Current management of gestational trophoblastic disease

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Abstract

Gestational trophoblastic disease incorporates a spectrum of disorders ranging from benign to malignant subtypes. At one end of the condition, hCG level monitoring is all that is required, whereas other patients require combination chemotherapy regimens and surgery to cure the disease. The diagnosis can have profound effects on both the patient and her family and it is essential this is recognised and managed appropriately. Although rare, clinicians in non-specialist units are expected to inform patients of their diagnosis and explain the management steps prior to being referred to a specialised Trophoblastic centre and unfortunately, patients may be given inaccurate or incomplete information and use the Internet as their primary source of information. This article intends to explain the diagnosis itself (incidence, genetics, subtypes), clinical presentation and management, whilst answering some of the most commonly encountered questions asked by affected patients.

Keywords gestational trophoblastic disease; management; molar pregnancy

Introduction

Gestational trophoblastic disease (GTD) has historically been described as 'God's first cancer and man's first cure'. GTD is a rare but serious condition, affecting women of childbearing age with an incidence of 1:714 live births. The diagnosis encompasses a heterogeneous group of placental trophoblastic diseases; subdivided into benign (partial (PHM) and complete hydatidiform moles (CHM)) and neoplastic subtypes classified as Gestational Trophoblastic Neoplasia (GTN), which include invasive mole, choriocarcinoma, placental site- (PSTT) and epithelioid trophoblastic tumours (ETT). There are only three specialist referral centres for GTD in the United Kingdom, namely Ninewells Hospital in Dundee, Weston Park Hospital in Sheffield and Charing Cross Hospital in London. Only two of these centres; (Weston Park and Charing Cross Hospital) have established units for the screening, monitoring and treatment of patients with Gestational trophoblastic neoplasia (GTN). It is likely that Obstetrics and Gynaecology trainees will see a handful of cases throughout their career, and it is important to manage and counsel these women and their partners accurately and compassionately at such a difficult time.

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Incidence (Table 1)

Demographics

The risk of GTD is around 20 times higher in teenagers aged <15 years and over 200 times greater in women aged >50 years compared to those aged between 20 and 35 years. The most common underlying theory is that the probability of fertilising an abnormal oocyte is much higher at the extremes of reproductive age. A study by Savage et al., compared the rates of molar pregnancy and chemotherapy requirement to National (Department of Health) age-related pregnancy statistics. Amongst women diagnosed with partial and complete molar pregnancies, the highest risk occurred in women ≥50 years, with the risk of a complete hydatidiform mole as high as 1 in 8 patients. A peak in incidence at the opposite end of the reproductive spectrum (women aged 13 years) was seen for complete, but not partial moles. The risk of complete hydatidiform mole was seen to decline gradually until the age of 36 years, after which the incidence gradually increased. The risk of a partial molar pregnancy gradually increased with age. Chemotherapeutic requirement increased in women with a partial hydatidiform mole until age 30–34 years, before declining thereafter. In complete hydatidiform moles the chemotherapeutic requirement increased steadily with age, peaking at ≥50 years. Interestingly, there was not a corresponding peak in chemotherapy treatment amongst teenagers.

There is insufficient evidence to imply a relationship between gravidity, parity and the risk of GTD, often due to the presence of confounding risk factors (e.g.: maternal age) within the analyses. There is conflicting data regarding the role of female infertility and menstrual disorders upon the risk of GTD; some studies have reported higher rates, while others have not found an association. One group observed significantly higher rates of GTD amongst women who had undergone assisted reproductive techniques, specifically intrauterine insemination using donor semen. The role of smoking upon the risk of GTD is controversial, with some studies showing longer durations of smoking to be associated with an increased incidence of trophoblastic disease. Despite this, several subsequent papers have failed to identify a correlation.

Ethnicity has an important role in the incidence of GTD, yet the exact underlying mechanism remains unknown. Black women are ~50% less likely to develop GTD, whilst the highest rates occur in patients originating from Asia, especially the Philippines and Japan. The blood group of the patient and her partner is an interesting risk factor, as this was previously deemed one of the most important variables and historically included in prognostic scoring systems for GTN throughout the world. The highest risk for GTN development involved women of blood group B or AB with an incompatible partner blood group, i.e.: O or A. It is this patient and partner incompatibility that seems to be the main causative factor, yet in 2000 the International Society for the Study of Trophoblastic Disease

Incidence of GTD and GTN according to histological subtype

	Partial hydatidiform mole (GTD)	Complete hydatidiform mole (GTD)	Invasive mole (GTN)	Choriocarcinoma (GTN)	PSTT (GTN)	ETT (GTN)
Incidence	1 in 695 pregnancies	1 in 945 pregnancies	15–20% following CHM, 0.5–1.7% following PHM.	Europe & USA: 0.02–0.05/1000 pregnancies. SE Asia: 0.4–2/1000 pregnancies. 2–3% following complete hydatiform mole, <0.5% after partial hydatiform mole	1 per 100,000 pregnancies Accounts for 1–2% of GTN	Accounts for < 1% of GTN. ~90 cases published in the literature.

Table 1

(ISSTD) removed this risk factor from the prognostic scoring system due to a lack of definitive evidence regarding it's influence on outcome.

Histology and immunohistochemistry

GTD is characterised by abnormal trophoblastic proliferation, leading to an excess of highly vascular placental tissue. This is evident at the time of surgical evacuation, whereby copious amounts of tissue is removed, often associated with higher than average blood loss; potentially reaching several litres. Macroscopically, the hyperplastic trophoblast forms hydropic, transparent grape-like clusters, which characteristically invade into the myometrium in malignant subtypes forming bulky haemorrhagic masses with varying degrees of necrosis (Figures 1 and 2). Uterine perforation and invasion into surrounding structures (bladder and rectum) may occur in invasive moles, choriocarcinoma, PSTT or ETT subtypes. In partial hydatidiform moles, an intact fetus, gestation sac, fetal parts or fetal erythrocytes may be identifiable, yet the fetus typically demises by eight to nine weeks gestation. This is due to the abnormal placental component, which causes growth restriction and non-viability of the associated fetus.

As would be expected from a spectrum of diseases ranging from benign to malignant subtypes, there is a corresponding continuum of syncytio-, cytotrophoblastic and cytological atypia; ranging from mild in partial hydatidiform moles to moderate to marked in complete and invasive moles, choriocarcinoma.

Histologically, partial hydatidiform moles are characterized by mild trophoblast proliferation (less compared to complete hydatidiform moles) in focal or circumferential areas. The villi are dentate and angulated, compared to complete moles, which have oval shaped, asymmetrical villi. There are occasional and more localised cistern formation and scallops as opposed to the widespread change seen in complete moles. Vasculature and enucleated red blood cells may be present and there is mild cytological atypia. In a complete mole there is marked, grossly abnormal trophoblastic proliferation, occupying a circumferential pattern that surrounds budding, hydropic villi, collapsed stromal blood vessels and stromal karyorrhectic fragments. The stroma is highly cellular and myxoid with evidence of apoptosis. Intervillous trophoblastic bridging is often present; yet different to partial hydatidiform moles, vasculature and nucleated red cells are absent. Unlike partial moles, complete molar pregnancies have marked cytological atypia, which may be difficult to distinguish from choriocarcinoma in some cases.

Histologically, invasive moles are similar to complete hydatidiform moles and choriocarcinoma, with hyperplastic cytotrophoblast, syncytial components and marked cellular atypia. However, unlike choriocarcinoma, invasive moles have chorionic villi, which in comparison to their benign complete mole counterparts are less swollen, more irregular and atypical in appearance. In choriocarcinoma, there are trimorphic sheets containing all three types of malignant trophoblastic cells, with evidence of focal pleomorphism, central necrosis and lymphovascular space invasion. The tumour lacks intrinsic stroma or vasculature, but comprises marked cytological atypia, with numerous mitotic figures.

Using immunohistochemistry complete and partial hydatidiform moles can be distinguished, as complete moles lack the maternally derived p57 gene due to paternal imprinting of this gene expression. Partial moles have p57 nuclear staining in both the villous stromal cells and cytotrophoblast. Choriocarcinomas have a distinctive immunohistochemical profile, displaying a high Ki-67 labelling index, often exceeding 90%.

Genetics

Partial and complete hydatidiform moles both arise at the point of fertilisation, yet these two subtypes are genetically distinct. Partial moles generally compose a triploid conceptus containing 69 chromosomes, and most commonly arise when an ovum is fertilized by two spermatozoa, otherwise known as a dispermic or diandric, monogynic partial hydatidiform mole (Figure 3). An alternative cause involves a disruption in gametogenesis during meiotic division to create a diploid spermatozoa or oocyte, whilst one in ten partial molar pregnancies result from a tetraploid conceptus or mosaic events.

Complete hydatidiform moles are diploid and androgenetic in origin; containing no fetal tissue due to an absence of maternal genetic material. Most (90%) have a 46XX karyotype; with 75% resulting from the fertilization of an empty ovum with a single sperm, which then duplicates its genetic material (monospermic complete hydatidiform mole). The genetic material within this ovum may have been lost either before or after fertilisation (Figure 4a). Approximately 25% of complete moles arise from the fertilization of an empty ovum by two sperms