University Of diyala
College Of Medicine
Education and Scientific Research

(Molar pregnancy And maternal age)

A project submitted to the council of University of Diyala College of Medicine in Partial fulfillment of the Requirements for the Degree of bachelor.

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Table of contents

1.Introduction

Hydatidiform moles (HMs) are forms of gestational trophoblastic disease (GTD) that involve villous formation. They are characterized histologically by aberrant changes within the placenta. Specifically, the chorionic villi in these placentas show varying degrees of trophoblastic proliferation and oedema of the villous stroma. Hydatidiform moles are categorized as either complete hydatidiform moles (CHMs) or partial hydatidiform moles (PHMs) based on biology and genetics[1]. Hydatidiform mole is the premalignant form of gestational trophoblastic neoplasia. It is of clinical and epidemiological interest because of its potential for significant consequences for women's health[2].Of the two forms of molar disease, complete hydatidiform moles are more clinically important as they have high propensity for persistence (requiring clinical intervention)or progression to choriocarcinoma.Of complete moles, 15–20% will continue on to develop gestational trophoblastic neoplasia, whereas <5% of partial moles do. Complete hydatidiform moles are androgenic gestations, typically diploid but occasionally tetraploid. Partial hydatidiform moles are triploid conceptuses with the extra haploid set of chromosomes being paternally derived. Both types of moles are typically followed clinically for persistence by serum hCG levels and clinical symptoms (e.g., vaginal bleeding and persistent pregnancy symptoms)[3].The incidence of molar pregnancy varies by geographical region. It is generally believed that the incidence is high in developing countries. The incidence is higher in women younger than 20 years and older than 40 years of age. It is also higher in nulliparous women, in patients of low economic status, and in women whose diets are deficient in protein, folic acid, and carotene[4].Besides age, history of failed pregnancy increases the incidence of GTD.For example, elective abortion and miscarriage are connected with increasing risk of molar pregnancy[1].Molar pregnancies are one etiology for pregnancy failure. The gold standard for a molar diagnosis is by histopathologic examination of the products of conception. The practice of routine histopathologic evaluation of tissue obtained at the time of abortion has been the subject of debate because some authors think that it is not necessary as the clinical significance of findings is low with low incidence of HM[5].The usual management of abortions is not sufficient to detect all molar pregnancies because tissue is not routinely submitted for histological examination especially in resource-limited regions [6].By routine histopathologic assessment of products of first-trimester spontaneous abortions, important pathologies such as molar pregnancy and placental trophoblastic neoplasia can be diagnosed [7].The histopathologic diagnosis of molar pregnancies can be difficult and often requires expertise in perinatal pathology [8].

1.1 Epidemiology

The incidence of molar pregnancy is about 1 in every 1500 to 2000 pregnancies among whites in the United States. There is a much higher incidence among Asian women in the United States (1 in 800) and an even higher incidence among women in Asia, for example, Taiwan (1 in every 125 to 200 pregnancies) [8].The risk for the development of a second molar pregnancy is 1% to 3%, or as much as 40 times greater than the risk for developing the first molar pregnancy.Although the cause of GTN is unknown, it is known to occur more frequently in women younger than 20 years and in those older than 40 years. It appears that GTN may result from defective fertilization, a process that is more common in both younger and older individuals. Diet may play a causative role. The incidence of molar pregnancy has been noted to be higher in geographic areas where people consume less β-carotene (a retinoid) and folic acid.[9]

1.2 ETIOLOGY and Risk factor

As described previously, hydatiform moles are divided into complete and partial moles. Complete mole is the most common type and does not contain fetal parts, whereas in a partial mole there might be identifiable fetal residues. Complete moles are typically diploid, whereas partial moles are triploid.[10] Complete moles tend to cause higher levels of the human chorionic gonadotropin (hCG), which is one of the main clinical features of this process. In complete moles, the karyotype is 46,XX 90% of the time and 46,XY 10% of the time. It arises when an enucleated egg is fertilized either by two sperms or by a haploid sperm that then duplicates and therefore, only paternal DNA is expressed.[11]On the other hand, in partial moles, the karyotype is 90% of the time triploid and either 69,XXX or 69,XXY. This karyotype arises when a normal sperm subsequently fertilizes haploid ovum duplicates and or when two sperms fertilize a haploid ovum. In partial moles, both maternal and paternal DNA is expressed.[12] Whilst the diagnosis of molar pregnancy is rare, there are two groups of women who have signifiscantly elevated risks of developing a molar pregnancy.At the extremes of the reproductive age, girls under the age of 15 years have a risk approximately 20 times higher than women aged 20–40, whilst women aged over 45 have a several hundred-fold higher risk than those aged 20–40.1 The increased risk for these groups is mainly for complete molar pregnancy, with the incidence of partial molar pregnancy changing less across the age groups.[13].

Certain risk factors increase the prevalence of molar pregnancies:

1.Extremes of maternal age.

2.Greater than 35 years old carries a five to ten-fold increased risk risk.

3.Early teenage years, usually less than 20 years old.

4.Previous molar pregnancy increases the risk 1% to 2% for future pregnancies.

5.Women with previous spontaneous abortions or infertilities.

6.Dietary factors including patients that have diets deficient in carotene (vitamin A precursor) and animal fats.

7.Smoking.

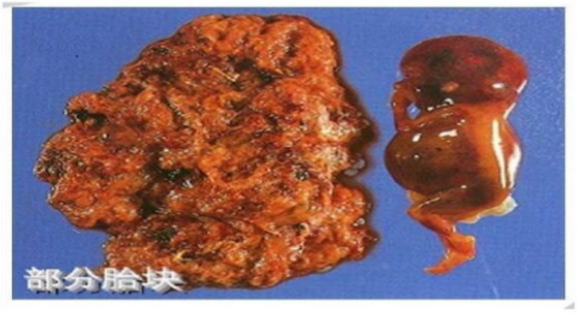
1.3 Age-related molar pregnancy risks

In England and Wales, between 2000 and 2009 , 5,793 patients with complete moles and 7,790 with partial moles were registered , compared with total of 8,242,511 conception [14].The overall molar pregnancy incidence was 1 for 607 conception (complete mole 1:1,423 ; partial mole 1:1,058) but with major variations with age . For complete moles the risk varied from <1:1,000 for ages 18 – 40, to 1:156 for women aged 45 and 1:8 for those aged 50 and above.[15].

1.4 Types of molar pregnancy

The types are categorized on the basis of gross morphology , histopathology and karyotype that are :-

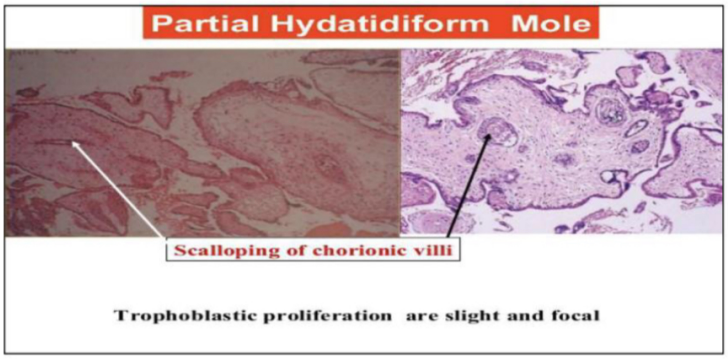
1.4.1 Partial mole : In this situation, two sperm fertilise the egg instead of one, creating 69 instead of 46 chromosomes. There is too much genetic material and the pregnancy develops abnormally, with the placenta outgrowing the baby. There may be evidence of a fetus but it will be abnormal and cannot survive.[16]



Partial hydatidiform mole with fetus

PATHOLOGIC FEATURES

Gross Findings:



▸Large hydropic vesicles admixed with nonmolar placental tissue

▸Fetus frequently with developmental abnormalities, particularly syndactyly

Microscopic Findings:

▸Enlarged villi admixed with small and normal-sized villi

▸Enlarged villi with scalloped borders and trophoblast inclusions

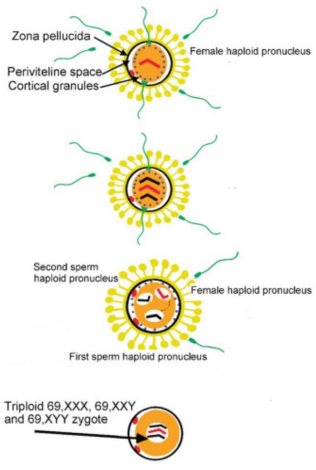
▸Less frequent or prominent cavitation than in CHM

▸Mild and focal syncytiotrophoblast hyperplasia with “lacy” or “moth-eaten” appearance

▸Evidence of fetal development including nucleated red blood cells in villous capillaries, chorionic plate, amnion, cord, or fetal tissues.

Genetic :

In the “incomplete” or partial mole, the karyotype is usually a triploid, often 69 XXY (80%). Most of the re-maining lesions are 69 XXX or 69 XYY. Occasionally mosaic patterns occur. These lesions, unlike complete moles, often present with a coexistent fetus. The fetus usually has a triploid karyotype and is defective. Genetic analysis of choriocarcinomas usually reveals aneuploidy or polyploidy, typical for anaplastic carcinomas.[17]



Triploidy of partial hydatidiform mole.

The risks of partial mole according to age :

the overall risk for a molar pregnancy is shown to be slightly increased, above average for young teenagers with a risk of 1:450 aged 16 ; relatively unchanged at <1:500 for women of the majority of the reproductive age group and then increases significantly for those aged >40, with a risk of 1:101 at age 45 and 1:8 for women aged >50[14].For partial moles, there is no excess risk at the younger age and the increasing risk that starts at age 25 years does so at a slow rate reaching only 1:630 at 40, 1:286 at 45 and 1:113 at 50.[15]

Table II. Age-related risk for a partial molar pregnancy in England and Wales 2000–09.

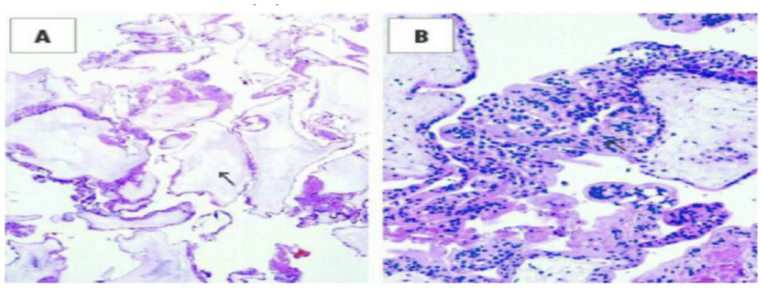
Age	Risk
13	1:1,876
14	1:1,417
15	1:1,424
16	1:1,266
17	1:1,466
18	1:1,455
19	1:1,566
20	1:1,638
21	1:1,488
22	1:1,342
23	1:1,317
24	1:1,453
25	1:1,113
26	1:1,217
27	1:1,152
28	1:1,064
29	1:1,063
30	1:959
31	1:991
32	1:980
33	1:924
34	1:992
35	1:903
36	1:778
37	1:880
38	1:770
39	1:794
40	1:639
41	1:650
42	1:496
43	1:459
44	1:491
45	1:286
46	1:281
47	1:307
48	1:472
49	1:192
≥ 50	1:113
Overall	1:1,058

1.4.2_Complete mole - **A complete mole is when one (or even two) sperm fertilises an egg cell which has no genetic material inside. Even if the father's chromosomes double up to make 46 in all, the balance of chromosomes from the mother and father is wrong. Usually the fertilised egg dies at that point but in rare cases it goes on to implant in the uterus. When it does, no embryo grows, only the trophoblast (the cells that will become the placenta) and that grows to fill the uterus with the molar.[16]**

PATHOLOGIC FEATURES

Gross Findings:

- **Uniformly large grape-like, transparent vesicles (if classic).**
- **No fetus or gestational sac in most cases.**



Complete hydatidiform mole. (A) Histological low power view showing numerous edematous villi with frequent cistern formation (arrow); (B) histological high power view showing hyperplastic trophoblast (arrow).**(10)**

Microscopic Findings:

Complete Hydatidiform Mole

- **Generalised hydropic change in villi with central cisterns**
- **Marked hyperplasia of villous cytotrophoblast and syncytiotrophoblast**
- **Hyperplasia of the intervillous and implantation trophoblast**
- **Striking cytologic atypia**
- **Absence of fetal tissues**

Early Complete Hydatidiform Mole

- **Bulbous "club-shaped" terminal villi**
- **Hyper cellular myxoid villous stroma with karyorrhexis**
- **Labyrinthine network of villous stromal canaliculi**
- **Focal hyperplasia of cytotrophoblast and syncytiotrophoblast**

Genetic :

The cytogenetic analysis of tissue obtained from molar pregnancies offers some clue to the genesis of these le-sions.complete moles Most hydatidiform moles are "complete" moles and have a 46 XX karyotype. Specialized studies indicate that both of the X chromosomes are paternally de- rived. This androgenic origin probably results from fertilization of an "empty egg" (i.e., an egg without chromosomes) by a haploid sperm (23 X), which then duplicates to restore the diploid chromosomal com-plement (46 XX). Only a small percentage of lesions are 46 XY. Complete molar pregnancy is only rarely asso-ciated with a fetus, and this may represent a form of twinning.[17]

The risk of complete mole in relation to age

In contrast, in complete moles there is a slightly increased risk for the young with a values of 1:699 at age 16, while at older ages, the increased risk rises much more rapidly from 1:1,248 at 40, to 1:157 at45 and 1:8 for >50. As a result of these differing changes with age, the ratio of complete mole to partial mole changes significantly with age, while the overall figure is 42% for those aged 13 –18 years, 63% are complete mole; aged 18 – 40 years 39%; aged 41 – 49 54% and aged >50, 93%.[14][15]

Table III. Age-related risk for a complete molar pregnancy in England and Wales 2000–09.

Age	Risk
13	1:234
14	1:515
15	1:463
16	1:699
17	1:914
18	1:1,012
19	1:1,165
20	1:1,423
21	1:1,419
22	1:1,509
23	1:1,643
24	1:1,741
25	1:1,592
26	1:1,469
27	1:1,649
28	1:1,727
29	1:1,681
30	1:1,852
31	1:1,812
32	1:1,931
33	1:1,647
34	1:1,923
35	1:2,151
36	1:2,244
37	1:1,740
38	1:1,446
39	1:1,454
40	1:1,248
41	1:993
42	1:589
43	1:350
44	1:320
45	1:157
46	1:80
47	1:56
48	1:30
49	1:19
≥ 50	1:8
Overall	1:1,423

1.5 Clinical features

Complete mole ,The typical clinical presentation of complete molar pregnancies has changed with the advent of high-resolution ultrasonography. Most moles are now diagnosed in the first trimester before the onset of the classic signs and symptoms[18][19][20].Vaginal bleeding , The most common classic symptom of a complete mole is vaginal bleeding. Molar tissue separates from the decidua, causing bleeding. The uterus may become distended by large amounts of blood, and dark fluid may leak into the vagina. This symptom occurs in 50% of cases. Hyperemesis ,Patients may also report severe nausea and vomiting. This is due to extremely high levels of human chorionic gonadotropin (hCG). This is reported to occur in 4% of patients diagnosed at 5-9 weeks of gestation, and in 23% when the diagnosis is made after 10 weeks' gestation. Hyperthyroidism, Signs and symptoms of hyperthyroidism can be present due to stimulation of the thyroid gland by the high levels of circulating hCG or by a thyroid stimulating substance (ie, thyrotropin) produced by the trophoblasts[21].Clinical hyperthyroidism has been reported in 3.7% of women with a hydatidiform mole diagnosed after the 10th week of gestation.Partial mole ,Patients with partial mole do not have the same clinical features as those with complete mole. These patients usually present with signs and symptoms consistent with an incomplete or missed abortion, including vaginal bleeding and absence of fetal heart tones.

1.6 Diagnosis

History and Physical

The presentation of the hydatiform mole is somewhat different in a complete mole versus a partial mole. In fact, most partial moles are diagnosed as spontaneous abortions that are later discovered after a pathology report is obtained from the fetal tissue.Since the advent of ultrasonography, the diagnosis of complete molar pregnancies has increased in the early stages of pregnancy, mainly during the first trimester. The most common symptom (in one study as high as 84% of patients) of a complete mole is vaginal bleeding in the first trimester, which is normally due to the molar tissue separating from the decidua, resulting in bleeding. The typical buzzword appearance of vaginal bleeding is described as a "prune juice" appearance. This is secondary to the accumulated blood products in the uterine cavity and resultant oxidation and liquefaction of that blood. Another symptom of a complete molar pregnancy is hyperemesis (severe nausea and vomiting), which is due to the high level of

the hCG hormone circulating in the bloodstream. Some patients also endorse passage of vaginal tissue described as grape-like clusters or vesicles. Late findings of the disease (after the first trimester around 14 to 16 weeks of pregnancy) including signs and symptoms of hyperthyroidism, including tachycardia and tremors, again caused by the high levels of circulating hCG. Other late sequelae are pre-eclampsia, which is pregnancy-induced hypertension and proteinuria and/or end-organ dysfunction occurring typically after 34 weeks of pregnancy. When a patient less than 20 weeks pregnant presents with signs and symptoms of pre-eclampsia, a complete molar pregnancy should highly be suspected. In very advanced cases, patients present with severe respiratory distress possible from embolism of the trophoblastic tissue into the lungs.The presentation of a partial hydatiform mole is usually less dramatic than that of a complete mole. These patients typically present as described before with symptoms similar to a threatened or spontaneous abortion, including vaginal bleeding. Since partial hydatiform moles have fetal tissue, on examination, these patients may have fetal heart tones evident on Doppler. On physical exam, in more than 50% of cases, uterine size discrepancy and date discrepancy usually takes place. In a complete mole, the uterus is usually larger than the expected gestational date of the pregnancy, whereas, in partial moles, the uterus can be smaller than the suggested date.[22]

Investigations

Ultrasound ‹the diagnosis of complete mole is characteristically described as having a(snowstorm)appearance, although many will be diagnosed as an incomplete or an embryonic pregnancy.Partial mole may show a coexisting live fetus, with only scattered cystic spaces in the placenta[23]. Characteristically the diagnosis of partial mole is made after histological review of curettage specimens from presumed incomplete or missed abortions[24].Quantitative serum β-HCG is elevated, usually >100 000 IU/L in the complete mole.Full blood count and liver and renal function tests & thyroxin level should be obtained.Chest radiography, CT scan, or an MRI may be required to exclude metastatic spread.ECG if tachycardia is present or the patient is older than 40 years of age[24].

1.7 Treatment

In case of a suspected mole, further investigations include a complete blood count, measurement of creatinine and electrolytes, liver - kidney - thyroid function tests, and a baseline quantitative beta-hCG measurement. A careful pelvic and abdominal ultrasound scan should be done to look for evidence of an invasive mole, exclude a coexisting pregnancy, and look for possible metastatic disease. Computed tomography or magnetic resonance imaging may provide further information. Chest radiography or computed tomography should be considered if there are symptoms that suggest pulmonary metastases [25].

Suction curettage is the preferred method of evacuation regardless of uterine size in patients who desire to preserve fertility [26].It is best to avoid prior cervical preparation, oxytocic drugs and sharp curettage or medical evacuation, to minimize the risk of dissemination of tissue leading to metastatic disease [27].Oxytocic agents and prostaglandin analogues are best used only after uterine evacuations when there is significant hemorrhage.Total abdominal hysterectomy is a reasonable option for patients who do not wish to preserve their fertility. Hysterectomy is particularly advisable for patients >40 years whose risk of developing GTD is significantly increased. Though hysterectomy eliminates the risk of locally invasive disease, it does not prevent metastases and reduces the subsequent risk of persistent trophoblastic disease by up to 50%[28]Guidelines from the Royal College of Obstetricians and Gynecologists and the British Blood Transfusion Society recommend that all Rhesus-negative women who have a molar pregnancy should be given 250 IU anti-D immunoglobulin after surgical evacuation [29].Chemotherapy Complete molar pregnancy is well recognized to have the potential for local invasion and distant spread. After evacuation, local uterine invasion occurs in about 15% and metastases in 4%. Complete molar pregnancy is usually divided into low and high risk for persistence based on signs and symptoms of marked trophoblastic proliferation at the time of evacuation, i.e.: hCG >100,000 mIU/Ml; excessive uterine enlargement; theca-lutein ovarian cyst >6 cm in diameter; older maternal age; a previous molar pregnancy. The risk of postmolar GTD is significant less with partial molar pregnancy and is seen in approximately 1-6% Unfortunately there are no distinguishing clinical or pathologic features for predicting persistence after complete molar pregnancy.Although controversial, the use of chemoprophylaxis at the time of evacuation of high-risk complete molar pregnancy has been shown to significantly decrease the development of GTD from approximately 50% to 10-15%. A number of chemotherapy regimens are used for treating the disease, but the best seems to be the association between methotrexate, actinomycin D and cyclophosphamide.

1.8 Follow-up

The aims of follow-up are to confirm successful treatment and to identify women with persistent or malignant GTD who may require adjuvant chemotherapy or surgery at an early stage. Persistent vaginal bleeding and above all elevation of serum beta-hCG levels are the main indicators of residual disease.The outcome of a partial hydatidiform mole after uterine evacuation is almost always benign. Persistent disease occurs in 1.2% to 4% of cases; metastasis occurs only in 0.1% of cases (30). In complete moles, these risks are approximately 5 times greater after treatment with uterine evacuation and 2-3 times greater after hysterectomy The risk of persistent or recurrent GTD is greatest in the first 12 months after evacuation, with most cases presenting within 6 months.A variety of hCG criteria have been used to diagnose postmolar gestational trophoblastic disease. Recently, the International Federation of Gynecologists and Obstetricians (FIGO) standardized the following hCG criteria for the diagnosis of postmolar gestational trophoblastic disease (31):

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.

Use of reliable hormonal contraception is recommended while hCG values are being monitored. Oral contraceptives do not increase the incidence of postmolar gestational trophoblastic disease or alter the pattern of regression of hCG values . 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. Although pregnancies after molar evacuation usually are normal gestations, pregnancy obscures the value of monitoring hCG levels during this interval and may result in a delayed diagnosis of postmolar malignant gestational trophoblastic disease. A new intrauterine pregnancy should be ruled out on the basis of hCG levels and ultrasonography, especially when there has been a long delay in follow-up of serial hCG levels and noncompliance with contraception. After completion of documented remission for 6-12 months, women who desire pregnancy may discontinue contraception, and hCG monitoring may be discontinued. Patients with prior partial or complete moles have a 10-fold increased risk (1-2% incidence) of a second hydatidiform mole in a subsequent pregnancy. Therefore, all future pregnancies should be evaluated by early obstetric ultrasonography.

1.9 Complication

1.Perforation of uterus during suction curettage due to increase size of uterus . If perforation is present , do the procedure under laparoscopic guidance.

2. Hemorrhage during evacuation .

3. Molar metastasis : Respiratory distress during surgery because of trophoblasticembolization to the lung leads to respiratory compromise and hypoxemia with pulmonary edema , the high risk factor is a uterus large than expected gestational age.

4. heart failure caused by anemia or iatrogenic fluid overload.

5. Choriocarcinoma : Malignant trophoblastic disease develops in 10-20% of molar.

pregnancy, quantitative HCG should be monitored carefully for 1 year , after complete mole the risk 1:10 ,partial mole 1:200 , therefore careful follow up of HCG is essential.

2.Conclusion

In the light of the present studies,aged older than 35 and below than 15 years seems a risk factor and vaginal bleeding is the commonest presenting symptom. Early booking of pregnant women to antenatal care clinics and routine first trimester ultrasound made diagnosis easier and earlier before complications appear.[32]

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