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GESTATIONAL TROPHOBLASTIC DISEASE

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INTRODUCTION

DEFINITION

Gestational Trophoblastic Disease (GTD) defines a group of conditions which develop from fetal chorionic tissue.[12] They result from abnormal proliferation of trophoblastic tissue in the developing human placenta.[10,36]

EPIDEMIOLOGY

1. Incidence

The incidence of hydatidiform mole is different. In the United States it ranges from 1 in 1200 to 1 in 2500 pregnancies.[9] In some Asian countries, the incidence of hydatidiform mole is much higher, as high as 1 in 82 pregnancies.[9] The incidence of choriocarcinoma [36] in Europe and North America is 1 in 40,000 pregnancies and 1 in 40 hydatidiform moles. [36] In Southeast Asia and Japan, choriocarcinoma rates are greater at 9.2 and 3.3 per 40,000 pregnancies, respectively. [36] Previously GTD was associated with significant morbidity and mortality. Hydatidiform moles were often associated with serious bleeding and other complicated medical problems before the development of early detection and effective uterine evacuation in 1970s. The outcome [36] for GTN was bad before the introduction of chemotherapy for its management about fifty years ago.

Choriocarcinoma had a mortality rate of almost 100% when metastases were present and about 60% even when a hysterectomy was done for non metastatic diseases. GTN is now one of the most curable solid tumors with a cure rate of more than 90% even with widespread metastatic disease.[36] The incidence and etiological factors associated with developing a type of GTD have been difficult to identify. The problem in collecting reliable epidemiological data can be related to many factors, such as inconsistencies in the definition of cases, lack of ability to describe the population at risk adequately, no centralized databases, lack of a carefully selected control group to compare possible risk factors and the rarity of the disease.[36]

2. Classification

Classification and terminology of gestational trophoblastic disease (GTD) are varied and can be confusing.[10] GTD can be divided into two main groups: hydatidiform mole and malignant trophoblastic neoplasm (GTN).[10] These two main groups are further classified histologically and clinically.[10]

Table 1: Classification of Gestational Trophoblastic Disease. [10]

HISTOLOGICAL CLASSIFICATION	CINICAL CLASSIFICATION
1. Hydatidiform mole : • Complete • Partial 2. Malignant gestational trophoblastic neoplasia(GTN) A. Post molar GTN • Non invasive trophoblastic proliferation • Invasive mole • Gestational choriocarcinoma • Placental site trophoblastic tumor B.Gestational choriocarcinoma C. Placental site trophoblastic tumor	1. Hydatidiform mole • Complete • Partial 1. Malignant gestational trophoblastic neoplasia(GTN): A. Non metastatic GTN B. Metastatic GTN • Low risk • High risk C. Placental site trophoblastic tumor

3. Risk factors

Risk factors for Hydatidiform moles

1. Age: Compared to the women with ages between 21- 35 the risk of complete mole is 1.9 times higher as well as 7.5 higher for women more than 40 years.[36]
2. Previous history of molar pregnancies: the risk of repeat molar pregnancy after 1 molar pregnancy is about 1-2%, or about 10-20 times the risk for the other population.[36]
3. History of previous spontaneous abortion: [36]this increases the risk 2-3 fold compared to women without a history of miscarriage.
4. Genetic: mutation in NALPR7 gene on chromosome 19q13.4 has been recently identified as the causative gene for familial recurrent hydatidiform mole.[14]
5. Ethnicity: more common in Asian and African women
6. Diet: there is an inverse relationship between the incidence of molar pregnancy and vitamin A (complete mole not partial mole), Folic acid, Beta carotene, protein and animal fat.[36]
7. Ovulation induction for infertility: the use and duration of fertility treatment may be associated with an increase in the incidence of molar pregnancies.[36]
8. Other risk factors like parity, blood group, paternal age, smoking and alcohol are still controversial.

Risk factors for Choriocarcinoma

1. Previous history of molar pregnancy: choriocarcinoma is about 1000 times more likely after a complete mole as compared to any other event of the pregnancy.[36] about 50% of molar pregnancies are followed by choriocarcinoma.[36]
2. Association with a previous abortion in 25% of the cases, ectopic pregnancy in 5% and a full term pregnancy in 20%.[36]
3. Ethnicity: more common in Asian and African women.[36]
4. Advanced maternal age.[25]
5. Long term oral contraceptive use and blood group type A.[36]

PATHOLOGY

Hydatidiform mole and GTN arise from the placental trophoblast. [36]The normal trophoblast consists of cytotrophoblast, syncyttiotrophoblast, and intermediate trophoblast. [36] Syncytiotrophoblast produces human chorionic gonadotropin (HCG), it invades the endometrial stroma with the implantation of the blastocyst. Cytotrophoblast functions to supply the syncytium with cells in addition to forming outpouchings that become the chorionic villi covering the chorionic sac.[36] The chorionic villi close to the endometrium and the basilar layer of the endometrium together form the functional placenta for maternal-fetal nutrition and waste exchange. Intermediate trophoblast is found at the implantation site, in the chorionic sac and villi. All three types of trophoblastic cells may cause GTD when they proliferate.[36]

GTD include four main clinicopathologic forms

1. Hydatidiform mole (molar pregnancy):

   [17] The Oxford medical dictionary mentions hydatid (Greek word for a drop of water) as the watery contents of the cysts. This term also originated from its similarity in appearance to the hydatid cyst of Echinococcosis.[17] [36] The essential characteristics to diagnose a hydatidiform mole are trophoblastic proliferation and the presence of hydropic villi which arise by distension of chorionic villi by fluid, associated with an absent or an abnormal fetus/embryo (complete or partial mole)

Complete mole: There is enlargement of the villi with an absence of any part of the fetus or embryonic tissue. The trophoblast is consistently hyperplastic with different degrees of atypia, and capillaries in villi are absent.[36]

About 90% of complete moles are 46XX, which arise from duplication of the chromosomes of the haploid sperm after fertilization of an ovum in which maternal genetic material has been lost or inactivated.[36] The other 10% of complete moles are 46 XY or 46 XX which arise from fertilization of an empty ovum by 2 sperms.[36] The risk of trophoblastic neoplasia following a complete mole is 15-20%.[36]

Partial mole: it consists of chorionic villi with focal edema which is different in size and shape, with a scalloping and prominent stromal trophoblastic inclusion, a functional villous circulation, and focal trophoblastic hyperplasia with mild atypia.[36] Partial moles are most commonly triploid in karyotype. They are usually 69, XXXY, which arise from fertilization of an apparently normal ovum by 2 sperms.[36] There is a small risk of post molar GTN after a partial mole which is estimated at about 5%.[36]

2. Invasive mole- This is a benign tumor. It arises from myometrial invasion of a hydatidiform mole by direct migration through tissue or venous extension. About 10-17% of hydatidiform moles will lead to an invasive mole, and about 15% of these will metastasize to the vagina or lung.[36]

3. Choriocarcinoma- is a malignant disease which shows abnormal trophoblastic hyperplasia and anaplasia, hemorrhage, necrosis, absence of chorionic villi, and direct invasion into the myometrium.[36] Vascular invasion results in distant spread to liver, lung, brain, kidney, vagina, pelvis, intestine, and spleen. Twenty five percent of cases are associated with term and preterm delivery, 25% follow abortion or tubal pregnancy, 50% follow from hydatidiform mole.[36]

4. Placental site trophoblastic tumor (PSTT)-This is extremely rare. It arises from the placental implantation site and is formed mainly from mononuclear intermediate trophoblasts without chorionic villi infiltration.[36] It appears in cords or sheets between myometrial fibers. Compared to choricarcinoma, it is associated with less vascular invasion, hemorrhage and necrosis.[36] Tumor cells stain positive for human placental lactogen. Epithelioid trophoblastic tumor is a rare variant of PSTT which develop from neoplastic transformation of chorionic type intermediate trophoblasts.[36]

The following table outlines the pathological and clinical features of the different types of gestational trophoblastic neoplasias.[36]

Table 2: Clinico-Pathologic Features of Gestational Trophoblastic Disease[36]

GESTATIONAL TROPHOBLASTIC DISEASE	PATHOLOGIC FEATURES	CLINICAL FEATURES
1.Hydatidiform mole, complete	46 XXY mainly: 46 XY Absent fetus/embryo Diffuse swelling of villi Diffuse trophoblastic hyperplasia Absent scalloping of the villi Absent trophoblastic stromal inclusion	15-20% trophoblastic sequale HCG often more than 100,000 mIU/ml Medical complications
2. Hydatidiform mole, partial	Triploid (69XXY, 69XYY, 69XXX) Abnormal fetus/embryo Focal swelling of villi Focal trophoblastic hyperplasia Scalloping of chorionic villi present Trophoblastic stromal inclusion present	<5% trophoplastic sequale HCG usually <100 mIU/ml Rare medical complications
3. Invasive mole	Myometrial invasion Swelling villi Hyperplastic trophoblast	15% metastatic- lung/vagina Most often diagnosed clinically, rather than pathologically
4. Choriocarcinoma	Abnormal trophoblastic hyperplasia and anaplasia Absent vill Hemorrhage, necrosis	vascular spread to distant sites-lung/brain/liver Malignant disease
5. PSTT	Tumor cells infiltrate myometrium with vascular/ lymphatic invasion Intermediate cells/ absent villi Less hemorrhage and necrosis Tumor cells stain positive for hPL	

DIAGNOSIS OF GESTATIONAL TROPHBLASTIC DISEASE

History

- Amenorrhoea
- Hyperemesis gravidarum
- Vaginal bleeding

Examination

- Uterine size – bigger for dates
- Adnexal mass
- Evidence of metastatic disease eg vaginal metastases

Investigations: [29]

1. Urine and serum HCG: as a base line and to assess the response to chemotherapy. HCG as a marker of this disease is discussed later in the text.
2. Full blood count
3. Renal and liver function tests
4. Thyroid function test
5. Clotting profile
6. Chest x-ray: to check for any lung metastasis.
7. Ultrasound of pelvis and liver: need to exclude pregnancy (which might be the cause of increase HCG) and also to assess the size of intrauterine lesion and to look for liver metastasis. The typical ultrasound findings have been elaborated on earlier in the text.
8. CT abdomen and thorax
9. CT or MRI brain: indicated if there are any neurological symptoms or any pulmonary metastasis.[29]
10. CSF: serum HCG: CSF: serum HCG more than 1:60 indicates central nervous system metastasis.[29]
11. Positron emission tomography (PET) - CT: to find the source of a rising HCG which could not be detected by other imaging tools.[29] This type of scan detects tumor tissue which has high glucose uptake and metabolic rate.

1. Ultrasonography

   This is the standard test used in the diagnosis of molar pregnancy.[17] In the first trimester, the appearance of a complete mole is relatively non specific. During the second and third trimester, the classic features of a snowstorm pattern or cluster of grapes or honeycomb appearance or multiple echoes (holes) can be seen due to diffuse hydropic swelling.[17] Partial mole shows more focal distribution of cystic spaces within the placenta and the presence of embryonic tissue with the ratio of transverse to antero-posterior diameter more than 1.5.[29] Diagnosis can be made usually by ultrasonography but the definitive diagnosis needs histopathological examination.[17]

2. Human chorionic gonadotropin (HCG)

   Human chorionic gonadotropin HCG is disease specific tumor marker which is released by both hydatidiform moles and gestational trophoblastic neoplasms.[36] It is a glycoprotein that consists of an α-subunit which resembles pituitary hormones like TSH, FSH, and LH and hormone specific β- subunit which is unique for placental production.[36]

   A single gene on chromosome 6 encodes for the α subunit and the gene that encodes for the β-subunit is on chromosome 9. [24] HCG has a molecular weight of 36 700 and consists 30% carbohydrate which makes it the highest carbohydrate content compare to other human hormones.[24] The plasma half life for HCG is 24 hours compared to LH, which is one hour.[24] That is because of its high sialic acid content which prevents uptake and degradation of HCG by the liver. The degree of sialylation of HCG in GTD is less than normal HCG.[24]

HCG is synthesized by the syncytiotrophoblast. Its secretion starts early in the pregnancy and reaches the highest level of around 30-100 u/l at 9-11 weeks of pregnancy and stays at that level for a few days.[24] Subsequently, the level starts to decline to 5-10 u/l at 20 weeks and stays at this level for the rest of the pregnancy.[24] The level is related to the size of the placenta which may be higher if there are multiple fetuses.[24] The normal HCG function is to maintain the corpus luteum for continued progesterone secretion which is essential for the maintenance of pregnancy in the first few weeks. Also, it stimulates fetal testicular secretion of testosterone to promote male sexual differentiation.[24]

HCG in normal pregnancy has several forms which include absent c terminal, nicked free β subunit, free β subunit, nicked free β subunit, hyperglycosylated nicked, and free α subunit.[36] The type of HCG in GTD is heterogeneous and degraded more than in the normal pregnancy.[36] In hydatidiform moles, the level of HCG is very high compared to normal pregnancy. Fifty percent of patients with a complete mole have HCG levels of more than 100,000 min/ml prior to evacuation of the uterus.[36] In partial moles, about 10% of the patients may have HCG levels of more than 100,000 min/ml prior to evacuation.[36]

There is no cut off level in diagnosing molar pregnancy but studies have shown that molar pregnancy should be considered if the level of HCG is more than two multiplies of the median. A second measurement should be done if a molar pregnancy is suspected.[36] It is important to note that other pregnancy conditions may present with a high HCG level. The differential diagnosis of a high HCG level should include multiple gestation, erythroblastosis fetalais and intrauterine infections.[36]

Post molar GTN diagnosis is made by finding a rising or plateau level of HCG after evacuation of the hydatidiform mole.[4,36] Choriocarcinoma usually has a high level of HCG when metastases are present. Placental site trophoblastic tumor

commonly has only slightly raised levels of BHCG.[36] False positive results can occur as result of proteolytic enzymes which produce nonspecific proteins and heterophile antibodies.[25,29, 36] These anti bodies are found in 3-4% of healthy people and can mimic HCG immunoreactivity. False positive results due to these antibodies can be excluded by: [29,36]

- Checking HCG level in the urine - these antibodies are not excreted in the urine
- Using different immunoassay to measure the level of HCG.

Another cause for false +ve results is the cross reactivity of LH with HCG. This can be investigated by measuring the level of LH or giving an oral contraceptive to suppress LH secretion.[36]

3. Pathological diagnosis:
   The definitive diagnosis is made by histological examination of curettage specimens or biopsy of metastatic lesions.[17]

   For the diagnosis of post molar GTN we need to get at least one of the following: [4]
   1. Raising HCG level for 4 consecutive readings over 3 weeks
   2. Raise in HCG ≥ 10 % for 3 readings over 2 weeks
   3. Persistence HCG six months post evacuation of a molar pregnancy
   4. Choriocarcinoma diagnosed by histopathology
   5. The presence of metastatic disease

Staging

A staging system based on the anatomical spread has been developed by FIGO (the International Federation of Gynecology and Obstetrics).[4,29] Physicians should use this system for comparison of data and research purposes.[4]

Table 3: Staging for gestational trophoblastic neoplasia: [4,29]

Stage	Description
I	Disease confined to uterus
II	Disease extends outside uterus but is limited to genital structures (adnexa, vagina, broad ligament)
III	Disease extends to lungs with or without genital tract involvement
IV	Disease involves other metastatic sites

CLINICAL PRESENTATIONS AND COMPLICATIONS

1. Vaginal bleeding
   This is the most common presentation of GTD.[17,36] The abnormal and rapid growth of trophoblastic tissue causes separation of blood vessels from the decidual bed which results in painless vaginal bleeding.[17,23] This blood loss may occur gradually and cause severe anemia despite the patient having a normal intravascular volume. Blood transfusion is needed to 32% - 45% of patients.[10]

2. Excessive uterine size
   This is the second most common presentation of GTD.[36] Because of abnormal proliferation of trophoblastic tissue, the size of the uterus will be bigger than the actual size expected for normal gestational age. Retained blood clots and trophoblastic tissue can distend the uterus and cause it to be larger than expected.

3. Hyperemesis gravidarum
   Patients often present with excessive nausea and vomiting which may cause electrolyte and metabolic disturbances. The etiology of hyperemesis gravidarum is unknown.[24] It may be related to BHCG but its role in causing hyperemesis is still unclear.[24]

4. Ovarian theca lutein cysts
   This occurs mostly in patients with high levels of HCG, usually more than 100,000 miu/ml.[10] It has been found that patients with a theca lutein cyst and a uterus size of more than 4weeks than expected for gestational age have a 50% chance of developing post molar GTN.[10] Complications include torsion, rupture, and infection.

5. Pre-eclampsia
   GTD should be suspected in pregnant patients with signs and symptoms of pre-eclampsia in early pregnancy-especially during the first and early second trimester.[10,17] Most patients with pre-eclampsia due to molar pregnancy have an excessively large uterus. [10]

6. Hyperthyroidism
   A normal HCG will have weak thyrotropic activity on TSH receptors.[28] However, because of increase thyroxin binding globulin levels in pregnancy, this will cause a small change in thyroid hormone activity.[24] The degree of the thryotropic effect of HCG is inversely proportional to its level of sialylation.[28] HCG which is secreted in GTD has less sialylation, thus resulting in more thyrotropic activity on TSH receptors.[24] The quanitity of HCG, the degree of desialylation (which is different between each GTD) and

the duration of GTD will determine the severity of hyperthyroidism- ranging from subtle features of hyperthyroidism on the one extreme to a thyroid storm on the other extreme.[28]

Patients with GTD induced hyperthyroidism typically have no features of Grave's Disease like ophthalmic disease, pretibial myxedema, and acropachy.[28] Clinical hyperthyroidism occurs in about 7% of molar pregnancies and biochemical hyperthyroidism is much higher at about 50%. When β HCG reaches more than 200 miu/ml, hyperthyroidism will occur.[28] Thyroid storm which is life threatening emergency, can occur at any stage in the perioperative period. A diagnostic scoring system has been developed for prompt diagnosis of this emergency.[28]

Table 4: Diagnostic Scoring System for Thyroid	
1. Thermoregulatory dysfunction	
Temperature:	
37.2–37.72°C (99–99.9°F)	5
37.78–38.28°C (100–100.9°F)	10
38.33–38.83°C (101–101.9°F)	15
38.89–39.39°C (102–102.9°F)	20
39.44–39.94°C (103–103.9°F)	25
40°C (104.0°F)	30
2. Central nervous system effects	
Absent	0
Mild	10
Agitation	
Moderate	20
Delirium	
Psychosis	
Extreme lethargy	
Severe	30
Seizure	
Coma	
3. Gastrointestinal-hepatic dysfunction	
Absent	0
Moderate	10
Diarrhea	
Nausea/vomiting	
Abdominal pain	
Severe	30
Unexplained jaundice	
4. Cardiovascular dysfunction	
Tachycardia	
90–109 beats/min	5
110–119 beats/min	10
120–129 beats/min	15
130–139 beats/min	20
≥140 beats/min	25
5. Congestive heart failure	
Absent	0
Mild	5
Pedal edema	
Moderate	10
Bibasilar rales	
Severe	15
Pulmonary edema	
Atrial fibrillation	
Absent	0
Present	10
6. Precipitant history	
Negative	0
Positive	10

[28] Scoring: < 25 = unlikely to be thyroid storm.
25–44 = suggestive of impending storm.
> 45 = highly suggestive of thyroid storm.

7. Acute cardiopulmonary distress

The incidence of acute pulmonary distress in molar pregnancy is around 27%.[9] It occurs more frequently in patients with a uterine of size greater than 16 weeks and in patients with very high HCG levels.[10] Signs and symptoms include tachycardia, chest pain, hypoxia, tachypnea, diffuse rales and chest radiographic features of bilateral pulmonary infiltration. Symptoms usually occur within 4-12 hours after evacuation but it can occur at any time during the perioperative period.[9] There are many causes for acute cardio-pulmonary distress: [10]

- Trophoblastic embolization (the main cause in more than 50% of the patients of GTD).
- High-output cardiac failure (which is from thyrotoxicosis).
- Pulmonary congestion (which is from severe anemia).
- Pregnancy induced hypertension.
- Aspiration pneumonitis.
- Sepsis.
- Blood transfusion and acute lung injury which usually manifest 6 hours after transfusion.
- Iatrogenic fluid overload.

8. Disseminated intravascular coagulation (DIC)

Consumption coagulopathy can occur as a result of activation of the coagulation cascade by factors released from abnormal trophoblastic tissue.[17] This may be due to placental tissue release of substances that have some thromboplastin properties.[17]

The clinical features of hydatidiform mole at presentation is summarized in the following table. The most common presentation is vaginal bleeding followed by increased uterine volume and hyperemesis gravidarum.[23]

Table 5: Clinical Features of Hydatidiform Mole.[23]

Author	Period	N	Vaginal bleeding	Increases uterine volume	Hyperemesis gravidarum	Theca lutein cysts	Pre-eclampsia
Soto-Wright et al	1965-1975	306	97%	51%	26%	Not available	27%
	1988-1993	74	84%	28%	8%	9%	1%
Berkowitz et al	1979-1984	81	73%	4%	Not available	0	3%
Coukos et al	1989-1997	24	75%	54%	0	0	0
Gemer et al	1988-1998	41	58%	15%	2%	Not available	0
Present series	1970-1982	311	74%	51%	34%	21%	3%
	1992-2004	189	51%	29%	26%	13%	1%

9. GTN Metastatic Symptoms

The most common sites for metastases of GTN are the lung and the vulvo-vaginal region.[33] Less common sites are the brain and the liver. Other rare sites are skin and bone.[33] The most common presentation of choriocarcinoma metastases to the lung is haemoptysis, chest pain and cough. There are three main types of pulmonary choriocarcinoma:[34]

1. Nodular lesions which may cavitate is found in 65-95% of the patients.[34]
2. Miliary or alveolar pattern with identified margins in 5-15%of patients.[34]
3. Pulmonary infarction and hypertension due to trophoblastic embolisation of the pulmonary artery.[34]

MANAGEMENT OF GTN

1. Chemotherapy

   Treatment is based on classification of patients which is based the prognostic scoring system recommended by FIGO (the International Federation of Gynaecology and Obstetrics).[4,25,29] This system scores patients into two categories. Patients with a score of 0-6 and considered to be low risk patients and will respond to a single agent chemotherapeutic regime.[4,29] Patients with a score of greater than 7 are considered to be high risk and will require a multidrug chemotherapeutic regime.[4,25,29]

Table 6: Scoring system for gestational trophoblastic neoplasia [4,10,25,29]

RISK FACTOR	SCORE			
	0	**1**	**2**	**4**
1. Age, y	≤39	>39	-	-
2. Antecedent pregnancy	mole	abortion	term	
3. Pregnancy event to treatment interval, months	<4	4-6	7-12	>12
4. Pretreatment hCG, mIU/mL	<103	103-104	104-105	>105
5. Largest tumor mass, including uterus, cm	<3	3-4	≥5	-
6. Site of metastases	None	Spleen kidney	GI tract	Brain, Liver
7. No. of metastases	-	1-4	5-8	>8
8. Previous failed chemotherapy	-	-	Single drug	≥ 2 drugs

A. Patients with low risk metastatic disease: include patients with stage I, stage II, stage III, score <7: [4,25,29]

These patients are treated with single agent chemotherapy (like Methotrexate or Actinomycin).[4] Survival rates with this regime approaches 100%.[4] There are different regimes which include different doses and routes of administration. The most effective regime is Methotrexate 25 mg im or iv daily for 5 days which is then repeated every 14 weeks.[4] Alternatively a folic acid protocol with a higher dose of Metotrexate 1.0-1.5 mg/kg IM alternating every other day with folic acid 0.1-0.15 mg/kg IM for 8 days repeated every 15-18 weeks is used.[4]

This is used to avoid the side effects of Methotrexate which include mucositis, stomatitis, skin rash, uterine bleeding, pleuritic chest pain, thrombocytopenia, abdominal pain, liver derangement and pericardial effusion.[4] Actinomycin D is used for patients with resistance to Methotrexate or who have contraindications to Methotrexate use (renal or hepatic compromise). Actinomycin D has more side effect than Methotrexate.[4]

Table 7: Chemotherapeutic Regimes for Low Risk GTN: [4]

CHEMOTHERAPY REGIMEN	Primary Remission Rate %
1. MTX 0.4 mg/kg (maximum 25 mg)/d IV or IM for 5 d; repeat every 14 d	87-93
2. MTX 30-50 mg/m2 IM weekly	49-74
3. MTX 1 mg/kg IM d 1, 3, 5, 7; Folinic acid 0.1 mg/kg IM d 2, 4, 6, 8; repeat every 15-18 d, or as needed	74-90
4. MTX 100 mg/m2 IVP, then 200 mg/m2 in 500 ml D5W over 12 h; Folinic acid 15 mg IM or PO q 12 h for 4 doses beginning 24 h after start of MTX; repeat every 18 d, or as needed	69-90
5. Act-D 10-13 _g/kg IV qd for 5 d; repeat every 14 d	77-94
6. Act-D 1.25 mg/m2 IV every 2 wk	69-90
7. Alternating MTX/Act-D regimens 1 and 5	100

Chemotherapy should continue (regardless of the regimen used) until the HCG level returns to normal level, then at least one course of chemotherapy should be given.[4] Treatment must be escalated to a multi agent regime, if there is no response to the single agent regime, if the HCG levels remain high or if metastases develop.[4]

B. Patients with high risk metastatic disease: include stage II, stage III stage IV, score ≥ 7: [4,25]

They are treated with multi agent chemotherapy with or without radiotherapy or surgery to achieve a cure rate of 80-90%.[4] The most common regime which is used as primary therapy for high risk GTN is EMA-CO.[4] This includes methotrexate, folic acid, actinomycin D, cyclophosphamide, and vincristine.
The response rate with this regime is 71-78% and long term survival rates are between 85-94%.[4]

Table 8: Regime for High Risk Metastatic Disease [4,25]

DAY	DRUG	DOSE
1	Etoposide Actinomycin D MTX	100 mg/m2 IV over 30 min 0.5 mg IVP 100 mg/m2 IVP, then 200 mg/m2 in 500 ml D5W over 12 h
2	Etoposide Actinomycin D Folic acid	100 mg/m2 IV over 30 min 0.5 mg IVP 15 mg IM or PO every 12 h for 4 doses starting 24 h after start of MTX
8	Cyclophosphamide Vincristine	600 mg/m2 IV 1.0 mg/m2 IVP

These patients should continue with at least 3 courses of this regimen after the HCG levels return to normal.[4]

2. Radiotherapy:
   The indication for radiotherapy is brain metastasis.[4,29] The cure rate with central nervous system metastasis ranges between 50-80%.[4] This depends on many factors like patient's symptoms, number, location and size of lesions.[4]

3. Surgery:
   Surgery is still indicated in some patients although GTN is sensitive to chemotherapy.[29] Surgery is indicated when there is resistance to chemotherapy, to control bleeding, to relieve obstructive symptoms like bowel and urinary obstruction due to large lesions, treat infection and to decrease the duration of chemotherapy treatment if fertility is not required.[29]

4. Selective arterial embolization:
   This is a non invasive procedure which may be used to control bleeding in vaginal, uterine and liver metastasis. It can be done under conscious sedation.[29] Complications range from mild eg. post embolization syndrome which includes fever, pelvic pain, and leucosytosis) to more severe eg iliac artery embolization can cause neurological problems in lower limbs and recto-vesico-vaginal fistula.[29]

Follow up:

- During treatment serum and urine HCG should be taken twice a week.
- On completion of therapy, serum and urine HCG should be taken weekly for 6 weeks.29
- After 6 weeks, repeat U/S pelvis, CT/MRI if they were abnormal.
- First year: Urine and serum HCG every 2 weeks in the first 6 months then just urine HCG every 2 weeks for the next 6 months. Contraception for at least the first 12 months.
- Second year: Urine HCG every month
- Third year: Urine HCG every 2 months
- Fourth year: Urine HCG every 3 months
- Fifth year: Urine HCG every 4 months.
- Sixth year and lifelong: Urine HCG every 6 months

Management of Hydatidiform Mole

The management of this condition requires a team approach. Discussion and communication between anaesthetist, obstetrician and endocrinologist must occur soon after the diagnosis of a molar pregnancy. This will allow adequate time for the work up and evaluation of these patients.

Surgical management

The treatment of choice for molar pregnancy is vacuum aspiration. It should be done with an oxytocin infusion 30 units/L running at rate 30 drops per minute after cervical dilatation or after starting the evacuation.[17] Oxytocin decreases the risk of haemorrhage and perforation. Curettage should be done after vacuum aspiration. Bagshawe and colleague [17] reported that when other methods, rather than vacuum aspiration, are used as the first choice for uterine evacuation, the risk of persistent trophoblastic disease increases. Hysterectomy should be considered for patients with severe uncontrolled bleeding, patients past child bearing age and those who have completed their family and want sterilization.[17]

Peri-operative Anaesthetic Concerns

The perioperative anaesthetic concerns include the following:

1. Hyperthyroidism:
   Stable patients with clinical hyperthyroidism should be treated with anti thyroid medications until a euthyroid state is achieved. Emergency patients with bleeding and severe hyperthyroidism should get a dose of a beta blocker and steroid to prevent thyrotoxic crisis. Another option in these patients is plasmapheresis which is used for rapid hormonal control by removing excess hormones.[27] On the other hand, it is an invasive procedure and patients need to be followed up closely because of the risk of a coagulopathy developing postoperatively.[27] Both Erbil et al [(20)] and Ozbey et al [(21)] have reported on the use of plasmapheresis in such patients.

Management of the thyroid storm: [26]

This may occur at any time during the perioperative period.

1. Admission to ICU with supportive therapy include fluid and electrolyte control, oxygen, acetaminophen for hyperpyrexia (avoid aspirin because it increase free thyroid hormones).
2. Treat congestive heart failure.
3. B-blocker as Propanolol or Esmolol.
4. Methimazol or PTU.
5. Lugol's solution or potassium iodide should be used 1 hour after PTU because iodide may cause reflex release of thyroid hormone.
6. Glucocorticoid. [(26)]

Table 9: Drugs used to treat a thyroid storm:[26]

DRUG	DOSE	MECHANISM OF ACTION
1. Anti thyroid drugs: A.Propylthiouracil (PTU) B.Methimazole (Tapazole)	300 mg every 6 hours orally or by NGT,[26] maximum dose per day 1.200-1.500 mg. 30 mg every 6 hours orally or by NGT,[26] maximum dose 120 mg per day	Prevent production of T4 and T3 in the thyroid gland and prevent conversion of T4 to T3 outside the gland. Prevent production of T4 and T3
2. Iodides A. Lugol's solution B.Solution of potassium iodide	10 drops three times a day orally or by NGT.[26] 8 drops every 6 hours orally or by NGT	Prevent release of thyroid hormone from the gland
3. Beta- blocker A. propranolol(inderal) B. Esmolol (Brevibloc)	1 mg/min IV as need then 60-80 mg every 6 hours orally or by NGT.[26] Loading dose of 250-500 mic/kg then infusion 50-100 mic/kg/min	Reduce hyper adrenergic symptoms and prevent conversion of T4 to T3
4. Glucocorticoids A. Dexamethazone (Decadron) B. Hydrocortisone	1mg/min IV as needed then 60-80 mg every 4 hours orally or by NGT. 100 mg IV every 8 hours	 Prevent conversion of T4 to T3

2. Acute cardiopulmonary distress
   This life threatening condition requires ICU support. Some patients may need mechanical ventilation, vasopressor drugs, and invasive monitoring. Because the main cause is trophoblastic embolization, an oxytocin infusion should be started after partial uterine evacuation.[10]
3. Massive blood loss and disseminated intravascular coagulation
   Two large IV lines, blood products, invasive arterial pressure CVP monitoring and vassopresor drugs should be considered. Oxytocin infusion decrease incidence of bleeding but on the other hand it may cause strong uterine contractions which may lead to trophoblastic embolization.
4. Hyperemesis Gravidarum
   Proper parenteral fluid and electrolyte replacement is the first step to treat hyperemesis gravidarum. Different anti emetics and vitamin supplementations can be given.[38] Hyperemesis gravidarum can cause benign and life threatening complications.[38] Benign complications include weight loss, acidosis from malnutrition, alkalosis from vomiting, dehydration, hypokalaemia, electrocardiographic abnormalities, muscle weakness, tetany, and psychological disturbances.[38]

Life threatening complications include oesophageal rupture due to severe vomiting, central pontine myelinolysis, retinal haemorrhage, renal damage, spontaneous Wernicke's encephalopathy, pneumomediastinum, epistaxis due to inadequate intake vitamin K, intrauterine growth retardation, and fetal death.[38]

5. Pre-eclampsia

   Pre anaesthetic examination should include accurate air way examination due to the increased risk of pharyngolaryngeal edema.[39] College of American Obstetricians and Gynecologists (ACOG) and the American Society of Anaesthesiologists (ASA) recommend that regional anaesthesia be used in pre-eclamptic patients without coagulopathy in order to decrease the need for general anesthesia should an emergent procedure become necessary.[39]

Although regional anaesthesia is related to a decrease in maternal mortality, general endotracheal anaesthesia (GETA) is still required in some cases.[39] There are some indications for GETA include coagulopathy, placental abruption, platelet count less than 80,000–100,000/μL in the pre-eclamptic patient, eclampsia and severe pulmonary edema.[39] Management of blood pressure carefully, especially during laryngoscopy and intubation.[39] Short-acting opioids, antihypertensives such as alfentanil or esmolol, and continuation of magnesium sulphate infusion may be useful to decrease the response to larygoscopy and intubation.[39]

Anaesthetic Management

Different anaesthetic techniques such as general anaesthesia, spinal anaesthesia and total intravenous anaesthesia have been reported in the literature.[2,11,17]

General Anaesthesia

General anaesthesia is preferred to provide haemodynamic stability during evacuation of the uterus because of the risk of rapid blood loss.[17] It is also preferred for haemodynamically unstable patients or patients with coagulopathy where spinal anaesthesia should be avoided.[17]If required, esmolol, alfentanil, or magnesium sulphate may be used to blunt the intubation response. In haemodynamically stable patients, thiopentone is the induction agent of choice because of its anti thyroid action.[17] In hemodynamically unstable patients, etomidate is the induction agent of choice.[17]

A non depolarizing muscle relaxant which does not cause histamine release should be used.[17] Depending on the size of the uterus a rapid sequence induction may need to be done. Both volatile and intravenous agents have been mentioned in the literature for the maintenance of anaesthesia.[2,17] However, again there is no clear evidence that advocates one technique over the other. Yoo K. Y et al [18] concluded that the volatile anaesthetics include Sevoflurane, Desflurane, Isoflurane, and Halothane inhibited the spontaneous contractility of isolated pregnant human uterine muscle in a dose-related manner. The degree of inhibition induced by Isoflurane was less to that of Halothane, whereas that induced by Sevoflurane and Desflurane was comparable.[18]

Total intravenous anaesthesia (TIVA): This technique has been documented in many case reports. E Eturk et al [(2)] reported using TIVA in a 25 year old woman

with a molar pregnancy at 12 weeks with hyperthyroidism. He used propofol, remifentanil and esmolol infusions. TIVA can cause a dose dependent decrease in blood pressure and heart rate which may be helpful in thyrotoxic patients [(2).] Also, TIVA can produce hypotension which may decrease blood loss during surgery. Eroglu et al [(2)] reported that TIVA with propofol and remifentanil abolished the endocrine stress hormone release and hemodynamic response to surgery.

Spinal anesthesia

The use of spinal anaesthesia in molar pregnancy with hyperthyroidism also has been reported. Solak and Aturk [11] reported that spinal anaesthesia in patients with hyperthyroidism due to molar pregnancy during evacuation was preferable to general anaesthesia. They mentioned many reasons: [11]

1. The sympathetic block induced by spinal anaesthesia can be helpful.
2. It avoids the tocolytic effect of volatile anaesthesia.
3. Ease of technique.
4. Avoid the effects of ventilation on the pulmonary system.
5. Complications like thyroid storm and cardiopulmonary distress are detected earlier as compared to general anaesthesia. [(11)]

FOLLOW UP [29]

Assess urine and serum HCG level every 2 weeks until the level of HCG returns to normal level then check urine HCG every 6 months.[29] Patients should remain on a contraceptive for a minimum of six months.[29]

CONCLUSION

The incidence of gestational trophoblastic disease varies greatly between countries. Many risk factors are associated with the cause of this disease but the exact cause of this problem is still unknown. Early diagnosis by evaluating clinical presentations, complete investigations, and careful histological and immunehistochemical studies are the main step to avoid critical complications. Communication between obstetricians, anesthesiologist and endocrinologist is essential.

The anaesthesiologist should evaluate these patients for critical complications of molar pregnancy. Different anaesthetic techniques such as general anaesthesia, spinal anaesthesia and total intravenous anaesthesia have been reported in the literature for the management of a molar pregnancy. Both volatile and intravenous agents have been mentioned in the literature for the maintenance of anaesthesia. However, there is no clear evidence that advocates one technique over the other.
Chemotherapy and surgical evacuation are the main part of the management of GTN and hydatidiform mole respectively. Follow up should be done for all patients to monitor the response to treatment.

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