CHAPTER e6 Neoplasia During Pregnancy

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Cancer develops during ~1 in every 1000 pregnancies. Of all the cancers that occur in women, less than 1% occur in pregnant women. The four cancers most commonly developing during pregnancy are cervical cancer, breast cancer, melanoma, and lymphomas (particularly Hodgkin's lymphoma); however, virtually every form of cancer has been reported in pregnant women (Table e6-1). In addition to cancers developing in other organs of the mother, gestational trophoblastic tumors can arise from the placenta. The problem of cancer in a pregnant woman is complex. One must take into account the possible influence of the pregnancy on the natural history of the cancer, the effects of the diagnostic and staging procedures, and the treatments of the cancer on both the mother and the developing fetus. These issues may lead to dilemmas: what is best for the mother may be harmful to the fetus, and what is best for the fetus may be harmful to the mother.

Another complicating issue in women who develop cancer during pregnancy is that many of the early symptoms of cancer are ignored in pregnant women. The many changes in a woman's body during pregnancy dull one's senses to changes that may be related to an underlying disease rather than the pregnancy. Thus, many cancers that occur in pregnancy present in advanced stages.

As a general rule, one should assume that no diagnostic or therapeutic intervention is safe in the first trimester of pregnancy other than surgery. If the mother develops life-threatening complications during the first trimester that require radiation therapy or systemic chemotherapy, and these interventions cannot be safely delayed, a recommendation should be made for an abortion. Indeed, radiation, even in the form of diagnostic radiography, should be avoided throughout pregnancy. No exposure to radiation is safe, and efforts to shield the fetus with barriers placed on the abdomen cannot block internal scatter radiation. It is safest to omit radiation exposure of any kind. Fortunately, its use is seldom an essential component of treatment before delivery.

Chemotherapy exposure is also to be avoided, if at all possible. It should never be given in the first trimester; a variety of single agents and combinations have been given in the second and third trimesters, without a high frequency of catastrophic effects to the pregnancy or the fetus, but data on safety are sparse. Maternal factors that may influence the pharmacology of chemotherapeutic agents include the 50% increase in plasma volume, altered absorption and protein binding, increased glomerular filtration rate, increased hepatic mixed function oxidase activity, and third space created by amniotic fluid. The fetus is protected from some agents by placental expression of drug efflux pumps, but decreased fetal hepatic mixed function oxidase and glucuronidation activity may prolong the half-life of agents that do cross the placenta. A database on the risks associated with individual chemotherapy agents is available on the Internet (*www.motherisk.org*).

The optimal management strategies have not been developed based on prospective clinical trials. Instead, a guiding principle has been to delay therapeutic interventions until as late as possible during the pregnancy. Delivery is recommended at 32 weeks. By and large, this approach minimizes exposure of the child to noxious cancer treatments, spares the mother complications of pregnancy, and is generally accomplished without an adverse impact on treatment outcome. Pregnancy appears to have little or no impact on the natural history of malignancies, despite the hormonal influences. Spread of the mother's cancer to the fetus (so-called vertical transmission) is exceedingly rare.

TABLE e6-1 Incidence of Malignant Tumors During Gestation

Tumor Type	Incidence per 10,000 Pregnancies[a]	% of Cases[b]
Breast cancer	1–3	25%
Cervical cancer	1.2–4.5	25%
Thyroid cancer	1.2	15%
Hodgkin's disease	1.6	10%
Melanoma	1–2.6	8%
Ovarian cancer	0.8	2%
All sites	10	100%

[a]These are estimates based on extrapolations from a review of more than 3 million pregnancies (Smith LH et al: Am J Obstet Gynecol 184: 1504, 2001).
[b]Based on accumulating case reports from the literature; the precision of these data is not high.

CERVICAL CANCER DURING PREGNANCY

The incidence of cervical cancer in pregnant women is roughly comparable to that of age-matched controls who are not pregnant. Invasive cervical cancer develops at a rate of about 0.45 in 1000 live births and carcinoma in situ is seen in 1 in 750 pregnancies. About 1% of women diagnosed with cervical cancer are pregnant at the time of diagnosis. Early signs of cervical cancer include vaginal spotting or discharge, pain, and postcoital bleeding that are also common features of pregnancy. Early visual changes in the cervix related to invasive cancer can be mistaken for cervical decidualization or ectropion (columnar epithelium on the cervix) due to pregnancy. Women diagnosed with cervical cancer during pregnancy report having had symptoms for 4.5 months on average.

Human papillomavirus (HPV) types 16 and 18 account for about 70% of cervical cancer. The rate of carriage of these serotypes can be reduced with the use of vaccination before exposure. Screening is recommended at the first prenatal visit and 6 weeks postpartum. The rate of cytologic abnormalities on Pap smear in pregnant women is about 5–8% and is not much different than the rate in nonpregnant women of the same age. Consensus guidelines dictate that specific tests are indicated based on the level of atypia seen on Pap smear. Atypical squamous cells of unknown significance (ASCUS) generally trigger HPV testing with colposcopy reserved for the subset of women with a high-risk HPV-type infection. By contrast, the presence of dysplasia is considered an indication for colposcopy regardless of HPV type. Women with either low- or high-grade squamous intraepithelial lesions (LSIL or HSIL) and HIV-infected women with ASCUS are recommended for colposcopy.

At colposcopy, any areas suspicious for invasive disease are biopsied. However, endocervical curettage is contraindicated in pregnant patients. The only indication for therapy of cervical neoplasia in pregnant women is the documentation of invasive cancer.

Accordingly, some physicians defer colposcopy in pregnant women until six weeks post-partum unless they are at high risk for invasive disease. Cervical intraepithelial neoplasia has a low risk of progression to invasive cancer during pregnancy (~0.4%) and many such lesions (36–70%) regress spontaneously postpartum. If invasive disease is suspected at colposcopy and the pregnancy is between 16 and 20 weeks, a cone biopsy may be performed to make the diagnosis; however, the procedure is associated with bleeding because of the increased vasculature in the gravid cervix and increases the risk of premature rupture of membranes and preterm labor two- to three-fold. Cone biopsy should not be done within 4 weeks of delivery.

Management of invasive disease is guided by the stage of disease, the gestational age of the fetus, and the desire of the mother to have the baby. If the disease is in early stage and the pregnancy is desired, it is safe to delay treatment regardless of gestational age until fetal maturity allows for safe delivery. If the disease is in advanced stage and the pregnancy is desired, the safety of delaying therapy is unproven. Abortion followed by definitive therapy is recommended for women with advanced cancer in the first or second trimester (see Chap. 97). In women in the third trimester with advanced disease, the baby should be delivered at the earliest possible time and followed immediately by stage-appropriate therapy. Most women with invasive cancer have early-stage disease. If the disease is microinvasive, vaginal delivery can take place and be followed by definitive treatment, usually conization. If a lesion is visible on the cervix, delivery is best done by caesarian section and followed by radical hysterectomy.

BREAST CANCER DURING PREGNANCY

Breast cancer occurs once in 3000 to 10,000 live births. About 5% of all breast cancers occur in women 40 years or younger. Among all premenopausal women with breast cancer, 25–30% were pregnant at the time of diagnosis. While early pregnancy is a protective factor against breast cancer in women as a whole, the breast cancers diagnosed during pregnancy are often diagnosed at a later stage of disease and so have a poorer outcome. The late diagnosis has at least two contributions. One is the more aggressive behavior of the cancer possibly related to the hormonal milieu (estrogen increases 100-fold; progesterone increases 1000-fold) of the pregnancy. However, about 70% of the breast cancers found in pregnancy are estrogen receptor–negative. Another factor is that early physical signs of the disease are often attributed to the changes that occur in the breast normally as a part of pregnancy. However, a breast mass in a pregnant woman is never normal. Younger women with breast cancer have a higher likelihood of having mutations in *BRCA1* or *BRCA2*. Pregnancy retains its protective effects in carriers of *BRCA1* mutations; such women with four or more children had a 38% reduction in breast cancer risk compared to nulliparous carriers. However, pregnancy seems to increase the risk of breast cancer among carriers of *BRCA2* mutations, particularly in the first 2 years after pregnancy. About 28–58% of the tumors express HER-2.

Primary tumors in pregnant women are 3.5 cm on average, compared to <2 cm in nonpregnant women. A dominant mass and a nipple discharge are the most common presenting signs and they should prompt ultrasonography and breast MRI exam (if available) followed by lumpectomy if the mass is solid and aspiration if the mass is cystic. Mammography is less reliable in pregnancy due to the increased breast density. Needle aspirates of breast masses in pregnant women are often nondiagnostic or falsely positive. Even in pregnancy, most breast masses are benign (~80% are adenoma, lobular hyperplasia, milk retention cyst, fibrocystic disease, fibroadenoma, and other rarer entities).

TABLE e6-2 Differences in Breast Cancers in Pregnant and Nonpregnant Women

	Pregnant	Nonpregnant
Tumor size	3.5 cm	2 cm
Estrogen receptor +	30%[a]	67%
HER-2 +	up to 58%	10–25%
Stage II, III	65–90%	45–66%
Lymph node +	56–89%	38–54%

[a]Lower measured levels could be in part artifactual due to the increased levels of estrogen in the milieu

Differences between pregnancy-associated breast cancer (often defined as cancer detected during the pregnancy and up to 1 year after delivery) are shown in Table e6-2. About 20% of breast cancers are detected in the first trimester, 45% in the second trimester, and 35% in the third trimester. Some argue that stage for stage, the outcome is the same for breast cancer diagnosed in pregnant and nonpregnant women.

Staging the axillary lymph nodes is currently somewhat controversial. Sentinel lymph node sampling is not straightforward in pregnant women. Blue dye has been carcinogenic in rats, and shielding the fetus from administered radionuclides is of unproven efficacy. For this reason, many surgeons favor axillary node dissection to stage the nodes. Largely due to the typical delay in diagnosis, axillary nodes are more often positive in pregnant than in nonpregnant women.

As with other types of cancer in pregnant women, diagnosis in the first trimester often triggers a recommendation for an abortion to allow definitive therapeutic intervention at the earliest possible time. While definitive local surgery is applicable in the first trimester, radiation therapy and chemotherapy are considerably more risky. Delay in administration of systemic therapy can increase the risk of axillary spread. In the second and third trimesters, chemotherapy (particularly anthracycline-based combinations) are both safe and effective (see Chap. 90). 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 the 33rd or 34th week 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 nurse 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. Indeed, a meta-analysis has suggested that pregnancy in breast cancer survivors may reduce the risk of dying from breast cancer by as much as 42%.

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, 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-alfa is toxic and its safety in pregnancy has not been documented. Agents active in advanced disease include dacarbazine, interleukin-2, ipilumimab (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 (see Chap. 87).

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

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

(See Chap. 110) Hodgkin's disease occurs mainly in the age range of people who are of child-bearing age. However, Hodgkin's disease is not more common in pregnant than nonpregnant women. Hodgkin's disease is diagnosed in approximately 1 in 6,000 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 as 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. 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 like 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, as 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. 341) 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.endo-society.org/guidelines/final/upload/Clinical-Guideline-Executive-Summary-Management-of-Thyroid-Dysfunction-during-Pregnancy-Postpartum.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 is not recommended in the first trimester. Patients with follicular cancer or early papillary cancer can be observed until the postpartum period. 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 T4 levels are higher during pregnancy but target therapeutic levels also increase (Table e6-3). 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 TSH level is lower than 2.5 mIU/L.

GESTATIONAL TROPHOBLASTIC DISEASE

(See Chap. 97) 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.

TABLE e6-3 Thyroid Function Test During Pregnancy (Mean Levels)

	Nonpregnant	First Trimester	Second Trimester	Third Trimester
TSH (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).

In general, if the serum level of beta-human chorionic gonadotropin (HCG) returns to normal after surgical removal (evacuation) of the mole, the illness is considered gestational trophoblastic disease. By contrast, if the 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 origin. Choriocarcinomas contain anaplastic trophoblastic tissue with both cytotrophoblast and syncytiotrophoblast features and no identifiable villi.

Moles can be partial or complete. Partial moles have a distinct molecular origin and usually are smaller tumors with less hydropic villi. 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 gestational trophoblastic disease often present with first-trimester bleeding and unusually large uterine size. Ultrasound shows absence of fetal parts or heart sounds. Patients are monitored by chest radiograph, pelvic examination, and weekly measurement of HCG levels.

Patients with molar pregnancies require suction curettage with postoperative HCG monitoring. In 80% of cases, HCG declines within 8–10 days. Patients should not become pregnant for at least 12 months. Women with invasive moles generally undergo hysterectomy followed by chemotherapy. 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.

Specific criteria have been developed to aid the decision about when disease becomes neoplasia:

1. Four consecutive increased HCG levels over the 3 weeks after evacuation surgery.
2. A rise in HCG of 10% or more on three consecutive values over 2 or more weeks.
3. The presence of choriocarcinoma.
4. Persistent HCG elevations 6 months after evacuation.

Patients without widely metastatic disease are generally managed with single-agent methotrexate (either 30 mg/m^2 IM weekly until HCG normalizes or 1 mg/kg IM every other day for 4 doses followed by leukovorin 0.1 mg/kg IV 24 hours after methotrexate), which cures >90% of patients. Patients with very high 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. 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.

FURTHER READINGS

Azim HA Jr et al: Treatment of the pregnant mother with cancer: A systematic review on the use of cytotoxic, endocrine, targeted agents, and immunotherapy during pregnancy. Part I: Solid tumors. Cancer Treat Rev 36:101, 2010

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Leslie KK (ed): Cancer complicating pregnancy. Obstet Gynecol Clin N Am 32: 533, 2005

Pentheroudakis G et al: Cancer, fertility and pregnancy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 21:v266, 2010