TABLE 124e-4 THYROID FUNCTION TEST DURING PREGNANCY (MEAN LEVELS)

	Nonpregnant	First Trimester	Second Trimester	Third Trimester
Thyroid-stimulating hormone (mIU/L)	1.38	0.91	1.03	1.32
Total thyroxine (μg/dL)	7.35	10.98	11.88	11.08

Source: Based on the National Health and Nutrition Examination Survey III (NHANES III) (OP Soldin et al: Ther Drug Monit 17:303, 2007).

GESTATIONAL TROPHOBLASTIC DISEASE

(See Chap. 117) Gestational trophoblastic disease encompasses hydatidiform mole, choriocarcinoma, placental site trophoblastic tumor, and assorted miscellaneous and unclassifiable trophoblastic tumors. Moles are the most common, occurring in 1 in 1500 pregnancies in the United States. The incidence is higher in Asia. In general, if the serum level of β-human chorionic gonadotropin (β-hCG) returns to normal after surgical removal (evacuation) of the mole, the illness is considered gestational trophoblastic disease. By contrast, if the β-hCG level remains elevated after mole evacuation, the patient is considered to have gestational trophoblastic neoplasia. Choriocarcinoma occurs in 1 in 25,000 pregnancies. Maternal age >45 years and prior history of molar pregnancy are risk factors. A previous molar pregnancy makes choriocarcinoma about 1000 times more likely to occur (incidence 1–2%).

Hydatidiform moles are characterized by clusters of villi with hydropic changes, trophoblastic hyperplasia, and absence of fetal blood vessels. Invasive moles are distinguished by invasion of the myometrium. Placental site trophoblastic tumors are composed mainly of cytotrophoblast cells arising at the site of placental implantation. Choriocarcinomas contain anaplastic trophoblastic tissue with both cytotrophoblast and syncytiotrophoblast features and no identifiable villi.

Moles can be partial, typically associated with fetal tissue, or complete, typically not associated with any fetal or embryonic tissue. Partial moles have a distinct molecular origin and usually are smaller tumors with less hydropic villi and considerably less potential for persistent or malignant disease. Partial moles result from fertilization of an egg by two sperm, resulting in diandric triploidy. Complete moles usually have a 46,XX genotype; 95% develop by a single male sperm fertilizing an empty egg and undergoing gene duplication (diandric diploidy); 5% develop from dispermic fertilization of an empty egg (diandric dispermy).

Women with molar gestations often present with first-trimester bleeding, disproportionately high serum β-hCG levels for menstrual age, unusually large uterine size for menstrual age, hyperemesis gravidarum, theca lutein cysts in the ovaries (due to β-hCG stimulation), and hyperthyroidism (due to cross-reactivity of β-hCG and TSH) and may develop preeclampsia before 20 weeks of menstrual age. Pelvic ultrasound imaging of complete moles shows absence of fetal parts, an enlarged echo-bright, hydropic placenta in an enlarged uterus, and enlarged multicystic ovaries. If the diagnosis is uncertain at the initial examination and the pregnancy is desired, then a serum β-hCG level should be obtained and the examination repeated in a week. If no embryo is seen within 7–10 days and the serum β-hCG is elevated, then this is a nonviable pregnancy that should be evacuated. Diagnosis of partial molar pregnancies can be more difficult because an embryo or fetus with visible heart motion is usually present, and the hydropic changes in the placenta, uterine enlargement, and elevations of β-hCG are not usually as dramatic. Although an embryo or fetus is present, it rarely grows normally with normal anatomy, and repeated ultrasound examinations usually make the diagnosis. Amniocentesis will also make the diagnosis by demonstration of triploidy.

Patients with molar pregnancies require prompt uterine evacuation with suction curettage, which may be complicated by very heavy bleeding. Following evacuation of complete moles, approximately 20% will result in persistent, invasive, or metastatic disease. Partial moles are considerably less likely (<5%) to result in persistent disease. Patients should be monitored with serial determinations of serum β-hCG until the values fall below the lower limit of the assay and remain low for at least 6 months. Patients should be advised not to become pregnant for at least 12 months.

A variety of criteria have been used to make the diagnosis of postmolar gestational trophoblastic disease, but current consensus guidelines as adopted by the International Federation of Gynecology and Obstetrics are listed below:

1. A β-hCG level plateau of four values plus or minus 10% recorded over a 3-week duration (days 1, 7, 14, and 21)
2. A β-hCG level increase of more than 10% in three values recorded over a 2-week duration (days 1, 7, and 14)
3. Persistence of detectable β-hCG for more than 6 months after molar evacuation

About half of choriocarcinomas develop after a molar pregnancy, and half develop after ectopic pregnancy or, rarely, after a normal full-term pregnancy. Disease is classified as stage I if it is confined to the uterus, stage II if disease is limited to genital structures (~30% have vaginal involvement), stage III if disease has spread to the lungs but no other organs, and stage IV if disease has spread to liver, brain, or other organs.

Patients without widely metastatic disease are generally managed with single-agent methotrexate (either 30 mg/m^2 IM weekly until β-hCG normalizes or 1 mg/kg IM every other day for four doses followed by leucovorin 0.1 mg/kg IV 24 h after methotrexate), which cures >90% of patients. Patients with very high β-hCG levels, presenting >4 months after a pregnancy, with brain or liver metastases, or failing to be cured by single-agent methotrexate are treated with combination chemotherapy. Etoposide, methotrexate, and dactinomycin alternating with cyclophosphamide and vincristine (EMA-CO) is the most commonly used regimen, producing long-term survival in >80% of patients. Brain metastases can usually be controlled with brain radiation therapy. The vast majority of choriocarcinomas can be cured with chemotherapy alone. Hysterectomy is reserved for women who have completed their child-bearing, women with chemotherapy-resistant disease in the uterus, and women with rare placental site trophoblastic tumors confined to the uterus because these tumors are less reliably sensitive to chemotherapy. Women cured of trophoblastic disease who have not undergone hysterectomy do not appear to have increased risk of fetal abnormalities or maternal complications with subsequent pregnancies.