chemotherapy (particularly anthracycline-based combinations) is both safe and effective (Chap. 108). Lumpectomy followed by adjuvant chemotherapy is frequently used; fluorouracil and cyclophosphamide with either doxorubicin or epirubicin have been given without major risk to the fetus. Taxanes and gemcitabine are also beginning to be used; however, safety data are sparse. Methotrexate and other folate antagonists are to be avoided because of effects on the fetal nervous system. Myelotoxic therapy is generally not administered after 33 or 34 weeks of gestation to allow 3 weeks off therapy before delivery for recovery of blood counts. Endocrine therapy and trastuzumab are unsafe during pregnancy. Experience with lapatinib is anecdotal, but no fetal malformations have been reported. Antiemetics and colony-stimulating factors are also considered safe. Women being treated into the postpartum period should not breast-feed their babies because of excretion of cancer chemotherapy agents, particularly alkylating agents, in milk.

Subsequent pregnancies following gestational breast cancer do not appear to influence relapse rate or overall survival. A meta-analysis found that pregnancy in breast cancer survivors was associated with a reduced the risk of dying from breast cancer by as much as 42%. This finding, however, is heavily confounded by the "healthy survivor effect"; women with more extensive or advanced disease are more likely to avoid pregnancy.

MELANOMA DURING PREGNANCY

Speculation about melanoma occurring during pregnancy based largely on anecdotal evidence and small case series concluded that it occurred with increased frequency, was more aggressive in its natural history, and was caused in part by the hormonal changes that also produced hyperpigmentation (so-called *melasma*) during pregnancy. However, more complete epidemiologic data suggest that melanoma is no more frequent in pregnant women than in nonpregnant women in the same age group, that melanoma is not more aggressive during pregnancy, and that hormones seem to have little or nothing to do with the etiology. Pregnant and nonpregnant women do not differ in the location of primary tumor, depth of primary tumor, tumor ulceration, or vascular invasion.

Suspicious lesions should be looked for and managed definitively with excisional biopsy during pregnancy. Wide excision with sampling of regional lymph nodes is warranted. If lymph nodes are involved, the course of action is less clear. Several agents have demonstrated some activity in melanoma, but none have been used during pregnancy. Adjuvant interferon α is toxic, and its safety in pregnancy has not been documented. Agents active in advanced disease include dacarbazine, IL-2, ipilimumab (antibody to CTLA-4), and in those with *BRAF* mutation V600E, a BRAF kinase inhibitor. In the setting of metastatic disease, abortion may be indicated so that systemic therapy can be initiated as soon as possible (Chap. 105).

Melanoma is one of the very few cancers that are well documented to metastasize transplacentally to the fetus, where it seems to have a predilection for the head and neck. It has a very grave prognosis in the offspring. Fortunately, transplacental spread is rare.

Pregnancy subsequent to the diagnosis and treatment of melanoma is not associated with an increased risk of melanoma recurrence.

HODGKIN'S DISEASE AND NON-HODGKIN'S LYMPHOMA DURING PREGNANCY

(See Chap. 134) Hodgkin's disease occurs mainly in the age range that coincides with child-bearing. However, Hodgkin's disease is not more common in pregnant than nonpregnant women. Hodgkin's disease is diagnosed in approximately 1 in 6000 pregnancies. It generally presents as a nontender lymph node swelling, most often in the left supraclavicular region. It may be accompanied by B symptoms (fever, night sweats, unexplained weight loss). Excisional biopsy is the preferred diagnostic procedure because fine-needle aspiration cannot reveal the architectural framework that is an essential component of Hodgkin's disease diagnosis. The stage at presentation appears to be unaffected by pregnancy. Women diagnosed in the second and third trimester can be treated safely with combination chemotherapy, usually doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). In general, the patient in the first trimester is asymptomatic, and a woman with a desired pregnancy can be followed until the second or third trimester when definitive multiagent chemotherapy can be safely given. Radiation therapy is not given during pregnancy and is not necessary for optimal management of the pregnant patient. If symptoms requiring treatment appear during the first trimester, anecdotal evidence suggests that Hodgkin's disease symptoms can be controlled with weekly low-dose vinblastine. Such an approach has been safely used to avoid termination of pregnancy. Pregnancy does not have an adverse effect on treatment outcome.

Non-Hodgkin's lymphomas are more unusual in pregnancy (approximately 0.8 per 100,000 pregnancies), but are usually tumors with an aggressive natural history, such as diffuse large B cell lymphoma, Burkitt's lymphoma, or peripheral T cell lymphoma. Diagnosis relies on an excisional biopsy of a tumor mass, not fine-needle aspiration. Staging evaluation is generally limited to ultrasound or MRI examinations. Diagnosis in the first trimester should prompt termination of the pregnancy followed by definitive treatment with combination chemotherapy, because aggressive lymphomas are not likely to be held at bay with single-agent chemotherapy. Women diagnosed in the second or third trimesters can be treated with standard chemotherapy, such as with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). The experience with rituximab in this setting is anecdotal. However, infants born of mothers who have received rituximab may have transient delay in B cell development that typically normalizes by 6 months. The treatment outcome is similar in lymphomas diagnosed in pregnant and nonpregnant women of the same clinical stage.

THYROID CANCER DURING PREGNANCY

(See Chap. 405) Thyroid cancer, along with melanomas, brain tumors, and lymphomas, are cancers that are increasing in incidence in the general population. Thyroid cancers are rising faster among women in North America than the other increasing tumor types. The Endocrine Society has developed practice guidelines to inform the management of patients with thyroid disease during pregnancy (*http://www.endocrine.org/~/media/endosociety/Files/Publications/Clinical%20Practice%20Guidelines/Thyroid-Exec-Summ.pdf*). Thyroid nodules 1 cm or larger are approached by fine-needle aspiration. If a malignancy is diagnosed, surgery is generally recommended in the second and third trimesters. However, surgical complications appear to be twice as common when the patient is pregnant. Because the growth of thyroid tumors is often indolent, surgery can safely be postponed until after the first trimester. Patients with follicular cancer or early papillary cancer can be observed until the postpartum period. The fetal thyroid begins trapping iodine by 12 weeks of gestation and does so with very high avidity. Even small doses of radioactive iodine given during pregnancy can completely ablate the fetal thyroid with serious consequences for the fetus and should be avoided throughout pregnancy. Radioactive iodine can be safely administered after delivery. Patients with a history of thyroid cancer who become pregnant should be maintained on thyroid hormone replacement during pregnancy because of the adverse impact of maternal hypothyroidism on the fetus. Women who are breast-feeding should not be treated with radioactive iodine, and women treated with radioactive iodine should not become pregnant for 6–12 months after treatment.

The assessment of thyroid function during pregnancy is challenging because of the physiologic changes that occur during pregnancy. Women who have previously been treated for thyroid cancer are at risk of hypothyroidism. The demand for thyroid hormone increases during pregnancy, and doses to maintain normal function may increase by 30–50%. Total T_4 levels are higher during pregnancy, but target therapeutic levels also increase (Table 124e-4). It is recommended that the upper and lower limits of the laboratory range be multiplied by 1.5 in the second and third trimester to establish a pregnancy-specific normal range. The target thyroid-stimulating hormone (TSH) level is <2.5 mIU/L.