Gestational Trophoblastic Neoplasia in the 1990s

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Major advances have been achieved during the past 40 years in the epidemiology, etiology, pathology, endocrinology, immunology, diagnosis, and treatment of molar pregnancy (MP) and gestational trophoblastic neoplasia (GTN). MP is now recognized as composing two distinct entities—complete and partial, with distinct histopathology, genetics, and clinical presentations. Proper management is dependent on a thorough understanding of each type. Early diagnosis and effective treatment of patients with GTN has resulted in 100 percent cure rates in non-metastatic disease and in the majority of patients with metastases. In most instances, resistant disease leading to death results from delayed diagnosis and overwhelming tumor burden. Moreover, in most instances successful treatment can be accomplished with preservation of fertility and normal pregnancy outcome anticipated. A rare variant of choriocarcinoma called placental site trophoblastic tumor (PSTT) has been described, which, although curable by surgery when localized, is usually fatal when disseminated. It is anticipated that during the decade of the nineties the scientific work in progress will lead to earlier diagnosis and improved survival in resistant cases.

Thirty-five years have elapsed since the first patient with metastatic choriocarcinoma was successfully treated with chemotherapy at the National Cancer Institute. Since that momentous occasion, which the late Arthur T. Hertig, Professor of Pathology, Harvard Medical School, called "God's first cancer, man's first cure," much has been accomplished in our understanding of this fascinating and enigmatic group of diseases.

The following is a summary of the current status of knowledge about this condition, which is now referred to as gestational trophoblastic neoplasia (GTN), emphasizing those aspects which are most important for the clinician to understand when confronted with a patient who is afflicted by this illness.

The topics to be discussed include evolving concepts of molar pregnancy, management of gestational trophoblastic tumors, staging and prognostic factors, placental site trophoblastic tumors, and the subsequent reproductive performance of women following treatment for molar pregnancy and gestational trophoblastic disease.

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EVOLVING CONCEPTS OF MOLAR PREGNANCY

Pathology

Molar pregnancy (MP) is composed of two separate entities, partial and complete, which are distinct in terms of histopathology, chromosome pattern, and clinical presentation. Chorionic villi in complete moles are diffusely hydropic and are enveloped by hyperplastic and atypical trophoblast [1]. Complete moles generally have no identifiable embryonic or fetal tissue. In contrast, partial moles are composed of two populations of chorionic villi. While some villi appear reasonably normal, others have hydropic swelling and focal trophoblast hyperplasia [2]. Hydropic villi may also have markedly irregular scalloping and stromal trophoblastic inclusions. Fetal embryonic tissues are often identified with partial moles, but these fetuses generally exhibit the malformations of triploidy, including syndactyly, hydrocephalus, and growth retardation [3]. Infrequently, fetuses associated with partial moles are live-born.

Chromosomal Pattern

Approximately 90 percent of complete moles have a 46 XX karyotype, and the molar chromosomes are of paternal origin [4–6]. Generally a haploid (23X) sperm fertilizes an ovum and then duplicates its own chromosomes; the maternal chromosomes may be either inactive or absent [7]. While most complete moles have a 46XX karyotype, 6–10 percent have a 46XY chromosomal pattern; again, all the chromosomes are paternal in origin [8]. The 46 XY complete mole apparently results from fertilization of an empty ovum by two separate sperm [9].

About two-thirds of partial moles have a triploid karyotype, resulting from fertilization of an apparently normal ovum by two sperm [10,11]. The remaining one-third of partial moles have a diploid karyotype (46XX or 46XY). It may, however, be difficult to differentiate partial mole from a twin gestation coexisting with a complete mole.

Experiments involving nuclear transplantation in mice provide important insights into the genesis of molar pregnancy [12]. Paternal or maternal nuclei from early germ cells were transferred to an egg in which the female pronucleus was removed. When "fertilized" eggs contained two maternal sets of chromosomes, the embryo developed to the 25-somite stage, with poor growth of extra-embryonic tissues. When "fertilized" eggs contained two paternal sets of chromosomes, like a complete mole, the embryo developed only to the six-somite stage and degenerated, and the trophoblastic growth was exuberant and hyperplastic. Therefore, the maternal genome is particularly important for regulating the growth and development of the embryo, while the paternal genome is crucial to controlling proliferation of extra-embryonic tissues. The central theme of molar trophoblastic neoplasia appears to be an excessive amount of paternal chromosomes, which induces trophoblastic hyperplasia.

Clinical Presentation

The most common presenting symptom in patients with complete mole is vaginal bleeding (97 percent) [13]. Half the patients present with signs and symptoms of marked trophoblastic growth, including excessive uterine size, high human chorionic gonadotropin (hCG) levels, and prominent ovarian theca lutein cysts. These patients

are also predisposed to develop such medical complications as toxemia (27 percent), hyperthyroidism (7 percent), and acute respiratory insufficiency (2 percent), which usually become clinically apparent following evacuation.

In contrast, a patient with partial mole usually does not exhibit the dramatic clinical features demonstrated by complete mole. Only 4–11 percent have excessive uterine enlargment. Theca lutein cysts, hyperthyroidism, respiratory insufficiency, and toxemia are rare. Furthermore, pre-evacuation hCG levels are normal or low in the majority of cases (94 percent). In fact, the pre-evacuation clinical diagnosis usually is either missed or incomplete abortion in over 90 percent and the diagnosis is made only after histologic review of curettage specimens.

Ultrasonic Findings

Complete molar pregnancy produces a characteristic vesicular sonographic pattern because of the marked generalized swelling of chorionic villi. Ultrasound may not, however, be able to identify small molar villi in the early first trimester or distinguish an early mole from degenerating chorionic villi. Correlation of the ultrasonic features with the hCG level is essential in establishing the correct diagnosis.

Ultrasonography has been less accurate in the diagnosis of partial molar pregnancy. Approximately 25 percent of patients with partial mole exhibit placental cystic spaces, and a fetus with multiple anomalies suggestive of triploidy will be noted in 10 percent of cases. A recent review of ultrasounds at the Brigham & Women's Hospital in 22 patients with partial moles and 33 first-trimester missed abortions reveal two sonographic findings which appear to correlate clinically with the histologic diagnosis of partial mole: cystic changes in the placenta, and > 1.5 ratio in the transverse to anterior-posterior diameter of the gestational sac. The latter finding may be part of the embryopathy of triploidy [16].

Persistent Disease Following Evacuation

Complete moles give rise to persistent GTN in about 20 percent of patients [17–19]. Patients who have signs of marked trophoblastic growth, including excessive uterine size, high hCG levels, and theca lutein cysts, have a 40–50 percent chance of developing persistent tumors which require intervention, and these are designated as high-risk moles. In contrast, only 4–7 percent of moles without signs of exuberant trophoblastic growth develop persistent disease and therefore are characterized as low-risk moles.

The risk of developing persistent GTN in patients with partial moles is approximately 3–4 percent, which is similar to that seen in complete moles without evidence of exuberant trophoblastic growth [20]. In a recent series from the New England Trophoblastic Disease Center (NETDC), patients with partial mole who developed persistent disease did not have pathologic or clinical features that distinguished them from other patients with partial mole [21]. Thus partial molar patients are generally considered to be low-risk. All of the patients with persistent tumor after partial mole had non-metastatic disease and achieved complete remission after one or two courses of single-agent chemotherapy. There are, however, reported cases of metastatic disease following partial moles, so careful follow-up after evacuation is essential, and a thorough examination for metastatic disease should be carried out before treatment is undertaken.

STAGING AND PROGNOSTIC FACTORS

The staging of GTN has been the subject of controversy among gynecologists for years, and there are no signs on the horizon of resolving the conflict. The first attempt at staging emerged from the clinical classification developed at the National Cancer Institute (NCI). All patients were divided initially into two groups on the basis of the extent of disease (i.e., non-metastatic versus metastatic) [22]. In 1965, an analysis of the first ten years' experience at the NCI led to the conclusion that patients with metastatic disease should be subdivided into good prognosis and poor prognosis on the basis of certain prognostic factors which included the duration of disease, the hCG level, the presence of brain or liver metastases, failed response to initial chemotherapy, and the type of antecedent pregnancy [23].

In 1985, the International Federation of Gynecologists and Obstetricians (FIGO) began to report data on GTN using an anatomic staging system which was based on postmortem studies in over 450 patients carried out by the Capital Hospital in Beijing by Sung and colleagues [24]. In this system, *stage I* includes all patients with tumor confined to the uterus. *Stage II* comprises all patients with tumor outside the uterus but localized to the vagina and/or pelvis. *Stage III* includes all patients with pulmonary metastases with or without uterine, vaginal, or pelvic involvement. *Stage IV* includes patients who have far-advanced disease with involvement of the brain, liver, kidneys, or gastrointestinal tract. Patients with stage IV disease are in the highest risk category because they are most likely to be resistant to chemotherapy. Stage IV tumors generally have the histologic pattern of choriocarcinoma and most commonly follow a non-molar pregnancy.

The main advantage of the FIGO staging system is the fact that it most closely resembles that used in the staging of other gynecologic malignancies. Its main drawback lies in the fact that it lacks a logical prognostic sequence on which to base therapy, since there are patients in each category who are at greater risk of developing drug resistance.

In order to resolve this problem, in 1983 the World Health Organization (WHO) endorsed the use of a prognostic scoring system, based on one developed by Bagshawe, which reliably predicts the potential for chemotherapy resistance [25]. In that system, high scores indicate greater potential for drug resistance and the need for intensive combination chemotherapy to attain remission.

A recent poll of members of the Society for Gynecologic Oncologists revealed that the NCI classification was the one most widely utilized by its members. Nonetheless, we feel that anatomic staging plays an important role in collecting and comparing data from different centers throughout the world.

MANAGEMENT OF GESTATIONAL TROPHOBLASTIC NEOPLASMS

The optimal management of GTN requires a thorough evaluation of the extent of disease, accurate pathologic interpretation of available material, availability of a reliable hCG assay, an understanding of the natural history of trophoblastic tumors, and familiarity with treatment protocols which have proven most effective in the past.

Diagnostic Tests

All patients with persistent tumors, regardless of the antecedent pregnancy, should undergo a thorough evaluation, including a complete history and physical

examination, baseline serum hCG levels, and hepatic, thyroid, and renal function tests. Basic metastatic work-up includes a chest X-ray, computed tomographic (CT) scan of the chest (if indicated), ultrasonography of the abdomen and pelvis, and head CT scan.

Duplex ultrasound has recently been shown to be capable of identifying focal areas of altered echogenicity within the uterus. When used in conjuction with Doppler scanning to detect focal areas of altered blood flow, it can be a valuable tool to identify otherwise occult metastases in various organs [26].

Cerebral metastases, which are associated with increased mortality and morbidity, have in the past proven difficult to diagnose. Two new techniques, however, have altered the prognosis of this complication dramatically because of earlier diagnosis— head CT scanning and the plasma:CSF hCG ratio. The Charing Cross Group have reported that a plasma:CSF hCG ratio of less than 60 strongly suggests central nervous system involvement [27]. It must be emphasized, however, that rapid changes in plasma hCG levels may not be promptly reflected in the cerebrospinal fluid (CSF), making a single plasma:CSF hCG ratio misleading.

Treatment

The treatment of GTN should be individualized. Once the pre-treatment evaluation is completed and the extent of disease determined, the patient should be assigned a stage and a prognostic score. In general, low-risk patients with both metastatic and non-metastatic disease usually respond to single-agent chemotherapy, while patients with high-risk disease should be treated primarily with combination chemotherapy.

Ninety percent of patients with stage I (non-metastatic) disease are curable with single-agent chemotherapy. Those patients who prove resistant to single-agent chemotherapy ultimately respond to combination chemotherapy. For this reason, the distinction between low-risk and high-risk prognostic scores in patients with stage I disease is not as important as it is in the other groups.

There does, however, exist a subset of stage I patients with histologically proven choriocarcinoma and a greater than average tumor burden, as reflected in hCG titers over 50,000 mIU/ml, who have generally proven resistant to single-agent chemotherapy and do best when treated with combination therapy initially. Pre-treatment dilation and curettage has proven extremely helpful in identifying this small group of patients, and for this reason this procedure should be a part of the initial work-up [28].

Primary surgical treatment in patients with stage I disease who no longer wish to preserve fertility is an acceptable alternative to chemotherapy alone. When primary hysterectomy is performed, adjunctive single-agent chemotherapy should be utilized in case viable tumor is disseminated at surgery and also to treat occult metastases. Data from the Southeastern Trophoblastic Disease Center reveals that occult pulmonary metastases are present on CT scans of the lung in about 40 percent of patients with presumed non-metastatic disease [29]. Chemotherapy may be safely administered at the time of hysterectomy without increasing operative morbidity.

The type of chemotherapy selected for patients with stage II and stage III disease should be based on the prognostic score. Low-risk patients in these categories are managed initially with single-agent chemotherapy despite the presence of metastatic

disease; however, high-risk patients should always be treated primarily with combination chemotherapy. The cure rate should approach 100 percent.

Special attention may need to be focused on the role of surgery in the management of stage II and stage III disease. Vaginal metastases may bleed profusely because they are highly vascular and friable. Bleeding may be controlled by packing the vagina and performing local excision. The administration of one or two courses of chemotherapy may result in marked tumor regression and reduce vascularity. Recently, the technique of angiographic embolization of the hypogastric arteries has proven to be a successful and less invasive technique.

Thoracotomy has a limited role in the management of stage III disease. Thoracotomy should be performed if the diagnosis is seriously in doubt, since some primary lung tumors can secrete hCG. Furthermore, if a patient has had a persistent viable solitary pulmonary nodule by chest CT despite intensive chemotherapy, pulmonary resection may be advantageous [30]. An extensive metastatic work-up should be obtained, however, to exclude other sites of persistent disease. It is important to emphasize that fibrotic nodules may persist indefinitely on chest roentgenogram after complete gonadotropin remission is achieved. These should not be surgically excised.

Hysterectomy may be required despite the desire to preserve fertility in patients with metastases in order to control uterine hemorrhage or sepsis. Furthermore, it has been reported that, in patients with bulky uterine tumor, hysterectomy may reduce the tumor burden and therefore limit the need for chemotherapy.

All patients with stage IV disease should be treated with intensive combination chemotherapy and the selective use of radiation therapy and surgery. Before 1975, the survival rate of patients with stage IV disease was approximately 30 percent. Since 1975, when primary combination chemotherapy was introduced, the complete remission rate has risen to over 90 percent. This dramatic improvement in survival resulted from a combination of factors, including the use of staging and prognostic scoring systems, earlier diagnosis because of improved imaging techniques, and the use of newer agents incorporated into well-proven protocols used intensively with radiation therapy and surgery.

The management of hepatic disease is particularly problematic and challenging. If a patient is resistant to systemic chemotherapy, hepatic arterial infusion of chemotherapy has been shown to achieve complete remission in selected cases. Hepatic resection may also be necessary to control bleeding or to excise resistant disease.

If cerebral metastases are detected, whole-brain irradiation is promptly instituted at the NETDC. The concurrent administration of chemotherapy and brain irradiation may reduce the risk of spontaneous cerebral bleeding. Brain irradiation may be both hemostatic and tumoricidal. Craniotomy may be required to provide acute decompression or to control bleeding. Infrequently, a solitary cerebral metastasis that is resistant to chemotherapy may be amenable to resection. Fortunately, patients with cerebral metastases who attain remission usually have no residual neurologic defects.

SINGLE-AGENT CHEMOTHERAPY

Single-agent chemotherapy with either Methotrexate®(Mtx) or actinomycin D (ACT D) has achieved comparable and excellent cure rates in both non-metastatic and metastatic disease. Mtx and folinic acid (Mtx-FA) rescue has been the preferred

single-agent protocol at the NETDC since 1974. Between 1974 and 1990, a total of 260 patients were treated with primary Mtx and FA rescue. Complete remission was obtained in 86 percent, and 60 percent required only one course to achieve remission. Mtx-FA rescue induced remission in 90 percent of patients with stage I disease and 60 percent of patients with low-risk stage II and stage III tumor. Resistance to Mtx was more common in patients with choriocarcinoma, when metastases were present, and when the pre-treatment hCG level was greater than 50,000 mIU/ml. The toxicity following Mtx-FA rescue was quite low, with thrombocytopenia, granulocytopenia, and hepatotoxicity occurring only in 2 percent, 6 percent, and 14 percent, respectively. No patients required transfusions or developed sepsis due to myelosuppression, and no patient experienced marked nausea or alopecia.

CHEMOTHERAPY ADMINISTRATION

When patients with low-risk disease are treated with single-agent chemotherapy, the hCG level is measured weekly after each course of chemotherapy. The hCG regression curve serves as the primary basis for determining the need for further treatment. After the first treatment, further chemotherapy is withheld as long as the hCG level is falling progressively. Additional single-agent chemotherapy is not administered at any predetermined or fixed interval time. Subsequent courses of chemotherapy are administered under the following conditions: when the hCG level plateaus for more than three consecutive weeks, re-elevates, or when the hCG level does not decline by one log within 18 days after completing the first treatment.

If a second course of Mtx-FA is necessary, the dosage of Mtx is unchanged if the patient's response to the first treatment is adequate. An adequate response is defined as a decline in the hCG level by one log following a course of chemotherapy. When the response to the first treatment is inadequate, the patient is considered to be resistant to Mtx and actinomycin D is then promptly substituted.

A relatively new drug, etoposide (VP16) has been demonstrated to be a highly effective anti-tumor agent in GTN [31–32]. A triple-therapy regimen which includes etoposide, Mtx-FA, and ACT D (EMA) has become the primary combination regimen at the NETDC.

Patients who require combination chemotherapy must be treated intensively to achieve remission. It is advisable to administer combination chemotherapy as frequently as toxicity permits (usually at two-week intervals) until the patient obtains three weekly normal hCG values. After the patient achieves normal hCG values, two additional courses of chemotherapy are administered to reduce the risk of relapse.

PLACENTAL SITE TROPHOBLASTIC TUMORS

In 1976, Kurman et al. described 12 patients with a variant of trophoblastic disease marked by a distinct and exaggerated placental site reaction [32]. The term "trophoblastic pseudotumor of the uterus" was coined to reflect the apparently benign nature of the lesion. In 1981, Twiggs et al. reported the death of a young woman with metastatic trophoblastic pseudotumor [33]. In 1981, Scully and Young published a reappraisal of these rare tumors and suggested the term "placental site trophoblastic tumor" (PSTT) to emphasize the potentially malignant nature of the lesion [34].

Diagnosing this rare form of trophoblastic disease and predicting its biologic behavior remain difficult despite knowledge of the histology of these lesions and continued reporting of series of patients.

Diagnosis

PSTT may complicate or follow normal pregnancy, abortion, or hydatidiform mole. Tumors are thought to arise from the intermediate trophoblastic cell. This trophoblast functions in implantation and the establishment of the uteroplacental circulation. Although the intermediate trophoblast can elaborate all placental proteins, the major protein secreted is human placental lactogen (hPL). Histologically, PSTT is characterized by mononuclear and occasionally multinuclear giant cells that infiltrate the uterus and its blood vessels. Chorionic villi are present very rarely.

PSTT can be distinguished from gestational choriocarcinoma by its monomorphic cell population and lack of necrosis and hemorrhage. Immunohistochemical studies demonstrate variable reactivity, with a minority of cells staining for hCG, and the majority staining for hPL.

Clinical Behavior

PSTT may follow any type of gestation. The symptoms can appear from weeks to years after termination of the pregnancy. Most patients present within the first three months with irregular vaginal bleeding. Rare presenting symptoms have been reported and include virilization, amenorrhea, and nephrotic syndrome [35,36,37].

The variable and often low hCG expression in PSTT may be accounted for by the paucity of syncytiotrophoblast. At the time of the clinical presentation, therefore, hCG values are often low and certainly below the levels usually encountered with other forms of GTN.

Patients found to have PSTT on dilation and curettage should undergo a complete work-up, including metastatic screening. The majority of patients, however, will be found to have non-metastatic disease.

The clinical behavior of PSTT remains enigmatic. Many patients can be cured with curettage alone, while others have died despite intensive multimodal therapy.

Metastases from PSTT occur mainly in the lungs, although metastases to lymph nodes, brain, liver, kidney, vagina, stomach, and spleen have been reported [37]. A major clinical dilemma in patients with PSTT is predicting which tumors have the greatest risk of developing metastases. Levels of hCG and hPL have been poor predictors of clinically aggressive behavior. Some authors have recommended the use of mitotic counts to predict tumors with an increased likelihood of metastases; however, mitotic counts vary substantially from endometrial curettings to hysterectomy specimens to metastatic lesions. Basing further therapy on mitotic counts from endometrial curettings therefore may be misleading. Using a proposed cutoff of more than four mitoses per 10 high-power fields to dictate when a hysterectomy should be performed may not be useful. Therefore, patients with PSTT and low mitotic counts may also develop disseminated tumors.

Treatment

Metastatic PSTT is an ominous sign since this tumor is relatively insensitive to aggressive cytotoxic chemotherapy. Although few if any long-term survivors with

metastatic PSTT have been reported, radiotherapy may have a role in providing local control of the tumor and palliating the symptoms. Early hysterectomy is recommended for treatment of non-metastatic disease and may also be useful in patients with metastases, since the uterus is usually infiltrated with tumor.

Serial hCG levels should be measured over long periods of time because metastases have been reported to occur as late as ten years after the presentation. Because little hCG is secreted, a large tumor burden may be present before the hCG levels are detectable.

SUBSEQUENT REPRODUCTIVE PERFORMANCE

Patients with GTN usually can achieve complete sustained remission without undergoing hysterectomy. After completing hormonal follow-up, most patients thereafter are confronted with a decision about attempting future pregnancy. Therefore, it is helpful to have data on later pregnancies to counsel these patients rationally.

The NETDC has collected data on later pregnancies for 30 years. When patients complete gonadotropin follow-up, they are requested to inform the Center about any later conceptions. Furthermore, every two to three years the Center mails questionnaires to all patients in the registry concerning their general health problems and later pregnancies. Patients are informed of the data from the questionnaires in our yearly newsletter.

Pregnancies After Complete Molar Pregnancy

Patients who were treated for complete mole at the NETDC had 1,162 later gestations between June 1, 1965, and December 31, 1989. These subsequent conceptions resulted in 803 term live births (69.1 percent), six stillbirths (0.05 percent), 84 premature deliveries (7.2 percent), and nine ectopic pregnancies (0.8 percent). Fifteen (1.3 percent) of the later gestations were either complete or partial moles. Major and minor congenital malformations were detected at birth in 35 (3.9 percent) of the infants; no particular anomaly was noted. First- and second-trimester spontaneous abortions developed in 190 (16.4 percent) and 18 (1.5 percent) of the pregnancies, respectively. The risk of stillbirth, prematurity, malformations, and spontaneous abortion was comparable to that in the general population.

The frequency of intrapartum complications was determined by assessing the primary cesarean section rate in later gestations. Primary cesarean section was performed in 49 (17 percent) of 288 later-term and premature deliveries between January 1979 and December 1989. Patients with complete mole, therefore, are not at greater than normal risk of needing cesarean delivery in later gestations.

Patients with complete hydatidiform mole were reassured that they can expect a normal reproductive outcome in the future.

Pregnancies After Partial Molar Pregnancy

Between June 1, 1965, and December 31, 1989, patients with partial molar pregnancy at the NETDC had 107 later gestations, resulting in 79 term live births (73.9 percent), one stillbirth (0.9 percent), one premature delivery (0.9 percent), and one ectopic pregnancy (0.9 percent). First- and second-trimester spontaneous abortions occurred in 16 (14.9 percent) and one (0.9 percent) pregnancies, respectively.

Only two (2.5 percent) of 81 term or premature infants had detectable major or minor congenital malformations. Primary cesarean section was performed in 13 (16.2 percent) of 80 term or premature births between January 1979 and December 1989.

Similarly, patients with partial molar pregnancy appear to have normal reproductive function subsequent to their evaluation.

Repeat Molar Pregnancy

Patients with molar disease (either partial or complete) are at increased risk of developing molar pregnancy in later conceptions [38,39]. The incidence of repeat hydatidiform mole has been reported as 0.6–2.0 percent in later pregnancies in North America and Asia [40–42]. Furthermore, Sand et al. reported that, after two episodes of gestational trophoblastic neoplasia, the risk of repeat disease rises to 28 percent [39].

We have observed every possible combination of repeat molar disease in our 15 patients with repeat moles [43]. Seven patients had consecutive complete moles, and two had repeat partial moles. Six patients developed both a complete and partial hydatidiform mole; five patients had an initial complete mole followed by a partial mole, and one patient had an initial partial mole followed by a complete mole. These patients may have a predilection for abnormal fertilization that causes either complete or partial mole.

Patients with repeat molar disease may ultimately have a normal pregnancy. Four of our patients with repeat mole later completed normal, full-term pregnancies. Lurain et al. also reported that five of eight patients with consecutive moles subsequently achieved normal, term gestations [43].

Patients with repeat moles are at increased risk of developing persistent GTN in later episodes of molar disease. Only one (7 percent) of our 15 patients with repeat mole developed persistent tumor after her first molar gestation; however, six patients (40 percent) developed persistent tumor after their second or third molar pregnancy. Parazzini et al. also observed a threefold increased risk of post-molar tumor in patients with repeat molar disease [44].

Pregnancies After Persistent GTN

Reports from the National Cancer Institute, Charing Cross Hospital (London), Beijing Union Medical College Hospital, and Hong Kong all indicate that patients with GTN who are managed successfully with chemotherapy can expect normal reproduction in the future [46–50]. Van Thiel et al. studied later gestations in 50 women with GTN who were treated at the NCI. Those women had 88 subsequent pregnancies that resulted in 71 full-term deliveries (81 percent), five spontaneous abortions (17 percent), and two stillbirths (2 percent). Congenital malformations were detected in only three full-term infants (4 percent). Ross also reviewed the experience at the NCI and observed no increase in congenital anomalies in later pregnancies in patients with GTN.

Walden and Bagshawe reported observing 64 later gestations in patients with GTN who were treated at Charing Cross Hospital. Those subsequent pregnancies concluded in 45 full-term deliveries (70.3 percent), ten spontaneous abortions (15.6 percent), five premature births (7.8 percent), and four stillbirths (6.3 percent). Only three full-term infants (4.7 percent) had congenital anomalies. The cumulative dose of chemotherapy had no effect upon subsequent fertility or fetal wastage.

The potential influence of chemotherapy upon later fertility and congenital anomalies was investigated further at Charing Cross Hospital by Rustin et al. Among 217 women who wished to conceive after chemotherapy for GTN, 200 (92 percent) conceived, and 187 (86 percent) succeeded in having at least one live birth. There was no significant difference in the ability to conceive or the outcome of later pregnancy in women over 30 as compared to those 30 or under. Women who received three or more drugs in combination were less likely to conceive or to have a live birth than were women who received methotrexate alone or methotrexate with one other agent. A total of 368 pregnancies resulted in 273 live births (74.2 percent), 53 spontaneous abortions (14.4 percent), eight stillbirths (2.2 percent), and two ectopic pregnancies (0.6 percent). Five (1.8 percent) of the live-born infants had major congenital anomalies.

Song and colleagues reviewed 355 subsequent pregnancies in patients treated with chemotherapy for GTN in Beijing. The subsequent gestations concluded in 279 term births (78.6 percent), 20 premature deliveries (5.6 percent), 26 spontaneous abortions (7.3 percent), three stillbirths (0.8 percent), and two ectopic pregnancies (0.6 percent).

Patients at the NETDC who received chemotherapy for GTN had 385 later conceptions between June 1, 1965, and December 31, 1989. Those pregnancies resulted in 275 term live births (71.4 percent), six stillbirths, 14 premature deliveries, and four ectopic pregnancies. Major or minor malformations were detected at birth in six (2 percent) of 295 term or premature infants. First- and second-trimester abortions occurred in 15 and 2 percent of the pregnancies, respectively. Primary cesarean section was performed for 14.8 percent of 189 term or premature deliveries between January 1979 and December 1989. The data from the NETDC on later pregnancies in patients with GTN are consistent with the experience reported from Washington, London, Beijing, and Hong Kong.

Management of Subsequent Pregnancies

Patients with GTN should be counseled that they generally have the same expectation for normal future pregnancies as does the average woman in the United States. After a patient has had a molar gestation, however, any future conception is at increased risk of developing GTN. It is therefore advisable for patients to undergo ultrasonography in the first trimester to confirm normal development. The placenta or products of conception from subsequent pregnancies should undergo careful pathologic examination. Furthermore, a serum hCG level should be obtained six weeks after the completion of any future gestation to exclude subsequent choriocarcinoma.

CONCLUSION

This review covers the most important aspects of molar pregnancy and GTN in the 1990s that physicians need to know in advising patients with this disease. Dramatic progress has occurred in the understanding and treatment of this group of diseases because of the tireless commitment of many investigators worldwide. It is expected that during the next decade additional progress will be made in the treatment of the small remaining group of patients with resistant disease, as newer diagnostic techniques and more effective agents are developed.

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