASTIC DISEASES.

The GTDs are unique because of their elaboration of ß-HCG which is invariably used as the tumour marker. The spectrum also produces other hormones-human placental lactogen (HPL) and human chorionic thyrotropin (HCT) responsible for features of hyperthyroidism seen in some of them.

hCG is an invariable secretory product of the trophoblastic cells. Serial measurement of the hCG level may be used to assess response to therapy and to determine need for further treatment. hCG is a glycoprotein composed of alpha (□) and beta (ß) subunits with MW of 37,000. The level of hCG after conception rises to a peak at between 70 and 90 days in a normal singleton pregnancy before falling to low levels. This is the basis of immunological tests for pregnancy. The ß-hCG is usually measured because some other hormones such as LH, FSH, and TSH also have □ and ß chains, with the □ subunit indistinguishable immunologically from those of hCG. The ß-hCG radioimmunoassay has permitted early diagnosis, careful assessment of therapy and assurance of complete sustained remission in gestational trophoblastic tumour.

MANAGEMENT.

INVESTIGATIONS

1.) Complete blood count with platelets; Anaemia is a common medical complication, thus it is important to know the baseline packed cell volume especially since she would be taken for surgery.

2.) It would be important to assess the clotting profile in order to exclude the development of a coagulopathy or to treat one if discovered.

3.) Liver function test

4.) Electrolyte, urea and creatinine are usually normal, but the baseline levels are essential in monitoring the patient.

5.) Ultrasound Scanning is an important standard criterion for identifying both complete and partial molar pregnancies. The classic image is of a snow storm appearance indicating hydropic chorionic villi. High resolution ultrasonography shows a complex intrauterine mass containing many small cysts.

6.) ß -HCG assay in serum and urine; hCG levels greater than 100,000 mIU/ml indicates exuberant trophoblastic growth and raises suspicion that a molar pregnancy should be excluded. It is important however to note that a molar

pregnancy may have a normal hCG level.
7.) Chest X-RAY; once a molar pregnancy is diagnosed. A baseline chest radiograph should be taken. The lungs are a primary site for malignant trophoblastic tumours.
8.) Amniography; this is a useful confirmatory test in centers where other sophisticated techniques are not available. A characteristic soap bubble appearance is seen.

TREATMENT
The patient should be stabilized and transfused if anaemic, rehydrated if indicated and all electrolyte imbalances corrected. Any coagulopathy should be corrected too.

The definitive treatment is evacuation of the uterus by dilatation and Suction curettage. Primary hysterectomy can be considered in older multiparous women. The role of prophylactic chemotherapy in hydatidiform mole is controversial.

FOLLOW UP
A chest X-Ray, ß -HCG assay should be done before discharge. It is important to monitor ß -HCG values serially to identify the rare patient who develops malignant disease. Follow up should be weekly for the first 8 weeks, monthly for the next 10 months, 3-6 monthly for one year and then yearly for life.
Any rise in ß -HCG levels should prompt a chest radiograph and a pelvic examination to facilitate early detection and metastases. Contraception is recommended for 1 year after evacuation. This is to monitor disease progression and to avoid conflicting results as hCG is needed to aid diagnosis. It is important to evaluate all future pregnancies early with ultrasonography because patients with a prior complete or partial mole have a ten fold risk of a second mole in a future pregnancy.

Complications include; Uterine hemorrhage, Coagulopathy, Infection, Recurrence, Malignant transformation,Theca lutein cyst.

Invasive mole.
This may regress spontaneously, but if there is evidence of progression, the treatment is same for choriocarcinoma.

MALIGNANT GTD
This includes retained mole, invasive mole, choriocarcinoma and metastatic GTD.
The diagnosis is made when a woman has rising hCG levels or develops metastases after a molar evacuation. Histological diagnosis of invasive mole or choriocarcinoma is the criteria for malignant GTD.

INVESTIGATIONS
The investigations are basically the same for HM above. HOWEVER, further investigations are prompted by metastatic symptoms.

STAGING
FIGO Staging
I Disease limited to the uterus
II Disease outside the uterus but limited to the genital structures
III Extension to the lungs
IV Other metastatic sites

Each of the stages can be further divided into sub stages
A with no risk factor
B with one risk factor
C with two risk factors

TREATMENT
The mainstay of treatment is chemotherapy.
In the management of choriocarcinoma, prognostic scoring system is usually employed to determine the treatment regime to be used. The score puts into consideration the various risk factors in choriocarcinoma. Patients are divided into low, medium and high risk groups based on this score.

SCORE				
Prognostic factor	**0**	**1**	**2**	**3**
Age	≤39	>39		
Interval (mths)*	<4	4-6	7-12	>12
Antecedent pregnancy	HM	Abortion/ectopic	Term pregnancy	
hCG level	$<10^3$	10^3-10^4	10^4-10^5	
ABO Blood Group. (Female/male)	A/O	O/A	B	AB
Largest tumour(cm)	<3	3-5		
Site of metastasis		Spleen, kidney	GIT, Liver	Brain
Number of metastasis		1-3	4-8	8
Chemotherapy			single drug	multiple drugs

WHO Prognostic scoring of GTD
**Interval between antecedent pregnancy and start of chemotherapy.*

Low risk ≤4 Medium risk 5-7 High risk ≥8

The exact combination varies from centre to centre. However, most are methotrexate- based. Other useful agents include Actinomycin D, 6-mercaptourine, etoposide, cis-platin, cyclophosphomide, vincristine, hyroxyurea, doxorubicin, bleomycin and fluorouracil.

Before commencing, the haemogram of the patient should be noted. PCV less than 30%, WBC less than 2,500cells/mm^3, and platelets less than 100,000 cells/mm^3 are contraindications. The FBC, E/U/Cr should be monitored serially.
Side effects of the drugs include: alopecia, angular stomatitis, anaemia, diarrhoea, thrombocytopenia,

immunosuppression, skin discolouration, hemorrhagic cystitis, abdominal discomfort.

Surgery would be indicated if it is resistant to chemotherapy, if there is uncontrollable hemorrhage or uterine perforation. The use of immunotherapy and radiotherapy has been reported in some quarters[4]. It is important to follow these patients up. This is similar to that of molar pregnancy. The 5-year survival rate is between 70% - 100% depending on the risk group.

CONCLUSION

Gestational trophoblastic disease remains a challenging subject which though has been present for a long time, is still evolving. Prompt presentation and early diagnosis would modify the outcome and thankfully, it is sensitive to chemotherapy.

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