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REVIEW ARTICLE

Hydatidiform mole

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SUMMARY

This article critically reviews the current understanding of the origin of hydatidiform mole. The pathogenesis, clinical presentation and diagnosis is discussed. Suction curettage and close patient follow up reduces the mortality and morbidity of the patients with this disease.

INTRODUCTION

Changes have occurred over the years in the understanding of the pathogenesis, classification and follow up management of benign gestational trophoblastic disease (Hydatidiform mole).

Hydatidiform mole is a benign gestational trophoblastic neoplasm which can potentially progress to choriocarcinoma.[6] It arises from placental chorionic tissue of foetal origin, i.e. trophoblastic tissue. If in the normal formation of the placenta during pregnancy the trophoblastic tissue becomes highly proliferative this can result in the formation of a hydatidiform mole.

Trophoblastic tissue invades the myometrium and maternal blood vessels during the implantation and development of the placenta resulting in the formation of lakes. This increases the absorptive surface area for the maternofoetal transfer. During this invading process some trophoblastic cells enter the uterine veins and blood stream resulting in embolization of trophoblasts to the lungs. During parturition embolization of trophoblasts also occurs.

The presence of trophoblasts in the lungs therefore does not mean invasive malignancy.

Trophoblastic tissue of a mole like trophoblasts of a normal placenta produce a wide range of hormonal and protein compounds. The range includes oestrogen, progesterone, human placental lactogen, prolactin, preg-

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nancy specific globulin B1 SP1 and human chorionic gonadotrophin.[13] HCG is a glycoprotein molecule made up of two chains A and B sub units. HCG is similar to the pituary glycoproteins LH+FSH except its B subunit. Apart from the gestational trophoblastic disease (Hydatidiform mole, Choriocarcinoma) there are HCG producing tumours. These are malignant teratoma, embryonic tumours and dsysgeminoma. Dysgeminoma produces HCG when it contains giant syncytio-trophoblasts. The human chorionic gonadotrophin (HCG) has superseded all the other molar products as a perfect tumour market. HCG is used in the diagnosis and follow up management of hydatidiform mole. As long as the tumour cells are alive HCG will be produced and the quantity in urine or serum correlates with the number of viable tumour cells[1]. Specific radioimmunoassay methods have been developed to measure the B subunit of HCG and thus differentiation between HCG and LH/FSH/TSH can be made accurately particularly at low levels of these hormones.

Hydatidiform mole is classified into two distinct clinical types based on pathological and cytogenic studies. The two types are complete (classical) and partial moles.[14]

Complete moles: Complete moles have a macroscopic appearance of a large tumour with clusters of translucent vesicles filled with fluid i.e. the grape like vesicles.

The vesicles are one centimetre in diameter on average. On microscopy the villi are oedematous and avascular. The trophoblasts are hyperplastic with anaplasia. There is no microscopic or macroscopic evidence of any embryo, amniotic membranes or umbilical cord.[7] The absence of foetal vessels differentiate a complete from a partial mole. Complete moles have been shown to be androgenetic. A proportion of complete moles give rise to persistent disease or malignant transformation.

Partial mole: A partial mole is characterised by a normal chorionic villi with macroscopic or microscopic evidence of a foetus. Microscopically normal placental tissue with focal trophoblastic hyperplasia scattered within the placenta is found. Foetal vessels are seen. A partial mole has to be differentiated from hydropic degenerative changes in an abortion. Cytogenetic studies have demonstrated triploid chromosomal constitution as discussed below. Partial moles are thought not to give rise to persistent or malignant transformation.

Invasive mole (*Chorioadenoma destuens*): This occurs when trophoblastic cells invade into or through the uterine wall. Although embolisation of trophoblasts can occur these are not metastases. In choriocarcinoma sheets of malignant trophoblastic cells can be identified without any villous structure. The cells are large, anaplastic, irregular syncytial giant cells..

The risk of malignancy of gestational trophoblastic disease cannot be determined from the pathological appearance of the trophoblastic cells. The management of molar pregnancy depends on the HCG levels rather than its malignant potential on the histological appearances.

Pathogenesis of hydatidiform mole: The exact cause of hydatidiform mole remains unknown and it is thought to be a multistage process. The pathogenetic process is established at the time of conception linked to a defective ovum resulting in abnormal structure and function of the trophoblasts.[12] Serial ultrasonographic studies of early pregnancy supports the theory that a molar pregnancy arises from an abnormal blighted ovum embryo which is followed by accumulation of fluid in the villi and trophoblastic proliferation.[10]

Cytogenetic studies of molar chromosomes has led to the discovery that the majority of complete moles have paternal chromosomal karyotype of 46 XX. The two X chromosomes are derived from the male partner. This results from fertilisation of an empty ovum by haploid sperm with 23 X chromosomes.

Subsequent duplication of the fertilised egg results in a 46 XX diploid number.

A 46 XY karyotype has been demonstrated in a minority of complete moles. This occurs from dispermia i.e. two spermatoza with 23 XY and 23 XX fertilises an empty egg. The mechanism of how the female haploid chromosomes are lost is not known. Partial moles on the other hand were found to have triploid or trisomy chromosomal pattern.[9] This occurs when a normal egg is fertilised by two sperm (double paternal contribution).

Studies have shown a higher incidence of the disease in the older age group i.e. over 40 years[5] and the young age group under 20 years. Bagshawe (1986) showed that the risk of hydatidiform mole was six times greater in pregnancies occurring under 15 years of age and 400 times greater for those over 50 years. Previous molar pregnancy increases the risk of another molar preg-

nancy. Various authors have found different recurrence rates; one in 150, one in 50 and one in 76[2]. The Charing Cross (UK) series have shown that one molar pregnancy increases the risk of a second one by 10 fold and a second molar pregnancy is associated with a further 10 fold increase of another hydatidiform mole.

The incidence of hydatidiform mole in the world is variable due to genetic, geographical, racial and environmental influence. The disease is more common in the Fast East; Indonesia one in 200 pregnancies whilst in the United Kingdom the incidence is reported as one in 500 pregnancies.[15] Parity has not been shown to be a high risk factor in hydatidiform mole.[2]

A high index of suspicion is required to diagnose hydatidiform mole before the passage of the pathognomonic grape like products because the signs and symptoms are often those of early pregnancy. Hydatidiform mole should be considered in the differential diagnosis of vaginal bleeding in early pregnancy. The vaginal bleeding in hydatidiform mole commonly occurs around the 12 weeks of pregnancy. Severe life threatening haemorrhage leading to hypovolaemic shock and deaths have been reported. Management of hydatidiform mole has to be in a hospital with sufficient blood bank back up.

Hyperemesis gravidarum is a common symptom. The vomiting associated with hydatidiform mole is due to high circulating HCG levels and the enlarging uterus pressing on the abdominal viscera.

The early onset of PET before 20 weeks of pregnancy is a strong pointer to molar pregnancy. A 70 pc incidence of pre-eclampsia in association with a large rapidly growing uterus has been documented. Pre-eclampsia in association with hydatidiform mole is due to excessive trophoblastic activity and hormonal imbalance although Scott *et al* attributes the cause to the presence of paternally derived chromosomes in molar pregnancy.

Hyperthyroidism associated with molar pregnancy is due to the production by trophoblastic cells of a thyrotropin hormone which stimulates thyroid hormone production. In the mild form of the disease; tremor, tachycardia or nervousness can occur. In severe thyrotoxicosis however congestive cardiac failure, goitre or weight loss can develop. Evacuation of the molar pregnancy is usually accompanied by spontaneous resolution of the thyrotoxicosis.

A partial mole can co-exist with a live foetus and thus a foetal heart can be heard.[4] Generally the foetus associated with a partial mole tends to die in early gestation.

Uteri greater than 16 weeks or four weeks greater than the missed period are associated with a higher incidence of trophoblastic embolization.

The diagnosis of embolization can be confirmed by the demonstration of villous trophoblasts in the pulmonary vasculature at autopsy or from blood obtained from the pulmonary artery by Swan Ganz Catheter. The incidence of embolization has been found to be 2,6 pc and 5,4 pc.[17] Patients who develop pulmonary embolization subsequently develop trophoblastic neoplasia. Fourteen pc and 20 pc incidence were found by Curry *et al* and Howie respectively.[5]

Ovarian cysts found in association with large for dates uteri have a high incidence of malignant trophoblastic sequelae. The ovarian cysts are the theca lutein which are caused by a high HCG level.

A positive pregnancy test is not diagnostic of a hydatidiform mole and neither is one HCG titer.

The HCG titer in normal singleton pregnancy show a wide variation and rises from the first week of conception to peak between 50-70 days, falling thereafter to low levels. The levels fall after 80 to 90 days of pregnancy.[5]

The peak serum levels are in the region of 120-160 iu/ml. High HCG levels are also found in molar pregnancies and racial difference in HCG titers have been demonstrated. In multiple pregnancy the HCG levels are higher. Due to this wide titer variation the diagnosis of molar pregnancy cannot be made on a single sample. Sequential samples showing progressive increase in HCG titers or titers over 1 000 iu/ml are suggestive of hydatidiform mole.[15,16] However, this method has been superceeded by ultrasound scanning of the uterus as a diagnosis of molar pregnancy in those centres with ultrasound.

Ultrasound scanning can be used in the first trimester and can be repeated if the diagnosis is in doubt. In centres where the ultrasound machine is available, it should be used as a standard diagnostic technique for molar pregnancy.

The features of hydatidiform mole on ultrasound scanning are:-

a) Snow storm appearance - this picture is produced by the echoes from the vesicular molar tissue. Small white dots and dashes are seen on the scan.
   However, early placental development can mimic the presence of a hydatidiform mole and this necessitates scanning the entire cross section of the uterus to exclude the presence of foetal parts.

b) In hydatidiform mole, no foetal echoes or foetal heart can be demonstrated. In multiple pregnancy misdiagnosis can occur because the size of the uterus will not be proportional to the gestation. Serial repeat ultrasound studies are advisable when a developing foetus is suspected. Misdiagnosis are rare in experienced ultrasonographer's hands.

Ultrasound scanning is useful in the diagnosis of a partial mole especially in the presence of a viable foetus.

Large homogenous solid ovarian teratoma, lymphoma or dysgerminoma can be misdiagnosed as hydatidiform mole on ultrasonography.[8]

X ray of the pelvis at 16 weeks can be helpful in centres where ultrasound scan is not available. At 16 weeks the foetal skeleton will show on X ray. In multiple pregnancy or wrong dates the foetal skeleton may not show.

DIC is a known complication of hydatidiform mole. DIC is caused by embolization of trophoblasts to the lungs where they release thromboplastin substances into the circulation. Thromboplastin stimulates fibrin and platelet deposition into the blood vessels leading to consumption coagulatory.

Spontaneous abortion of a mole does occur and is associated with a low complication rate. In young patients dilatation suction curettage is the primary treatment when the cervix is closed. Suction curettage is the method preferred for the molar evacuation[3] because of the following advantages:-

a) Rapid evacuation of the uterus is achieved with minimal blood loss.
b) The danger of perforating the uterus is minimised as the instrument is blunt and no force is needed.
c) The danger of blood vessel injury is minimised and this reduces the chances of trophoblastic embolization. The direction of the evacuation is outward into the suction tubing.
d) Suction curettage and spontaneous abortion are associated with a low risk of requiring chemotherapy for gestational malignancy when compared to patients who had a medical induction with oxytocin, prostaglandin or hysterotomy.[2] Displacement of trophoblasts into the intravascular space by uterine contraction or manipulation occurs and this could account for the necessity to use chemotherapy.
e) Suction curettage can be safely used for large uterine sizes. The uterus contracts immediately with or without the help of oxytocin making further curettage safer.

DIC following rapid suction evacuation has been reported. Hysterectomy can be considered in older women who have completed their family but however it does not eliminate the post molar incidence of malignancy. Close follow up using HCG measurement will still need to be done. Hysterectomy decreases the chance of precipitating trophoblastic embolization since manipulation of the uterus is minimal.

In 90 pc of women with molar pregnancy, the trophoblasts regress after the evacuation.[2] However, in a small proportion up to 10 pc of the tissue persists in the uterus or elsewhere for years and it is important to recognise these women.

Close follow up of molar pregnancy is of paramount importance. Complete mole should be followed up for the first two years and partial mole for at least six months.[2] Follow up is aimed at early detection of persistent disease so that chemotherapy can be initiated early thus improving the prognosis.

Bagshawe (1986) estimates that 7 to 7,5 pc of patients with molar pregnancy require chemotherapy after evacuation of the uterus. In the United States of America, the figures are much higher ranging from 20 pc to 26 pc.

Indications for chemotherapy for patients who have had a hydatidiform made are as follows:[1]

1. Urinary HCG values greater than 30 000 iu/l HCG/ 24 hour urine serum greater than 20 000 iu/l at four to six weeks after evacuation of the mole.
2. Progressively rising HCG at any time post evacuation of a mole.
3. Raised HCG at any time post evacuation of the mole.
4. Evidence of intracranial, hepatic, gastro-intestinal metastases.
5. Pulmonary metastases with persisting or rising HCG values.
6. Persistent uterine haemorrhage with a raised HCG value.

Systems to improve follow up of patients with molar disease have been set up in the United Kingdom. Patients with hydatidiform mole are registered at regional centres. The registration process aims at improving data collection and providing economical centralised HCG measurement. Counselling of the

patients can be done and this increases patient compliance. The knowledge of the natural history of the disease is enhanced. At each follow up visit, history of vaginal bleeding, vomiting and haemoptysis is obtained. Abdominal examination for vaginal secondaries, subinvoluted uterus and presence of thecalutein cysts will be determined.

Follow up B HCG determinations should be done twice weekly until normal HCG levels then monthly for six months and twice monthly for one year. A pregnancy test is only useful when positive but has no value in accurately assessing the course of the disease when negative. The sensitivity of the biologic/immunological pregnancy test in current use is in the region of 850-5 000 iu/l HCG titer.[11] The normal pituitary HCG levels in the presence of a functioning gonads is less than four iu/l.[11] Since the current biologic/immunological tests cannot be measured below 850 iu/l, HCG measurement can be done by radioimmunoassay in the four iu/l to 850 iu/l range. This gap of HCG levels is important for follow up of molar disease as well as monitoring choriocarcinoma chemotherapy. Since LH/FSH cannot be differentiated from HCG, measurement of B subunit HCG is necessary. The radioimmunoassay of the B subunit has become more precise and sensitive. Automation of the technique enables frequent samples to be measured from a large number of patients. Background interference in the radioimmunoassay HCG has been demonstrated in urine and it is essential that serum measurement are used. Thus the more sensitive radioimmunoassay of HCG should be used in the follow up.

The main concern of a molar pregnancy is progression to invasive mole or to the aggressive malignant choriocarcinoma. The majority of trophoblasts (90pc) die out spontaneously after an evacuation of the uterus and about 10 pc persist. Four pc of molar pregnancies develop into choriocarcinoma (4,34) whilst up to 57 pc of choriocarcimona arise from hydatidiform mole.[13]

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