Current management of gestational trophoblastic disease

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Abstract

Gestational trophoblastic disease is a rare pregnancy-related disorder. It comprises of partial mole, complete mole, choriocarcinoma, placental site trophoblastic tumour and epithelioid trophoblastic tumour. Novel immunohistochemical technologies have helped in the diagnosis of the disease and some of the genes may also serve as prognostic markers. Partial and complete moles can be treated by suction evacuation and most patients do not require further treatment. However, 10–20% of them may develop gestational trophoblastic neoplasia. The International Federation of Obstetrics and Gynaecology has adopted a staging system with incorporation of the modified World Health Organization scoring system. Low-risk disease is treated by single-agent chemotherapy while high-risk disease is treated by multi-agent chemotherapy. The overall cure rate is more than 90% and most patients can preserve fertility and anticipate normal pregnancy outcomes. Nevertheless, the disease can recur. Referral to a specialist centre is important to ensure proper monitoring and management.

Keywords choriocarcinoma; gestational trophoblastic disease; gestational trophoblastic neoplasia; hydatidiform mole; management

Introduction

Gestational trophoblastic disease (GTD) consists of a spectrum of pregnancy-related disorders ranging from benign hydatidiform mole to malignant conditions. In the report by the International Federation of Obstetrics and Gynaecology (FIGO) in 2012, gestational trophoblastic neoplasia (GTN) replaces the terms including chorioadenoma destruens, metastasizing mole, and choriocarcinoma, though a histological verification is still desirable. GTN also represents a condition when there is a plateau comprising of at least four persistently elevated human chorionic gonadatrophic (hCG) levels (day 1, 7, 14 and 21), or sequential rise of hCG for two weeks (day 1, 7 and 14) or longer, or lung metastases diagnosed by chest X-ray. Non-metastatic trophoblastic neoplasia refers to diseases localised within the uterus, while metastatic GTN refers to diseases spreading to other sites such as vagina, lungs, liver and brain. Placental-site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT) have distinct pathological and clinical presentation and should be classified separately. GTD was once a fatal disease. But with the advances in the disease diagnosis, better hCG assay, availability of effective chemotherapy, >90% patients can be treated successfully without the need of surgery even in the presence of metastatic diseases.

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Hydatidiform mole

Epidemiology

Hydatidiform mole can be classified into complete (CHM) and partial (PHM) moles. Molar pregnancy is rare, and its incidence varies from 11.5 per 1000 deliveries in Indonesia to less than one per 1000 deliveries in the United States. In the United Kingdom, the incidence of CHM is 1–3 in 1000 pregnancies and that of PHM is 3 in 1000 pregnancy. The accuracy of these epidemiological data depends on reliability of the diagnostic techniques and the availability of a vigilant registry system. Besides, the incidence of molar pregnancy may be under-estimated if the tissue masses are not saved for histological examination after miscarriage or termination of pregnancy.

Molar pregnancy is more common at the extremes of ages. The risk of recurrent molar pregnancy increased to 1–1.8% after one molar pregnancy and to 15–20% after two molar pregnancies. Recent genetic studies also showed that mutation in NLRP7 (formerly known as NALP7) gene on chromosome 19q13 and rarely KHDC3L on chromosome 6, is associated with familial recurrent hydatidiform mole which is an autosomal recessive disorder causing CHM of diploid and biparental in origin. In addition, the use of oral contraceptive pills had been implicated to lead to an increased risk of molar pregnancy and such risk appears to increase with the duration of the use of the pills. On the other hand, the relationship of vitamin A precursor carotene deficiency, late menarache, light menstrual flow, parity, blood group, paternal age, smoking and alcohol consumption with molar pregnancy remains unclear.

Pathology

Cytogenetic studies have shown that CHM has a diploid karyotype and is paternal in origin. 80–90% of CHM are the result of fertilisation of an empty ovum by a haploid sperm which then duplicates its chromosomes. Hence, the karyotype configuration of the CHM zygote is 46, XX. In the remaining cases, an empty ovum is fertilised by two haploid sperms resulting in 46, XX or XY. In PHM, a haploid ovum is fertilised by two sperms. The zygote, therefore, becomes triploid containing 69, XXY, XXX and rarely XYY.

Although less conspicuous in early gestation, CHM is characterised by gross villous vesicles, diffuse hydropic villi and trophoblastic hyperplasia with stromal hypercellularity and

karyorrhoectic debris. The cytotrophoblasts may show nuclear pleomorphism. In contrast, gross villous vesicles are only occasionally seen in PHM and the hydropic villi tend to be smaller and less numerous compared with CHM. Trophoblastic hyperplasia is less obvious and there may be scalloping of chorionic villi and trophoblastic stromal pseudo-inclusion. Normal gestational products like gestational sac, embryo, foetus, foetal erythrocyte or placenta may be present. p57 (KIP2) is a paternally imprinted gene and is maternally expressed. CHM is composed of paternal DNA and so there is absence of p57 (KIP2) nuclear staining in the cytotrophoblasts and villous stromal cells. On the other hand, since PHM and hydropic abortion contain maternal DNA, p57 (KIP2) is positive. Ploidy analysis using in situ hybridisation, flow cytolmetry or short tandem repeat genotyping can determine the paternal or maternal origin of the polymorphic alleles. Thus, it is possible to distinguish between androgenetic diploidy, diandrogenic triploidy and biparental diploidy in the diagnsosis of CHM, PHM and non-molar pregnancy.

Presentation

The most common presentation of molar pregnancy is vaginal bleeding complicating pregnancy. Some may also have passage of vesicles and the uterus may be larger than date on examination. With more popular use of early ultrasound and hCG measurement, molar pregnancy can be diagnosed earlier. Therefore, florid symptoms like hyperemesis gravidarum, hyperthyroidism, early-onset pre-eclampsia, thromboembolism, large ovarian theca lutein cysts and neurological and chest symptoms due to brain and lung metastasis are rarely seen nowadays.

Investigation

Ultrasound, especially transvaginal scan with Doppler flow, may help to detect molar pregnancy. CHM may be diagnosed by features such as anembryonic pregnancy, delayed miscarriage and snow-storm appearance. The suspicion of PHM may be raised when soft markers like cystic spaces in placenta, ratio of transverse to antero-posterior diameters of the gestational sac more than 1.5 are present. In general, the detection rate of molar pregnancy by ultrasound is poor. In one retrospective study involving more than 1000 patients, the sensitivity, specificity, positive predictive value and negative predictive value of ultrasound in detecting hydatidiform mole were 44%, 74%, 88% and 23%, respectively. Therefore, the diagnosis of GTD can only be reliably made with histological examination and it should be performed after every non-viable pregnancy.

Human chorionic gonadotrophin

hCG is a glycoprotein produced by syncytiotrophoblasts containing α and β subunits joined by non-covalent bonds. In normal pregnancy, most hCG is intact. In GTD, there is a higher proportion of β-hCG compared with that in normal pregnancy. Various forms of β-hCG exist in GTD, including free-β, β-core, nicked free-β and carboxyl-terminal fragments. Therefore, an ideal hCG assay for GTD should detect all portions of β-hCG, particularly the free beta subunit, hyperglycosylated hCG (hCG-H), nicked hCG, and hCG missing the terminal carboxyl segment. False-positive and false-negative results can occur. Phantom hCG (pseudohypergonadotropinemia) is a result of the presence of heterophilic antibodies in serum that react with the animal-derived antigens used in commercial hCG immunoassay kits giving rise to a falsely elevated hCG. Heterophilic antibodies may be present in approximately 3.4% of healthy individuals. If there is discrepancy with the clinical presentation, hCG levels should be rechecked with a different immunoassay. The other easy alternative is to measure the urine hCG or its derivatives (free-β subunit or β-core fragment) either quantitatively or qualitatively because heterophilic antibodies have a large molecular size and are not excreted into the urine. So if the serum hCG is persistently positive while the urine hCG is negative, it implies the presence of interference with the serum hCG immunoassay. The lack of linear parallelism with serial serum dilutions can also help to corroborate the presence of false-positive hCG, as heterophilic antibodies react with reagents in the immunoassay and not hCG. Serum can also be pre-absorbed to eliminate the heterophilic antibodies. If the serum hCG returns to negative after the pre-absorption, inference with the immunoassay is confirmed. Low level of pituitary-derived hCG may also be detected in serum in 1.3% peri-menopausal and 6.7% post-menopausal women due to the lack of oestrogen and progesterone negative feedback on the luteinizing hormone and follicle-stimulating hormone (FSH) production. Interpretation of the concurrent FSH level and the use of oral contraceptive pills to suppress the pituitary may be useful to determine the origin of the hCG production.

On the other hand, high dose hook effect can occur with a falsely low serum hCG level. When the serum hCG level is too high, there are not enough antibodies in the solution to bind the hCG molecules and hence much of them are being washed away without being measured. If a very high hCG level is suspected, the laboratory should be informed and the serum should be diluted before measurement.

In a retrospective study on 153 patients, 46% of the patients with CHM had hCG level over 100,000 IU/l before evacuation. However, a cut-off level for diagnosing pregnancy is not known, though some studies showed that molar pregnancy was likely if the hCG level was higher than two multiples of the median or more than 80,000 mIU/ml.

Treatment

Suction evacuation of the uterus can aid histological diagnosis and treatment. Cervical priming immediately before uterine evacuation does not increase the need of subsequent chemotherapy. Medical induction is not recommended for molar pregnancy because of the theoretical risk of myometrial contraction and tumour embolism through the venous system. Besides, medical induction might incur higher risk of incomplete abortion and hence the need of subsequent chemotherapy. Nevertheless, medical abortion may be considered in PHM at second trimester because the foetal parts may obstruct the evacuation and the risk of persistent trophoblastic disease after the procedure is low. Because the uterus is usually vascular and bigger than date, uterine evacuation should be performed by an experienced gynaecologist. If the gestation is more than 16 weeks, the evacuation should be performed in a trophoblastic disease centre. In case of heavy bleeding during the procedure, oxytocic agents can be given, preferably after the evacuation has been completed. Anti-D prophylaxis should be given where appropriate.