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Overview on the updates in vesicular molar pregnancy

***Corresponding Author: Sultan Ahmed Naif Almansour**

General Practice - Medical Affairs Supervisor at Hospital Affairs Directorate In Aljouf Health, Northern Saudi Arabia.

Email: sualmansour@moh.gov.sa

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Abstract

Gestational trophoblastic disease (GTD) is one of the rare human tumors that originates in placental tissue and can be cured even with extensive metastases. GTDs include a variety of interrelated tumors, including full and partial moles, invasive moles, choriocarcinomas, and placental trophoblast tumors, which have different tendencies to infiltrate and spread locally. Most GTDs develop after a bruise, but can follow a previous pregnancy. Transvaginal ultrasonography, routine beta CG, and current approaches to chemotherapy can cure most women with gestational trophoblastic malignancies and maintain reproductive function.

***Keywords*:** trophoblast gestational disease; human chorionic gonadotropin; chemotherapy.

Introduction

Gestational trophoblastic disease (GTD) is a group of uncommon conditions associated with pregnancy. Histologically, it includes the premalignant partial (PHM) and complete hydatidiform mole (CHM), as well as the malignant invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). The GTD spectrum has recently been expanded to also include atypical placental site nodule (APSN) as 10%–15% may coexist with or develop into PSTT/ETT [1].

The most common form of GTD is vesicular mole pregnancy, also known as molar pregnancy. A molar pregnancy occurs when the placenta doesn't develop normally. Instead, a tumor forms in the uterus and causes the placenta to become a mass of fluid-filled sacs, also called cysts. About 1 in every 1,000 pregnancies (0.1 percent) is a molar pregnancy. This kind of pregnancy usually doesn't last because the placenta typically can't nourish or grow a baby at all. In rare cases, it may also lead to health risks for mom.

A molar pregnancy is also called a mole, a hydatidiform mole, or gestational trophoblastic disease. The patient can have this pregnancy complication even if she have had a typical pregnancy before. And, the good news is the patient also can have a completely normal, successful pregnancy after having a molar pregnancy. 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 [2].

Types of vesicular mole

There are 2 types of hydatidiform moles: complete and partial.

1. The complete hydatidiform mole is usually diploid and entirely androgenetic in origin. Most have 46,XX karyotype; a few have a 46,XY karyotype. A complete molar pregnancy consists of diffuse hydropic chorionic villi with trophoblastic hyperplasia, forming a mass of multiple vescicles. There is usually no evidence of a fetus and minimal embryonal development.

2. The partial hydatidiform mole is usually triploid, with one maternal and two paternal haploid sets, either from dispermic fertilization or from fertilization with an unreduced diploid sperm. There is usually a fetus and a large placenta. The hydropic villi show a less florid appearance than is seen with

a complete hydatidiform mole and are interspersed with normal chorionic villi. The fetus usually dies within a few weeks of conception, and a recent review did not identify any case in which a fetus of paternal (diandric) origin survived to term [3]. Very rarely, a partial molar pregnancy develops with two maternal and one paternal haploid set (digynic). In these cases, the placenta is small, the villi show minimal hydropic changes, and the fetus is growth-restricted. Some of these pregnancies have been reported to result in live births, with subsequent early neonatal death [4].

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 [5]. There is a probability of presence of choriocarcinoma in molar pregnancy patients, as of 3,000 women with partial hydatidiform moles, 0.1% had a choriocarcinoma. Persistent trophoblastic disease or malignant complications are much more common with a complete molar pregnancy than with a partial hydatidiform mole. The incidence of these complications is approximately 8% and 0.5% respectively, compared with a risk of 1:50,000 after a full-term pregnancy.

Risk factors of vesicular mole

Clinical studies have been carried out to identify risk factors for molar pregnancy and discover whether factors differ in CHM or PHM.

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 35 years of age as they have 2-3 fold increased risk of developing complete molar pregnancy [7], which makes the risk escalates up to 7 fold for women older than 40 years, which could be attributed to higher susceptibility of ovum from old women to abnormal fertilization. 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 [6]. History is also known as an important risk factor for molar pregnancy, as if the patient has had a molar pregnancy in the past, she is more likely to have another one. 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 [2]. Old paternal age, history of spontaneous abortion or previous gestational trophoblastic disease, low dietary intake of carotene and vitamin A deficiency [8], certain ABO blood groups and smoking have been reported to carry a higher risk of CHM development.

Epidemiology of vesicular mole

Although epidemiological studies have reported a wide variation in the incidence of hydatidiform mole, in most parts of the world it is 1 per 1000 pregnancies [9]. In high-income countries, the incidence of complete mole is approximately 1-3 per 1000 pregnancies and the incidence of partial mole is about 3 per 1000 pregnancies [10].

Due to high incidence of molar pregnancy in some populations, studies have associated low socio economic status with high incidence of GTD [11]. These situations tend to have decreased with time due to the advances in medical monitoring and better sources of food. After one molar pregnancy, the chance of a second complete or partial mole is 1-2%. The risk of a third molar pregnancy increases substantially to 15-20% and is not decreased by changing partners and may be related to familial or sporadic biparental molar disease [15]. More generally, it is considered that the risk of an additional mole in the next pregnancy is approximately 5-10 fold higher than the baseline risk for the "normal" population [16]. However, the spontaneous rejection of mole formation has also been observed.

GTD incidence is three to four times higher in Asia, Africa and Latin America than in North America and Europe. GTD incidence has remained relatively constant at 1 to 2 per 1000 deliveries in Europe and in United States [7]. However, despite substantial economic achievements over the recent years, Japan yet shows a relatively high frequency (3 in 2000 deliveries in 2000 and 1/500 pregnancies in 2003) of molar pregnancy. On the other hand, GTD occurs in a rate of 28 per 1000, 8.5 per 1000, 9.8 per 1000 and 2 per 1000 in Pakistan, Brazil, Finland and Sweden respectively [7,12]. As documented, Hispanics and Native Americans residing in the United States and certain population groups in South East Asia show a higher incidence of molar pregnancy compared to the rest of the population living in the same countries [13]. Considering the global statistics, genetic, nutritional and environmental factors also seem to play roles in GTD development [12]. The incidence of Hydatidiform Mole in Hamadan in west of Iran was estimated 3.34 per 1000 pregnancies between 1997 and 2006. Among the cases with mole, 53.29% were complete and 46.71% were partial mole [14].

The CHM are more frequently invasive than PHM. This malignant change in molar pregnancies seems to be associated with the male origin of the DNA [16]. The possibility that heterozygous moles arising from 2 sperm fertilising the "empty egg" may have a higher risk of malignant change is another observation [17]. Approximately 80% of the HM is self-limiting i.e., prevents itself from becoming invasive. The proportion of HM which change into invasive moles ranges from 7-17% or in rare cases 2-5% to a choriocarcinoma; a malignant, rapidly growing and metastatic cancer [18]. 60% of all the choriocarcinoma are not preceded by a clinically recognized HM [19]. The CHM carry approximately a 15% risk of malignant change, while the PHM have a much lower risk of malignant change; approximatly 0.5-1%. The fact that these HM can be repetitive with different male partners rather suggests an underlying oocyte problem.

Clinical presentation of vesicular mole

A molar pregnancy may feel just like a typical pregnancy at first. However, you'll likely have certain signs and symptoms that something is different.

Patients usually present with second trimester vaginal bleeding and a uterus greater than the gravid date. As diagnosis is often made in the first trimester with ultrasound examination, complications such as hyperemesisgravidarum, pre-eclampsia, and hyperthyroidism are less common. If there is vaginal passage of the gestational product, vesicles may be seen.

Pelvic pain and pressure may be found because the tissues in a molar pregnancy grow faster than they should, especially in

the second trimester. the stomach may look too large for that early stage in pregnancy. The fast growth can also cause pressure and pain. The hormone hCG is made by the placenta. It's responsible for giving many pregnant women a certain amount of nausea and vomiting. In a molar pregnancy, there may be more placenta tissue than normal. The higher levels of hCG might lead to severe nausea and vomiting. The typical honeycomb appearance of a complete mole is rarely seen, especially in the first trimester. Typically, there is absence of fetal parts, cystic appearance of the placenta, and a deformed gestational sac that may appear like a spontaneous abortion. Hence, some molar pregnancies are only diagnosed on histologic examination after evacuation for a spontaneous abortion.

Diagnosis of vesicular mole

Sometimes a molar pregnancy is diagnosed when the patient go for your usual pregnancy ultrasound scan. Other times, the doctor will prescribe blood tests and scans if you have symptoms that might be caused by a molar pregnancy. On the other hand, diagnosis of a molar pregnancy might be suspected based on a number of clinical features: abnormal vaginal bleeding in early pregnancy is the most common presentation; uterus large for dates (25%); pain from large benign theca-lutein cysts (20%); vaginal passage of grape-like vescicles (10%); exaggerated pregnancy symptoms including hyperemesis (10%), hyperthyroidism (5%), early preeclampsia (5%).

Nowadays ultrasound scan often permits to diagnose molar pregnancy before 12 weeks, showing a fine vascular or honeycomb appearance. Later a complete mole is characteristically described as snowstorm appearance of mixed echogenicity, representing hydropic villi and intrauterine hemorrhage. The ovaries often contain multiple large theca-lutein cysts as a result of increased ovarian stimulation by excessive beta-hCG [20]. High levels of hCG in the blood might also be a sign of a molar pregnancy. But some molar pregnancies may not raise hCG levels, and high hCG is also caused by other standard kinds of pregnancies, like carrying twins. In other words, your doctor won't diagnose a molar pregnancy based on hCG levels alone.

Ultrasound diagnosis of partial mole is more difficult: the fetus may be still viable, but may show signs consistent of triploidy, such as unusually early growth restriction or developmental abnormalities. There may be only scattered cystic spaces within the placenta, and ovarian cystic changes usually much less pronounced. In case of doubt, the scan should be repeated in 1 to 2 weeks.

In women with a complete mole, the quantitative serum beta-hCG level is higher than expected, often exceeding 100,000 IU/L. In case of a partial mole, the level of beta-hCG is often within the wide range associated with normal pregnancy and the symptoms are usually less pronounced. For these reasons the diagnosis of a partial mole is often missed clinically and made from subsequent histologic assessment of the abortive material [21].

Histopathology of vesicular mole

Grossly, CHM consists of hydropic villi to semi-transparent vesicles of variable sizes with absence of normal placenta. Early complete hydatidiform moles have minimal or no gross evidence of abnormal villi.

In microscopic evaluation, CHM, which represents approximately 75% of molar pregnancies involves diffuse edematous villi and trophoblastic hyperplasia in the entire placenta [22]. Macroscopically, no fetal tissue or amnion development is observed. As apparent from the term partial HM, the extent of villous edema, trophoblastic proliferation and signs and symptoms are comparatively lower than that of CHM. Furthermore, partial moles contain fetal tissue and amnion in addition to placental tissue.

Management and treatment of vesicular mole

A molar pregnancy can't grow into a normal, healthy pregnancy. patient must have treatment to prevent complications. This can be really, really hard news to swallow after the initial joys of that positive pregnancy result.

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 [23]. Suction evacuation and curettage, ideally performed under ultrasound guidance, is the preferred method of evacuation of a molar pregnancy independent of uterine size if maintenance of fertility is desired. It is recommended that a 12-14 mm suction cannula is used and that an intravenous oxytocin infusion is started at the onset of suction curettage and continued for several hours postoperatively to enhance uterine contractility.

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 [24]. Oxytocic agents and prostaglandin analogues are best used only after uterine evacuations when there is significant hemorrhage.

Because the risk of bleeding increases with uterine size, blood for transfusion should be available when the uterus is greater than 16 weeks in gestational size. Rh immune globulin should be given to Rh-negative women at the time of molar evacuation as RhD factor is expressed on the trophoblast. Judicious use of appropriate evacuation equipment and techniques, access to blood products, careful intraoperative monitoring, and early recognition and correction of complications results in improved outcomes [25,26] If there is no persistent bleeding, a second evacuation is usually not needed.

Prophylactic administration of either methotrexate or actinomycin D chemotherapy at the time of or immediately following molar evacuation is associated with a reduction in the incidence of postmolar GTN to 3%-8%. However, it should be limited to special situations in which the risk of postmolar GTN is much greater than normal or where adequate hCG follow-up is not possible [27]. The risk of recurrence is low (0.6%-2%) after one molar pregnancy, although much increased after consecutive molar pregnancies [28]. Mutations in NLRP7 and KHDC3L have been reported in women with recurrent molar pregnancy [29].

Role of surgery in vesicular mole treatment

Hysterectomy is an alternative to suction curettage if child-

bearing is complete. Surgery may have an important role in the management of GTN. Hysterectomy can be considered in uncontrolled uterine bleeding, although it can often be avoided with the use of uterine artery embolization. Laparotomy may be needed to stop bleeding in organs such as the liver, gastrointestinal tract, kidneys, and spleen. Neurosurgery is needed if there is bleeding into the brain or increased intracranial pressure. The resection of an isolated drug-resistant tumor may also be curative.

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% [30].

In addition to evacuating the molar pregnancy, hysterectomy provides permanent sterilization and decreases the need for subsequent chemotherapy by eliminating the risk of local myometrial invasion as a cause of persistent disease. Medical induction of labor and hysterotomy are not recommended for molar evacuation, since these methods increase maternal morbidity and the development of postmolar GTN requiring chemotherapy.

Follow up

Follow-up hCG monitoring every 1-2 weeks is essential for early diagnosis of and management of postmolar GTN. On the other hand, postmolar GTN rarely occurs after the spontaneous return of hCG levels to normal, allowing for a shortened follow-up period for most women. Hence, a single additional confirmatory normal hCG measurement 1 month after first hCG normalization is recommended for a PHM and monthly hCG measurements should be obtained for only 6 months after hCG normalization for a CHM [25].

Termination of pregnancy is not indicated if accidental pregnancy occurs during surveillance after the hCG level has returned to normal. In addition, data now show that it is safe to recommend oral contraceptives [31].

Role of chemotherapy in vesicular mole treatment:

If the molar pregnancy falls into a higher risk category due to cancer potential or because the patient had difficulty getting proper care for whatever reason, she may receive some chemotherapy treatment after the D&C. This is more likely if the hCG levels don't go down over time [32].

Role of radiotherapy in vesicular mole treatment:

Radiotherapy has a limited role in GTN, except in treatment of brain metastasis, although its efficacy compared with intrathecal methotrexate is controversial [33].

Conclusions

The general understanding of the natural history and management of molar pregnancy has advanced considerably in recent years. The key-role in obtaining a high cure rate becomes an early diagnosis and the subsequent strictly follow-up. Efforts are still necessary to develop effective new second-line therapies for patients with drug-resistant disease

References

1. Kaur B, Short D, Fisher RA, Savage PM, Seckl MJ, Sebire NJ. Atypical placental site nodule (APSN) and association with malignant gestational trophoblastic disease; a clinicopathologic study of 21 cases. Int J GynecolPathol. 2015; 34: 152-158.
2. J. O. W. Schorge, J. O. Schorge, K. D. Bradshaw, L. M. Halvorson, J. I. Schaffer, and M. M. Corton, Williams Gynecology, McGraw-Hill, New York City, NY, USA, 2008.
3. Petignat P, Billieux MH, Blouin JL, Dahoun S, Vassilakos P. Is genetic analysis useful in the routine management of hydatidiform mole? Hum Reprod. 2003; 18(2): 243–9.
4. Fryns JP, van de Kerckhove A, Goddeeris P, van der Berger H. Unusually long survival in a case of full triploidy of maternal origin. Hum Genet. 1977; 38(2): 147–55.
5. J. Fu, F. Fang, L. Xie et al., Prophylactic chemotherapy for hydatidiform mole to prevent gestational trophoblastic neoplasia. Cochrane Database of Systematic Reviews. 2012; 11(9): p. CD007289.
6. A. Igwegbe and G. Eleje, Hydatidiform mole: A review of management outcomes in a tertiary hospital in south-east Nigeria. Annals of Medical and Health Sciences Research. 2013; 3(2): 210.
7. M. Loukovaara, E. Pukkala, P. Lehtovirta, A. Leminen Epidemiology of hydatidiform mole in Finland, 1975 to 2001. Eur J Gynaecol Oncol. 2005; 26: 207-208.
8. F. Parazzini, C. La Vecchia, G. Mangili, C. Caminiti, E. Negri, G. Cecchetti, et al. Dietary factors and risk of trophoblastic disease Obstet Gynecol. 1988; 158: 93-99.
9. Hancock BW, Seckl MJ, Berkowitz RS. Gestational Trophoblastic Disease. 4th edn. ISSTD website; 2015. Available at: http://test.registraid.com/gtd-book.html. Accessed May 2, 2018.
10. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. Lancet. 2010; 376: 717-729.
11. N.J.F.R. Sebire, M. Foskett, H. Rees, M.J. Seckl, E.S. Newlands Risk of recurrent hydatidiform mole and subsequent pregnancy outcome following complete or partial hydatidiform molar pregnancy. BJOG. 2003; 110: 22-26.
12. A. Almasi, F. Almassinokiani, P. AkbariFrequency of molar pregnancies in health care centers of tehran. Iran J Reprod Infertil. 2014; 15: 157-160.
13. B.W. Tham, J.E. Everard, J.A. Tidy, D. Drew, B.W. Hancock Gestational trophoblastic disease in the Asian population of Northern England and North Wales. BJOG. 2003; 110: 555-559.
14. S Aghababaii, F Shobeiri, SM. Hosseinipanah HYDATIDIFORM mole: A statistical survey in West of Iran. J Postgrad Med Inst. 2016; 30: 80-83.
15. Tuncer ZS, Bernstein MR, Wang J, Goldstein DP, Berkowitz RS. Repetitive hydatidiform mole with different male partners. Gynecol Oncol. 1999; 75: 224-6.
16. Savage PM, Sita Lumsden A, Dickson S, Iyer R, Everard J, Coleman R, Fisher RA, Short D, Casalboni S, Catalano K, et al. The relationship of maternal age to molar pregnancy incidence, risks for chemotherapy and subsequent pregnancy outcome. J Obstet Gynaecol. 2013; 33: 406-11.
17. Baasanjav B, Usui H, Kihara M, Kaku H, Nakada E, Tate S, Mitsuhashi A, Matsui H, Shozu M. The risk of post-molar gestational

trophoblastic neoplasia is higher in heterozygous than in homozygous complete hydatidiform moles. Hum Reprod. 2010; 25: 1183-91,

18. Lurain JR, Brewer JI, Torok EE, Halpern B. Natural history of hydatidiform mole after primary evacuation. Am J Obstet Gynecol 1983; 145: 591-5

19. Kani KK, Lee JH, Dighe M, Moshiri M, Kolokythas O, Dubinsky T. Gestatational trophoblastic disease: multimodality imaging assessment with special emphasis on spectrum of abnormalities and value of imaging in staging and management of disease. Curr Probl Diagn Radiol. 2012; 41: 1-10.

20. Benson CB, Genest DR, Bernstein MR, et al. Sonographic appearance of first trimester complete hydatidiform moles. J Ultrasound ObstetGynecol. 2000; 16: 188-91.

21. Soper JT, Mutch DG, Schink JC. American College of Obstetricians and Gynecologists. Diagnosis and treatment of gestational trophoblastic disease: ACOG Practice Bulletin No. 53. GynecolOncol. 2004; 93(3): 575-85.

22. D. Williams, V. Hodgetts, J. Gupta Recurrent hydatidiform moles Eur J Obstet Gynecol Reprod Biol. 2010; 150: 3-7.

23. Schlaerth JB, Morrow CP, Montz FJ, d'Abling G. Initial management of hydatidiform mole. Am J Obstet Gynecol. 1988; 158: 1299-306.

24. Stone M, Bagshawe KD. An analysis of the influences of maternal age, gestational age, contraceptive method, and the mode of primary treatment of patients with hydatidiform moles on the incidence of subsequent chemotherapy. Br J ObstetGynaecol. 1979; 86(10): 782-92.

25. Lurain JR. Gestational trophoblastic disease I: Epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. Am J ObsetGynecol. 2010; 203: 531-539.

26. Berkowitz RS, Goldstein DP. Clinical practice. Molar pregnancy. N Engl J Med. 2009; 360: 1639-1645.

27. Wang Q, Fu J, Hu L, et al. Prophylactic chemotherapy for hydatidiform mole to prevent gestational trophoblastic neoplasia. Cochrane Database Syst Rev. 2017; (9): CD007289.

28. Sebire NJ, Fisher RA, Foskett M, Rees H, Seckl MJ, Newlands ES. Risk of recurrent hydatidiform mole and subsequent pregnancy outcome following complete or partial hydatidiform molar pregnancy. BJOG. 2003; 110: 22-26.

29. Murdoch S, Djuric U, Mazhar B, et al. Mutations in NALP7 cause recurrent hydatidiform moles and reproductive wastage in humans. Nat Genet. 2006; 38: 300-302.

30. Bahar AM, el-Ashnehi MS, Senthilselvan A. Hydatidiform mole in the elderly: hysterectomy or evacuation? Int J GynaecolObstet. 1989; 29(3): 233–8.

31. Costa HL, Doyle P. Influence of oral contraceptives in the development of post-molar trophoblastic neoplasia–a systematic review. GynecolOncol. 2006; 100: 579-585.

32. Zakaria A, Hemida R, Elrefaie W, Refaie E. Incidence and outcome of gestational trophoblastic disease in lower Egypt. Afr Health Sci. 2020; 20(1): 73-82.

33. Taymaa May, Donald P, Goldstein, Ross S Berkowitz. Current Chemotherapeutic Management of Patients with Gestational Trophoblastic Neoplasia. Chemotherapy Research and Practice. 2011; 806256: 12.