

Gestational trophoblastic disease

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LEARNING POINTS

- Contemporary hydatidiform moles most commonly present as early pregnancy failure.
- Following a diagnosis of hydatidiform mole, patients require hCG follow-up to detect persistent trophoblastic neoplasia, which follows about 15% of complete hydatidiform moles and about 0.5% of partial hydatidiform moles.
- Most cases of persistent trophoblastic neoplasia can be treated successfully with relatively nontoxic chemotherapeutic regimens.
- Abnormal vaginal bleeding or other unusual symptoms following any type of pregnancy should raise suspicion for possible trophoblastic disease.

Introduction

Gestational trophoblastic disease refers to a range of defined entities including complete and partial hydatidiform mole, invasive mole, and the malignant tumors choriocarcinoma, placental site trophoblastic tumor, and its variants. In the context of abortion care, chief concerns are the reliable detection of hydatidiform mole and prevention of morbidity through identification of persistent gestational trophoblastic neoplasia (pGTN) [1]. Diagnosis of pGTN typically requires human chorionic gonadotropin (hCG) surveillance following uterine evacuation of hydatidiform moles; rising or plateauing hCG levels signal pGTN that may require chemotherapy. The aim of this chapter is not to review all aspects of gestational trophoblastic disease but rather to focus on early diagnosis of hydatidiform mole (HM) and its subsequent management, including screening after induced abortion or medical management of early pregnancy failure. Complications of GTN are best managed in specialist tertiary referral centers.

Epidemiology of hydatidiform mole

In the USA and Western Europe, hydatidiform mole occurs in approximately 1 in 500 to 1 in 1,200 pregnancies [2]. The incidence of both complete (CHM) and partial (PHM) hydatidiform mole varies by ethnicity, being greater in women

of Asian origin. Incidence is also strongly associated with extremes of maternal age, with a small peak in relative risk in the early teens and a much larger peak occurring among women in their late forties [3]. All hydatidiform moles carry a risk of developing pGTN, which occurs following about 15% of CHM and 0.5% of PHM [4].

Genetics of hydatidiform moles

Hydatidiform moles represent a phenotype of abnormal placental development due to overexpression of paternally derived genes, and they are therefore abnormalities of imprinting. Complete and partial hydatidiform moles are genetically distinct. Complete moles are almost always diploid, with the genetic material exclusively of paternal origin. They derive from fertilization of an anucleate oocyte, either by a haploid sperm that undergoes duplication inside the oocyte or, more rarely, by two sperm. Partial moles are almost exclusively triploid, with one maternal and two paternal contributions to the genome. They usually arise from dispermic fertilization of an apparently normal oocyte (Fig. 19.1).

Presentation of moles and their early identification

According to classical dogma, PHM is associated with the presence of a fetus and coexistent patchy hydatidiform change of the placenta, whereas CHM lacks significant fetal development and demonstrates diffuse placental hydropic change. However, modern understanding of these pathologies negates such a simple distinction. Indeed, some cases of CHM show histologic evidence of early fetal-type

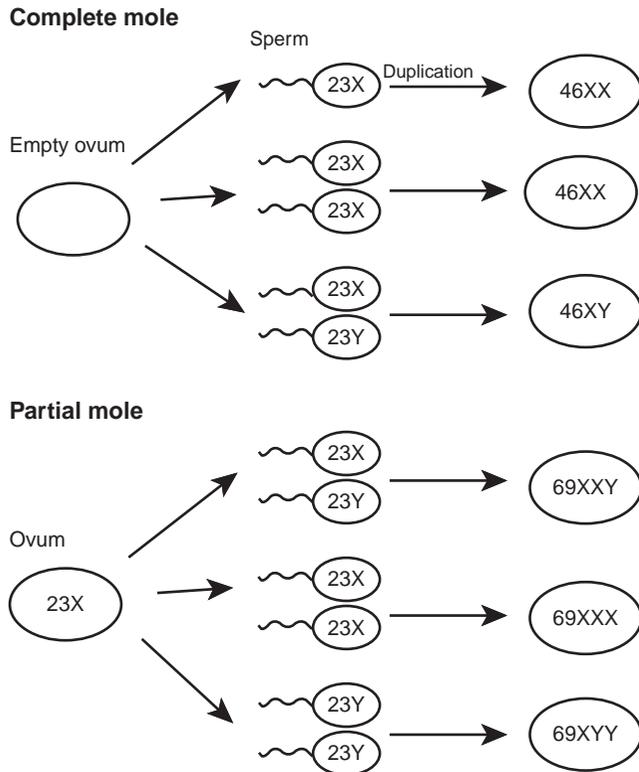


Figure 19.1 Cytogenetic origin of hydatidiform moles. Most complete moles are diploid (46 chromosomes) and androgenetic (i.e., the genetic material is exclusively of paternal origin). They arise from fertilization of an “empty” oocyte by either a haploid sperm that undergoes duplication or, rarely, by two haploid sperm. Partial moles are almost always triploid (69 chromosomes), and contain both maternal and paternal genetic contributions. Partial moles arise from fertilization of an apparently normal haploid ovum by two haploid sperm. (Reprinted with permission from Altieri A, Franceschi S, Ferlay J, Smith J, La Vecchia C. Epidemiology and aetiology of gestational trophoblastic diseases. *Lancet Oncol* 2003; 4:670–678.)

development [5], whereas most women with PHM present as early pregnancy failure without a clinically or sonographically identifiable fetus [6]. The changing clinical, sonographic, and histopathologic descriptions of these conditions require revised and updated criteria for their identification and diagnosis.

Pathology of hydatidiform moles

Molecular genetic analysis is the gold standard for the definitive diagnosis and subtyping of hydatidiform mole, although histopathologic examination remains the most common method of diagnosis for practical purposes. The diagnostic pathologic feature of molar pregnancy is abnormal proliferation of villus trophoblast. However, complete moles and partial moles each have distinctive histologic characteristics, even in the first trimester [7–9].

Classic second-trimester complete moles exhibit marked villus hydrops with extensive circumferential villus tro-

phoblast hyperplasia and central “cistern” formation. However, most contemporary moles are evacuated in the first trimester when these features are not developed. The histopathologic diagnostic features at this early stage include a characteristic abnormal “budding” villus architecture with abnormally distributed villus trophoblast hyperplasia, a relative lack of villus hydrops, sheets of pleomorphic extravillous trophoblast, collapsed villus blood vessels, and marked stromal karyorrhectic debris, as well as abnormal extravillous trophoblastic invasion [8,9]. In addition, tests based on genetic characteristics of the HM subtypes may assist in the diagnosis of early CHM. The imprinted gene $p57^{KIP2}$ shows high levels of expression in cells with maternal nuclear DNA content, but it is repressed in cells that contain only paternal DNA. Therefore, normal placenta and PHM show nuclear positivity on immunostaining of villi with antibody to $p57^{KIP2}$, whereas androgenetic CHM does not [10,11].

Classic second-trimester partial moles exhibit a dual population of normal-sized and hydropic villi with focal trophoblast hyperplasia. In the first trimester, the changes are usually patchy and mild with limited villus hydrops and cistern formation, numerous vessels containing nucleated fetal red cells, patchy vascular “pseudoangiomatoid” change, abnormally shaped “scalloped” or “dentate” villi, and the presence of trophoblastic pseudo-inclusions and villus stromal fibrosis. Trophoblast hyperplasia is patchy and in an abnormal distribution, often with a vacuolated appearance (Fig. 19.2).

In some cases, a definite diagnosis of early PHM may not be possible without the use of ancillary techniques such as assessment of ploidy using *in situ* hybridization or flow cytometry [12] or microsatellite polymorphism analysis (not available in routine practice) [13]. This requirement is especially true when limited material is submitted for examination. Furthermore, conceptions affected by other aneuploidies may appear histologically similar to PHM, although they lack the abnormal trophoblast hyperplasia of hydatidiform mole.

Changes in the clinical presentation of hydatidiform mole

In traditional obstetric and gynecologic teaching, patients with CHM presented with vaginal bleeding or passage of vesicles per vagina, uterine enlargement greater than expected for gestational age, and abnormally high levels of serum hCG. Potential medical complications included preeclampsia, hyperthyroidism, hyperemesis, anemia, or massive ovarian theca-lutein cysts [14].

However, with the increasing use of ultrasonography to assess uncomplicated pregnancies and those that present with vaginal bleeding, this classical presentation occurs rarely [15]. Most contemporary moles are evacuated before 12 weeks’ gestation (around 10 weeks in the UK) [16,17]. This change in management has decreased dramatically the number of molar pregnancies presenting with the symptoms

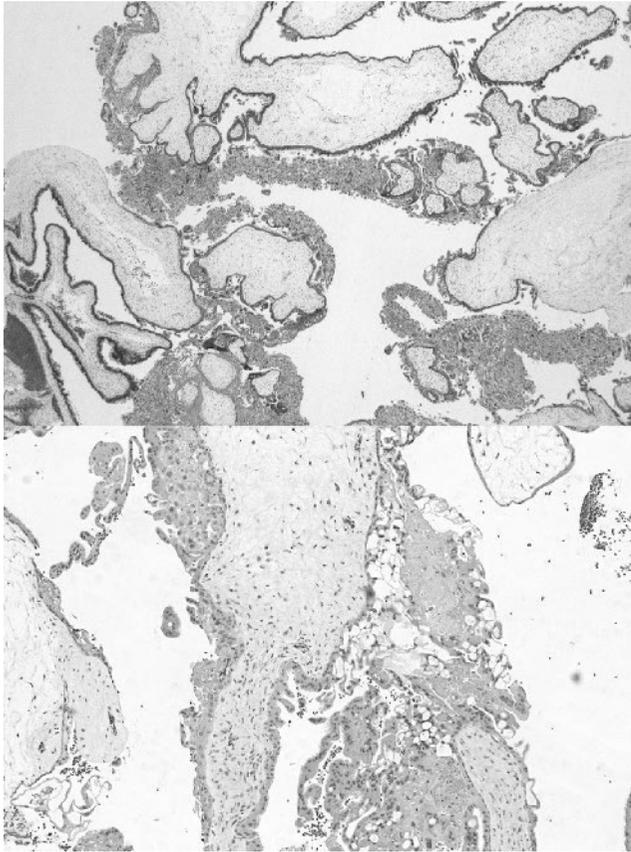


Figure 19.2 Photomicrographs of complete hydatidiform mole (top) and partial hydatidiform mole (bottom) demonstrating histopathologic features of abnormal budding architecture, cellular stroma with debris and abnormal trophoblast hyperplasia (complete mole), and abnormal irregularly shaped villi with trophoblastic pseudoinclusions and abnormal trophoblast proliferation (partial mole). H&E, original magnifications $\times 20$.

and signs induced by overgrowth of trophoblast and excessive hCG secretion. In one study of women with confirmed CHM, 40% were entirely asymptomatic with the condition detected by routine sonography, whereas the remaining 60% presented with vaginal bleeding; only 2% reported symptoms such as hyperemesis, and no women reported any other systemic manifestations [18].

The role of ultrasonography in the diagnosis of hydatidiform mole

Although now seldom seen, the characteristic sonographic findings of second-trimester hydatidiform mole include a uterine cavity filled with a central heterogeneous mass with anechoic spaces of varying sizes and shapes (e.g., a “snowstorm” appearance) without associated fetal development (Chapter 6) [19]. In addition, theca-lutein ovarian cysts can occur secondary to high hCG levels, producing either a “soap bubble” or “spoke wheel” appearance

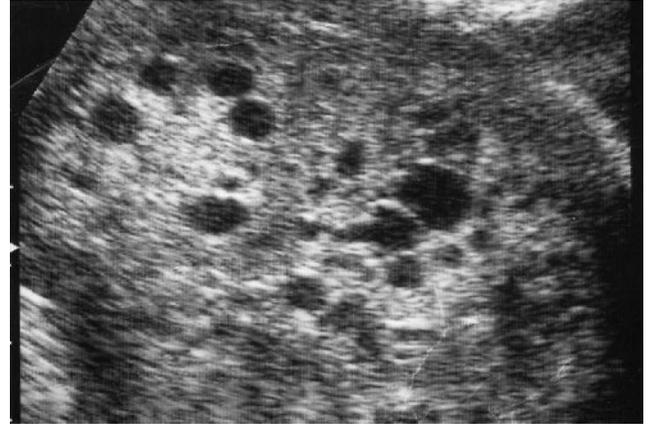


Figure 19.3 Early partial hydatidiform mole most commonly appears as an anembryonic pregnancy on ultrasonography. Occasionally, it manifests as multiple cystic spaces in the placenta, as shown in this ultrasound image.

of the enlarged ovaries. In the first trimester, hydatidiform changes on ultrasound examination are less readily apparent (Fig. 19.3).

Multiple studies have examined the ability of ultrasound to detect hydatidiform mole in early pregnancy, with initial reports suggesting detection rates of up to 80% for CHM. When PHM or CHM was not suspected prior to pathologic examination, the most common initial sonographic diagnosis was anembryonic pregnancy [20–24]. These early reports were based on small series from specialist centers.

Two recent larger studies found that in routine practice, preevacuation ultrasonography performed during the first or early second trimester correctly identified only 40 to 60% of molar pregnancies [16,25]. The largest study reviewed the preevacuation ultrasound findings in more than 1,000 consecutive patients referred to a UK regional trophoblastic disease unit for histologic review of possible or probable hydatidiform mole [16]. All cases of gestational trophoblastic disease suspected clinically, sonographically, or on the basis of histopathologic findings are registered at the center, allowing for the greatest possible ascertainment. The median gestational age at evacuation was 10 weeks (range 5 to 27 weeks). The final diagnosis was hydatidiform mole in 859 (82%) cases, including 253 (29%) CHM and 606 (71%) PHM.

Overall, only 40% of women with confirmed hydatidiform mole had a preevacuation ultrasound diagnosis suggesting molar pregnancy, including about 80% of CHM and 30% of PHM; the remaining cases appeared sonographically as anembryonic pregnancies. A nonsignificant trend occurred toward increasing ultrasound detection rate with advancing gestational age; sonographic features of hydatidiform mole were reported in 35% of cases before 14 weeks'

gestation, compared to approximately 60% after this time. Of note, more than 10% of the cases identified as molar on ultrasound examination were in fact nonmolar hydropic abortions on histologic review. Based on this study, the sensitivity, specificity, and positive and negative predictive values for routine preevacuation ultrasound examination for hydatidiform mole are 44, 74, 88, and 23%, respectively. Because a proportion of early moles are simply not yet hydropic enough to be evident on ultrasound examination, current techniques will likely never result in 100% detection rates [9,26].

Occasionally, routine ultrasound examination demonstrates the presence of a morphologically normal fetus in association with apparent “molar” change of the placenta. These findings may represent a pregnancy with placental mosaicism for CHM [27] or a dichorionic twin pregnancy with a CHM and a normal co-twin. Partial mole is unlikely because triploid PHM rarely progresses, and the fetus is almost never structurally normal. In one large series of CHM/co-twin cases, the risk of pGTN was comparable to that reported following singleton CHM, and it did not differ between women who continued the pregnancy and those who had immediate uterine evacuation. However, pregnancy continuation was associated with several complications, including spontaneous abortion, later fetal demise, and preterm delivery [28]. Diffuse cystic sonographic “molar” changes of the placenta in association with an apparently normal fetus in the second or third trimester are usually due to placental mesenchymal dysplasia rather than hydatidiform mole [29].

Detection of hydatidiform mole in the abortion care setting

Most pregnancy terminations and pregnancy failures occur during the first trimester, and treatment options include aspiration or medical regimens. Appropriate management of these conditions will lessen the chance of missing an undiagnosed mole that may subsequently present with pGTN [30,31]. Data based on cases of pGTN following terminations of pregnancy suggest that delayed diagnosis results in poorer outcomes. Women presenting with clinical symptoms of pGTN have significantly more complications, morbidity, and requirements for radical surgery and combination chemotherapy than women identified by postevacuation hCG surveillance protocols [31].

Detecting early hydatidiform mole and its possible sequelae presents challenges, however. Tissue is not always available for histopathological examination. With home-based medical treatment regimens for induced abortion or early pregnancy failure, patients typically expel the products of conception outside of the clinical setting. Moreover, only 22% of North American abortion providers routinely submit tissue for pathological examination following surgical abortion [32]. Even when tissue is submitted, pathologists with-

out special expertise in gestational trophoblastic disease may have problems identifying the subtle morphologic changes of early moles. Indeed, studies have shown poor interobserver correlation between pathologists, particularly in distinguishing partial moles from nonmolar hydropic abortions [33,34].

Because most early molar pregnancies are partial moles that present sonographically as anembryonic gestations [16], the most comprehensive approach would include universal ultrasound examination to identify any nonviable conceptions, followed by aspiration and formal histopathologic tissue analysis by specialists in placental pathology. However, such a policy is cost-prohibitive, especially because PHM rarely results in persistent disease. Moreover, this strategy excludes patients who prefer home-based medical methods of pregnancy termination.

Urine pregnancy testing postabortion can detect persistently elevated hCG levels that may signal complications including failed abortion, incomplete abortion, or the rare case of pGTN [31]. Following complete induced abortion, hCG levels decline rapidly at first and then more gradually; low-sensitivity urine pregnancy tests are usually negative by 2 to 3 weeks after surgical abortion, whereas sensitive tests may take 4 weeks or more (Chapter 6). A persistently positive test in the absence of other complications may signify pGTN. In this case, serum quantitative hCG levels should be followed every 1 to 2 weeks to assure that they return to normal or until pGTN is confirmed by persistently elevated hCG levels [35]. Because pGTN can occur after nonmolar gestations, hCG testing is advised for patients who have unexplained persistent abnormal bleeding 6 weeks following any pregnancy outcome [1,36].

For a variety of reasons, including that many women do not return for follow-up after induced or spontaneous abortion, some cases of HM will inevitably escape detection. A few cases of pGTN resulting from undiagnosed HM at the time of abortion have been reported [30,31]. Fortunately, given the rarity of molar pregnancy and the less than 1% risk that PHM will progress to pGTN, overall morbidity from undetected early HM is likely to be very low.

Management of hydatidiform mole

Uterine evacuation

Prompt uterine evacuation constitutes the initial management of hydatidiform mole. Use of suction rather than sharp curettage minimizes the risk of uterine perforation [37]. Evacuation of large moles is facilitated by adequate dilation using osmotic dilators and a large-bore cannula. To control bleeding following uterine aspiration, we recommend using a single dose of ergotamine to induce a sustained contraction. In general, clinicians should avoid repeated evacuations; they increase the risk of uterine perforation, and persistent molar tissue may be deeply invasive and

likely to require chemotherapy [17]. Ultrasound examination, either B mode or combined with color Doppler flow assessment, may help confirm uterine evacuation or identify residual trophoblastic tissue [38–40]. Neither the American College of Obstetricians and Gynecologists (ACOG) nor the Royal College of Obstetricians and Gynaecologists (RCOG) supports medical methods of uterine evacuation for patients with suspected hydatidiform mole [1,36,41].

Follow-up hCG surveillance

All patients diagnosed with CHM or PHM require follow-up with serial hCG measurements for the early detection of pGTN. Serum monitoring provides the most accurate way of determining when the hCG falls to normal. The ACOG recommends measuring serum hCG within 2 days of evacuation, every 1 to 2 weeks while elevated, and then monthly for an additional 6 months [36]. The protocol followed at the trophoblastic disease center at Charing Cross Hospital, London, is as follows: hCG is measured in serum and urine every 2 weeks until normal and then in urine monthly until the end of the follow-up period. If the hCG becomes negative within 56 days (8 weeks), then we follow the patient for a total of 6 months from the time of molar evacuation. In contrast, follow-up is extended for a full 6 months of negative hCG values if hCG first normalizes more than 56 days after molar evacuation. We use the same periods of follow-up regardless of the type of hydatidiform mole [35]. Other centers in the world may vary this regimen; some use a shorter duration of follow-up, particularly for PHM [42]. Abbreviated follow-up may help overcome problems with patient compliance [43]; however, it also presents a small risk of missing pGTN with its rare but life-threatening complications, and therefore warrants further investigation.

Because cancer can produce multiple forms of hCG that are not all found in normal pregnancy, hCG assays used in cancer optimally would detect all forms of hCG. In addition to reported false-positive problems [44], most commercial assays are prone to false-negative results because they fail to detect variant forms of hCG [45]. Efforts are under way to develop a new generation of appropriate hCG assays for use in cancer.

Patients who have had a molar pregnancy are at increased risk for a subsequent hydatidiform mole and development of pGTN following any future pregnancy, even if nonmolar, due to reactivation of latent trophoblast [46]. Therefore, hCG surveillance is critical following any subsequent pregnancy, regardless of outcome. Reliable contraception is recommended during the initial follow-up period because a subsequent pregnancy complicates the interpretation of a rising hCG level, and the hormonal effects of pregnancy may reactivate latent trophoblastic disease. Use of the combined oral contraceptive pill (OCP) in this setting has been marked by controversy. Early experimental studies suggested that administration of exogenous hormones could stimulate GTN

growth, and some observational studies reported an increased risk of pGTN in women using OCPs. However, a recent systematic review of the literature, including two randomized trials, failed to support this conclusion [47]. Moreover, the World Health Organization designates all hormonal contraceptive methods as Category 1 (no reason to deny) for women with benign or malignant gestational trophoblastic disease [48]. Nonetheless, some centers, including those in the UK, recommend avoiding hormonal contraception at least until hCG levels have returned to normal [17].

Persistent gestational trophoblastic neoplasia

Forms of pGTN

Persistent GTN complicates about 15% of CHM and about 0.5% of PHM [4,35]. The various forms of pGTN include noninvasive trophoblastic proliferation, invasive mole, choriocarcinoma, and placental site trophoblastic tumor.

Invasive mole occurs when villi from a CHM (or rarely PHM) penetrate into the myometrium or the uterine vasculature. Occasionally, villi penetrate through the full thickness of the myometrium (percreta), leading to uterine perforation or local pelvic extension. In contrast to choriocarcinoma, invasive mole contains distinct molar chorionic villi. The condition usually manifests clinically as pGTN following initial evacuation of a molar pregnancy, with persistent heavy vaginal bleeding and raised hCG levels. Sonography demonstrates focal areas of increased echogenicity within the myometrium [49] (Fig. 19.4). These findings mimic those of placental site trophoblastic tumor but they occur concurrently, or soon after, a proven molar gestation. Treatment usually involves standard chemotherapy



Figure 19.4 Ultrasonographic appearance of an invasive complete hydatidiform mole, showing a localized uterine mass with multiple echolucent cystic spaces and Doppler imaging demonstrating peripheral blood flow. See Plate 19.1.

protocols or surgery; adjunctive local ultrasound-guided injection of methotrexate also has been described [50].

Choriocarcinoma is a malignant neoplasm that exhibits differentiation toward villus cytotrophoblast and syncytiotrophoblast in the absence of chorionic villus structures. Choriocarcinoma occurs in approximately 1 in 20,000 pregnancies [36], and it can follow CHM, PHM, normal pregnancy, stillbirth, spontaneous abortion, or ectopic pregnancy. The incidence of choriocarcinoma after CHM is about a thousand-fold greater than that following a nonmolar pregnancy. Choriocarcinoma either presents as pGTN in patients on hCG surveillance or as clinically apparent, often metastatic, disease in other patients. Uterine choriocarcinoma appears as a hemorrhagic nodule, which metastasizes early to cervix, vagina, or distant sites. Unexplained intracerebral hemorrhage or acute cor pulmonale in a woman of childbearing age should always raise suspicion of choriocarcinoma.

Placental site trophoblastic tumor (PSTT) is distinct from choriocarcinoma both pathologically and clinically, growing more slowly and remaining localized often for several years. Placental site trophoblastic tumors tend to produce less hCG than choriocarcinoma. Spread is initially to adjacent structures and lymph nodes, although PSTT also can metastasize. Many PSTT will respond to aggressive chemotherapy regimens. The cure rate is high if the disease is detected within 4 years of the causative pregnancy, but patients presenting after this period almost universally succumb to the disease. Overall experience with PSTT is still limited [51].

Diagnosis and evaluation of pGTN

Persistent GTN typically presents as either plateauing or rising hCG concentrations during hCG surveillance (Fig. 19.5) or, uncommonly, with symptoms due to localized or metastatic disease. Although several staging systems have been suggested for pGTN, the FIGO 2000 Staging and Risk Factor Scoring System for GTN represents a unified worldwide system to allow comparison of outcome and treatment data across centers [52]. According to this system, any of the following criteria suffices for the diagnosis of postmolar pGTN:

- Plateauing hCG ($\pm 10\%$) for four measurements over a 3-week period or longer
- Rising hCG on three consecutive weekly measurements, over a period of 2 weeks or longer
- Histologic evidence of choriocarcinoma
- hCG exceeding 20,000 IU/L 4 weeks postuterine evacuation (because of the risk of uterine perforation)
- hCG level remaining elevated for 6 months or more postevacuation.

Identification of pGTN warrants further investigation to stage the disease. After a molar pregnancy, most women simply require a current serum hCG level, chest x-ray, and a pelvic Doppler ultrasound. Identification of a lesion on chest x-ray prompts further delineation by chest CT, as well as

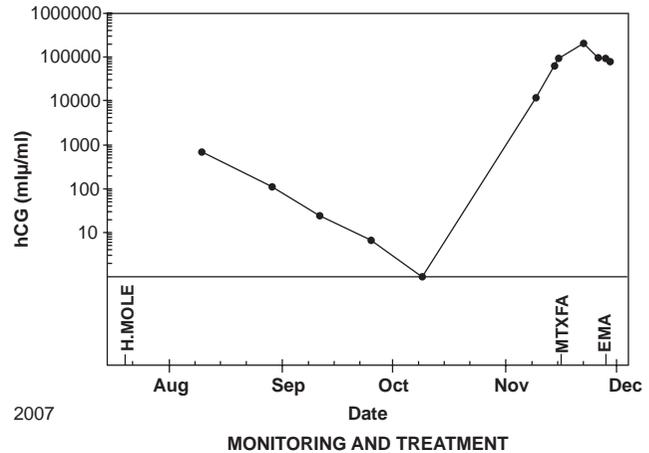


Figure 19.5 Plot of serum hCG concentrations following evacuation of an early complete hydatidiform mole, demonstrating a gradual fall in hCG levels followed by a marked increase, indicating persistent GTN requiring chemotherapy. H Mole = hydatidiform mole; MTXFA = methotrexate, folinic acid; EMA = etoposide, methotrexate, and actinomycin D.

brain MRI to help exclude CNS spread. If the brain MRI is normal, then a lumbar puncture to assess the cerebrospinal fluid serum hCG ratio helps exclude occult CNS disease. Specialists use the results of these studies to determine the stage and prognostic score to assign patients to high- or low-risk groups for developing disease that is resistant to single drug chemotherapy [53]. Other indications for treatment of pGTN include vaginal or intra-abdominal bleeding; metastases in the lung or vagina exceeding 2 cm; or metastases in the brain, gastrointestinal tract, or liver.

Treatment of low-risk patients

Most women who develop pGTN after a molar pregnancy will be low-risk, meaning that their disease has a low probability of becoming resistant to single-drug therapy with either methotrexate or actinomycin D. A variety of protocols exist [54–56] but no randomized trials have established the optimal agent or regimen [57].

Due to its favorable safety/side effect profile, methotrexate is used most commonly with or without folinic acid rescue. A nonrandomized study suggests that daily or alternate daily methotrexate treatment over a week is superior to weekly or less-frequent pulsed administrations [58]. At Charing Cross, we administer 50 mg of methotrexate intramuscularly on days 1, 3, 5, and 7 alternating with 15 mg of folinic acid orally 30 hours postmethotrexate on days 2, 4, 6, and 8, repeated every 2 weeks. Once the serum hCG has normalized, methotrexate treatment is continued for three further cycles (i.e., for 6 weeks of normal hCG levels). We estimate that 10^5 cancer cells may remain when hCG levels first become normal, so stopping therapy early increases relapse rates. The schedule is well tolerated with no alopecia. The incidence of mucositis, the most common toxicity, fell

from 20% to less than 2% by increasing the folinic acid rescue from 7.5 to 15 mg [56]. Other less-frequent side effects include serositis and derangement in liver and renal function. Myelosuppression occurs rarely, and no second malignancies have yet been reported.

Several schedules also have been developed using actinomycin D. Daily administration for 5 days every 2 weeks is more efficacious and better tolerated than pulsed or bi-weekly single-dose regimens [58]. The short-term toxicity of actinomycin D exceeds that of methotrexate but, like methotrexate, it probably has no significant long-term sequelae [56].

The most sensitive indicator of methotrexate resistance is a plateau or rise in serum hCG levels over three or more values. The level of hCG at which resistance develops may guide the choice of salvage chemotherapy. At Charing Cross, we achieve high cure rates using single-agent actinomycin D if the hCG is less than 100 IU/L. If initial therapy was actinomycin D, a switch to methotrexate may be curative. Both actinomycin D failures and those patients developing methotrexate resistance with an hCG exceeding 100 IU/L can be cured with etoposide, methotrexate, and actinomycin D (EMA) combined with cyclophosphamide and vincristine (CO) [56].

Treatment of high-risk patients

Combination chemotherapy is the treatment of choice for high-risk patients. The most widely used regimen based on EMA/CO has remission rates of 80 to 95% [59,60]. EMA/CO chemotherapy is more toxic than single-agent therapy; short-term side effects include reversible alopecia, mucositis, myelosuppression, and peripheral neuropathy. Such high-risk treatment increases the risk of second tumors approximately 1.5-fold compared to the general population. A review of 275 high-risk patients at Charing Cross Hospital treated with EMA/CO chemotherapy showed a cumulative 5-year survival of 86%, with no deaths from GTN beyond 2 years after the initiation of chemotherapy. Presence of metastatic disease, especially combined liver and brain metastases, was associated with poor prognosis [59].

Patients with resistant GTN can still be salvaged after primary treatment failure, usually by a combination of further chemotherapy and surgical removal of resistant disease. As an adjunct to surgery or when surgery is not appropriate, we use a weekly alternating regimen of etoposide and cisplatin (EP) alternating with 1 day of EMA. This combination is toxic but effective, with salvage rates greater than 80% [61]. No other treatment regimens utilized thus far have proven as effective as EP/EMA.

Follow-up postchemotherapy

Following successful treatment, patients are followed up with regular serum and urine hCG measurements weekly for 6 weeks, biweekly for 3 months, and then with dimin-

ishing frequency until they require only biannual urine samples. In the UK, we continue follow-up indefinitely because we are uncertain when it is safe to stop. Current information indicates that the overall relapse rate is about 3%, with most relapses occurring within the first year of follow-up. We advise women not to conceive for 12 months, as pregnancy would mask early detection of relapsed disease and the preceding chemotherapy poses an increased risk of congenital anomalies.

Conclusion

With advances in technology and clinical practice over the last two decades, presentation of hydatidiform mole has moved from the second trimester to the earlier weeks of gestation. Because early moles lack the characteristic features of classic moles, this evolution is testing the limits of our current diagnostic modalities and opening up new avenues of clinical inquiry and research. By remaining clinically astute and aware of changes in the rapidly evolving field of gestational trophoblastic disease, abortion providers and other women's health practitioners can play an important role in decreasing morbidity from this rare but important set of disorders.

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