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Gestational trophoblastic disease

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KEYWORDS
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Staging;
Treatment;
Placental-site trophoblastic tumour

Summary
Gestational trophoblastic disease is a disease of the proliferative trophoblastic allograft and includes partial mole (PM), complete hydatidiform mole (CM), invasive and metastatic mole, choriocarcinoma, placental-site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). Suction evacuation is recommended to terminate CM or PM. PM or CM should be monitored with serum human chorionic gonadotrophin, and effective contraception should be advised for at least 6 months. About 10–20% of patients with molar pregnancy may progress to gestational trophoblastic neoplasia (GTN) which requires chemotherapy. At the 2000 International Federation of Obstetrics and Gynecology (FIGO) meeting, recommendations were made on the criteria for diagnosing GTN and on methods of investigation. Staging was revised to include a modified World Health Organization risk score. The first-line chemotherapy for low-risk GTN is methotrexate and, for high-risk GTN, EMA-CO is recommended. In PSTT and ETT, surgery plays a more important role than chemotherapy. Referral of patients to a centre with experience in treating GTN is important to ensure a good outcome.

Introduction

Gestational trophoblastic disease (GTD) is a disease of the proliferative trophoblastic allograft and includes partial mole (PM), complete hydatidiform mole (CM), invasive mole, metastatic mole, choriocarcinoma (CC), placental-site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT; Table 1). Although CC, PSTT and ETT are definitely neoplastic, the various types of molar pregnancies are basically benign. Only 10–20% of patients with molar pregnancy may progress with a potential to develop malignant disease if left untreated. At the 2000 International Federation of Obstetrics and Gynecology (FIGO) meeting, the term 'gestational trophoblastic neoplasia' (GTN) was recommended for patients whose serum human chorionic gonadotrophin (HCG) level failed to regress in the absence of a normal pregnancy. These patients, similar to those with CC, need chemotherapy treatment. Some centres would further classify GTN to non-metastatic and metastatic GTN and/or low and high risk (Table 1). These patients, especially low-risk GTN, have a good prognosis if treated properly. Hence referral to a centre with experience in treating GTN is important to ensure a good outcome.

Epidemiology

The incidence of GTD is higher in Asia and Latin America than in Western countries. The incidence of molar pregnancy in South Asia ranges from 3.2 to 9.9 per 1000

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Table 1 Classification of gestational trophoblastic disease.

Histological classification
Partial mole
Complete mole
Invasive mole
Metastatic mole
Choriocarcinoma
Placental-site trophoblastlc tumour
Epithelioid trophoblastic tumour
Clinical classification of gestational trophoblastlc neoplasla
Non-metastatic
Metastatlc
and/or
Low risk
High risk

gestations, and in North America the range is 0.6–1.1 per 1000 gestations. However, there seems to be a decrease in incidence in molar pregnancy in some countries such as South Korea and Japan, probably because of an improvement in socio-economic status and a decrease in women conceived at an advanced age or in grand multiparas.

The gathering of data on the incidence of GTD is difficult as the number of pregnancies should include term and preterm deliveries of live and dead babies, ectopic pregnancies, miscarriages (including those that have gone unnoticed with no histological proof) and molar pregnancies. Depending on the reliability of a country's reporting system, errors may occur in both the numerator and the denominator. In fact, in many reported incidences of GTD, a hospital-based delivery rate was used and this may not be representative of the country. Generally speaking, GTD is not a common disease.

Mole

Risk factors for molar pregnancy

Molar pregnancy is more common in women who get pregnant at very young or advanced ages and in grand multiparas. Use of oral contraceptives was generally associated with an increased risk of GTD, with relative risks ranging from 1.1 to 2.6. A recent report showed that a diet low in vitamin A has also been implicated, although the result was not conclusive. Paternal age, smoking, alcohol intake, blood group and infection have no effect on the incidence of GTD. A history of previous molar pregnancy increases the chance of molar pregnancy by 10-fold.

Histological and clinical classification

Histologically, PM is different from CM in the degree of trophoblastic proliferation and the presence of fetal parts or fetal red blood cells. However, in the absence of obvious fetal parts, PM may be misdiagnosed as CM. Conversely, florid hydropic changes of placental villi in missed abortion may be mistaken for PM. Cytogenetic and biomolecular technology can help to differentiate miscarriages from PM, and PM from CM. The majority of CMs have a 46XX genotype with both Xs from paternal origin, identifiable from genetic markers. The majority of PMs are triploid (69XXY) and have both paternal and maternal genetic markers.

Mole is a benign condition. However, it may behave like a malignant disease. Mole can invade locally into the myometrium and even cause perforation of the uterus. Histological diagnosis of invasive mole is usually made on a hysterectomy specimen as it cannot be made based on uterine evacuate. Mole can also metastasize to vagina or lung. Metastatic mole has been diagnosed incidentally on excised vaginal or lung nodules or at autopsy. Spontaneous regression of these metastatic molar tissues has been reported in the past and hence these are not truly malignant. With our increasing understanding of the behaviour of mole, surgical excision of the uterus or ectopic molar tissues becomes a rarity, and histological confirmation is no longer possible. However, from epidemiological studies, a certain percentage of moles may change and behave like malignant disease or even change to a CC histologically. Their typical presentation is a failure of regression of the serum HCG level, and if not treated by chemotherapy, the disease will progress and eventually develop into CC. The term 'GTN' is used to describe this disease entity. GTN can occur following molar or normal pregnancy. Often, no tumour can be found, even on intensive investigation—a non-metastatic GTN; but metastatic lesions can develop—a metastatic GTN. The aggressiveness of the disease depends on a number of prognostic factors such as interval between diagnosis and antecedent pregnancy, age, level of serum HCG, types of antecedent pregnancy (molar or normal), size and number of metastases, and site of metastasis. Many different clinical classifications have been used to classify GTN into different prognostic groups. In 2000, a consensus recommendation on the staging and classification of GTN was adopted by FIGO and will be discussed below.

Clinical management (Table 2)

The classical presentation of molar pregnancy is abnormal vaginal bleeding (75%) in a large-for-gestation uterus (50%) with absence of fetal pulsation. Associations with complications like early onset preeclampsia, anaemia, thromboembolism, hyperthyroidism, hyperemesis gravidarum and large lutein cysts are less commonly seen, especially in developed countries. This could be due to the widespread use of sensitive pregnancy tests and early diagnosis of pregnancy. The use of ultrasound, especially transvaginal ultrasound, in patients with abnormal bleeding during early pregnancy leads to an early diagnosis of molar pregnancy and its termination. Nevertheless, these complications could be life-threatening and should be borne in mind when managing patients with late first or second trimester molar pregnancy. Although there has been an increase in the early