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Molar Pregnancy and other Gestational Trophoblastic Diseases

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INTRODUCTION

Gestational trophoblastic disease (GTD) is a placental disease: it arises from abnormal proliferation of trophoblastic cells in the placenta. When GTD persists or recurs it is often called gestational trophoblastic neoplasm (GTN). The spectrum of GTD includes:

- Complete and partial hydatidiform molar pregnancies: the most common form of GTD invasive mole (GTN).
- Choriocarcinoma, placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT) which are all malignant degenerations of placental tissue. Very rarely no antecedent pregnancy can be identified. PSTT and ETT are rare and are not discussed further in this book.

Most, but not all GTD produce β-human chorionic gonadotropin (hCG), which is also produced in normal pregnancies and can be detected with a urine pregnancy test (UPT).

Complete mole

This is the most frequent form (80% of GTD). Its chromosomal pattern is mostly 46XX and all chromosomes are paternal: often an 'empty' ovum is fertilized by a single sperm that duplicates, but sometimes two sperm cells fertilize an 'empty' ovum. No fetus is present in a complete molar pregnancy. In 15–20% of the complete hydatidiform moles, the trophoblastic tissue persists and causes persistent/invasive mole or choriocarcinoma.

Partial mole

In partial mole, two sperm cells fertilize a normal ovum resulting in a 69XYY, XXX or XXY chromosome pattern. Often a fetus or fetal tissue is present. Only 0.5–2% of partial moles develop into invasive moles[1].

INCIDENCE

Molar pregnancies are rare: approximately 1 in every 400–800 pregnancies is a complete or partial molar pregnancy. Choriocarcinoma and persistent trophoblastic neoplasm are even rarer with an incidence of approximately 1 : 50,000 pregnancies. Risk factors for GTD are:

- Teenage pregnancies
- Pregnancies in women above the age of 35 years
- History of molar pregnancy: the risk of recurrence is 1% after one molar pregnancy and 15–20% after two molar pregnancies[1]
- Smoking
- Blood group A, B or AB
- Nulliparity
- Use of oral contraceptives (no higher chance in persistent/invasive mole)
- History of infertility.

SIGNS AND SYMPTOMS

Early signs and symptoms of GTD are severe hyperemesis, vaginal blood loss in first trimester of pregnancy, anemia, rapid growth of the uterus and early pre-eclampsia (before 20 weeks' gestation). Abdomen distention may be a sign of theca-lutein cysts or ascites; some women have respiratory failure or seizures (due to eclampsia or brain metastasis). In a number of women small grape-like particles are born vaginally. Five per cent of women present with hyperthyroidism; hCG has thyroid-stimulating activity.

In partial moles these symptoms are less pronounced as the hCG levels are lower compared to complete moles.

EXAMINATION

The uterus is enlarged for the gestational age and very soft on bimanual palpation. Sometimes there is some dilatation of the cervical os or the grape-like particles may be visible during speculum examination. A vaginal metastasis can be present.

On vaginal examination metastasis in the vagina can be palpated. One needs to stress that vaginal examinations should be gently performed and once metastases are found in the vagina no further examinations should be allowed since torrential hemorrhage can occur. Remember the vaginal metastases are like icebergs. A small component is found above the surface with a much bigger volume of disease subepithelial.

INVESTIGATIONS

On ultrasound in complete moles a classical picture of a 'snowstorm' is seen. No fetus or amniotic fluid is present. Often in the ovaries enlarged theca-lutein cysts are present (detection rate is 56%[2]). During vaginal ultrasound look for invasion into the myometrium and/or adnexa. In these situations, the risk of uterine perforation and severe bleeding may occur if one tries to evacuate a uterus. Some regard these patients as having invasive molar pregnancies and it may be safer to give them chemotherapy as for choriocarcinomas.

In partial molar pregnancies the ultrasound diagnosis is more complicated: cystic spaces can be seen in the placenta (Swiss cheese appearance). Sometimes multiple ovarian cysts are seen; this is caused by hormonal stimulation by hCG of the ovaries. Often a fetus with or without cardiac activity is present (detection rate of ultrasound is much lower than in complete mole).

The hormonal level of β-hCG in blood and urine is increased (more than two times the median). Measuring the level of β-hCG in blood is often not possible in low-resource settings, but UPT are often available, and may be positive. However a false-negative UPT can be seen in molar pregnancies; therefore blood β-hCG levels are the gold standard in diagnosis and follow-up.

It is advisable to do a chest X-ray in patients with GTD to exclude lung metastasis.

Histological examination from suspicious abortion tissue is the most reliable investigation and should always be carried out if abortion tissue looks abnormal. In settings where histology is impossible it is advisable to do a UPT 4 weeks after evacuation with suspicious tissue. When the UPT is positive 4 weeks post-evacuation, a GTD should be suspected and follow-up of UPT for 12 months is recommended (see paragraph on follow-up).

As chemotherapy may be required, in these patients HIV status needs to be determined as well as CD4 count, as chemotherapy treatment will be complicated in patients with poor immunity and a CD4 count < 200[3]. Anti-retroviral therapy can be administered concurrently with chemotherapy.

TREATMENT

Suction evacuation is the treatment of choice (level of evidence 2C). This can be done by both conventional suction curettage as well as by manual vacuum aspiration (MVA) and preferably should take place in a hospital with blood transfusion possibilities and ideally with an intensive care unit (ICU) department as trophoblastic embolization during evacuation is an emergency requiring ventilation and must be differentiated from cardiac failure, thyroid storm, and acute respiratory distress syndrome (ARDS). Be prepared for massive blood loss [cross-match at least 2 units of blood, have 2 intravenous (IV) drips running] and if you use MVA have at least two MVA sets and one or two assistants who empty the syringes all the time for you, so you can act fast in order to minimize blood loss. Use the largest MVA cannula of 12 mm. If the uterus becomes more empty, blood loss diminishes, the uterus feels gritty and some foam is seen in the MVA. If possible, check this with ultrasound during the procedure. Give oxytocin only at the end of the procedure when the uterus is empty because there is some concern that oxytocics given early can lead to persistent GTD. In patients with uncontrollable vaginal bleeding after suction evacuation, hemorrhage can be controlled by balloon tamponade such as with the Bakri balloon (or low-resource adaption: put condom around indwelling bladder catheter and fill the condom with several hundred milliliters of IV fluid) that is used in post-partum hemorrhages. Sometimes uterine artery ligation or hysterectomy is used to stop blood loss. Major complications of evacuation are blood loss

and uterine perforation. The patient who has severe bleeding from a vagina metastasis may benefit from vaginal packing. Do not try to remove vaginal metastasis because this will bleed profusely.

In partial molar pregnancies it is good practice to give 1000 IU anti-D anti-globulin to Rhesus-negative patients if available. In complete molar pregnancies there are no fetal blood cells and this is not necessary.

Follow-up

Women should receive reliable anti-conceptives after evacuation of a molar pregnancy for at least 1 year because a new pregnancy will interfere with follow-up.

- In resource-rich settings: check serum β-hCG every second week after evacuation of a molar pregnancy until it normalizes, then check it monthly for 1 year: when plateauing or rising hCG GTN is diagnosed[4]. Plateaued hCG is defined as four successive comparable measurements of hCG in 3 weeks. Rising hCG is defined as two consecutive increases in hCG concentration of ≥10%.
- In resource-poor settings the only way to detect recurrence is often UPT and ultrasound. You can start performing monthly ultrasounds 1 month after evacuation. The UPT should be performed once monthly starting from the third to fourth months until 1 year after evacuation of a molar pregnancy. The normal time for the hCG to normalize is 99 days in complete moles and 59 days in partial moles.

Prophylactic chemotherapy for high-risk disease

This is a highly controversial subject and in most situations not the standard practice; nevertheless it is administered in some low-resource settings because doctors fear that patients will not return for follow-up. Two trials showed that in women at high risk for persistent GTD the recurrence rate drops from around 50% to 14% with chemotherapy.

High-risk factors for developing persistent mole are:

- Very high levels of hCG (in case you can check this in the serum >100,000 IU/l)
- Significant enlargement of the uterus
- Large theca-lutein cysts on ultrasound (>6 cm).

Chemoprophylactic drugs are single agent methotrexate or dactinomycin and might be appropriate prophylaxis in women who are difficult to follow-up (Level of evidence 2B).

Twin pregnancies

In twin pregnancies with one viable fetus and one complete molar pregnancy, women might want to continue the pregnancy until term. Pregnancy might be complicated with preterm deliveries, ongoing vaginal blood loss, early and severe pre-eclampsia and intrauterine fetal death. Around 19–57% of these women develop GTN requiring (multiple cycles of) chemotherapy. In only 25–40% of these twin pregnancies, will a live baby be born.

Indications to start chemotherapy[4]

- Where β-hCG estimation is available, plateauing or rising hCG GTN
- In resource-poor settings: positive UPT 4 months after evacuation or earlier if signs of molar pregnancy re-occur on the ultrasound
- Choriocarcinoma
- Evidence of metastasis (check vagina and chest X-ray as these are the most common sites)
- When serum hCG ≥20,000 IU/l 4 weeks after evacuation and when hCG is still present 6 months after evacuation: chemotherapy is advised[4].

Persistent gestational trophoblastic neoplasm

Persistent disease is seen in 15–20% of complete moles[5]: 15% have local recurrence, 4% metastatic disease. Metastatic disease is most often in the lungs (80%), followed by vaginal metastasis, metastasis in liver and in the brain (10%, often in choriocarcinoma). Patients with liver and brain metastasis most often have concurrent lung and liver metastasis. Partial moles have in 0.5–2% local recurrence (generally not distant metastasis)[6].

Most patients are detected because they were followed up after evacuation by hCG measurements. Signs and symptoms of persistent GTD are vaginal blood loss. On ultrasound often a mass is visible in the uterus.

Risk factors for developing GTN after evacuation of GTD are large theca-lutein cysts (ovaries >5 cm), extremely enlarged uterus, women above 40 years, previous GTD, very high hCG levels.

Choriocarcinoma

Choriocarcinoma develops after normal pregnancies in 1 in 50,000, abortions in 1 in 15,000 and after complete molar pregnancies in 1 in 40. As normal pregnancies and abortions are more common than molar pregnancies – 50% of the choriocarcinomas develop after a mole, 25% after an abortion/ectopic pregnancy and 25% after a normal pregnancy.

Choriocarcinoma is more aggressive than persistent GTN: many patients have widespread metastasis at the moment of diagnosis. Signs and symptoms are: vaginal blood loss and signs of metastatic disease like coughing, shortness of breath, pain in the upper abdomen due to liver metastasis and cerebral symptoms due to brain metastasis. On examination women have an enlarged uterus and ovarian cysts; 30% have vaginal metastasis. On ultrasound a mass is seen in the uterus, sometimes extending outside the uterus.

Pretreatment staging and scoring of persistent mole and choriocarcinoma

Minimum required investigations include:

1. Vaginal ultrasound (look for intrauterine and extrauterine signs of disease, it is very good in your follow-up if you have a marker lesion).
2. Chest X-ray: metastasis?
3. Vaginal examination to detect vaginal metastasis.
4. When chest X-ray is negative and no vaginal metastases are found in asymptomatic patients with persistent mole, they do not require brain and liver imaging. When metastasis on chest X-ray or in vaginal examination, and in all choriocarcinoma patients, imaging of liver (ultrasound) and brain (computed tomography/magnetic resonance imaging) are advised, but of course this also depends on the local availability and referral possibilities.

After the staging (Table 1) you can calculate the prognostic score index (PSI) (Table 2). Women with PSI ≤6 need single-agent chemotherapy, women with a PSI ≥7 need multiple drug chemotherapy.

Table 1 The current FIGO staging of gestational trophoblastic neoplasia (GTN)

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

Table 2 Prognostic score index (PSI) of gestational trophoblastic neoplasia/disease (WHO/FIGO)

	PSI			
	0	*1*	*2*	*4*
Age	–	≤40 years	>40 years	–
Antecedent term pregnancy	Hydatidiform mole	Abortion	Term	–
Intervals (months) from index pregnancy	<4	4–6	7–12	>12
Pretreatment hCG (mU/ml)	$<10^3$	10^3–10^4	$>10^4$–10^5	$>10^5$
Largest tumor size including uterus	–	3–4 cm	5 cm	–
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
No. of metastases identified	0	1–4	5–8	>8
Previously failed chemotherapy	–	–	Single drug	Two or more drugs

Score ≤6 = low risk; score ≥7 = high risk.

Prognosis of persistent mole and choriocarcinoma

The cure rate for women who received appropriate chemotherapy is high: the cure rate in women with a PSI ≤6 is almost 100%; the rate for women with a PSI ≥7 is 95%. In 90% of the women the PSI is ≤6, and single-agent chemotherapy should be available on a regional level.

Single-agent chemotherapy

Single-agent chemotherapy is given for low-risk GTN (Table 2, PSI ≤6). Before each administration of the next cycle of methotrexate (MTX), perform a UPT or hCG level in the blood.

Methotrexate

Two schedules are used:

1. *Weekly MTX* is given in a dose of 1 mg per kg body weight intramuscularly (IM), weekly. If available, 24 h after MTX leucovorin (folinic acid 0.1 mg/kg) can be given to reduce toxicity of MTX. Leucovorin is not readily available in low-resource countries and not absolutely indicated for this intermediate dose of MTX. The MTX is repeated every week (8th day). When hCG in serum or UPT is negative, four more consolidation courses of MTX are given.
2. *Bi-weekly MTX* (Charing Cross schedule): the regimen of MTX (50 mg IM every 48 h for four doses on days 1, 3, 5 and 7) with folinic acid rescue (15 mg orally 30 h after MTX on days 2, 4, 6 and 8) regimen is effective and is well tolerated. Courses are repeated every 2 weeks on day 15. After normalization of hCG three more courses are given.

MTX is effective in more than 90% of the patients in International Federation of Obstetrics and Gynecology (FIGO) stage 1 and in 70% of patients with FIGO stage 2 disease. Side-effects are mild: nausea, vomiting, serositis, mucositis, blepharitis or conjunctivitis. Instruct your patient on good oral hygiene! MTX is excreted by the kidneys and can be hepatotoxic: check hemoglobin, leukocytes, thrombocytes, and liver and kidney function before the next administration if possible.

Dactinomycin (actinomycin-D)

This is given at 1.25 mg/m^2 (see Chapter 31 on dose of chemotherapy. You can calculate the body surface area with a free internet tool: http://www.miniwebtool.com/bsa-calculator/metric/), maximum 2 mg IV every 2 weeks. It is less toxic than MTX, but not that easily available. The dactinomycin is repeated every 2 weeks (15th day) and two consolidation courses are given after hCG in serum or the UPT is negative for 4 weeks.

A meta-analysis showed that MTX was less effective than dactinomycin in reaching primary remission in low-risk persistent molar pregnancies (relative risk 3.00, 95% confidence interval 1.10–8.17)[7]. A combination therapy of MTX and dactinomycin was no more effective than single-agent chemotherapy but increased the toxicity[7].

- Resource-poor setting: follow-up after single-agent chemotherapy can be done with monthly UPT for the duration of 1 year. Make sure that the patient uses adequate anticonception (combined oral contraceptive, depot-Provera®, Omplanon® or Norplant®).
- Resource-rich setting: serum hCG after normalization should be measured monthly. Patients with MTX resistance and with hCG in serum ≤100 IU/l can be switched to dactinomycin. When hCG >100 IU/l, they should receive multidrug chemotherapy.

Multiagent chemotherapy

Indications for multiagent chemotherapy are:

- Patients with persistent high-risk trophoblastic disease (Table 2, PSI ≥7)
- Patients with failed single-agent treatment.

There are several regimens for high-risk GTN, but no randomized controlled trial (RCT) has proved the superiority of one schedule above another[8]. Usable regimens are:

- *EMA/CO* (Table 3): this is the treatment of choice in many settings. It is a schedule that should be repeated every 2 weeks until remission (negative UPT, disappearance of all radiological disease) and is than generally repeated for three more cycles (6 weeks). Toxicity is relatively low. In one study all patients had alopecia, rarely hematological toxicity and mild gastro-

Table 3 EMA/CO schedule for persistent high-risk gestational trophoblastic neoplasia (GTN) or patient with failed single-agent chemotherapy for persistent low-risk GTN

Etoposide	100 mg/m^2 IV over 30 min	Day 1 and 2
Methotrexate (MTX)	100 mg/m^2 IV push followed by 200 mg/m^2 IV over 12 h	Day 1
Actinomycin-D	0.5 mg IV bolus	Day 1 and 2
Leucovorin (folinic acid)	15 mg orally every 12 h for 4 doses	24 h after start MTX
Cyclophosphamide	600 mg/m^2	Day 8
Vincristine	1.0 mg/m^2	Day 8

intestinal symptoms. In the long term: 83% of the patients had normal pregnancies after EMA/CO[1] treatment and 2% had developed a secondary malignancy. Complete remission rate was 78–91%[9]. Before administration of drugs, test hCG in serum or urine, Hb, white cell count and if possible platelet count.

- A convenient schedule for resource-poor setting multiagent chemotherapy is depicted in Table 4. It is less expensive than EMA/CO, but no RCT has been done to compare the two schedules! Repeat this course every 21 days. Before administration of drugs, test hCG in serum or urine, Hb, white cell count and if possible platelet count.
- *EMA/EP* – second-line chemotherapy: even in failure of EMA/CO a high cure rate (81%) can be obtained by the more toxic EMA/EP (Table 5). As EMA/EP has high toxicity it should be given by doctors with experience.

Table 4 Low-resource schedule for multiagent chemotherapy for persistent high-risk gestational trophoblastic neoplasia (GTN) or patient with failed single-agent chemotherapy for persistent low-risk GTN

Methotrexate	15 mg/m^2 IM	Day 1
Vincristine	1 mg/m^2 IV in 500 ml normal saline in 60 min	Day 1
or Actinomycin D	2 mg/m^2	
Cyclophosphamide	1000–1500 mg/m^2	Day 1
Methotrexate	15 mg/m^2 IM	Day 2
Methotrexate	15 mg/m^2 IM	Day 3
Methotrexate	15 mg/m^2 IM	Day 4

Table 5 EMA/EP schedule is a second-line chemotherapy treatment for persistent high-risk gestational trophoblastic neoplasia (GTN) or patient with failed single-agent chemotherapy for persistent low-risk GTN that did not respond to EMA/CO

Etoposide	100 mg/m^2 IV over 30 min	Day 1
Methotrexate (MTX)	300 mg/m^2 IV over 12 h	Day 1
Actinomycin-D	0.5 mg IV bolus	Day 1 and 2
Leucovorin (folinic acid)	15 mg orally every 12 h for 4 doses	24 h after start MTX
Etoposide	150 mg/m^2 IV	Day 8
Cisplatin	75 mg/m^2 IV over 12 h	Day 8

Surgery for persistent gestational trophoblastic disease

Some surgical treatment options for persistent GTD are:

- A second suction curettage in patients with persistent GTN might lower the number of necessary chemotherapy cycles[10], but this is not established yet in low-resource settings. Be careful to avoid uterine perforation.
- Hysterectomy reduces the risk of persistent GTD in low-risk women (PSI ≤6) and should be considered for selected patients wishing sterilization at molar evacuation. Hysterectomy can be done in cases of only local recurrence and no wish to save fertility. It can be useful in low-risk persistent GTD[11]. Women with high-risk persistent GTD (PSI ≥7) often already have

metastatic disease for which they need chemotherapy. Hysterectomy in molar pregnancies can be difficult!
- Vaginal metastases are highly vascular. Biopsy or resection of these lesions should not be undertaken since bleeding can be abundant.
- Metastasectomy can be considered in selected patients[11].

Radiotherapy

Brain metastasis can be treated with chemoradiation. You could refer a patient with (isolated) brain metastasis to your national radiotherapy center.

KEY POINTS

- In women with persistent blood loss after abortion and pregnancy, GTN should be excluded: do a pregnancy test!
- Persistent mole is an easily curable malignancy and should be treated as soon as the diagnosis is made and staging is done.
- Single-agent chemotherapy include MTX and dactinomycin and are highly effective in curing women with persistent low-risk molar pregnancies.
- High-risk persistent GTN can still be cured by multiagent chemotherapy.
- In women who do not wish to conceive anymore, a hysterectomy can cure local disease, but is not effective against metastasis.

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Further reading

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