

9

PRESENTATION AND MANAGEMENT OF MOLAR PREGNANCY*Ross S Berkowitz and Donald P Goldstein*

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 (2, 3 and 4) 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 clinical 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.* and Kohorn also noted a high incidence of vaginal bleeding in 312 (89%) of 347 and in 188 (94%) of 200 patients with molar pregnancy, respectively. [5,6]. 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.* reported that theca lutein cysts were clinically palpable in 102 (26.4%) of 386 patients with molar pregnancy[7]. Kohorn also observed theca lutein cysts in 20% of patients with molar pregnancy[6]. However, Santos-Ramos *et al.*, using ultrasound observed theca lutein ovarian cysts >5 cm in diameter in 23 (46%) of 50 patients with molar pregnancy[8].

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 hyperstimulation 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]. 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. Curry *et al.* 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 is more common. Calton *et al.* measured thyroid function tests in 11 patients with molar pregnancy before and after evacuation[15]. Pre-evacuation, all patients had elevated values for thyroidal ¹³¹I uptake and serum free thyroxine; the thyroid function tests rapidly returned to normal after evacuation even before the hCG level became undetectable.

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[16]. Kenimer *et al.* reported that highly purified hCG appeared to have intrinsic thyroid-stimulating activity[17]. Positive correlations have been reported in some studies between serum hCG levels and serum total thyroxine (T₄) or triiodothyronine (T₃) concentrations. However, Nagataki *et al.* found no correlation between serum hCG and free T₄ in 10 patients

with molar pregnancy[18]. 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 T₄ or T₃ index values[19]. 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. Thyroid storm is characterized by hyperthermia, delirium, coma, atrial fibrillation and cardiovascular collapse. 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 is usually observed 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[20].

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 h 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.

In recent years, patients with complete mole are being more frequently managed at our Center before they develop the classic signs and symptoms. Recent changes in the clinical presentation of complete mole may be due to changing clinical practice such as the frequent use of hCG measurement and vaginal probe ultrasound in early pregnancy in women with vaginal staining and even in asymptomatic women.

Soto-Wright *et al.* reviewed the presentation of 74 patients with

complete mole who underwent uterine evacuation at the NETDC between 1988 and 1993[21]. 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. It is important to emphasize that the incidence of post-molar gestational trophoblastic tumor 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. Among the entire group of 74 patients, 19 (25.7%) patients developed post-molar persistent tumor. Similarly, Paradinas *et al* has reported that most recent cases of complete mole are diagnosed in the first trimester in the United Kingdom[22]. While patients with first trimester complete mole generally do not present with the classic signs and symptoms, the risk for post-molar tumor remains unchanged.

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[23]. Excessive uterine size was noted in only three (4%) patients and hyperemesis, hyperthyroidism, prominent theca lutein ovarian cysts and respiratory insufficiency served 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[24,25]. 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. 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[26]. 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[27]. 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[28]. A complete mole may be better differentiated from a missed abortion by considering the hCG value at the time of the ultrasound.

Ultrasonography may also contribute to the detection of partial hydatidiform mole. Naumoff *et al.* reviewed the ultrasound findings in 19 patients with partial mole who curettage[29]. 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 ultrasound in patients with partial mole to determine if sonographic criteria could be established to detect partial mole before evacuation[30]. Ultrasound from 22 partial moles and 33 first-trimester missed abortions were reviewed independently by three radiologists who were unaware of the pathological 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%.

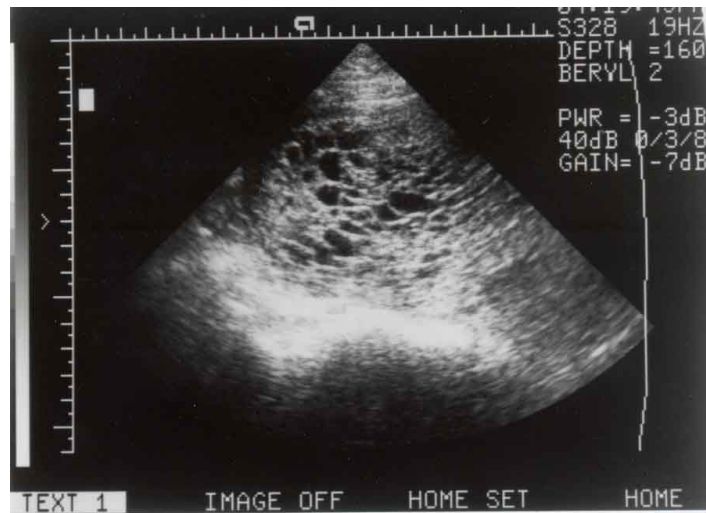


Figure 9.1 Ultrasound of a complete molar pregnancy showing diffuse vesicular change in the chorionic tissue.

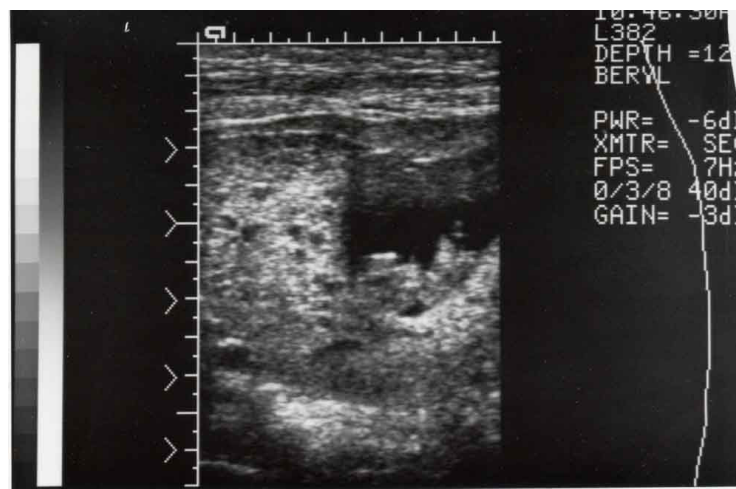


Figure 9.2 Ultrasound of a partial molar pregnancy showing a fetus and focal cystic spaces in the placenta

9.3.2 hCG MEASUREMENT

Markedly elevated hCG levels are commonly seen in patients with complete molar pregnancy. Genest *et al.* reviewed the clinical and pathological characteristics of 153 cases of complete mole managed at the NETDC between 1980 and 1990[31]. Pre-evacuation hCG levels were greater than 100 000 U/l in 46% of the patients. Similarly, Menczer *et al.* reported that 30 (41%) of 74 patients with molar pregnancy had pre-evacuation hCG values greater than 100 000 U/l[32]. The measurement of a high hCG level (>100 000 U/l) may therefore suggest the diagnosis of a complete molar pregnancy, particularly when associated with vaginal bleeding and uterine

enlargement.

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 U/l[21]. Czernobilsky *et al.* also reported that only one (6%) of 17 patients with partial mole had a preevacuation urinary hCG level greater than 300 000 U/l[25].

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[33,34]. Complete moles have higher serum levels of percentage free α hCG than do partial moles (2.4 versus 1.0; $p < 0.005$). In contrast, partial moles have higher serum levels of percentage free β hCG than do complete moles (0.85 versus 0.17; $p \leq 0.0005$). The mean ratios of percentage free β hCG to α hCG in complete and partial mole are 20.9 and 2.4, respectively ($p < 0.005$).

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 and thyroid tests performed in addition to routine blood work and urinalysis. 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*. 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, it does not prevent metastatic disease and therefore gonadotropin followup is required.

In patients who wish to retain fertility, suction curettage is the preferred method of evacuation regardless of uterine size[35,36]. An oxytocin infusion should be started before anesthesia induction to increase myometrial tone and facilitate contraction and thus decrease blood loss. Concern has been expressed that oxytocin may promote metastasis of trophoblastic tissue. However, it has been reported that uterine stimulation before evacuation did not increase the risk of persistent tumor. The cervix should be carefully dilated to accommodate a cannula appropriate for the volume of trophoblastic tissue. A 12mm cannula is generally satisfactory 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. However, it is best to proceed promptly to uterine evacuation. 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 be placed on top of the fundus to assess uterine size and to massage the uterus. When suction evacuation is thought to be complete sharp curettage should be performed to remove any residual chorionic tissue. 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. Goldstein reported that chemoprophylaxis reduced the risk of persistent tumor from 20% to 8% and eliminated metastases[37]. Similarly, Kashimura *et al.* noted that chemoprophylaxis in patients with complete mole reduced the frequency of post-mole tumor from 18% to 7%[38]. Fasoli *et al.* also observed that prophylactic chemotherapy reduced the risk for post-molar disease from 9% to 3%[39]. 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.* conducted a prospective, randomized trial of the use of prophylactic chemotherapy in patients with complete mole[40]. 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 also recently performed a prospective, randomized trial of prophylactic actinomycin D in 60 patients with high-risk complete mole[41]. The frequency of post molar tumor in the chemoprophylactic group was 13.8% and in the control group was 50%.

At our Center, 93 patients with high-risk complete mole were treated with prophylactic actinomycin D and only 10 (11%) developed persistent disease[42]. 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.

Chemoprophylaxis may be particularly useful in patients with high-risk complete mole when hormonal follow-up is either unavailable or unreliable. Molar pregnancy is more prevalent in certain global regions such as Asia and Africa where medical follow-up may be less available[43].

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. Patients with partial mole are at a lower risk of developing post-molar tumor. Therefore, in patients with partial mole who rapidly attain non-detectable weekly hCG values (less than seven weeks post-evacuation), monthly hCG follow-up may be discontinued after three months.

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[44]. However, data from our Center and the Gynecologic Oncology Group indicate that oral contraceptives do not increase the risk for post-molar persistent tumor[45,46]. 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[47]. However, they observed that oral contraceptives containing more than 50 µg of estrogen may be associated with an increased risk of post-molar disease. Ho Yuen and Burch 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[48]. Additionally, the dose of estrogen used was not significantly associated with a risk of developing gestational trophoblastic tumor. 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.

9.5 PERSISTENT GESTATIONAL TROPHOBLASTIC TUMOR AFTER COMPLETE MOLAR PREGNANCY

Complete molar pregnancy is well recognized to have a risk of developing persistent gestational trophoblastic tumor. However, the incidence of persistent tumor after complete mole has been reported from 8% to 29%[1,5,13,49-51]. 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[49]. The criteria for diagnosing post-molar tumor were as follows:

hCG >20000 U/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[39,52]. 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 post-molar tumor 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 is some variation in the definition of persistence[53]. The criteria for diagnosing persistent tumor after mole in the USA are 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. The use of less stringent diagnostic criteria for post-molar tumor in the USA is 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[54]. Similarly, Kim *et al.* noted that 36 (27%) of 133 patients with complete mole were lost to follow-up in Korea[40]. Massad *et al.* 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[55].

Several studies have shown that the risk for developing post-molar tumor 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[56].

At the NETDC, we reviewed the outcome of 858 patients with complete mole to assess prognostic factors for persistent tumor. Signs of marked trophoblastic growth such as excessive uterine size, theca lutein cysts >6 cm in diameter and pre-evacuation hCG level >100000 U/l were present in 352 (41%) patients. Non-metastatic and metastatic gestational trophoblastic tumor developed in 31% and 8.8% respectively of 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. 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[40].

The risk for post-molar tumor has also been observed to be increased in patients of older age. Tow[57] and Xia *et al.*[58] 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[59]. Complete moles in older women are more commonly aneuploid, and aneuploidy may be a risk factor for persistent tumor[60]. Martinet *et al.* reported that 10 (77%) of 13 aneuploid complete moles developed

persistent tumor[61].

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[62]. Between June 1965 and November 2001, we treated 34 patients with repeat molar gestations at our Center[59]. 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 (44.4%) of 18 complete 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[64—67]. Genest *et al.* reviewed the histopathological characteristics and clinical outcome of 153 complete moles who were managed at our Center between 1980 and 1990[31]. 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 β hCG value was predictive of an increased risk of post-molar tumor but the study did not distinguish between complete and partial moles[68]. However, we observed that the measurement of free β hCG did not identify our patients with complete mole who were particularly at risk of developing persistent tumor[34]. The mean percentage free β hCG and β hCG 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[69]. Post-molar disease was observed in heterozygous and homozygous complete moles in 50% and 4% of cases, respectively. However, other investigators have not confirmed that heterozygous complete moles are associated with an increased risk of persistent tumor[70, 71].

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[72-74]. 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[75]. 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[76].

Table 9.1 Postmolar gestational trophoblastic tumor (GTT) in the USA

Authors	No. of patients	Non-Metastatic GTT (%)	Metastatic GTT (%)	Total GTT (%)
Goldstein and Berkowitz [1]	858	14.7	4.0	18.7
Lurain et al. [50]	738	16.3	3.0	19.3
Curry et al. [5]	347	16.6	3.5	20.1
Morrow et al. [51]	121	23.1	3.3	26.4
Kohorn [11]	127	26.0	3.1	29.1

Table 9.2 Persistent gestational trophoblastic tumor 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. [23]	25	1	0
Szulman and Surti [25]	49	2	0
Wong and Ma [78]	35	4	2
Ohama et al. [79]	56	0	0
Bolis et al. [80]	86	2	0
Seckl et al. [81]	857	4	0
Lage et al. [82]	310	17	0
Goto et al. [83]	349	10	3
Total	1823	40 (2.2%)	5 (0.3%)

9.6 PERSISTENT GESTATIONAL TROPHOBLASTIC TUMOR 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 persistent tumor[77]. As more data accumulated, it has been apparent that the risk of persistent tumor following a partial mole is appreciably lower. Table 9.2 summarizes the data from eight studies: 51 (1.2%) of 3966 patients with partial mole developed persistent tumor [2,24,25,78-83].

All of our patients with persistent tumor following partial mole had non-metastatic disease. Similarly, in the collected series in Table 9.2, only 6 (12%) patients had metastases. While Goto *et al.* reported three patients with pulmonary metastases, all three patients had barely detectable metastases on computed tomography[83].

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[77]. 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.

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[84]. 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[26]. Genest *et al.* re-evaluated 19 cases of presumed non-triploid partial moles by repeating ploidy analysis and reviewing the pathology[85]. 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[86]. We recently 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[87]. 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.

Matsui *et al.* [88] 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.

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 1278 subsequent pregnancies between June 1965 and November 2001[63]. These later conceptions resulted in 877 (68.6%) term live births, seven (0.5%) stillbirths, 95 (7.4%) premature deliveries and 11 (0.9%) ectopic pregnancies. Spontaneous abortion occurred in 229 (17.9%) conceptions and major and minor congenital anomalies were detected in 40 (4.1%) infants. Primary Cesarean section was performed in 70 (18.8%) of 373 later term and premature deliveries between January 1979 and November 2001. Importantly, chemoprophylaxis had no adverse effect on later pregnancy experience. Similarly, Ho *et al.* and Kashimura *et al.* reported that patients receiving chemoprophylaxis have a normal later reproductive experience[38, 89].

After partial mole, our patients had 251 later gestations between June 1965 and November 2001 [63]. These subsequent pregnancies resulted in 189 (75.3%) term live births, one (0.4%) stillbirth, four (1.6%) premature deliveries and one (0.7%) ectopic pregnancy. Spontaneous abortion occurred in 39 (15.5%) pregnancies and major and minor congenital anomalies were diagnosed in only three (1.5%) infants. Primary Cesarean section was performed in 29 (14.9%) of 194 term or premature deliveries. 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[90]. After one molar pregnancy, the risk of having molar disease in a future conception is about 1%[91,92]. Between June 1965 and November 2001, we treated 34 patients with repeat molar pregnancy at our center[63]. 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[93]. The experience in these six patients suggests that a primary oocyte problem may contribute to the development of molar pregnancy.

Following two molar pregnancies, 22 patients at our Center had 35 later pregnancies resulting in 20 (57.1%) full term deliveries, 7 (20%) molar pregnancies (6 complete, one partial), three spontaneous abortions, three therapeutic abortions, one intrauterine fetal demise and one ectopic pregnancy. Therefore, among our patients with two molar pregnancies, the risk of developing molar disease in a subsequent conception was 20%. Bagshawe *et al.* also reported that the

risk of molar disease following two episodes of molar pregnancy was 15%[91]. However, patients with repeat mole can achieve normal full-term pregnancies. Similarly, Lurain *et al.* reported that five of eight patients with repetitive mole later achieved normal term gestation[94].

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. A careful pathological review should also be performed on the placenta or products of conception from later pregnancies. 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[95]. 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.

REFERENCES

1. Goldstein D.P. and Berkowitz, R.S. (1982) The diagnosis and management of molar pregnancy, in *Gestational Trophoblastic Neoplasms: Clinical Principles of Diagnosis and Management*, Saunders, Philadelphia, Ch. 7, pp. 143—75.
2. Vassilakos, P., Riotton, G. and Kajii, T. (1977) Hydatidiform mole: two entities. *Am. J. Obstet. Gynecol.*, 127, 167—70.
3. Szulman, A.E. and Surti, U. (1978) The syndromes of hydatidiform mole. I. Cytogenetic and morphologic correlations. *Am. J. Obstet. Gynecol.*, 131, 665—71.
4. Szulman, A.E. and Surti, U. (1978) The syndromes of hydatidiform mole. II. Morphologic evolution of the complete and partial mole. *Am. J. Obstet. Gynecol.*, 132, 20—7.
5. Curry, S.L., Hammond, C.B., Tyrey, L. *et al.* (1975) Hydatidiform mole: diagnosis, management, and long-term follow up of 347 patients. *Obstet. Gynecol.*, 45, 1—8.
6. Kohorn, E.I. (1984) Molar pregnancy: presentation and diagnosis. *Clin. Obstet. Gynecol.*, 27, 181—91
7. Montz, F.J., Schlaerth, J.B. and Morrow, C.P. (1988) The natural history of theca lutein cysts. *Obstet. Gynecol.*, 72, 247—51.

8. Santos-Ramos, R., Forney, J.P. and Schwartz, BE. (1980) Sonographic findings and clinical correlations in molar pregnancy. *Obstet. Gynecol.*, 56, 186—92.
9. Osathanondh, R., Berkowitz, R., de Cholnoky, C. *et al.* (1986) Hormonal measurements in patients with theca lutein cysts and gestational trophoblastic disease. *J. Reprod. Med.*, 31, 179—82.
10. Ho, P.C., Wong, L.C. and Ma, 1-1K. (1986) Plasma prolactin, progesterone, estradiol and human chorionic gonadotropin in complete and partial moles before and after evacuation. *Obstet. Gynecol.*, 67, 99—106.
11. Kohorn, EI. (1982) Hydatidiform mole and gestational trophoblastic disease in Southern Connecticut. *Obstet. Gynecol.*, 59, 78—84.
12. Berkowitz, R.S., Goldstein D.P. and Bernstein, MR. (1980) Laparoscopy in the management of gestational trophoblastic neoplasms. *J. Reprod. Med.*, 24, 261—4.
13. Berkowitz, R.S. and Goldstein, D.P. (1993) The management of molar pregnancy and gestational trophoblastic tumors, in *Gynecologic Oncology*, 2nd edn (eds R.C. Knapp and R.S. Berkowitz), McGraw-Hill, New York, 1993, pp. 328—38.
14. Depue, R.H., Bernstein, L., Ross, R.K. *et al.* (1987) Hyperemesis gravidarum in relation to estradiol levels, pregnancy outcome and other maternal factors: a seroepidemiologic study. *Am. J. Obstet. Gynecol.*, 156, 1137—41.
15. Galton, V.A., Ingbar, S.H., Jimenez-Fonseca, J. *et al.* (1971) Alterations in thyroid hormone economy in patients with hydatidiform mole. *J. Clin. Invest.*, 50, 1345—54.
16. Nisula, B.C. and Taliadouros, G.S. (1980) Thyroid function in gestational trophoblastic neoplasia: evidence that the thyrotropic activity of chorionic gonadotropin mediates the thyrotoxicosis of choriocarcinoma. *Am. J. Obstet. Gynecol.*, 138, 77—85.
17. Kenimer, J.G., Hershman, J.M. and Higgins, H.P. (1975) The thyrotropin in hydatidiform moles is human chorionic gonadotropin. *J. Clin. Endocrinol. Metab.*, 40, 482—91
18. Nagataki, S., Mizuno, M., Sakamoto, S. *et al.* (1977) Thyroid function in molar pregnancy. *J. Clin. Endocrinol. Metab.*, 44, 254—63.
19. Amir, S.M., Osathanondh, R., Berkowitz, R.S. *et al.* (1984) Human chorionic gonadotropin and thyroid function in patients with hydatidiform mole. *Am. J. Obstet. Gynecol.*, 150, 723—8.
20. Twiggs, L.B., Morrow, C.P. and Schlaerth, J.B. (1979) Acute pulmonary complications of molar pregnancy. *Am. J. Obstet. Gynecol.*, 135, 189—94
21. Soto-Wright, V, Bernstein, M.R., Goldstein, D.P., Berkowitz, R.S. (1995) The changing clinical presentation of complete molar pregnancy. *Obstet Gynecol.*, 86, 775-779
22. Paradinas F.J., Browne P, Fisher R.A., Foskett M., Bagshawe K.D., Newlands E. (1996) A clinical histopathological and flow

- cytometric study of 149 complete moles, 146 partial moles and 107 non-molar hydropic abortions. *Histopathology*, 28: 101-109.
23. Berkowitz, R.S., Goldstein, D.P. and Bernstein, MR. (1986) Natural history of partial molar pregnancy. *Obstet. Gynecol.*, 66, 677—81.
 24. Szulman, A.E. and Surti, U. (1982) The clinicopathologic profile of the partial hydatidiform mole. *Obstet. Gynecol.*, 59, 597—602.
 25. Czernobilsky, B., Barash, B. and Lancet, M. (1982) Partial moles: a clinicopathologic study of 25 cases. *Obstet. Gynecol.*, 59, 75—7.
 26. Mosher, R., Goldstein, D.P., Berkowitz, R.S., Bernstein, M.R., Genest, D.R. (1998) Complete hydatidiform mole, a comparison of clinicopathologic features, current and past. *J. Reprod. Med.*, 43,21-7.
 27. Benson, C.B., Genest, D.R., Bernstein, M.R., Soto-Wright, V., Berkowitz, R.S. (2000) Sonographic appearance of first trimester complete hydatidiform moles. *Ultrasound Obstet. Gynecol.*, 16, 188-191.
 28. Romero, R., Horgan, J.G., Kohorn, E.I. *et al.* (1985) New criteria for the diagnosis of gestational trophoblastic disease. *Obstet. Gynecol.*, 66, 553—8.
 29. Naumoff, P., Szulman, AF., Weinstein, B. *et al.* (1981) Ultrasonography of partial hydatidiform mole. *Radiology*, 140, 467—70.
 30. Fine, C., Bundy, AL., Berkowitz, R.S. *et al.* (1989) Sonographic diagnosis of partial hydatidiform mole. *Obstet. Gynecol.*, 73, 414—18.
 31. Genest, D., Laborde, O., Berkowitz, R.S. *et al.* (1991) A clinicopathologic study of 153 cases of complete hydatidiform mole (1980—1990): histologic grade lacks prognostic significance. *Obstet. Gynecol.*, 78, 402—9
 32. Menczer, J., Modan, M. and Sea, D.M. (1980) Prospective follow-up of patients with hydatidiform mole. *Obstet. Gynecol.*, 55, 346.—9
 33. Ozturk, M., Berkowitz, R., Goldstein, D. *et al.* (1988) Differential production of human chorionic gonadotropin and free subunits in gestational trophoblastic disease. *Am. J. Obstet. Gynecol.*, 158, 193—8
 34. Berkowitz, R., Ozturk, M., Goldstein, D. *et al.* (1989) Human chorionic gonadotropin and free subunits' serum levels in patients with partial and complete hydatidiform moles. *Obstet. Gynecol.*, 74, 212—16.
 35. Berkowitz, R.S., Goldstein, D.P. (1996) Chorionic tumours. *N. Engl. J. Med.*, 335, 1740-1748.
 36. Tidy J.A., Gillespie, A.M., Bright, N., Radstone, L.R., Coleman, R.E., Hancock, B.W. (2000) Gestational trophoblastic disease: A study of mode of evacuation and subsequent need for treatment with chemotherapy. *Gynecol. Oncol.*, 78, 309-312.
 37. Goldstein, D.P., (1971) Prophylactic chemotherapy of patients

- with molar pregnancy. *Obstet. Gynecol.*, 38, 817—22.
38. Kashimura, Y., Kashimura, M., Sugimori, H. *et al* (1986) Prophylactic chemotherapy for hydatidiform mole: five to 15 years follow-up. *Cancer*, 58, 624-9.
 39. Fasoli, M., Ratti, F., Francheschi, S. *et al* (1982) Management of gestational trophoblastic disease: results of a cooperative study. *Obstet. Gynecol.*, 60, 205—9.
 40. Kim, O.S., Moon, I-I., Kim, K.T. *et al.* (1986) Effects of prophylactic chemotherapy for persistent trophoblastic disease in patients with complete hydatidiform mole. *Obstet. Gynecol.*, 67, 690—4.
 41. Limpongsanurak, S. (2001) Prophylactic actinomycin D for high-risk complete hydatidiform mole. *J. Reprod. Med.*, 46, 110-116.
 42. Berkowitz, R.S., Goldstein, D.P., Dubeshter, B. and Bernstein, MR. (1987) Management of complete molar pregnancy. *J. Reprod. Med.*, 32, 634-9
 43. Palmer, J.R. (1994) Advances in the epidemiology of gestational trophoblastic disease. *J. Reprod. Med.*, 39, 155—62.
 44. Stone, M. and Bagshawe, K.D. (1979) An analysis of the influences of maternal age, gestational age, contraceptive method, and the mode of primary treatment of patients with hydatidiform moles on the incidence of subsequent chemotherapy. *Br. J. Obstet. Gynecol.*, 86, 782—92.
 45. Berkowitz, R.S., Goldstein, D.P., Marean, A. and Bernstein, MR. (1981) Oral contraceptives and postmolar trophoblastic disease. *Obstet. Gynecol.*, 58, 474—7
 46. Curry, S., Schlaerth, J., Kohorn, F. *et al.* (1989) Hormonal contraception and trophoblastic sequelae after hydatidiform mole (a Gynecologic Oncology Group study). *Am. J. Obstet. Gynecol.*, 160, 805-11.
 47. Ho Yuen, B. and Burch, P. (1983) Relationship of oral contraceptives and the intrauterine contraceptive devices to the regression of concentrations of the beta subunit of human chorionic gonadotropin and invasive complications after molar pregnancy. *Am. J. Obstet. Gynecol.*, 145, 214-17
 48. Deicas, R.E., Miller, D.S., Rademaker, A.W. and Lurain, J.R. (1991) The role of contraception in the development of postmolar gestational trophoblastic tumor. *Obstet. Gynecol.*, 78, 221—6
 49. Bagshawe, K.D. (1993) Trophoblastic neoplasia, in *Cancer Medicine*, 3rd edn (eds J.F. Holland, F. Frei III, R. Bast, Jr *et al*, Williams & Wilkins, Baltimore, pp. 1691—968.
 50. Lurain, J.R., Brewer, J.I., Torok, FE. and Halpern, B. (1983) Natural history of hydatidiform mole after primary evacuation. *Am. J. Obstet. Gynecol.*, 145, 591—5.
 51. Morrow, C.P., Kletzky, O.A., DiSaia, PT. *et al* (1977) Clinical and laboratory correlates of molar pregnancy and trophoblastic disease. *Am. J. Obstet. Gynecol.*, 128, 424—30.

52. Franke, H.R., Risse, E.K.J., Kenemans, P. *et al.* (1983) Epidemiologic features of hydatidiform mole in the Netherlands. *Obstet. Gynecol.*, 62, 613-16.
53. Kohorn, E.I. (1993) Evaluation of the criteria used to make the diagnosis of non-metastatic gestational trophoblastic neoplasia. *Gynecol. Oncol.*, 48, 139-A7.
54. Schlaerth, J.B., Morrow, C.P., Kletzky, O.A. *et al.* (1981) Prognostic characteristics of serum human chorionic gonadotropin titer regression following molar pregnancy. *Obstet. Gynecol.*, 58, 478—82.
55. Massad, L.S., Abu-Rustum, N., Lee, S.S., Renta, V. (2000) Poor compliance with post-molar surveillance and treatment protocols by indigent women. *Obstet. Gynecol.*, 96, 940-4.
56. Morrow, C.P. (1984) Post-molar trophoblastic disease: diagnosis, management and prognosis. *Clin. Obstet. Gynecol.*, 27, 211—20.
57. Tow, W.S.H. (1966) The influence of primary treatment of hydatidiform mole on subsequent course. *J. Obstet. Gynaecol. Br. Commonw.*, 73, 544—52.
58. Xia, Z., Song, H. and Tang, M. (1980) Risk of malignancy and prognosis using a provisional scoring system in hydatidiform mole. *Chin. Med. J.*, 93, 605—12.
59. Tsukamoto, N., Iwasaka, T., Kashimura, Y. *et al.* (1985) Gestational trophoblastic disease in women aged 50 or more. *Gynecol. Oncol.*, 20, 53-61.
60. Tsuji, K., Yagi, S. and Nakano, R.I. (1981) Increased risk of malignant transformation of hydatidiform moles in older gravidas: a cytogenetic study. *Obstet. Gynecol.*, 58, 351—5.
61. Martin, D.A., Sutton, G.P., Ulbright, T.M. *et al.* (1989) DNA content as a prognostic index in gestational trophoblastic neoplasia. *Gynecol. Oncol.*, 34, 383-8.
62. Parazzini, F., Mangili, G., Belloni, C. *et al.* (1988) The problem of identification of prognostic factors for persistent trophoblastic disease. *Gynecol. Oncol.*, 30, 57—62.
63. Garner, E.O., Lipson, E., Bernstein, M.R., Goldstein, D.P., Berkowitz, R.S. (2002) Subsequent pregnancy experience in patients with molar pregnancy and gestational trophoblastic tumor. *J. Reprod. Med.* 47, 380-6.
64. Hertig, A.T. and Sheldon, W.H. (1947) Hydatidiform mole: a pathologico-clinical correlation of 200cases. *Am. J. Obstet. Gynecol.*, 53, 1 —36.
65. Driscoll, S.G. (1977) Gestational trophoblastic neoplasms: morphologic considerations. *Hum. Pathol.*, 8,529—39.
66. Elston, C.W. and Bagshawe, K.D. (1972) The value of histological grading in the management of hydatidiform mole. *J. Obstet. Gynaecol. Br. Commow.*, 79, 717—24.
67. Tow, W.S. and Yung, R.H. (1967) The value of histologic grading in the prognostication of hydatidiform mole. *J. Obstet. Gynaecol. Br. Commonw.*, 74, 292—3.

68. Khazaeli, MB., Hedayat, MM., Hatch, K.D. *et al.* (1986) Radioimmunoassay of free-beta subunit of human chorionic gonadotropin as a prognostic test for persistent trophoblastic disease in molar pregnancy. *Am. J. Obstet. Gynecol.*, 155, 320—4.
69. Wake, N., Fujino, T., Hoshi, S. *et al.* (1987) The propensity to malignancy of dispermic heterozygous moles. *Placenta*, 8, 319—26.
70. Lawler, S., Fisher, R. and Dent, J. (1991) A prospective genetic study of complete and partial hydatidiform moles. *Am. J. Obstet. Gynecol.*, 164, 1270-7
71. Mutter, CL., Pomponio, R.J., Berkowitz, R.S. and Genest, DR. (1993) Sex chromosome composition of complete hydatidiform moles: Relationship to metastasis. *Am. J. Obstet. Gynecol.*, 168,1547—51.
72. Fulop, V., Mok, S.C., Genest, D.R., Szigetvari, I., Cseh, I., Berkowitz, R.S. (1998) C-myc, c-erb B-2, cfms and bcl2 oncoproteins: Expression in normal placenta, partial and complete mole and choriocarcinoma. *J. Reprod. Med.*, 43, 101-110.
73. Fisher R.A., Newlands, E.S. (1998) Gestational trophoblastic disease: Molecular and genetic studies. *J. Reprod. Med.*, 43, 87-97.
74. Vegh, G.L., Tuncer, Z.S., Fulop V., Genest, D.R., Mok, S.C., Berkowitz, R.S. (1999) Matrix metalloproteinases and their inhibitors in gestational trophoblastic diseases and normal placenta. *Gynecol. Oncol.*, 75, 248-253.
75. Tuncer, Z.S., Vegh, G.L., Fulop, V., Genest, D.R., Mok, S.C., Berkowitz, R.S. (2000) Expression of epidermal growth factor receptor – related family products in gestational trophoblastic diseases and normal placenta and its relationship to development of post-molar tumor. *Gynecol. Oncol.*, 77, 389-393.
76. Sukcharoen, N., Multirangura, A., Limpongsanurak, S. Telomerase (1999) Activity in complete hydatidiform mole. *J. Reprod. Med.*, 44, 465-470.
77. Rice, L.W., Berkowitz, R.S., Lage, J.M. and Goldstein, D.P. (1990) Persistent gestational trophoblastic tumor after partial hydatidiform mole. *Gynecol. Oncol.*, 36, 358—62.
78. Wong, L.C. and Ma, H.K. (1984) The syndrome of partial mole. *Arch. Gynecol.*, 234, 161—6.
79. Ohama, K., Deda, K., Okamoto, F, *et al.* (1986) Cytogenetic and clinicopathologic studies of partial moles. *Obstet. Gynecol.*, 68, 259-62.
80. Bolis, G., Belloni, C., Bonazzi, C. *et al.* (1988) Analysis of 309 cases after hydatidiform mole: different follow-up program according to biologic behavior. *Tumori*, 74, 93-6.
81. Seckl, M.J., Fisher, R.A., Salerno, F., Rees, H., Paradinas, F., Foksett, M., Newlands, E.S. (2000) Choriocarcinoma and partial hydatidiform moles. *Lancet* 356, 36-39.
82. Lage, J.M., Berkowitz, R.S., Rice, LW. *et al.* (1991) Flow cytometric analysis of DNA content in partial hydatidiform moles

- with persistent gestational trophoblastic tumor. *Obstet. Gynecol.*, 77, 111—15.
83. Goto, S., Yamada, A., Ishizuka, T. and Tomoda, Y. (1993) Development of postmolar trophoblastic disease after partial molar pregnancy. *Gynecol. Oncol.*, 48, 165-70.
 84. Teng, N. and Ballon, S.C. (1984) Partial hydatidiform mole with diploid karyotype: report of three cases. *Am. J. Obstet. Gynecol.*, 150, 961—4.
 85. Genest, D.R., Ruiz, R.E., Weremowicz, S., Berkowitz, R.S., Goldstein, D.P. Dorfman, D.M (2002). Do non-triploid partial hydatidiform moles exist? A histological and flow cytometric re-evaluation of non-triploid specimens. *J. Reprod. Med.* 47, 363-8.
 86. Vejerslev, L.O., (1991) Clinical management and diagnostic possibilities in hydatidiform mole with co-existent fetus. *Obstet. Gynecol. Surv.*, 46, 577-88.
 87. Steller, MA., Genest, DR., Bernstein, MR. *et al.* (1994) Clinical features of multiple conception with partial or complete molar pregnancy and coexisting fetuses. *J. Reprod. Med.*, 39, 147—54.
 88. Matsui, H., Sekiya, S., Hando, T., Wake, N., Tomoda, Y. (2000) Hydatidiform mole co-existent with a twin live fetus: a national collaborative study in Japan. *Human Reprod.*, 15, 608-11.
 89. Ho, P.C., Wong, L.C. and Ma, H.K. (1985) Return to ovulation after evacuation of hydatidiform mole. *Am. J. Obstet. Gynecol.*, 153, 638-42.
 90. Brandes, J.A. and Peretz, A. (1965) Recurrent hydatidiform mole. *Obstet. Gynecol.*, 25, 398— 400.
 91. Bagshawe, K.D., Dent, J. and Webb, J. (1986) Hydatidiform mole in England and Wales 1973-1983. *Lancet*, ii, 673-7
 92. Rice, L.W., Lage, J.M., Berkowitz, R.S. *et al.* (1989) Repetitive complete and partial hydatidiform mole. *Obstet. Gynecol.*, 74, 217—19.
 93. Tuncer, Z.S. Bernstein, M.R., Wang, J., Goldstein, D.P., Berkowitz, R.S. (1999) Repetitive hydatidiform mole with different male partners. *Gynecol. Oncol.*, 75, 224-26.
 94. Lurain, J.R., Sand, P.K., Carson, S.A. and Brewer, J.I. (1982) Pregnancy outcome subsequent to consecutive hydatidiform moles. *Am. J. Obstet Gynecol.*, 142, 1060—1.
 95. Tuncer, Z.S., Bernstein, M.R., Goldstein, D.P., Lu, K.H., Berkowitz, R.S. (1999) Outcome of pregnancies occurring within 1 year of hydatidiform mole. *Obstet. Gynecol.*, 94, 588-90.