

**Review article**

**A review on gestational trophoblastic disease**

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**Abstract**

Molar pregnancy occurs when the fertilization of the egg by the sperm goes wrong and leads to the growth of abnormal cells or clusters of water filled sacs inside the womb. This condition is one of a group of conditions known as gestational trophoblastic tumours (GTTs). Molar pregnancies used to be called hydatidiform mole but now most people call them molar pregnancies. Molar pregnancies are rare but they are the most common type of gestational trophoblastic tumour. In the UK, about 1 in 590 pregnancies is a molar pregnancy. In Asian women, molar pregnancies are about twice as common as in Caucasian women. Most molar pregnancies are benign. They can spread beyond the womb in some women, but are still curable. Molar pregnancies can either be complete or partial. In case of complete mole, no parts of foetal tissue are formed. In case of partial mole there may be some foetal tissue in the womb, alongside the molar tissue. By measuring the levels of  $\beta$ hCG in blood and urine in high dilution helps to diagnose a molar pregnancy; an ultrasound scan can also diagnose many women with molar pregnancy. The molar tissue needs to be surgically removed. Afterwards, in around 10 to 15 out of 100 women, some molar tissue remains in the deeper tissues of the womb or other parts of the body. This is called a persistent gestational tumour. Invasive mole, choriocarcinoma, and placental site trophoblastic tumor (PSTT) termed as "gestational trophoblastic neoplasia" (GTN), which can progress, invade, metastasize, and lead to

death if left untreated. These women need to have chemotherapy completely get rid of the abnormal cells.

**Key Words :** Molar pregnancy, beta HCG, persistent gestational tumour, choriocarcinoma

**Introduction**

Gestational trophoblastic disease (GTD) is a spectrum of cellular proliferations arising from the placental villous trophoblasts encompassing four main clinicopathologic forms : hydatidiform mole (complete and partial), invasive mole, choriocarcinoma and placental site trophoblastic tumor (PSTT). The term "gestational trophoblastic neoplasia" (GTN) has been applied collectively to the latter three conditions, which can progress, invade, metastasize, and lead to death if left untreated.<sup>1</sup> GTD was historically associated with significant morbidity and mortality. Hydatidiform moles were often accompanied by serious bleeding and other medical complications prior to the development of early detection and only treatment was effective uterine evacuation in the 1970s. The outcomes for GTN were likewise poor before the introduction of chemotherapy into their management 50 years ago.<sup>2</sup>

The mortality rate for invasive mole approached 15%, most often because of hemorrhage, sepsis, embolic phenomena, or complications from surgery. Choriocarcinoma had mortality rate of almost 100% when metastases were present and approximately 60% even when hysterectomy was done for apparent no metastatic disease. Gestational trophoblastic neoplasms are now some of the most curable of all solid tumors, with cure rates 90% even in the presence of widespread metastatic disease.<sup>3,4</sup>

These tumours are rare, and they appear when cells in the womb start to proliferate uncontrollably. The cells that form gestational trophoblastic tumours are called trophoblasts and come from tissue that grows to form the placenta during pregnancy. Choriocarcinoma is very sensitive to chemotherapy, and has a very good prognosis. GTD can simulate pregnancy, because the uterus may contain fetal tissue, albeit abnormal. This tissue may grow at the same rate as a normal pregnancy and produces chorionic gonadotropin, a hormone which is measured to monitor fetal well-being. While GTD overwhelmingly

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affects women of child-bearing age, it may rarely occur in postmenopausal women.<sup>5</sup>

Gestational trophoblastic disease (GTD) may also be called gestational trophoblastic tumour (GTT). As persistent elevation of beta HCG may also be referred to as gestational trophoblastic neoplasia (GTN).

Very rarely a twin pregnancy will show a normal developing baby and a molar pregnancy at the same time. This happens in less than 1 in 100 cases of GTT.<sup>6</sup> The risk of developing persistent trophoblastic disease is higher in this situation. For many women it is possible for the pregnancy to continue. Reports show that in about 25 to 40 out of every 100 of these cases the healthy baby can be delivered and survives. But if someone has complications she may not be able to go ahead with the pregnancy. This is obviously a very difficult situation where invariably risks involved. They may refer to one of the national molar pregnancy treatment centers for advice. It needs proper counseling for further treatment and follows up.<sup>7</sup>

GTD is the common name for five closely related tumours one benign tumour and four malignant tumours. The benign tumour called hydatidiform mole. First a fertilized egg implants into the uterus, but some cells around the fetus the chorionic villi do not develop properly. The pregnancy is not viable, and the normal pregnancy process turns into a benign tumour. There are two subtypes of hydatidiform mole: complete hydatidiform mole and partial hydatidiform mole.<sup>8</sup> The four malignant tumours are invasive mole, choriocarcinoma, placental site trophoblastic tumour, epithelioid trophoblastic tumour. All five closely related tumours develop in the placenta & arise from trophoblastic cells. The trophoblast is the membrane that forms the wall of the blastocyst in the early development of the fetus. In a normal pregnancy, trophoblastic cells aid the implantation of the fertilized egg into the uterine wall. But in GTD, they develop into tumour cells.<sup>9</sup>

### Incidence

Overall, GTD is a rare disease. Nevertheless, the incidence of GTD varies greatly between different parts of the world. The reported incidence of hydatidiform mole ranges from 23 to 1299 cases per 100,000 pregnancies. The incidence of the malignant forms of GTD is much lower, only about 10% of the incidence of hydatidiform mole. The reported incidence of GTD from Europe and North America is significantly lower than the reported incidence of GTD from Asia and South America. One proposed reason for this great geographical variation is differences in healthy diet in the different parts of the

world e.g. carotene deficiency.<sup>9,10</sup> However, the incidence of rare diseases such as GTD is difficult to measure, because epidemiologic data on rare diseases is limited. Not all cases will be reported, and some cases will not be recognized. In addition, in GTD, this is especially difficult, because one would need to know all gestational events in the total population. Yet, it seems very likely that the estimated number of births that occur at home or outside of a hospital has been inflated in some reports.<sup>11</sup>

### Etiology

Hydatidiform moles are abnormal conceptions with excessive placental development. Conception takes place, but placental tissue grows very fast, rather than supporting the growth of a fetus.<sup>12</sup> Complete hydatidiform moles have no fetal tissue and no maternal DNA. A single sperm duplicates and this duplicated sperm fertilizes an empty ovum, or, two sperms fertilize an empty ovum (dispermic fertilization). An empty ovum is a maternal egg which has no functional maternal DNA. Partial hydatidiform moles have a fetus or fetal cells. They are triploid in origin, i.e. one set of maternal haploid genes and two sets of paternal haploid genes. They almost always occur following dispermic fertilization of a normal ovum (fertilization of one egg by two sperm). Malignant form of GTD is very rare. About 50% of malignant forms of GTD develop from a hydatidiform mole.<sup>13</sup>

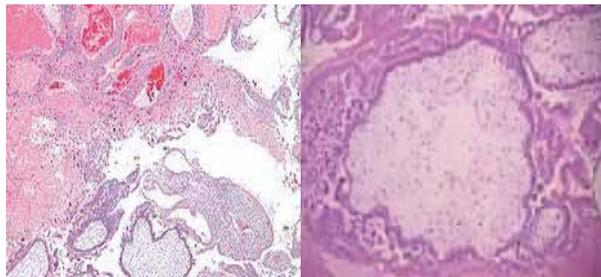
### Risk Factors

Two main risk factors increase the likelihood for the development of GTD - firstly the woman being under 20 years of age or over 35 years of age, and secondly history of previous GTD.<sup>14</sup> Although molar pregnancies affect women of all ages, women under 16 years of age have a six times higher risk of developing a molar pregnancy than those aged 16–40 years, and women 50 years of age or older have one in three chance of having a molar pregnancy. Being from Asia/of Asian ethnicity is an important risk factor. The ABO blood groups of the parents appear to be a factor in choriocarcinoma development, i.e. women with blood group A have been shown to have a greater risk than blood group O women.<sup>15</sup>

### Diagnosis

Cases of GTD can be diagnosed through routine tests given during pregnancy such as blood tests and ultrasound, or through tests done after miscarriage or abortion. Vaginal bleeding, enlarged uterus, pelvic pain or discomfort, and hyperemesis are the most common symptoms of GTD. But GTD also leads to elevated serum human chorionic gonadotropin hormone (HCG). Since pregnancy is by far the most common

cause of elevated serum HCG, clinicians generally first suspect a pregnancy with a complication. However, in GTD, the beta subunit of HCG means beta HCG is also always elevated.<sup>16</sup> Therefore, if GTD is clinically suspected, serum beta HCG is also measured. The initial clinical diagnosis of GTD should be confirmed histologically, which can be done after the evacuation of pregnancy in women with hydatidiform mole however, malignant GTD is highly vascular.<sup>17</sup> Histopathology of hydatidiform mole stained with hematoxylin and eosin shows villi of different sizes. Villous in the center exhibits marked edema with a fluid-filled central cavity which is known as cistern. Marked proliferation of the trophoblasts is observed. The syncytiotrophoblasts stain purple, while the cytotrophoblasts have a clear cytoplasm and bizarre nuclei. No fetal blood vessels are in the mesenchyme of the villi. (Figure-1)



**Figure-1:** Histopathology of hydatidiform mole stained with hematoxylin and eosin

### Treatment

Treatment is always necessary. The treatment for hydatidiform mole consists of the evacuation of pregnancy.<sup>18-20</sup> Evacuation will lead to the relief of symptoms, and also prevent later complications. Suction curettage is the preferred method of evacuation. Hysterectomy is an alternative if no further pregnancies are wished for by the female patient. Hydatidiform mole also has successfully been treated with systemic intravenous methotrexate.<sup>21</sup> The treatment for invasive mole or choriocarcinoma generally is the same. Both are usually treated with chemotherapy. Methotrexate and dactinomycin are among the chemotherapy drugs used in GTD.<sup>22-25</sup> Only a few women with GTD suffer from metastatic gestational trophoblastic disease which has poor prognosis. Their treatment usually includes chemotherapy. Radiotherapy can also be given to places where the cancer has spread, e.g. the brain.<sup>26</sup>

Women who undergo chemotherapy are advised not to conceive for one year after completion of treatment. These women also are likely to have an earlier menopause. It has

been estimated by the Royal College of Obstetricians and Gynaecologists that the age of menopause for women who receive single agent chemotherapy is advanced by 1 year and by 3 years for women who receive multi agent chemotherapy.

### Follow up

Follow up is necessary in all women with gestational trophoblastic disease, because of the possibility of persistent disease, or because of the risk of developing malignant uterine invasion or malignant metastatic disease even after treatment in some women with certain risk factors.<sup>27,28</sup> The use of a reliable contraception method is very important during the entire follow up period, because the follow-up depends on measuring beta HCG. If a reliable contraception method is not used during the follow-up, there can be great confusion if HCG rises. When the patient become pregnant again, the level of  $\beta$  hCG rises & there is great confusion wheather the gestational trophoblastic disease is still present or the patient is pregnant. Therefore, during the prescribed follow up period, the patients must not become pregnant.

In women who have a malignant form of GTD, HCG concentrations stay the same or it rises. Persistent elevation of serum beta HCG levels after a non-molar pregnancy like normal pregnancy, whether term pregnancy, preterm pregnancy, ectopic pregnancy or abortion, always indicate persistent GTD. In rare cases, a previous GTD may be reactivated after a subsequent pregnancy, even after several years. Therefore, the beta HCG tests should be performed also after any subsequent pregnancy in all women who had a previous GTD, 6 and 10 weeks after the end of any subsequent pregnancy.

Women with persistent abnormal vaginal bleeding after any pregnancy, and women developing acute respiratory or neurological symptoms after any pregnancy, should also undergo HCG testing, because these may be signs of a undiagnosed GTD.

### Prognosis and staging

Women with a hydatidiform mole have an excellent prognosis. Also women with a malignant form of GTD usually have a very good prognosis. Choriocarcinoma, for example, is an uncommon, yet almost always curable cancer. Although choriocarcinoma is a highly malignant tumour and a life threatening disease, it is very sensitive to chemotherapy. Virtually all women with non-metastatic disease are cured and retain their fertility. Prognosis is also very good for those with metastatic cancer, in the early stages, but fertility may be lost. Hysterectomy means surgical removal of the uterus can also be offered to

patients > 40 years of age or those for whom sterilization is not an obstacle.<sup>24</sup> Only a few women with GTD have a poor prognosis, those having stage IV GTN (gestational trophoblastic neoplasia) according to the The Federation Internationale de Gynécologie et d'Obstétrique (FIGO) staging system.<sup>25</sup>(table-I) The risk can be estimated by scoring systems such as the modified WHO Prognostic scoring System, where scores between 1 and 4 from various parameters are summed together.<sup>29</sup> FIGO and the AJCC have designated staging to define gestational trophoblastic neoplasia; the FIGO system is most commonly used.<sup>30</sup> Some tumor registrars encourage the recording of staging in both systems.

**Table-I :** Gestational trophoblastic neoplasia (GTN)

FIGO	Anatomical Staging
I	Disease confined to the uterus.
II	Outside of the uterus, but limited to the genital structures (adnexa, vagina, and broad ligament)
III	Extends to the lungs, with or without known genital tract involvement
IV	All other metastatic sites

**Table-II :** Modified WHO prognostic scoring system as adapted by FIGO

Scores	0	1	2	4
Age	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from index pregnancy	<4	4–6	7–12	>12
Pretreatment serum hCG (iu/1)	<10 <sup>3</sup>	10 <sup>3</sup> –10 <sup>4</sup>	10 <sup>4</sup> –10 <sup>5</sup>	>10 <sup>5</sup>
Largest tumor size (including uterus)	<3	3–4 cm	≥5 cm	–
Site of metastases	lung	Spleen, kidney	Gastrointestinal	Liver, brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	≥2 Drugs

**Becoming pregnant again**

Most women with GTD can become pregnant again and can have children again. The risk of a further molar pregnancy is low. More than 98% of women who become pregnant following a molar pregnancy will not have a further hydatidiform mole or be at increased risk of complications. In the past, it was seen as important not to get pregnant straight away after a GTD. Specialists recommended a waiting period of 6 months after the HCG levels become normal. Recently, this standpoint has been questioned. New medical data suggest that a significantly shorter waiting period after the HCG levels become normal is reasonable for approximately 97% of the patients with hydatidiform mole.<sup>30</sup>

The risk of a repeat GTD is approximately 1 in 100, compared with approximately 1 in 1000 risk in the

general population. Especially women whose HCG levels remain significantly elevated are at risk of developing a repeat GTD.<sup>26</sup>

**Persistent trophoblastic disease**

The term persistent trophoblastic disease (PTD) is used when after treatment of a molar pregnancy; some molar tissue is left behind and again starts growing into a tumour. Although PTD can spread within the body like a malignant cancer, the overall cure rate is nearly 100%. In the vast majority of patients, treatment of PTD consists of chemotherapy. Only about 10% of patients with PTD can be treated successfully with a second curettage.<sup>31</sup>

**GTD coexisting with a normal fetus : twin pregnancy**

In some very rare cases, a GTD can coexist with a normal fetus. This is called a twin pregnancy. These cases should

be managed only by experienced clinics, after extensive consultation with the patient. Because successful term delivery might be possible, the pregnancy should be allowed to proceed if the mother wishes, following appropriate counseling. The probability of achieving a healthy baby is approximately 40%, but there is a risk of complications, like pulmonary embolism and pre-eclampsia. Compared with women who simply had a GTD in the past, there is no increased risk of developing persistent GTD after such a twin pregnancy.<sup>25-27</sup> In few cases, a GTD had coexisted with a normal pregnancy, but this was discovered only incidentally after a normal birth.<sup>28</sup>

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