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PRESENTATION AND MANAGEMENT OF MOLAR PREGNANCY

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Our understanding of the cytogenetics, epidemiology, pathology and clinical management of hydatidiform mole has advanced considerably over the past 40 years. It is now well recognized that molar pregnancy comprises two distinct entities, complete and partial, which differ on the basis of chromosomal pattern, gross and microscopic histopathology and clinical presentation. Other chapters in this text review the current status of the cytogenetics, epidemiology and pathology of molar disease. In this chapter, our focus will be on the presentation, diagnosis and principles of management of patients with complete and partial hydatidiform mole.

9.1 PRESENTATION OF COMPLETE MOLAR PREGNANCY AND MANAGEMENT OF COMPLICATIONS

The following description of the classical presentation of complete mole is partially based upon our experience with 308 patients between 1965 and 1975 at the New England Trophoblastic Disease Center (NETDC)[1]. The experience from our center is consistent with the published observations of other investigators. However, partial mole was initially distinguished from complete mole by Vassilakos *et al.* in 1977 and Szulman and Surti in 1978 on the basis of karyotype and histopathology [2—4]. It is therefore important to note that all studies concerning molar pregnancy which include patients before 1980 may have included some patients with partial mole. However, the vast majority of patients with molar pregnancy in studies before 1980 most likely involved cases of classic complete hydatidiform mole, since most cases of partial mole were interpreted as being non-molar abortions.

9.1.1 VAGINAL BLEEDING

Vaginal bleeding is the most common presenting symptom in patients with complete mole, occurring in 97% of our cases. Curry *et al.* [5] and Kohorn[6] also noted a high incidence of vaginal bleeding in 312 (89%) of 347 and in 188 (94%) of 200 patients with molar pregnancy, respectively. Molar chorionic villi may disrupt maternal vessels by separating from the decidua and the endometrial cavity may be

distended by large volumes of retained blood. Retained blood may undergo oxidation and 'prune juice-like' fluid may leak from the uterine cavity. Because bleeding may be prolonged, considerable and occult, 54% of our patients were anemic at presentation (hemoglobin <10 g/100 ml).

9.1.2 EXCESSIVE UTERINE ENLARGEMENT

The uterine size was palpably larger than gestational age in 51% of our patients with complete mole. Uterine size was larger than dates by four weeks in 46% and 38% of patients with complete mole in the studies by Curry *et al.* and Kohorn [5,6]. The endometrial cavity expands because of both retained blood and chorionic tissue. Excessive uterine size is usually associated with markedly elevated levels of human chorionic gonadotropin (hCG) from trophoblastic overgrowth.

9.1.3 THECA LUTEIN OVARIAN CYSTS

The reported frequency of theca lutein ovarian cysts varies depending upon whether the diagnosis is established by clinical or ultrasound examination. Montz *et al.* [7] reported that theca lutein cysts were clinically palpable in 102 (26.4%) of 386 patients with molar pregnancy. Kohorn also observed theca lutein cysts in 20% of patients with molar pregnancy [6]. However, Santos-Ramos *et al.* [8] using ultrasound observed theca lutein ovarian cysts >5 cm in diameter in 23 (46%) of 50 patients with molar pregnancy.

Theca lutein ovarian cysts are usually bilateral and multicystic, containing amber-colored or serosanguineous fluid. Though usually in the 6-12 cm range, they may reach substantial proportions of larger than 20 cm in size. While theca lutein cysts are generally noted at the time of presentation, they may enlarge substantially after uterine evacuation.

Theca lutein cysts result from hyper-stimulation of the ovaries by high circulating blood levels of hCG and are detected almost exclusively in patients with very high serum hCG values [9,10]. Infrequently these patients may develop other signs of ovarian hyperstimulation such as ascites or pleural effusions. When this occurs, fluid and electrolyte disturbances may require management.

Montz *et al.* reviewed the clinical records of 102 patients with molar pregnancy and theca lutein ovarian cysts to define their natural history [7]. The mean regression time for these cysts was eight weeks. Only two patients experienced an acute surgical complication involving ovarian torsion or rupture. Similarly, Kohorn reported that three (2.3%) of 127 patients with molar pregnancy developed torsion of ovarian theca lutein cysts[11]. Given the low risk of torsion, theca lutein cysts can be followed conservatively. However, if patients have severe symptoms of respiratory compromise, pelvic pressure or pain, theca lutein cysts may be decompressed by either ultrasound-directed percutaneous or laparoscopic aspiration. Laparoscopy may also be

utilized to successfully manage cases of incomplete ovarian torsion or rupture [12].

9.1.4 TOXEMIA

Pre-eclampsia including hypertension, edema and/or proteinuria was observed in 27% of our patients with complete mole. Curry *et al.* reported pre-eclampsia in 12% of patients with molar disease in the Duke series [5]. Eclamptic convulsions occur rarely. In our experience toxemia was limited almost exclusively to patients with markedly elevated hCG values and excessive uterine enlargement. These authors also noted that 81% of their patients with toxemia had excessive uterine size.

9.1.5 HYPEREMESIS GRAVIDARUM

Hyperemesis requiring antiemetic therapy developed in 26% and 20% of patients with molar pregnancy treated at our Center and at the Yale Center [11,13]. Five (2%) of our patients required hospitalization for correction of marked electrolyte disturbances. Hyperemesis also appears to be associated with high hCG levels and excessive uterine size. Depue *et al.* have proposed that hyperemesis results from elevated serum estrogen levels [14].

9.1.6 HYPERTHYROIDISM

Clinically evident hyperthyroidism was detected in 7% of our patients with complete mole. However, laboratory evidence for hyperthyroidism was more common. Galton *et al.* measured thyroid function tests in 11 patients with molar pregnancy before and after evacuation [l5]. Pre-evacuation, all patients had elevated values for thyroidal ^{131}I uptake and serum free thyroxine; the thyroid function tests rapidly returned to normal after evacuation even before the hCG level became undetectable. Similarly, Norman, *et al.*[16] studying the thyroid status of 27 African patients found that when serum hCG reached a level of about 100,000 IU/L 13 of 16 patients were biochemically hyperthyroid; at serum levels of 300,000 IU/L most patients were clinically thyrotoxic. A feature of hyperthyroidism associated with molar pregnancy is that whereas T4 is invariably raised, the T3:T4 ratio tends to be low and TSH levels were not increased.

Hyperthyroidism occurs almost exclusively in patients with very high hCG levels. Some authors have suggested that hCG is the thyroid stimulator in patients with molar pregnancy[17]. Kenimer *et al.* reported that highly purified hCG appeared to have intrinsic thyroid-stimulating activity[18]. Positive correlations have been reported in some studies between serum hCG levels and serum total thyroxine (T_4) or triiodothyronine (T_3) concentrations. However, Nagataki *et al.* found no correlation between serum hCG and free T_4 in 10 patients

with molar pregnancy [19]. Similarly Amir *et al.* measured thyroid function tests in 47 patients with complete mole and observed no significant correlation between serum hCG levels and free T_4 or T_3 index values [20]. The identity of the thyrotropic factor in molar pregnancy is therefore still controversial.

Patients with untreated or poorly controlled hyperthyroidism may develop thyroid storm at the time of anesthesia induction and evacuation [21]. Thyroid storm is characterized by hyperthermia, delirium, coma, atrial fibrillation, and acute pulmonary edema associated with cardiac failure. While blood samples should be drawn for laboratory confirmation, the diagnosis of thyroid storm must be made clinically so that treatment can be promptly instituted. The administration of β-adrenergic blocking agents prevents or rapidly reverses many of the cardiovascular and metabolic complications of thyroid storm. A pulmonary artery catheter may also be helpful to monitor cardiovascular status and guide fluid replacement.

9.1.7 RESPIRATORY INSUFFICIENCY

Two per cent of our patients with complete mole developed respiratory insufficiency. Pulmonary compromise generally only develops in patients with high hCG levels, excessive uterine size and very large theca lutein cysts. Twiggs *et al.* reported that 12 (27%) of 44 patients with a molar pregnancy of at least 16 weeks size developed pulmonary complications[22].

Patients may present with tachycardia, tachypnea and anxiety or confusion in the recovery room after molar evacuation. Arterial blood gases may show evidence of hypoxia and respiratory alkalosis. Auscultation of the chest usually reveals diffuse rales and chest roentgenogram may show bilateral pulmonary infiltrates. The signs and symptoms of respiratory distress usually resolve within 72 hours with appropriate cardiovascular and respiratory support. However, it is important to recognize that some patients may require temporary mechanical ventilation to provide adequate oxygenation. While embolization of molar tissue to the pulmonary vasculature may contribute to respiratory distress, it may also result from the cardiovascular complications of toxemia, thyroid storm and massive fluid replacement.

9.1.8 CHANGING CLINICAL PRESENTATION OF COMPLETE MOLAR PREGNANCY

The clinical presentation of complete molar pregnancy as outlined above has changed considerably over the last decades. Patients with complete mole are being more frequently diagnosed in the first trimester before they develop the classic signs and symptoms due to the frequent use of hCG measurement and vaginal probe ultrasound in early pregnancy in women with vaginal staining and even in asymptomatic women [23,24].

Soto-Wright *et al.* reviewed the presentation of 74 patients with complete mole who underwent uterine evacuation at the NETDC

between 1988 and 1993 and compared it to an earlier cohort (1965-1975) [25]. Vaginal bleeding continued to be the most common presenting symptom, occurring in 62 (84%) patients. However, excessive uterine size (size> gestational age), anemia (hemoglobin <10g/dl) and toxemia were noted in only 21(28%), four (5%) and one (1.3%) patient, respectively. Additionally, hyperemesis was observed in only six (8%) patients and no patient had clinical hyperthyroidism or respiratory insufficiency. Patients with complete mole in the recent series were diagnosed earlier in gestation. The mean gestation age at diagnosis in the earlier (1965—1975) and recent series was 16.5 and 11.8 weeks, respectively. Despite the earlier diagnosis, it is important to emphasize that the incidence of post-molar gestational trophoblastic neoplasia did not change in the recent series; 15 of 64 (23%) patients with complete mole, who did not receive chemoprophylaxis, developed post-molar persistent tumor.

Similar findings have been reported from a number of other centers [26-30]. Paradinas *et al.* [26] has reported that most recent cases of complete mole are diagnosed in the first trimester in the United Kingdom. While patients with early diagnosis of complete mole have decreased presentation of classical symptoms, the incidence of post-molar tumor was unaffected. Felemban et al. [31] reported that at King Fahad Hospital in Riyadh, Saudi Arabia that current patients were more frequently diagnosed in the first trimester and had less frequent presence of classical symptoms, but no change in risk for post-molar tumor. Hou et al.[32] from Beijing have also observed similar findings in China. Globally, likely due to the increased availability of hCG testing and pelvic ultrasound, complete mole is now diagnosed more frequently in the first trimester, with less classical symptoms and no change in risk for post-molar tumor. Ben-Arie *et al.* [30] observed that currently with routine first trimester ultrasonography a significant proportion of patients with complete molar pregnancy are asymptomatic at the time of diagnosis.

Despite the general trend to earlier diagnosis of complete molar pregnancy Mangili *et al.* [33] have observed that failure of early detection in women ≥ 40 years is associated with a higher rate of severe complications.

9.2   PRESENTATION OF PARTIAL MOLAR PREGNANCY

Patients with partial mole usually do not present with the classical features of complete mole. We reviewed the medical records of 81 consecutive patients with partial mole to delineate its clinical presentation and natural history[34]. Excessive uterine size was noted in only three (4%) patients and hyperemesis, hyperthyroidism, prominent theca lutein ovarian cysts and respiratory insufficiency were observed in only one patient. The clinical diagnosis preoperatively was incomplete or missed abortion in 74 (91%) patients and molar pregnancy in only five (6%).

Other investigators have noted similar findings. Szulman and Surti and Czernobilsky *et al.* reported excessive uterine enlargement in

nine (11%) of 81 patients and in two (8%) of 25 patients with partial mole [35,36]. Toxemia was reported in both studies in only 4% of patients. Other medical complications of complete mole such as hyperthyroidism and theca lutein cysts are uncommon with partial mole. Szulman and Surti also observed that the clinical diagnosis prior to evacuation was incomplete or missed abortion in 92% of their patients. Characteristically, the diagnosis of partial mole is made after histological review of curettage specimens from presumed incomplete or missed abortions.

9.3   DIAGNOSIS

9.3.1 ULTRASOUND

Ultrasonography has proved to be an accurate and sensitive technique for the diagnosis of complete mole [23,37]. Complete mole produces a characteristic vesicular pattern due to generalized swelling of the chorionic villi (Figure 9.1). The chorionic villi in first trimester complete moles tend to be smaller and have less cavitation [38]. However, the majority of first trimester complete moles still demonstrate a typical ultrasound appearance of a complex, echogenic intra-uterine mass containing many small cystic spaces [39,40]. Among 24 cases of first trimester complete moles (mean gestational age 8.7 weeks), the initial sonographic interpretation was a complete mole in 17 (71%) cases. The specificity of the sonographic findings in complete molar pregnancy may be increased by correlation with the hCG level. A complete mole may be better differentiated from a missed abortion by considering the hCG value at the time of the ultrasound [41]. However, Seckin *et al.* [42] have reported that the initial beta-hCG levels and ultrasonographic mean lesion size did not predict the need for subsequent treatment.

Ultrasonography may also contribute to the detection of partial hydatidiform mole. Naumoff *et al.* reviewed the ultrasound findings in 19 patients with partial mole prior to curettage[43]. The following ultrasound findings were observed in these cases: excessively enlarged placenta, cystic spaces within the placenta, gestational sac which was either empty or contained amorphous echoes and growth-retarded fetus. Fine *et al.* studied ultrasounds in patients with partial mole to determine if sonographic criteria could be established to detect partial mole before evacuation [44]. Ultrasounds from 22 partial moles and 33 first-trimester missed abortions were reviewed independently by three radiologists who were unaware of the pathologic diagnoses. Each radiologist evaluated the appearance of the placenta, the shape, dimensions and contents of the gestational sac and the presence or absence of ovarian cysts. Two sonographic findings were significantly associated with the diagnosis of partial hydatidiform mole: cystic spaces in the placenta and ratio of transverse to anteroposterior dimension of the gestational sac >1.5 (Figure 9.2). These changes in the shape of the gestational sac may be part of the embryopathy of triploidy. There was high inter-observer correlation for both criteria.

When both criteria were present, the positive predictive value for partial mole was 87%. When both criteria were absent, the positive predictive value for missed abortion was 90%.
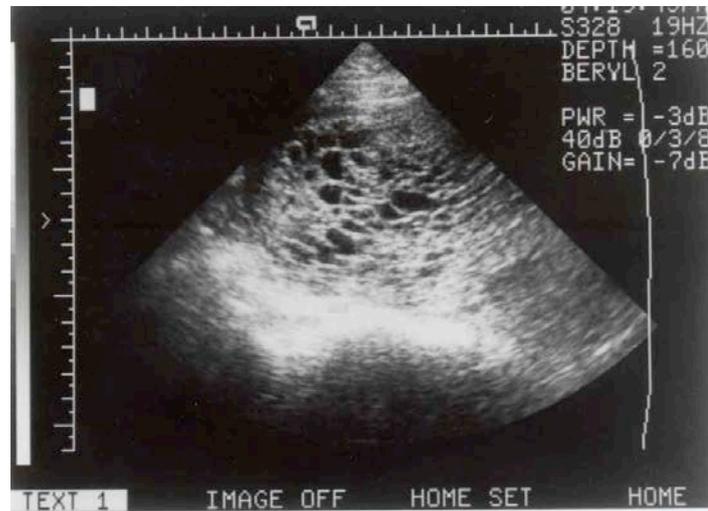

Figure 9.1 Ultrasound of a complete molar pregnancy showing diffuse vesicular change in the chorionic tissue.
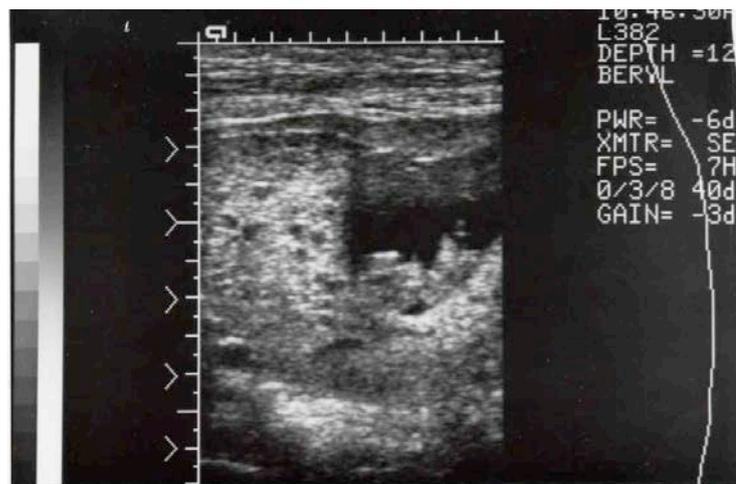

Figure 9.2 Ultrasound of a partial molar pregnancy showing a fetus and focal cystic spaces in the placenta

9.3.2 hCG MEASUREMENT

Markedly elevated hCG levels are commonly seen in patients with complete molar pregnancy[45,46]. Genest *et al.* [47] reviewed the clinical and pathological characteristics of 153 cases of complete mole managed at the NETDC between 1980 and 1990. Pre-evacuation hCG levels were greater than 100,000 IU/L in 46% of the patients. Similarly, Menczer *et al.* [48] reported that 30 (41%) of 74 patients with complete molar pregnancy had pre-evacuation hCG values greater than 100,000 IU/L. The measurement of a high hCG level (>100,000 IU/L) may therefore suggest the diagnosis of a complete molar

pregnancy, particularly when associated with vaginal bleeding and uterine enlargement [45].

In contrast, partial hydatidiform mole is less commonly associated with markedly elevated hCG values. Only two (6%) of 30 patients with partial mole at our center had pre-evacuation hCG levels greater than 100,000 IU/L [34]. Czernobilsky *et al.* [36] also reported that only one (6%) of 17 patients with partial mole had a pre-evacuation urinary hCG level greater than 300,000 IU/L.

Studies using monoclonal antibodies with high sensitivity and specificity for measuring hCG and its free subunits suggest that trophoblastic cells in complete and partial moles differ significantly in the manner in which they secrete the free subunits of hCG[45,49,50]. Complete moles have higher serum levels of percentage free beta hCG than do partial moles (2.4 versus 1.0; p<0.005). In contrast, partial moles have higher serum levels of percentage free alpha hCG than do complete moles (0.85 versus 0.17; p≤0.0005). The mean ratios of percentage free βhCG to αhCG in complete and partial mole are 20.9 and 2.4, respectively (p<0.005).

Thomas *et al.* analyzed the pre-evacuation hCG glycoforms in women with complete moles and persistent post-molar trophoblastic disease and found glycoform profiles that might be of use in the prediction of persistent trophoblastic disease [51].

9.4 TREATMENT

When a diagnosis of complete or partial molar pregnancy has been made, the patient should be evaluated for the presence of medical complications, including anemia, toxemia, hyperthyroidism and respiratory insufficiency. All patients should have baseline hCG performed in addition to routine blood work and urinalysis. Since earlier diagnosis is associated with fewer medical complications, Knowles *et al.* [52] has recommended simplifying the pre-evacuation testing strategy for suspected molar pregnancy to include only a complete blood count, baseline serum hCG level, and blood type with antibody screen. Further testing would depend on subsequent clinical assessment.

After the patient has been medically evaluated and stabilized, a decision must be made concerning the most appropriate method of evacuation. If the patient no longer desires to preserve fertility, hysterectomy may be performed with the mole *in situ* [53,54]. Prominent ovarian theca lutein cysts can be aspirated at the time and the ovaries conserved. It is important to inform the patient that while hysterectomy eliminates the complications of local invasion and reduces the chance of developing persistent trophoblastic disease to 3-5%, it does not prevent metastatic disease and therefore gonadotropin follow-up is still required [54].

In patients who wish to retain fertility, suction curettage is the preferred method of evacuation regardless of uterine size [55,56]. An oxytocin infusion should be started at the time of anesthesia induction to increase myometrial tone and facilitate contraction and thus

decrease blood loss. The concern that oxytocin may promote meta-stasis of trophoblastic tissue has not been shown to increase the risk of persistent tumor [46]. The cervix should be carefully dilated to accommodate a cannula appropriate for the volume of trophoblastic tissue. The use of prostaglandin agents to facilitate dilation is utilized by some clinicians in primigravida women. The selection of a cannula should be commensurate with the uterine size. For uterine size >10 cm the use of a 12mm cannula is generally recommended because it allows rapid evacuation and involution of the uterus. During dilatation, brisk bleeding may be encountered due to passage of copious amounts of blood retained in the endometrial cavity. Evacuation of the uterine contents expediently reduces overall blood loss. After the initiation of suction evacuation, the uterus generally shrinks rapidly and bleeding is well controlled. If the uterus is larger than 14 weeks size, one hand may massage the fundus to facilitate its contraction. When suction evacuation is thought to be complete, a gentle sharp curettage with the largest available curette should be performed to remove any residual chorionic tissue. Some surgeons prefer to use intraoperative sonography to monitor the procedure to determine when evacuation is complete. Patients who are Rh negative should receive Rh immune globulin at the time of evacuation because the RhD factor is expressed on trophoblast.

9.4.1 CHEMOPROPHYLAXIS

The use of prophylactic chemotherapy at the time of molar evacuation remains controversial. However, several investigators have reported that chemoprophylaxis reduces the incidence of post-molar tumor[57-64]. Goldstein reported that chemoprophylaxis with actinomycin D reduced the risk of persistent tumor from 20% to 8% and eliminated metastases [57]. Similarly, Kashimura *et al.* [58] noted that chemoprophylaxis in patients with complete mole reduced the frequency of post-mole tumor from 18% to 7%. Fasoli *et al.* [59] also observed that prophylactic chemotherapy reduced the risk for post-molar disease from 9% to 3%]. However, one of the main objections of exposing all patients with molar pregnancy to chemoprophylaxis is that only a small minority are at risk for persistence.

Kim *et al.* [60] conducted a prospective, randomized trial of the use of prophylactic chemotherapy in patients with complete mole. Seventy-one patients with complete mole were randomized to be treated with either molar evacuation alone or molar evacuation with prophylactic methotrexate and folinic acid. Patients were categorized as either high or low risk based upon prognostic factors for the development of persistent disease (a thorough discussion of these prognostic factors will be given later in this chapter). Among patients with high-risk complete mole, prophylactic chemotherapy reduced the incidence of post-molar tumor from 47% to 14%. Among patients with low-risk complete mole, prophylactic chemotherapy did not influence the incidence of persistent disease (7.7% versus 5.6%). However, patients who developed persistent tumor after prophylactic methotrexate subsequently required more courses of therapeutic

methotrexate to attain remission. Limpongsanurak [61] also performed a prospective, randomized trial of prophylactic actinomycin D in 60 patients with high-risk complete mole. The frequency of post-molar tumor in the chemoprophylactic group was 13.8% and in the control group was 50%. Uberti *et al.* [65] reported that single dose actinomycin D reduced postmolar gestational trophoblastic neoplasia by 76% in 29/60 adolescents with high-risk hydatidiform mole, and by 46% in a larger patient cohort. Post-molar GTN was diagnosed in two (6.9%) adolescents in the study group and in 9 (29%) patients in the control group. Adverse effects of chemotherapy were minor. In the follow-up, when post-molar GTN was diagnosed, severity of disease was not increased, compliance with follow-up was not reduced, and reproductive outcomes after discharge were similar [66].

At our Center, 93 patients with high-risk complete mole were treated with prophylactic actinomycin D and only 10 (11%) developed persistent disease [62]. All 10 patients had non-metastatic tumor. Six patients were treated with methotrexate for persistent tumor and five required only one course of methotrexate to attain remission. In order to avoid drug resistance, it may be important to use a different chemotherapeutic agent for therapy following failed chemoprophylaxis. The risk for chemoprophylaxis failure was increased in patients with particularly high pre-evacuation hCG levels.

A Cochrane Database Review by Fu *et al.* [67] concluded that prophylactic chemotherapy may reduce the risk of progression to gestational trophoblastic neoplasia in women with complete moles who are at high-risk of malignant transformation; however current evidence in favor of prophylactic chemotherapy is limited by poor methodological quality and small size of the available studies The main concern expressed is that prophylactic chemotherapy may increase drug resistance, delay treatment of gestational trophoblastic neoplasia, and expose women unnecessarily to toxic side effects.

Chemoprophylaxis may be particularly useful in patients with high-risk complete mole when hormonal follow-up is either unavailable or unreliable as in adolescents or in certain global regions such as Asia and Africa where medical follow-up may be less available [63].

9.4.2 FOLLOW-UP

Patients with both complete and partial molar pregnancy should be monitored with serial hCG values after evacuation to assure that they achieve complete sustained remission. Patients are followed with weekly hCG levels until non-detectable for three weeks and then monthly hCG levels until non-detectable for six months. After achieving a non-detectable serum hCG level (hCG <5 IU/L), the risk of developing relapse after both complete and partial mole appears to be very low [68-71]. Data from multiple centers including the Charing Cross Hospital, University of Texas Southwestern, Hungary, Australia, the Netherlands and our center indicate in several thousand women with molar pregnancy that the risk of relapse is less than one percent after achieving non-detectable hCG levels [68-77]. For example, in

1986 Bagshawe *et al.* [72] reported that 27/4754 patients with mole (<1%) developed relapse after achieving at least one non-detectable hCG value of less than 5 IU/L in serum and/or less than 25 IU/L in urine. Among clinical series published since 2004, only one patient with mole in more than 1000 patients developed persistent tumor after attaining non-detectable serum hCG values. The most recent sizable series concerning the development of gestational trophoblastic neoplasia after attaining hCG normalization is from Charing Cross [78]. Among 22,053 women monitored for molar pregnancy between 1980 and 2008, only 29 (1 in 760) developed gestational trophoblastic neoplasia after hCG normalization. If the hCG normalized within 56 days after evacuation, the risk of gestational trophoblastic neoplasia was 1 in 1536 compared to 1:464 when hCG normalized in greater than 56 days. The mean time to first raised hCG level after normalization was 449 and 462 days in the <56 and >56 day groups, respectively. Due to the long interval to the hCG rise after normalization, it is possible that some of these cases were new molar conceptions. It is possible that hCG follow-up can be safely abbreviated after molar evacuation without compromising patient's health.

Patients with partial moles may be particularly suitable for shortened duration of gonadotropin surveillance because of their low-risk of persistence. Lavie *et al.* [73] retrospectively reviewed the clinical follow-up of 163 patients with partial moles and concluded that a single undetectable hCG level after evacuation is sufficient follow-up to ensure remission in patients with partial moles. Schmitt *et al.* [79] in a prospective cohort study on 2008 patients registered at the French Trophoblastic Disease Centre found that the risk of persistent post-molar gestational trophoblastic neoplasia after hCG normalization was 0.34% after a complete mole, 0% after a partial mole, and 0.36% after a multiple pregnancy with co-existing mole. On this basis they concur that after normalization of the hCG, monitoring of partial mole can be stopped safely while it should be continued for complete mole and multiple pregnancy with co-existing mole.

Patients with molar pregnancy must be encouraged to use reliable contraception during the entire interval of hCG monitoring. An intrauterine device should be avoided before gonadotropin remission because of the risk of uterine perforation with invasive tumor. Therefore, patients are confronted with the choice of barrier methods or steroidal contraception when they desire to preserve fertility

Stone and Bagshawe reported in 1979 that the use of oral contraceptives prior to gonadotropin remission increased the frequency of post-molar tumor two - to threefold [80]. However, data from our Center and the Gynecologic Oncology Group indicate that oral contraceptives do not increase the risk for post-molar persistent tumor [81,82]. Importantly, the Gynecologic Oncology Group study was a randomized prospective trial. Interestingly, Ho Yuen and Burch also reported that the use of oral contraceptives containing 50 μg or less of estrogen was not associated with an increased risk of post-molar persistent tumor [83]. However, they observed that oral contraceptives containing more than 50 μg of estrogen may be

associated with an increased risk of post-molar disease. These authors speculated that the conflicting data concerning the use of oral contraceptives and the risk of developing post-molar tumor may be explained by differences in the dosage of estrogen. Deicas *et al.* reviewed the experience from the John I. Brewer Trophoblastic Disease Center and concluded that the use of oral contraceptives significantly reduced the incidence of post-molar tumor [84]. Additionally, the dose of estrogen used was not significantly associated with a risk of developing gestational trophoblastic tumor. Costa and Doyle [85] performed a systematic review of all published series concerning oral contraceptive use after molar evacuation and found no clear evidence for an association between oral contraceptive use after molar evacuation and risk for persistent gestational trophoblastic neoplasia. Therefore, we believe that following molar evacuation patients may be safely prescribed oral contraceptives during the entire interval of hormonal follow-up. Current formulations of oral contraceptives generally contain 50 μg or less of estrogen in the form of ethinyl estradiol or mestranol.

Poor compliance with post-molar surveillance and treatment protocols is associated with poorer outcomes due to advanced disease. Indigent women treated at urban, public hospitals are the group most likely to fail to comply with standard protocols for a number of reasons including cost, transportation issues, and inadequate understanding of the disease. The use of injectable medroxyprogesterone is strongly recommended for post-molar contraception in this population [86]
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9.5 GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN) AFTER COMPLETE MOLAR PREGNANCY

Complete molar pregnancy is well recognized to have a risk of developing gestational trophoblastic neoplasia (GTN). However, the incidence of persistent tumor after complete mole has been reported from 8% to 29% [1,5,13,87-90]. This marked variation in the reported incidence of post-molar tumor results from differences in diagnostic criteria.

On the basis of the follow-up of more than 7000 patients, Bagshawe reported that only 7.9% of patients with molar pregnancy required chemotherapy at the Charing Cross Hospital [87]. The criteria for diagnosing post-molar tumor were as follows:
- hCG >20000 IU/L more than four weeks after evacuation,
- progressively rising hCG values with a minimum of three rising values over two to three weeks,
- metastasis to the brain, liver, kidney, gastrointestinal tract or lungs (larger than 2 cm in diameter or three or more in number) or
- persistent hCG level four to six months after evacuation.

Using similar criteria, Fasoli *et al* from Italy and Franke *et al* from

Holland reported that 9% and 10% of patients respectively developed post-molar tumor [59,90]. Importantly, the data from England, Italy and Holland represent the experience when patients with molar disease are followed with an organized and systematic regional or national registry and health care system.

In the USA the incidence of gestational trophoblastic neoplasia is reported from 18% to 29% (Table 9.1). Most centers in the USA define persistent post-molar disease by the presence of a re-elevation or persistent plateau in hCG for at least three consecutive weeks. However, it is important to acknowledge that even amongst American centers there has been some variation in the definition of persistence [91]. The criteria for diagnosing persistent tumor after mole in the USA has been therefore considerably less stringent than the criteria followed in England or elsewhere in Europe. Clearly, some patients who receive chemotherapy for post-molar tumor in the USA would have achieved remission if gonadotropin follow-up continued in the absence of therapy. Agarwal *et al.* [92] retrospectively identified 76 women at Charing Cross Hospital who had persistently high hCG concentrations six months after molar evacuation and found that 65/66 (98%)spontaneously returned to normal without chemotherapy. The use of less stringent diagnostic criteria for post-molar tumor in the USA was partly motivated by the concern that some patients may be lost to follow-up. Schlaerth *et al.* reported that 19 (19%) of 99 patients with molar pregnancy were lost to follow-up at the University of Southern California [93]. Similarly, Kim *et al.* noted that 36 (27%) of 133 patients with complete mole were lost to follow-up in Korea [60]. Massad *et al.* [86] reported that among 40 indigent patients with molar pregnancy, 5 (13%) were lost to follow-up before remission and 16 (40%) were lost before completing 6 months of follow-up. The establishment of international criteria for diagnosing post-molar gestational trophoblastic neoplasia by FIGO should eliminate the global variation in reporting this condition [94].

Several studies have shown that the risk for developing GTN is increased in patients with signs and symptoms of marked trophoblastic proliferation: excessive uterus enlargement, markedly elevated hCG values and prominent ovarian theca lutein cysts as well as associated medical factors such as toxemia, hyperthyroidism and respiratory insufficiency. Curry *et al.* reported that post-molar disease developed in 49% of patients with prominent theca lutein ovarian cysts and in 57% of patients with ovarian cysts and large-for-dates uteri [5]. These findings were confirmed and extended by other investigators. Morrow also observed the occurrence of post-molar tumor in 55% of patients with theca lutein ovarian cysts or uterine size greater than 20 weeks [95]. Ayhan *et al.* [96] applied multivariate analysis in 82 patients and identified hCG level, age and history of previous mole as the most powerful indicators of persistent disease.

At the NETDC, we reviewed the outcome of 858 patients with complete mole to assess prognostic factors for GTN. Signs of marked trophoblastic growth such as excessive uterine size, theca lutein cysts >6 cm in diameter and pre-evacuation hCG level >100,000 IU/L were present in 352 (41%) patients. Non-metastatic and metastatic ges-

tational trophoblastic neoplasia developed in 31% and 8.8% respectively in these patients. In contrast, 506 (59%) patients with complete mole did not present with signs and symptoms of marked trophoblastic proliferation. Non-metastatic and metastatic disease developed in only 3.4% and 0.6% respectively of these patients [25]. Patients with complete mole who present with excessive uterine size, ovarian cysts and/or markedly elevated hCG values are therefore considered as high risk for developing post-molar tumor. Similarly, Kim *et al.* observed post-molar persistent disease in 47.4% of high-risk and only 7.7% of low-risk complete moles using the same clinical risk criteria [60].

The risk for gestional trophoblastic neoplasia has also been observed to be increased in patients of older age. Tow [97] and Xia *et al* [98] reported that 37% and 33% respectively of women over 40 with molar pregnancy developed persistent tumor. Tsukamoto *et al.* also observed that 56% of women over 50 developed post-molar tumor [99]. Complete moles in older women are more commonly aneuploid, and aneuploidy may be a risk factor for persistent tumor [100]. Martin et al reported that 10 (77%) of 13 aneuploid complete moles developed persistent tumor [101]. Elias *et al.* [102,103] has observed that advanced maternal age appears to increase a patient's risk of developing gestational trophoblastic neoplasia after complete mole and suggests that more aggressive upfront management should be considered in this age group. In a cohort of 82 patients with complete mole from ages 40-49, 36 of 68 (53%) patients treated by D and C alone developed gestational trophoblastic neoplasia. Markedly elevated hCG levels >175,000 IU/L appeared to constitute an "ultra high-risk" group for whom prophylactic chemotherapy or hysterectomy should be especially considered. In another study of 22 patients with complete mole over age 50, these authors observed that 9 of 15 (60%) patients with complete mole initially treated with dilation and evacuation alone developed gestational trophoblastic neoplasia. In contrast to patients with advanced age, adolescents (<age 20 years) do not appear to have a higher risk of developing post-molar disease requiring more aggressive initial management. Braga *et al.* [104] studied the clinical presentation and outcome in 220 adolescent patients with molar pregnancy and noted a significantly decreased risk of developing gestational trophoblastic neoplasia.

Patients with repetitive molar pregnancy are also at increased risk of developing persistent tumor in their later episodes of molar pregnancy. Parazzini *et al.* reported a threefold increased risk of post-molar tumor in patients with repetitive molar pregnancy [105]. Between July 1965 and May 2013, we treated 39 patients with repeat molar gestations at our Center [106]. Each patient had at least two documented molar pregnancies and each molar gestation was diagnosed as either partial or complete on the basis of established histopathological criteria. Persistent tumor developed following the first mole in 4 (20%) of 20 complete moles. However, post-molar tumor occurred following the second mole in 8 (40%) of 20 complete moles and in 2 (11.7%) of 17 partial moles.

Conflicting data exist concerning the potential prognostic

significance of the histopathological features of complete molar pregnancy. While some authors have indicated that histological features significantly predict the risk of persistent tumor, other investigators have suggested that histological grading has no prognostic value[107-110]. Genest *et al* reviewed the histopathological characteristics and clinical outcome of 153 complete moles who were managed at our Center between 1980 and 1990 [47]. No patient received prophylactic chemotherapy and all histological material was reviewed independently by two pathologists. The histological grade of the complete mole did not correlate significantly with any index of clinical outcome evaluated.

Khazaeli *et al.* reported that a high free βhCG value was predictive of an increased risk of post-molar tumor but the study did not distinguish between complete and partial moles [111]. However, we observed that the measurement of free βhCG did not identify our patients with complete mole who were particularly at risk of developing persistent tumor [45]. The mean percentage free βhCG and βhCG level did not differ significantly between patients with complete mole who attained spontaneous remission and those who developed post-molar tumor.

Wake *et al.* noted that the risk of persistent tumor was increased in complete moles with a heterozygous genotype [112]. Post-molar disease was observed in heterozygous and homozygous complete moles in 50% and 4% of cases, respectively. Baasanjav *et al.* [113]]has also observed in 28 consecutive molar pregnancies that all three cases of heterozygous complete moles and only 6/24 (25%) of homozygous moles required chemotherapy. However, other investigators have not confirmed that heterozygous complete moles are associated with an increased risk of persistent tumor [114,115].

Several investigators have reported altered expression of growth regulatory factors in complete mole and have noted a relationship between the expression of some growth regulatory factors and development of persistent tumor [116-118]. Strong immunostaining of epidermal growth factor receptor and c-erbB-3 in the extravillous trophoblast of complete mole was found to be significantly correlated with the development of post-molar tumor [119]. Telomerase activity has been reported in 12 (57.1%) of 21 complete moles with varied intensity and telomerase activity may be associated with persistent post-molar tumor [120]. Petts *et al.* [121] recently reported a study which showed that histopathologic features and immunohistochemical staining with antibodies for growth factors that had been reported to be prognostic for developing post-molar tumor in early hydatidiform moles were not found to be predictive for increased risk of post-molar gestational trophoblastic neoplasia (GTN). However, Nagymanyoki *et al.* by studying immunolocalization of CD31, determined that complete moles with high microvessel density had significantly greater risk of developing GTN[122].

It is possible to utilize the hCG regression curve to develop criteria

that determine a patient's risk of developing GTN or achieving remission within a few weeks after molar evacuation. Growdon *et al.* [123] reported that an hCG level of >199 mIU/ml in the third through eight weeks following partial molar evacuation was associated with at least a 35% risk of GTN. Wolfberg *et al.* [124] demonstrated that post-evacuation hCG values could predict the development of GTN in patients with complete mole. Within three weeks of molar evacuation, more than half of the women with complete mole had their risk of GTN modified to either >50% or <9%. Other investigators have also shown that the use of the hCG regression rate has proven to be an effective tool in predicting the risk of post-molar gestational trophoblastic neoplasia [125-128].

Table 9.1 Post-molar gestational trophoblastic neoplasia (GTN) in the USA

Authors	No. of patients	Non-Metastatic GTN (%)	Metastatic GTN (%)	Total GTN (%)
Goldstein and Berkowitz [1]	858	14.7	4.0	18.7
Lurain et al. [88]	738	16.3	3.0	19.3
Curry et al. [5]	347	16.6	3.5	20.1
Morrow et al. [89]	121	23.1	3.3	26.4
Kohorn [11]	127	26.0	3.1	29.1

Table 9.2 Gestational trophoblastic neoplasia (GTN) after partial hydatidiform mole

Series	No. of patients	No. with post-molar tumor	No. with metastases
Vassilakos et al. [2]	56	0	0
Czernobilsky et al. [36]	25	1	0
Szulman and Surti [35]	49	2	0
Wong and Ma [130]	35	4	2
Ohama et al. [131]	56	0	0
Bolis et al. [132]	86	2	0
Seckl et al. [133]	3000	15	1
Feltmate et al. [134]	390	22	1
Goto et al. [135]	349	10	3
Hancock et al. [136]	3189	14	2
Wielsma et al.[75]	344	6	0
Total	7579	76(1.0%)	9 (0.1%)

9.6 GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN) AFTER PARTIAL MOLAR PREGNANCY

Between January 1979 and January 1989, 16 (6.6%) of 240 patients who were followed for partial mole at our Center developed gestational trophoblastic neoplasia [129]. As more data accumulated, it has been apparent that the risk of GTN following a partial mole may be

appreciably lower. Table 9.2 summarizes the data from eleven studies: 76 (1.0%) of 7579 patients with partial mole developed GTN [2,,35,36,75,130-136]. Only one of our patients with GTN following partial mole had metastatic disease. Similarly, in the collected series in Table 9.2, only 9 (0.1%) patients had metastases. While Goto *et al.* [135] reported three patients with pulmonary metastases, all three patients had barely detectable metastases on computed tomography. Our patients with partial mole who developed persistent disease did not have pathological or clinical features that distinguished them from other patients with partial mole[129]. Fifteen (94%) of the patients were thought to have a missed abortion prior to evacuation. Only one patient presented with the classic signs and symptoms of molar disease, including excessive uterine size, high hCG levels and ovarian theca lutein cysts. A recent update of our experience with partial moles found that 22 of 390 patients (5.6%) developed GTN and that pre-evacuation clinical symptoms did not distinguish patients at risk for persistence [134].

Teng and Ballon reported three patients with diploid partial mole who developed persistent tumor and suggested that diploid partial moles may have a high risk for post-molar disease [137]. However, it is questioned whether true non-triploid partial moles exist. It may be difficult to distinguish pathologically a partial mole from a hydropic abortion or an early complete mole [37]. Genest *et al.* [138] re-evaluated 19 cases of presumed non-triploid partial moles by repeating ploidy analysis and reviewing the pathology. Following thorough re-evaluation, no case remained classified as a diploid partial mole.

9.7   MULTIPLE CONCEPTION WITH COMPLETE OR PARTIAL MOLAR PREGNANCY AND COEXISTING FETUSES

The estimated incidence of twin pregnancy consisting of a complete mole and coexisting fetus is one per 22,000—100,000 pregnancies [139]. We described our experience with eight cases of twin pregnancy with complete mole and a coexisting fetus and reviewed 14 additional published cases by other investigators [140]. Additionally, we described one case of a partial mole coexisting with a normal placenta and fetus. As compared with singleton complete moles, pregnancies consisting of complete moles and coexisting fetus are diagnosed later, have more markedly enlarged uteri and have higher pre-evacuation hCG values. Importantly, persistent tumor developed in 12 (55%) of 22 patients. There are limited data to guide antenatal management of multiple gestations consisting of complete mole and coexisting fetuses. Five (23%) fetuses survived and no fetal anomalies have been described. Prompt termination of pregnancy may be necessary if severe toxemia or other medical complications arise. The occurrence of multiple gestation containing a molar pregnancy may increase with greater use of ovulation induction [141].

Matsui *et al.* [142] reported 18 patients with proven androgenetic complete mole co-existent with a twin live fetus in a national collaborative study in Japan. Persistent tumor developed in 9 (50%) patients and metastases were detected in 6 (33%) cases. Among the 13 patients, who intended to continue the pregnancy, the pregnancy was terminated in 10 patients due to either maternal complications (toxemia and/or hemorrhage) or intrauterine fetal demise. Fishman *et al.* [143] reported the results in 7 women with complete hydatidiform mole and coexisting normal fetus treated at the John I. Brewer Trophoblastic Disease Center. Four patients required uterine evacuation before 20 weeks' gestation because of vaginal bleeding or medical complications, one required emergency hysterotomy because of hemorrhage at 24 weeks, and two women delivered normal, viable infants at 26 and 34 weeks. Four of the seven women required chemotherapy for treatment of non-metastatic disease. Massardier *et al.* [144] reporting the experience from the French Trophoblastic Disease Reference Center, observed that 3/14 (21%) women delivered a healthy child and 7/14 (50%) required chemotherapy. The most recent and largest report concerning twin pregnancies with complete mole and normal co-twin is from the Charing Cross

and Weston Park Gestational Trophoblastic Disease Centers [145]. Between 1998 and 2011, 90 patients were managed with a twin pregnancy with complete mole and normal co-twin. Among 51 patients deciding to continue pregnancy, 29 (57%) delivered a live baby at a median age of 34 weeks. Gestational trophoblastic neoplasia developed in 24 of 90 (26.7%) pregnancies and there were no maternal deaths.

9.8 PREGNANCIES AFTER MOLAR PREGNANCY

Since our Center was established in 1965, we have been committed to collecting data about later pregnancy experience. All patients and referring physicians are requested to keep us informed about subsequent pregnancies when they complete gonadotropin follow-up. Questionnaires are mailed to all of our patients every two to three years concerning later pregnancies and general health problems.

   Our patients who were treated for complete mole had 1388 subsequent pregnancies between July 1965 and December 2013 [106]. These later conceptions resulted in 949 (68.4%) term live births, seven (0.5%) stillbirths, 103 (7.4%) premature deliveries and 11 (0.8%) ectopic pregnancies. Spontaneous abortion occurred in 256 (18.4%) conceptions and major and minor congenital anomalies were detected in 40 (3.8%) infants. Importantly, chemoprophylaxis had no adverse effect on later pregnancy experience. Similarly, Ho et al. [146] and Kashimura et al. [58] reported that patients receiving chemoprophylaxis have a normal later reproductive experience.

   After partial mole, our patients had 357 later gestations between June 1965 and December 2013 [106]. These subsequent pregnancies resulted in 260 (72.8%) term live births, one (0.3%) stillbirth, eight (2.2%) premature deliveries and two (0.6%) ectopic pregnancy. Spontaneous abortion occurred in 64 (17.9%) pregnancies and major and minor congenital anomalies were diagnosed in only four (1.5%) infants. Therefore, in general patients with both complete and partial mole can anticipate normal future reproductive outcomes.

   However, patients with molar disease are at increased risk of developing molar pregnancy in subsequent conceptions [147]. After one molar pregnancy, the risk of having molar disease in a future conception is about 1% [72,148**].** Between June 1965 and December 2013, 39 patients with repeat molar pregnancy were treated at our center [106]. We observed every possible combination of repeat complete and partial molar gestation. In six cases, the medical records clearly indicated that the patient had a different partner at the conception of different molar pregnancies [149]. The experience in these six patients suggests that a primary oocyte problem may contribute to the development of molar pregnancy. Following two molar pregnancies, 25 patients at our Center had 40 later pregnancies resulting in 25 (62.5%) full term deliveries, 7 (17.5%) molar pregnancies (6 complete, one partial), three spontaneous abortions (7.5%), three therapeutic abortions (7.5%), one intrauterine fetal demise(2.5%) and one ectopic pregnancy (2.5%). Therefore, among our patients with two molar pregnancies, the risk of developing molar disease in a subsequent conception was 17.5%.

   Bagshawe *et al.* also reported that the risk of molar disease following two episodes of molar pregnancy was 15% [72]. Sebire, *et al.* [150] updating data from the same institution reported that subsequent pregnancy was molar in 27 of 2578 (1.9%) patients with a previous complete mole including 22(81%) complete moles and 5 (19%) partial moles. Of 2627 patients with a history of a partial mole the subsequent pregnancy was molar in 25 (1.7%) including 17 (68%) partial moles and 8 (32%) complete moles. The overall risk of molar pregnancy was 1.8% which represented a 20-fold increase compared to the general population. Among 27 cases with repeat complete moles three had later molar pregnancies indicating a recurrence rate after two previous complete moles of 10%.   Lurain *et al.* reported that five of eight patients with repetitive mole later achieved normal term gestation [151]. Although molar pregnancy can be repetitive, most patients with repeat mole can achieve normal full-term pregnancies.

Because of the increased risk of later molar disease, we advise our patients with molar pregnancy to undergo ultrasound in the first trimester of subsequent pregnancies to confirm normal gestational development. Additionally hCG should be measured six weeks after the completion of any future pregnancy to exclude choriocarcinoma. While all patients with molar pregnancy are encouraged to use reliable contraception during gonadotropin follow-up, some patients conceive before follow-up is completed. Seventy patients at our Center became pregnant prior to completion of six months of gonadotropin follow-up [152]. All of these patients achieved at least one non-detectable hCG level. Thirteen patients were lost to follow-up. No patient developed persistent tumor. Full term delivery with no congenital anomalies was documented in 35 (61.4%) patients. Pregnancies occurring before the completion of hCG follow-up in patients with molar pregnancy may be allowed to be continued under careful surveillance as long as the patient achieved at least one non-detectable hCG value.

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