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MOLAR PREGNANCY

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ABSTRACT

Hydatidform Mole comprises 90% of gestational trophoplastic disease (GTD) cases. It consists of complete mole (CM) and partial mole (PM). In CM the majority of cases are 46XX androgenetic karyotype with no fetus, while PM are ttriploid karyotype (69, XXY) in the majority of cases with an abnormal fetus. Familial recurrent hydatidiform mole: it is a rare autosomal recessive condition which runs in families. The chromosomes are biparental, unlike the usual androgenetic origin. Several risk factors have been evaluated; maternal age and previous molar pregnancy were the most common. The clinical presentation of CM has changed in the last 2 decades with vaginal bleeding as a common symptom due to earlier diagnosis by first trimester ultrasonography (USG). Most of CM moles are diagnosed in first trimester; a typical appearance of a complex echogenic intrauterine mass containing small cystic spaces is suggestive. Occasionally, cystic lesions are noted in placenta on USG of PM. USG detected both CM and PM before the evacuation in less than 60% of cases, so histological examination of product of conception is essential for the diagnosis. Suction evacuation is the standard treatment irrespective of uterine size. The serum hCG level is a sensitive indicator in follow up the disease process, including treatment response and detection of persistent GTD and relapse. Several risk factors are well known to increase the risk for GTD include: a preevacuation hCG level (> than 100,000 IU/L), Age >40 years, large for date uterine size and presence of thecan-lutein cyst (>6 cm).

KEYWORDS: Molar pregnancy, Complete Mole, Partial Mole, GTD.

Historic overview

Molar pregnancy (MP) also called hydatidform mole (HM). Around 400 B.C, Hippocrates first described hydatidiform mole as “dropsy of the uterus”. He explained their formation through the consumption of dirty water by the pregnant women. A.D.600, “a uterus filled with bladderlike objects” was described by Aetius of Armida. The description of hydatid - mole first used by William Smelie in 1752, he describes this pathology as “a bunch of grapes” consisting of different sizes.[1,2] In the 18th century; Velpeau and Boivin, first documented the disease as “cystic dilations of chorionic villi”. Sanger, described it as a malignant tumor derived from the decidua. Marchand described that these tumors are related to pregnancy and they are proliferation of the syncytium and cytotrophoblast. In beginning of 19th century, excessive levels of gonadotropic hormone in the urine of patients with mole were documented by several authors interested in this topic.[3]

Pathological classification

HM belongs to gestational trophoblastic disease (GTD) which is a heterogeneous group of interrelated lesions arising from the trophoblastic epithelium of the placenta. HM comprise 90% of GTD cases. HM is made up of two distinct entities, complete hydatidiform mole (CM) and partial hydatidiform mole (PM). MP, although benign, is considered to be premalignant because they have the potential to develop into a malignancy. Malignant GTD are invasive mole and choriocarcinoma. All GTD are characterized by high production of human chorionic gonadotropin (hCG) and ability to metastasize. Placental site trophoblastic tumor is locally malignant GTD characterized by being locally invasive and usually produces low levels of hCG. GTD was associated with significant morbidity and mortality before the discovery of effective chemotherapy approximately 50 years ago. At present, GTNs are among the most curable of all solid tumors, with survival rates approaching 100 %.[4] This review will concentrate on hydatidform mole pregnancy only.

Epidemiology

There is wide range of difference in incidence in different regions of the world. in North America and Europe, the incidence of HM to range from 0.57–1.1 per 1000 pregnancies, whereas studies in Southeast Asia and Japan have suggested an incidence as high as 2.0 per 1000 pregnancies, 1 per 250 pregnancies in Philippines, and much higher in Taiwan, 1 per 125 pregnancies.[5,6] In

UK, the incidence is around one per 1000 pregnancies.[7] Recent report from Japan showed a decreased incidence to figures similar to Europe and USA 1 per1000 pregnancies.[8] These variations may be attributed to the difference in the reporting data source, whether population‑based or hospital‑based. The other factors that may be responsible for this variation in the occurrence of molar pregnancy include race or ethnic group, socioeconomic and nutritional factors.[9]

Genetics and Pathology

HM is the result of a pregnancy with an abnormal karyotype due to an abnormal fertilization leading to abnormal proliferation of placental villi associated with an absent or an abnormal fetus/embryo.

Complete mole: The majority of cases are 46XX androgenetic karyotype result from the fertilization of an empty ovum with one haploid sperm which duplicates leading to karyotype of paternal origin,[4,10] but fewer cases are 46XY result from dispermic fertilization of an empty ovum.[11] The molar chromosomes are derived completely from the father, while the mitochondrial DNA has a maternal origin.[12]

Partial hydatidiform: Most partial moles result from the fertilization of a normal ovum by 2 sperms, leading to a triploid karyotype (69, XXY), less common triploid karyotypes (69XXX or 69XYY).[13]

Familial recurrent hydatidiform mole: is defined when patient had more than 2 consecutive moles, it is a rare condition which runs in families. Genetic mapping has shown that the gene responsible for this condition is located in a 1.1 Mb region on chromosome 19q13.4.[14]

The chromosomes are biparental, unlike the usual androgenetic origin.[15] The condition is autosomal recessive, mutations have been identified in over 50 families of bipaternal CM, it includes deletions, insertions, duplications and amino acid substitutions of leucine-rich region of *NLRP7*, suggestive that this region is essential for normal function.[15,16] This results in dysregulation of imprinting in the female germ line with abnormal development of both embryonic and extraembryonic tissue. Pregnancies in these women will always result in molar pregnancy; eighteen consecutive molar pregnancies have been reported in the literature.[17] Oocyte donation in these women is the only way to achieve normal pregnancy.[18]

Etiology and risk factors

Several risk factors have been evaluated; maternal age and previous molar pregnancy were the most common.

Maternal age

CM commonly occurs in extreme reproductive age women, while PM is not.[6] Girls younger than 15 years are at 20 times higher risk when compared to women aged 20-40 and women older than 45 years are at several hundred-fold higher risk when compared to women age 20-40.[19] It is well known that oocytes of older women are more susceptible to abnormal fertilization when compared to younger women.

History of previous molar pregnancy

A patient with history of MP will increase her risk by 1%, or 10-20 times the risk for the general population.[20,21] After two molar pregnancies, the risk of a third mole is 15–20%[22]

Many other risk factors have been postulated like ethnicity, geographic area, dietary factors and blood groups. Molar pregnancy is more common in Asian, it has been shown that race or ethnicity are risk factor for both CM and PM.[23] However, the incidence is falling in Asian countries, this could be related to an improvement in socioeconomic and dietary factors as animal studies have shown that diet can reset genetic outline.[24] For example, in South Korea, the incidence of molar pregnancies has dropped from 4.4:1000 pregnancies in the 1960s to 1.6:1000 pregnancies in1990s, and in Saudi Arabia, the incidence has fallen in 1988 from 1.5:1000 pregnancies to 0.9:1000 pregnancies in 2017.[9,25]

CLINICAL PRESENTATION

Complete mole

The clinical presentation of CM has changed in the last 2 decades.[21] Historically; the classical presentation in second trimester such as large for date uterine enlargement, pre-eclmpsia, hyperemsis gravidarum, thyrotoxicosis, anemia, excessive enlargement of the ovaries by theca-lutein cyst are rarely seen due to earlier diagnosis by first trimester ultrasonography (USG).[26] Vaginal bleeding is the commonest symptom; most patients are diagnosed before complications appear due to implementation of routine first trimester USG and referral of any pregnant patients with bleeding to USG.[27] Most of the complications associated with CM are a consequence of elevated hCG.

Partial mole

Unlike CM, no changes in clinical presentation had occurred. Patients usually present late in first trimester or early second trimester as missed or incomplete abortion with vaginal bleeding as a common symptom.

Diagnosis

Ultrasonography (USG)

The classical “snow storm appearance” on USG in second trimester of pregnancy is diagnostic but it is rarely seen nowadays because most of CM mole are diagnosed in first trimester, a typical appearance of a complex, echogenic intrauterine mass containing small cystic spaces is suggestive.[26] Occasionally, cystic lesions are noted in placenta on USG of PM. However, USG detected both CM and PM before the evacuation in less than 60% of cases.[4,27] Histological examination of product of conception is essential for the diagnosis.[6]

Quantitative hCG measurement

CM is characterized by hyperplasia of trophoplastic cells which produce hCG in high amount. hCG level >100,000 IU/L is typically suggestive of CM, while PM infrequently present with elevated hCG. Less than 50% of patients with CM and 7% of patients with PM will have hCG >100.000 IU/L.[28,29] Measurement of hCG is also important for follow up post evacuation or termination for detection of GTD if hCG rises or plateaus. This is evident when the level is markedly elevated, and the uterine size is large for date.[30]

Treatment

Suction evacuation is the standard treatment irrespective of uterine size. The procedure should be done or supervised by a senior obstetrician. Preparation before surgery include a plain chest x-ray to rule out trophoblastic emoblisation to lungs, blood group and rhesus, type and cross match 2 units of packed red blood cells, complete laboratory testing of hemoglobin, hematocrit, renal, liver and thyroid function test. Medical induction to ripen the cervix should be avoided since it can induce contractions and increase the risk of trophoblastic embolisation.[31] Once dilation of cervix id done and suction started, oxytocin should be given to prevent bleeding. Suction should be done gently to avoid uterine perforation. For rhesus (RhD) negative patient should be given immunoglobulin at the time of evacuation because the RhD antigen is present in trophoblasts.[31]

Follow up after evacuation

The serum hCG level is a sensitive indicator for following the disease process, including treatment response and detection of persistent GTD and relapse. It is estimated that 15-20% with CM and 1-5% with PM will progress to GTD.[32,33] In developed countries, patients are booked to registry centers for close monitoring of hCG. With this organization, fewer patients are lost to follow up, early diagnosis of GTD is made and further treatment can be initiated. The numbers of patients with seriously advanced GTD are falling as countries improve their technique for management of these patients.[30] However, when the hCG concentration falls rapidly to normal after uterine evacuation, women are at low risk of developing subsequent GTD.[4,34]

The American College of Obstetricians and Gynecologists suggests that patients with HM should obtain hCG levels 48 hours after evacuation and every 1 to 2 weeks until levels are normal for two consecutive time. Once undetectable levels are reached, follow-up measurements are made at monthly intervals for an additional 6 months.[35]

In UK all women with HM or GTD are registered for monitoring and treatment in 3 distributed centers across the country. The Royal college of Obstetrician and Gynecologist adopted different guidelines: after registration, follow-up consists of serial estimation of hCG levels, either in blood or urine specimens. Normalization of hCG is expected within 56 days, if hCG has normalized within 56 days after evacuation then follow up will be for 6 months from the date of evacuation. If hCG has not normalized within 56 days of evacuation, then follow-up will be for 6 months from normalization of the hCG.[32,36] During the follow up patient should be instructed not to get pregnant, initially barrier methods are recommended until normalization of hCG, Oral contraceptive pills (OCP) are not recommended at this stage due to suppression effect on endogenous luteinizing hormone, which may interfere with the measurement of hCG.[37] Once hCG is normalized, OCP is a good choice to continue the follow up period, studies have shown that OCP do not increase the risk of GTD.[38,39] Frequent pelvic examinations are performed while hCG values are elevated to monitor the involution of pelvic structures and to aid in the early identification of vaginal metastases. PM has low risk of progression to GTD, discontinuation of surveillance after first normalization of hCG is recommended and patient can be allowed to fall pregnant.[40]

Because of the increased risk molar disease in patients with CM, USG examination and hCG level is recommended in the first trimester of a subsequent pregnancy to confirm that the pregnancy is normal, hCG levels are measured 6 weeks postpartum to exclude disease recurrence and placenta should be evaluated histologically[41]

Management of special cases

CM or PM with normal twin is uncommon condition. The diagnosis can be done by USG. If the pregnancy is uncomplicated with normal karyotype, after appropriate counseling regarding the increased risks for obstetric complications like hemorrhage, preeclampsia, preterm delivery and GTD, the pregnancy can be allowed to continue if patient desires.[42] In a series of 90 patients with CM and normal twin pregnancies 57% delivered a live baby at a median of 34 weeks gestational age. GTN developed 26.7% pregnancies, and there were no reported maternal deaths.[43] Following delivery, the placenta should be evaluated histologically and serial hCG level, similar to management of a woman with a singleton CM.

Diagnosis of post molar GTD

Several risk factors are well known to increase the risk for GTD include: a pre-evacuation hCG level (> than 100,000 IU/L), Age >40 years, large for date uterine size (.>20 weeks sized) and presence of theca-lutein cyst (>6 cm).[44] The International Federation of Gynecologists and Obstetricians (FIGO) standardized the following hCG criteria for the diagnosis of postmolar gestational trophoblastic disease: An hCG level plateau of four values ±10% recorded over a 3-week duration (days 1, 7, 14, and 21). An hCG level increase of more than 10% of three values recorded over a 2-week duration (days 1, 7, and 14). Persistence of detectable hCG for more than 6

months after molar evacuation.[45] Rising or plateaued hCG is an indication to start chemotherapy. If patient is under close surveillance with high hCG after 6 months of evacuation but falling level, is not an indication to start chemotherapy. If hCG is >20,000 IU/L 4 weeks or more after evacuation, there is increase risk of uterine perforation and hemorrhage, some centers recommend chemotherapy.[4] Another indication for chemotherapy is when GTD, namely coriocarcinoma, is diagnosed based on histological examination, or in case of suspected metatsatsis to distatnt organs and high hCG level in a young woman in childbearing age.

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