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FAMILY PLANNING (A ROE AND S SONALKAR, SECTION EDITORS)

Molar Pregnancy: Epidemiology, Diagnosis, Management, Surveillance

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Abstract

Purpose of Review This review describes recommendations for the diagnosis and management of molar pregnancy, with focus on emerging evidence in recent years, particularly as it pertains to nuances of diagnosis, risk stratification, and surveillance of post-molar malignant trophoblastic disease.

Recent Findings Topics discussed include advances in histopathologic diagnosis of molar pregnancy to standardize analysis, most recent estimations of post-molar pregnancy malignancy, and updated surveillance guidelines.

Summary Hydatidiform molar pregnancy, resulting from an abnormal fertilization event, is the proliferation of abnormal pregnancy tissue with malignant potential. With increased availability of first trimester ultrasound, early detection of molar pregnancy has increased. While challenging to diagnose radiologically and histologically at early stages, standardization of tissue analysis allows improved detection and increased accuracy of incidence estimate for both complete and partial molar pregnancy. Treatment of molar pregnancy requires evacuation of tissue. Prophylactic chemotherapy or repeat curettage have been explored but not favored. As new molecular markers are sought, our ability to predict malignant transformation following molar pregnancies will allow for more streamlined surveillance. Recent data support a reduction in the length of surveillance following normalization of human chorionic gonadotropin levels after evacuation.

Keywords Molar pregnancy · Hydatidiform mole · Complete mole · Partial mole · Gestational Trophoblastic Disease · Surveillance

Introduction

Gestational trophoblastic disease (GTD) encompasses both benign and malignant entities resulting from abnormal proliferation of placental trophoblasts. The most commonly diagnosed GTD is hydatidiform mole, or molar pregnancy, which encompasses two related, but genetically distinct, forms of abnormal pregnancy: complete and partial moles. Both have potential for malignant transformation, though this risk is considerably higher for complete moles (15%) compared to their partial counterparts (1%) (Table 1) [1•]. Malignant forms of GTD, more commonly referred to as gestational trophoblastic neoplasia (GTN), include invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. GTN can occur after any form of pregnancy, including ectopic, spontaneous abortions, and term pregnancies. Most cases of GTN, however, occur following a molar pregnancy and are most commonly diagnosed based on a rise or plateau of beta human chorionic gonadotropin (hCG) levels (Table 2) [2].

In the past two decades, there have been several notable reviews covering the spectrum of gestational trophoblastic disease [3•, 4–7]. This review will highlight important clinical aspects of molar pregnancy specifically, with a focus on new developments in diagnosis and surveillance in the past 5 years. While prognosis for molar pregnancy is excellent, difficulty in predicting malignant transformation has traditionally led to a lengthy and burdensome healthcare follow-up. As our understanding of these entities evolve, new possibilities for detection and surveillance may reduce this burden for both patients and the healthcare system.

This article is part of the Topical Collection on *Family Planning*

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Table 1 Characteristics of Complete versus Partial Hydatidiform Moles

	Complete mole	Partial mole
Karyotype	Diploid: 46 XX > 46 XY	Triploid: 69 XXY/69 XYY/69 XXX
Histopathologic Features	Absence of fetal tissue **Diffuse** hydropic villi and atypical trophoblastic hyperplasia	Fetal tissue **Focal** hydropic villi and trophoblastic hyperplasia
hCG	> 100,000 mIU/mL	< 100,000 mIU/mL
Clinical Signs	Vaginal bleeding, uterus size > dates, hyperemesis, preeclampsia < 20 weeks, theca lutein cysts	Vaginal bleeding
Imaging	**Diffuse** hydropic swelling/ multiple echoes & no fetus Snowstorm, honeycomb or swiss cheese pattern	**Focal** cystic spaces within placenta, increased transverse diameter of sac, amniotic fluid, fetal parts
Risk of GTN overall	15–20%	1–5%
Risk of GTN after hCG normalization	0.35%	0.03%

Epidemiology

International estimates of molar pregnancy incidence range from 0.6–8 in 1000 [8]. The true incidence of molar pregnancy is difficult to assess given the rarity of this disease and reliance on laboratory trends over time. Additionally, unrecognized molar pregnancies may present very early and be ultrasonographically indistinguishable from spontaneous abortions. In a large study analyzing products of conception using single nucleotide polymorphism microarray of over 22,000 clinical miscarriages, 3% (710) were molar pregnancies. Of the molar pregnancies detected, more than 65% were not detected by ultrasound or standard histopathology [9]. Given pathologic assessment of products of conception is not standard practice, the true incidence of molar pregnancies is likely underestimated.

Personal history of molar pregnancy is an important risk factor, and risk rises exponentially with subsequent molar pregnancies. For instance, following an initial molar pregnancy, the risk of recurrence is 1.5% and increases to 25% after two molar pregnancies [10, 11]. In families with recurrent molar pregnancy, genetic links have been identified, particularly including mutations in NLRP7 and KHDC3L genes [2].

Extremes of maternal age have also been identified as a significant risk factor for development of complete molar pregnancy. In a large retrospective cohort study, Gockley et al. compared patients with complete or partial molar pregnancy to those with singleton live births. Adolescents and women > 40 years of age were 7 and 2 times more likely, respectively, to develop a complete molar pregnancy than those 20–39 years of age [12]. In contrast to the strong bimodal correlation of complete molar pregnancy risk with age, incidence of partial moles did not vary with maternal age in

Table 2 Society guidelines for post-molar surveillance

	Surveillance guidelines
FIGO[5]	- hCG q1-2 weeks - PHM: single additional normal hCG measurement 1 month after first normal - CHM: monthly hCG for 6 months after normalization
ESMO[2]	- hCG q2 weeks until normal then urine hCG monthly - If hCG normalizes in < 56 days, monitor hCG levels for 6 months from uterine evacuation - If hCG normalizes in > 56 days, monitor hCG levels monthly for 6 months from normalization
NCCN[68]	- hCG q1-2 weeks until normalized (3 consecutive normal assays). Then, hCG should be measured twice in 3-month intervals to ensure levels remain normal
RCOG[56]	- PHM: single additional normal hCG 1 month after first normal - CHM: If hCG normalizes in < 56 days, monitor hCG levels for 6 months from uterine evacuation if hCG normalizes in > 56 days, monitor hCG levels for 6 months from normalization
SGO[57]	- hCG weekly after evacuation until normalization then: - CHM: monitor hCG for 3 months - PHM: monitor hCG for 1 month

PMH partial hydatidiform mole, *CMH* complete hydatidiform mole, *FIGO* International Federation of Gynaecology and Obstetrics, *ESMO* European Society for Medical Oncology, *NCCN* National Comprehensive Cancer Network, *RCOG* Royal College of Obstetricians and Gynaecologists, *SGO* Society of Gynecologic Oncology

this study. Other studies have reached similar conclusions [12–14].

Data regarding risk factors such as diet, smoking status, oral contraceptive use, and blood type have been largely inconsistent [15–17]. Similarly, geography and molar pregnancy risk is limited by heterogeneity in study methodology, diagnostic techniques, and referral biases. Conflicting data exist regarding the association of race and ethnicity and molar pregnancy incidence. In an age-adjusted analysis, Melamed et al. described higher rates of complete moles in Asian women compared to White women while an opposite relationship was seen in partial mole incidence [18]. Although adjusted for age, other potentially confounding factors (gravidity, history of prior mole, socioeconomic status) were not addressed in analysis. Male factors, though understudied, may also play a role in the incidence of molar pregnancy. A small study in Iran demonstrated paternal occupational exposure to dust and soil was associated with increased rates of complete molar pregnancy in their partners [16].

Genetics

A hallmark of both complete and partial moles is excess paternal genetic material. A complete mole is formed from fertilization of an empty ovum by diploid paternal genome from a duplicated haploid sperm (46 XX), or more rarely, dispermic fertilization leading to a diploid karyotype (46 XX > 46 XY). A partial mole has a triploid karyotype (69 XXY) as a result of duplication of the haploid paternal genome with maternally derived genetic material [2]. Rarely, hydatidiform moles originating from tetraploid zygotes (XXYY or XXXY, most with three paternal genome sets) or biparental complete hydatidiform moles have also been identified [19, 20].

These fertilization events lead to abnormal proliferation of cytotrophoblasts and syncytiotrophoblasts, creating edematous placental villi described grossly as grape-like clusters, thus titled hydatidiform, given the cystic spaces (see Fig. 1A, B). Genes identified in patients with recurrent molar pregnancy have led to theories about dysfunction of maternal imprinting causing an imbalance in trophoblast proliferation [21, 22].

Mutations in genes related to oocyte DNA methylation, NLRP7, PADI6, and KHDC3L, have been identified in patients with recurrent molar pregnancy [2, 23]. While molar pregnancies genetically have paternal predominance, mutation in these maternal genes causes defects in maternal imprinting, allowing for paternally driven overgrowth of trophoblasts. While patients with spontaneous molar pregnancy have future reproductive outcomes similar to the

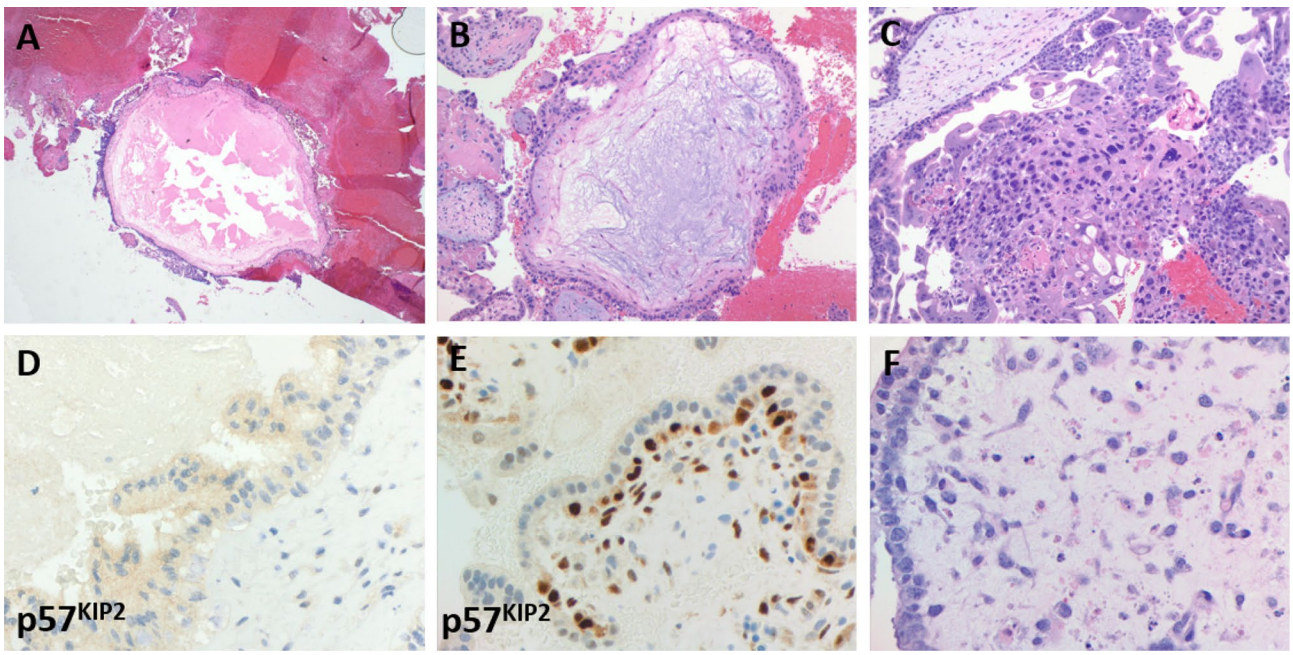

Fig. 1 Histologic Appearance of Molar Pregnancies. (**A**) Abnormal proliferation of villous trophoblasts in molar pregnancies causes cystic degeneration of bulbous villi, leading to cavitation/cistern formation and the appearance of grape-like clusters at gross evaluation. (**B**) Partial molar pregnancies will also exhibit hydropic villi with cystic degeneration, which can appear identical to that seen in complete molar pregnancies. (**C**) Syncytiotrophoblast hyperplasia and marked cytologic atypia are more commonly seen in complete than partial moles. Histologic distinction between complete and partial molar pregnancies often relies on evaluating expression of the paternally imprinted gene, p57, which is lost in cytotrophoblasts of complete moles (**D**) and is retained in those of partial moles (**E**). (**F**) Karyorrhexis of villous stromal cells may be a subtle finding in early molar pregnancies

general population, those with genetic predispositions are at increased risk of recurrent spontaneous abortions [24]. Patients with NLRP7 mutation have a 1.8% probability of obtaining a normal pregnancy [10]. Rare cases of families with NLRP7 or KHDC3L mutations, familial recurrent hydatidiform mole, have been described with > 75% of pregnancies resulting in complete mole [2, 20, 21]. Case studies of successful subsequent pregnancies have been achieved with donated ova [10, 23, 24].

Diagnosis

Clinical presentations of molar pregnancies have changed over time due to earlier disease detection, likely as a result of first trimester ultrasonography [25]. Few now experience what was previously viewed as "classic" molar symptoms, caused by elevations in hCG > 100,000 mIU/mL, including symptoms of hyperemesis, hyperthyroidism, theca lutein cysts, early development of preeclampsia, and uterine size greater than gestational age. As hCG levels generally are higher with complete molar pregnancy rather than partial, these symptoms were historically more common with complete moles [25]. Vaginal bleeding is now the most common presenting symptom for women with molar pregnancies [26]. While not specific to molar pregnancy, very high hCG levels increase clinical suspicion for molar pregnancy; however, this finding should not be interpreted independent of ultrasound findings.

Given the use of hCG as a tumor marker, it is important to consider causes of false results. Most notable is the "hook effect" marked by a false negative caused by hCG levels so high (typically > 500,000 mIU/mL) that the assay antibodies are saturated preventing accurate detection [27]. Causes of false elevations are described in cases of perimenopausal pituitary expression or heterophile antibodies [28].

Distinguishing between complete and partial molar pregnancies is critically important for characterization of risk of malignant transformation but may present challenges. Despite improvement in ultrasound sensitivity and predictive value, diagnostic findings are subtle in early pregnancy. As with the classic symptoms, the ultrasound findings of honeycombing or snowstorm appearance are less common [26]. In a large observational study comparing rates of ultrasound- versus histopathologic-diagnosed molar pregnancy, ultrasound was found to be 70% sensitive and 99% specific in identifying molar pregnancy. Ultrasound was more sensitive for complete moles compared to partial moles (88.2% (95% CI 78.2, 94.2) vs 56.0% (95% CI 44.7, 66.7)) [29, 30]. Lack of standard diagnostic criteria makes radiologic distinction from spontaneous abortion difficult at early gestational ages [29, 31]. The diagnosis becomes even more challenging as partial moles may contain similar pathology features as pregnancies with abnormal villous morphology related to other genetic abnormalities, early non-molar gestation, or early pregnancy loss [30]. However, histologic findings such as marked trophoblast atypia and syncytiotrophoblast hyperplasia, can aid in the distinction between complete and partial moles (Fig. 1C).

Given challenges in radiologic diagnosis, pathologic assessment is critical; however, similar to ultrasonography, distinguishing features are less defined at earlier gestations. Molar pregnancy may be identified too early to capture classic histologic features but may be suggested by the presence of karyorrhexis in villous stromal cells, representing the beginning stages of cavitation (Fig. 1F). Diagnostic algorithms have been proposed to improve identification and reduce inter- and intra-observer variation seen even amongst gynecologic pathologists [31, 32]. p57 immunohistochemistry and PCR-based DNA genotyping have been core advances in the histopathologic analysis of molar specimens [23]. Given the purely paternal genetic material in complete hydatidiform moles, the absence of p57, a protein from a *maternally* expressed gene for a cyclin-dependent kinase inhibitor, is used to distinguish a complete mole (purely androgenetic) from a partial mole or non-molar gestation (Fig. 1D, E) [3•, 33]. A triploid karyotype is nonspecific for partial moles, occurring in up to 10% of spontaneous abortions; thus, karyotyping is not sufficient for diagnosis. Genotyping uses polymerase chain reaction amplification to compare gene fragments between the products of conception and maternal tissue (extracted from evacuation procedure) to identify the genetic origin of the potential molar pregnancy [23]. Gene fragments not matching maternal DNA are presumed to be paternal in origin. Products of conception with diandric triploidy are consistent with a partial mole whereas biparental diploidy or digynic triploidy confirms a non-molar abortus. Several algorithms have been proposed combining p57 immunohistochemistry and confirmatory genotyping to reduce subjectivity of diagnosis based solely upon morphology [31, 32]. Histologic morphology can be used to triage the need for p57 immunohistochemistry; however with high suspicion for partial mole or non-molar abortus, molecular genotyping is needed for definitive diagnosis.

As surveillance guidelines evolve to account for risk of malignancy, diagnostic algorithms may begin to include risk stratification as well [34]. Accurate diagnosis of molar pregnancy is essential for risk stratification as we know complete and partial molar pregnancies carry a very different risk of malignant transformation [6]. Even within complete moles, researchers have identified distinct microRNA profiles relating to regulation of apoptosis between moles which progressed to GTN and those that did not. Mechanisms such as microRNA (miRNA) regulation or apoptotic index may serve as individualized predictors for progression to GTN [35, 36]. Molecular biomarkers of disease progression

could someday offer refined risk stratification and therefore another method of surveillance of molar pregnancy progression to GTN.

Management

Initial treatment of molar pregnancy often begins with uterine evacuation to remove the genetically abnormal tissue. Given the availability of electric suction curettage in the USA, manual vacuum aspiration (MVA) is used less commonly; however, if suction curettage is not available, MVA has been demonstrated to have equivalent success with regard to tissue removal and risk of uterine synechia formation [37]. Even with electric suction curettage, rates of complete evacuation are low for molar pregnancies compared to their non-molar counterparts (~87% vs ~98%, respectively) [37].

According to the International Federation of Gynaecology and Obstetrics (FIGO), further considerations for the evacuation of molar pregnancy include Rh immune globulin, based upon maternal Rh status, and use of peri-procedural uterotonics to reduce the risk of hemorrhage. Patients with uterine size > 16 weeks have increased risk of uterine perforation, hemorrhage, and pulmonary compromise [4]. Induction of labor or hysterotomy is not recommended due to increased risk of maternal morbidity [3•, 38].

Hysterectomy is an alternative management strategy, particularly for patients who have completed childbearing or those over 40 whose risk of treatment complications and malignant transformation is significantly higher [13]. While studies agree that hysterectomy does not completely eliminate risk of GTN development, data is conflicting about the magnitude of risk reduction [39•, 40–41]. Giorgione et al. demonstrated that there was no difference in GTN development or need for chemotherapy between hysterectomy and uterine evacuation in women over 40 with complete molar pregnancies. There may have been selection bias, however, as the patients undergoing hysterectomy may have been higher risk than the comparison group–even after multivariate analysis they were older and had higher pre-procedure hCG [40]. In contrast, a systematic review and meta-analysis by Zhao et al. demonstrated a risk reduction in post-molar GTN of more than 80% following hysterectomy compared to those receiving uterine evacuations [39•]. No prospective data exists on this topic.

Despite increased detection rates at earlier gestational ages, rates of post-molar GTN have not decreased over the years [26]. Prophylactic chemotherapy and second curettage have both been studied as a means of reducing the risk of malignant transformation [4, 42]. There is insufficient evidence to support prophylactic chemotherapy for all molar pregnancy [43–45]. Given reduction in the risk of post-molar GTN, it is offered in the UK for patients with high-risk molar pregnancy (hCG levels ≥ 20,000 mIU/mL 4 weeks after molar evacuation) [2, 46]. This practice has not been widely adopted due to the increased morbidity, potential for chemoresistance, and medical cost [44]. Routine second curettage has not demonstrated reduction in progression to post-molar GTN, though it may have a role as an alternative to immediate chemotherapy in patients with low-risk GTN [47].

Twin gestation with concurrent molar and normal fetal pregnancy represents a unique situation, as uterine evacuation and disruption of the normal pregnancy may be undesired or legally restricted depending on local abortion policies. Multiple gestations that include a molar pregnancy are rare. While up to 60% may result in a live birth, they carry a higher risk of transformation to GTN (20–45%) as well as higher risk of antenatal maternal complications (up to 80%) including preeclampsia, hyperthyroidism, preterm delivery, and intrauterine fetal demise [48]. Elective termination does not reduce the risk of post-molar GTN [49]. Given increasing prevalence of assisted reproductive technology for fertility and therefore potential for pregnancies with multiple gestations, this rare complication may be relevant for further studies [48].

Surveillance

Following surgical management, hCG levels are monitored for development of GTN (Table 2). Not all surveillance guidelines reflect the differences in rates of malignant transformation for partial and complete moles. Historically, guidelines included serum hCG testing every 1–2 weeks until normalized, and then testing in 1–2 month intervals for 6–12 months. Not surprisingly, these guidelines are burdensome for patients; several studies report that only 18% of patients complete the recommended follow-up [1•, 50•, 51]. In a prospective study on psychological impact of gestational trophoblastic disease, 47% of patients reported feelings of anxiety and 70% reported feeling distressed during the surveillance period. Interestingly, this study noted prior pregnancy loss and higher parity as protective factors for future reproductive concerns and adaptation problems [52]. Level of reproductive concern appears related to magnitude of psychologic impact with several studies demonstrating better emotional functioning in patients with prior children before molar pregnancy, as well as in those with successful conception attempts following surveillance [53, 54].

hCG surveillance recommendations following molar pregnancies are evolving in response to a growing body of evidence suggesting the risk of GTN following hCG normalization (typically defined by an hCG < 5 mIU/ml) is rare

[55]. A recent systematic review found a 0.35% cumulative incidence of GTN development after hCG normalization following a complete molar pregnancy. This rate was even lower for partial moles (0.03%) [1•]. More than half of the instances of malignant transformation presented outside of the current standard surveillance window. Given the rarity of malignancy following hCG normalization, reducing or eliminating surveillance in this instance was found to be cost-effective and clinically reasonable in a subsequent modeling study [50•]. A single hCG test 3 months after uterine evacuation was found to be a cost-effective alternative [50•].

The updated 2018 FIGO guidelines for post-molar surveillance have shortened follow-up for partial moles to one hCG following normalization but continue to recommend a more prolonged surveillance strategy for complete moles (Table 2) [50•, 55]. The American College of Obstetricians and Gynecologists (ACOG) has withdrawn a prior practice bulletin on molar pregnancy and instead now refers to the most recent FIGO recommendations. The Royal College of Obstetricians and Gynaecologists (RCOG) limits hCG follow-up for partial molar pregnancies to two hCG levels following normalization. For complete molar pregnancies, 6 months of surveillance is still recommended by this group [56]. Proposed guideline modifications center on continued risk stratification allowing a more individualized surveillance approach. In a recent SGO review regarding gestational trophoblastic disease, recommendations were to monitor hCG weekly until normalization and then continue follow-up for 3 months for complete mole or 1 month for partial mole [57]. The timing of hCG normalization may also be useful in determining surveillance strategies. Several studies suggest risk of malignant transformation is very low for patients who reach normal hCG levels within 56 days of uterine evacuation [1•, 55]. Some data also indicate the speed of hCG decline following evacuation may be related to risk of developing GTN [1•]. Others have used slope of free hCG to successfully model the prediction of GTN progression earlier than gold standard FIGO GTN diagnostic criteria in 38% of patients [58]. Genetic signatures and biomarkers represent potential future ways to risk stratify [35, 36].

As this is a disease of reproductive age women, implications for future fertility are an important component of care. For women with advanced maternal age, delaying future pregnancy for a lengthy surveillance period may have an adverse fertility impact. Patients are counseled to avoid pregnancy during the surveillance period given the interference with using hCG as a tumor marker. Historically, conflicting data existed regarding the safety of hormonal contraception during surveillance period; however, based upon more recent studies, guidelines support the use of hormonal contraception even before hCG normalization [59–62]. There is sparse data regarding timing and safety of IUD placement for post-molar contraception; however, most societies suggest safe placement can be performed following hCG normalization [56, 63].

In a small retrospective study of patients who conceived after hCG normalization but during the post-molar surveillance period, 75% resulted in live birth with no reports of fetal anomalies or persistent gestational trophoblastic neoplasia [64]. Thus, termination for pregnancy during post-molar surveillance period is not necessary but close observation is recommended. Upon completing post-molar hCG surveillance, women planning pregnancy must be counseled of the increased risk for recurrent mole particularly following a complete mole. Studies suggest that after a single molar pregnancy, a patient will have similar reproductive outcomes to the general population [65–67].

Conclusions

Hydatidiform moles are rare proliferations of placental tissue caused by abnormal fertilization events. Pregnant persons at extremes of age are at increased risk for molar pregnancy, as well as those with prior molar pregnancy. First trimester ultrasound has led to earlier detection leading to challenges in histopathologic identification by morphology alone. New methods of diagnosis utilize the genetically distinct characteristics of complete and partial moles and may be incorporated to reduce the risk of misdiagnosis. Treatment of molar pregnancy involves removal of abnormal molar tissue and surveillance for risk of malignant transformation of residual tissue, more common in complete moles than in partial moles. As long follow-up is burdensome to patients and the medical system, surveillance guidelines are evolving to incorporate risk stratification. Future research to identify biomarkers of malignant potential will help further refine risk stratification.

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Declarations

Ethics Approval Not applicable, this article does not contain any studies with human or animal subjects performed by any of the authors.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance

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