Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole

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Gestational trophoblastic disease includes hydatidiform mole (complete and partial) and gestational trophoblastic neoplasia (invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor). The epidemiology, pathology, clinical presentation, and diagnosis of each of these trophoblastic disease variants are discussed. Particular emphasis is given to management of hydatidiform mole, including evacuation, twin mole/normal fetus pregnancy, prophylactic chemotherapy, and follow-up.

Key words: chemotherapy, choriocarcinoma, gestational trophoblastic disease, gestational trophoblastic neoplasia, hydatidiform mole

Gestational trophoblastic disease (GTD) is a spectrum of cellular proliferations arising from the placental villous trophoblast encompassing 4 main clinicopathologic forms: hydatidiform mole (complete and partial), invasive mole, choriocarcinoma, and placental site trophoblastic tumor (PSTT) (Table). The term "gestational trophoblastic neoplasia" (GTN) has been applied collectively to the latter 3 conditions, which can progress, invade, metastasize, and lead to death if left untreated.

GTD was historically associated with significant morbidity and mortality. Hydatidiform moles were often accompanied by serious bleeding and other medical complications prior to the development of early detection and effective uterine evacuation means in the 1970s. The outcomes for GTN were likewise poor before the introduction of chemotherapy into their management 50 years ago. The mortality rate for invasive mole approached 15%, most often because of hemorrhage, sepsis, embolic phenomena, or complications from surgery. Choriocarcinoma had a mortality rate of almost 100% when metastases were present and approximately 60% even when hysterectomy was done for apparent nonmetastatic disease. Gestational trophoblastic neoplasms are now some of the most curable of all solid tumors, with cure rates >90% even in the presence of widespread metastatic disease.[1-3]

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★ EDITORS' CHOICE ★

Epidemiology

The incidence and etiologic factors contributing to the development of GTD have been difficult to characterize. The problems in accumulating reliable epidemiologic data can be attributed to a number of factors, such as inconsistencies in case definitions, inability to adequately characterize the population at risk, no centralized databases, lack of well-chosen control groups against which to compare possible risk factors, and rarity of the diseases.[4]

Epidemiologic studies have reported wide regional variations in the incidence of hydatidiform mole.[5] Estimates from studies conducted in North America, Australia, New Zealand, and Europe have shown the incidence of hydatidiform mole to range from 0.57–1.1 per 1000 pregnancies, whereas studies in Southeast Asia and Japan have suggested an incidence as high as 2.0 per 1000 pregnancies.[6] Investigations into possible ethnic and racial differences leading to an increased incidence of hydatidiform mole among American Indians, Eskimos, Hispanics, and African Americans as well as various Asian populations have not been able to attribute them to genetic traits, cultural factors, or simply differences in reporting.[7-9]

Data with respect to choriocarcinoma incidence rates are even more limited. Collection of data on the incidence of choriocarcinoma has been more difficult not only for reasons similar to those encountered with hydatidiform moles, but also because of the rarity of choriocarcinoma and the difficulty in clinically distinguishing postmolar choriocarcinoma from invasive mole. In Europe and North America, choriocarcinoma affects approximately 1 in 40,000 pregnancies and 1 in 40 hydatidiform moles, whereas in Southeast Asia and Japan choriocarcinoma rates are higher at 9.2 and 3.3 per 40,000 pregnancies, respectively. The incidence rates of both hydatidiform mole and choriocarcinoma have declined over the past 30 years in all populations.[10,11]

Several potential etiologic risk factors have been evaluated for the development of complete hydatidiform mole.[12] The 2 established risk factors that have emerged are extremes of maternal age and prior molar pregnancy. Advanced or very young maternal age has consistently correlated with higher rates of complete hydatidiform mole. Compared

TABLE
Clinicopathologic features of gestational trophoblastic disease

Gestational trophoblastic disease	Pathologic features	Clinical features
Hydatidiform mole, complete	46,XX (mainly); 46,XY Absent fetus/embryo Diffuse swelling of villi Diffuse trophoblastic hyperplasia	15-20% trophoblastic sequelae hCG often >100,000 mIU/mL Medical complications
Hydatidiform mole, partial	Triploid (69, XXY; 69, XYY; 69 XXX) Abnormal fetus/embryo Focal swelling of villi Focal trophoblastic hyperplasia	<5% trophoblastic sequelae hCG usually <100,000 mIU/mL Rare medical complications
Invasive mole	Myometrial invasion Swollen villi Hyperplastic trophoblast	15% metastatic–lung/vagina Most often diagnosed clinically, rather than pathologically
Choriocarcinoma	Abnormal trophoblastic hyperplasia and anaplasia Absent villi Hemorrhage, necrosis	Vascular spread to distant sites–lung/brain/liver Malignant disease
PSTT	Tumor cells infiltrate myometrium with vascular/lymphatic invasion Intermediate cells/absent villi Less hemorrhage and necrosis Tumor cells stain positive for hPL	Extremely rare hCG levels less reliable indicator Relatively chemoresistant Mainly surgical treatment

hCG, human chorionic gonadotropin; *hPL*, human placental lactogen; *PSTT*, placental site trophoblastic tumor.

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to women aged 21-35 years, the risk of complete mole is 1.9 times higher for women both >35 years and <21 years as well as 7.5 times higher for women >40 years.[13,14] Prior hydatidiform mole predisposes to another molar pregnancy. The risk of repeat molar pregnancy after 1 mole is about 1%, or about 10-20 times the risk for the general population.[15,16] Familial clusters of biparental complete hydatidiform moles associated with novel missense NLRP7 gene mutations on chromosome 19q have also been identified.[17] Another reported obstetric risk factor for both complete and partial moles is a history of spontaneous abortion, giving women a 2- to 3-fold increased risk of a molar pregnancy compared to women without a history of miscarriage.[12] Although many possible environmental etiologies for complete mole have been studied, the only consistent association has been an inverse relationship between β-carotene and animal fat dietary intake and the incidence of molar pregnancy.[18,19] Ovulation induction for fertility may also be associated with an increase in pregnancies consisting of a normal fetus or fetuses and a molar gestation.

Risk factors for choriocarcinoma include prior complete hydatidiform mole, ethnicity, and advanced maternal age. Choriocarcinoma is approximately 1000 times more likely after a complete mole than after another pregnancy event. The risk is also increased in women of Asian and American Indian descent as well as African Americans. Similar to molar pregnancies, the median age of women with choriocarcinoma is higher than that for normal pregnancies.[11] There also seems to be an increased risk of choriocarcinoma in women with long-term oral contraceptive use and blood group A.[5,20]

Pathology

Molar pregnancies and gestational trophoblastic neoplasms all take their origin from the placental trophoblast. Normal trophoblast is composed of cytotrophoblast, syncytiotrophoblast, and intermediate trophoblast. Syncytiotrophoblast invades the endometrial stroma with implantation of the blastocyst and is the cell type that produces human chorionic gonadotropin (hCG). Cytotrophoblast functions to supply the syncytium with cells in addition to forming outpouchings that become the chorionic villi covering the chorionic sac. The villous chorion adjacent to the endometrium and basalis layer of the endometrium together form the functional placenta for maternal-fetal nutrient and waste exchange. Intermediate trophoblast is located in the villi, the implantation site, and the chorionic sac. All 3 types of trophoblast may result in GTD when they proliferate.[21,22]

Hydatidiform mole

Hydatidiform mole refers to an abnormal pregnancy characterized by varying degrees of trophoblastic proliferation (both cytotrophoblast and syncytiotrophoblast) and vesicular swelling of placental villi associated with an absent or an abnormal fetus/embryo. Two syndromes of hydatidiform mole have been described based on both morphologic and cytogenetic criteria.[23,24] Complete hydatidiform moles undergo early and uniform hydatid enlargement of villi in