124e Neoplasia During Pregnancy

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Cancer complicates ~1 in every 1000 pregnancies. Of all the cancers that occur in women, less than 1% complicate pregnancies. The four cancers that most commonly complicate pregnancies 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 124e-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 (1) the possible influence of the pregnancy on the natural history of the cancer, (2) effects on the mother and fetus of complications from the malignancy (e.g., anorexia, nausea, vomiting, malnutrition), (3) potential effects of diagnostic and staging procedures, and (4) potential effects of cancer treatments on both the mother and the developing fetus. Generally, the management that optimizes maternal physiology is also best for the fetus. However, the dilemma occasionally arises that what is best for the mother may be harmful to the fetus, and what is best for the fetus may compromise the ultimate prognosis for the mother. The best way to approach management of a pregnant woman with cancer is to ask, "What would we do for this woman in this clinical situation if she was not pregnant? Now, which, if any, of those plans need to be modified because she is pregnant?"

Pregnancy is associated with a number of physiologic changes that frequently result in symptoms that may make it difficult to recognize symptoms or physical findings suggestive of a neoplasm. Increased sensitivity of central chemoreceptors to P_{CO_2} drives an increase in minute ventilation that many women perceive as dyspnea at rest or with minimal exertion. The combination of increased total body water, decreased colloid oncotic pressure, and some obstruction of venous return from the lower extremities causes demonstrable dependent edema in more than 50% of pregnant women. Decreased gastrointestinal motility due to high serum progesterone levels and mechanical compression from an enlarging uterus cause early satiety, gastroesophageal reflux, nausea, vomiting, and constipation. Hemorrhoids develop and often bleed. Breasts enlarge and increase in density and "lumpiness." These changes may result in delayed recognition and more advanced disease at diagnosis.

Physiologic changes in the maternal immune system necessary to facilitate retention of the fetal semi-allograft raise concerns that the relationship of a cancer with its host may be altered to the detriment of the maternal host. One half of all the genes necessary to create a new individual by sexual reproduction come from each parent. This provides the opportunity for many antigenic differences between the conceptus and the mother. Mammalian placentation has been a very successful method of reproduction, but it has necessitated some combination of both fetal and maternal evolutionary immune adaptations. These mechanisms are incompletely understood and remain an area of active investigation. It does seem likely, however, that this has been accomplished without a general, nonspecific blunting of the maternal immune response, which would be maladaptive to the mother. The multiple mechanisms likely include some "masking" of fetal antigens from recognition by the maternal immune system, blunting the maternal inflammatory response locally at the placental–maternal interface and induction of fetal-specific maternal immune tolerance to avoid rejection. Attention has turned to a subset of CD4+ induced, peripherally produced regulatory T cells that express the X chromosome encoded transcription factor Foxp3 (so-called *Tregs*). When these Foxp3 cells develop centrally in the thymus, they are termed "Tregs." When Foxp3-expressing cells develop peripherally, they are called "Pregs." These regulatory cells suppress the immune response against "self" and foreign antigens. They seem to be capable of suppressing the maternal response to paternal antigens expressed by the fetus and creating memory cells that retain tolerance to the same paternal antigens in subsequent pregnancies. Unfortunately, in a mouse model, the interleukin (IL) 10 produced by these cells enhanced susceptibility to infection by *Listeria* and *Salmonella*, while ironically not proving essential for retaining the fetal graft. Undoubtedly much remains to be learned about this critical immune balance.

TABLE 124e-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 (LH Smith 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.

RADIATION IN PREGNANCY

Exposure of developing fetuses to ionizing radiation may cause adverse fetal effects; awareness among physicians of this potential toxicity has resulted in a disproportionate aversion to diagnostic imaging in pregnancy. First, it must be stated that there are very useful imaging modalities (i.e., ultrasound and magnetic resonance imaging [MRI]) that do not use any ionizing radiation and are not associated with any demonstrable adverse fetal effects. There are three potential adverse fetal effects of ionizing radiation: teratogenesis (induction of anatomic birth defects), mutagenesis, and carcinogenesis. The fetus is most sensitive to teratogenesis during organogenesis in the first trimester. The dose of ionizing radiation necessary to induce birth defects in human fetuses is derived from studies of the survivors of the atomic bomb explosions and by extrapolation from controlled experiments in nonhuman mammals. From these data sources, it is clear that a minimum of 5 rem and more likely greater than 10 rem exposure is needed to induce birth defects in the first trimester. The fetal doses of radiation associated with some common diagnostic radiologic procedures are displayed in Table 124e-2. The data in Table 124e-2 show that no single procedure or selective combination of diagnostic procedures will exceed the very conservative 5 rem teratogenic threshold. Teratogenic effects later in pregnancy are largely limited to microcephaly and require exposures exceeding 25 rem. The reason for the disproportionate concern about radiation exposure and birth defects is that 2.5% of all fetuses are affected with birth defects without radiation exposure and, therefore, 2.5% of women undergoing any diagnostic imaging procedure will deliver malformed fetuses. Spontaneous mutations occur relatively infrequently, and high doses of radiation (>150 rem) are required to cause a demonstrable increase in that rate. The magnitude of the risk of carcinogenesis in offspring exposed as fetuses to diagnostic doses of radiation has been very difficult to

TABLE 124e-2 ESTIMATED FETAL EXPOSURE FROM SOME COMMON RADIOLOGIC PROCEDURES

Procedure	Fetal Exposure
Chest x-ray (2 views)	0.02–0.07 mrad
Abdominal film (single view)	100 mrad
Intravenous pyelography	≥1 rad[a]
Hip film (single view)	7–20 mrad
Barium enema or small bowel series	2–4 rad
CT scan of head or chest	<1 rad
CT scan of abdomen and lumbar spine	3.5 rad
CT pelvimetry	250 mrad

[a]Exposure depends on the number of films.

Abbreviation: CT, computed tomography.

Source: Data from FG Cunningham et al: General considerations and maternal evaluation. In *Williams Obstetrics*, 21st ed. New York: McGraw-Hill; 2001, pp. 1143–1158.