Chapter 10
Pregnancy in Cancer Patients and Survivors

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Introduction

Clinical medicine has improved the survival from cancers in childhood and young adulthood, leading invariably to the consideration of pregnancy in treated women. Prior therapy may have residual pathophysiologic effects that make pregnancy in cancer survivors complicated. In addition, pregnancy-related bodily changes may also make surveillance for recurrent malignancy challenging. Furthermore, pregnant women who receive a cancer diagnosis during pregnancy struggle with critical decisions that may impact their own survival and that of their unborn child. In many cases, there is conflict between the medical needs of mother and fetus. The aim of this chapter is to provide an overview of the management of pregnant women with a history of cancer and also discuss the management of women who are diagnosed with cancer during pregnancy.

Preconception Counseling

In order to provide optimal preconception counseling to cancer survivors, it is necessary to have detailed medical information regarding the patient's history. Specific information should include age at diagnosis, type of malignancy, stage, status of the cancer, prognosis, and the course of treatment. If radiation was used, the cumulative dose and field of irradiation should be known; if chemotherapy was administered, the specific chemotherapy regimens and cumulative doses should be determined.

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Understanding the specifics of cancer therapy will help determine the likelihood of end-organ dysfunction that could pose a risk to fetus or mother during pregnancy. It is also important to know whether the cancer is active or in remission, since this will dictate the type and frequency of surveillance. The risks and potential benefits of imaging for the surveillance of cancer must be weighed in each situation. For example, while a single serial radiologic study may expose a fetus to acceptable levels of radiation, serial computed tomography (CT) evaluations during pregnancy may pose significant fetal risk and can only be justified if there is a clear benefit to the mother. In the setting of active disease, concerns focus on the patient's prognosis. In patients who may be too ill to survive the pregnancy, pregnancy termination or early delivery may be justified for maternal health even though preterm delivery is associated with increased perinatal mortality or morbidity.

Pregnancy Physiology

An awareness of the expected changes in a woman's physiology during pregnancy allows clinicians to better understand the impact of cancer therapies on maternal and fetal health. Not only can this knowledge help clinicians predict how previously treated cancer survivors will tolerate the stress of pregnancy, it can also help clinicians understand the impact of cancer therapies administered during pregnancy, particularly in relation to clearance and metabolism of medications.

Key Cardiovascular Changes

Pregnancy increases the workload of the heart [1]. Cardiac output (CO) increases 30–50%, from 4.9 to 7 L/min. The increase in CO may start as early as 5 weeks gestation, peaking approximately at 25–30 weeks. The heart must handle an increased blood volume (see hematologic changes below) and the maternal heart rate increases early in the first trimester; in the third trimester, the heart rate may be 15–20 beats above the nonpregnant rate. The effect of progesterone on smooth muscle relaxation aids in increasing the capacitance of the peripheral blood vessels, which helps accommodate increasing blood volume but also results in a drop in systemic arterial pressure, often with a nadir in the second trimester around 24 weeks. A natural rise in blood pressure to prepregnancy or first-trimester ranges will occur as the patient enters the third trimester. The large gravid uterus can compress the aorta and inferior vena cava with a preferential caval effect. This leads to a reduction of blood return centrally, with a drop in CO by up to 25%, often manifested by a drop in blood pressure in the mother with accompanying nausea and discomfort when lying supine or fetal decelerations on monitoring related to decreased uterine perfusion.

Labor and delivery can also impact cardiac function. With each contraction, 300–500 ml of blood from the uterine circulation is returned transiently to the

maternal cardiac volume. After delivery and once the uterus is contracted, that volume is retained centrally, leading to an extra increase in CO by 10–15%. If a patient receives epidural anesthesia, the impact on the sympathetic nervous system will lead to vasodilation peripherally; the blood volume pooling into the extremities can lead to a decrease in CO. Special consideration of multiple gestations should also be made, as there is a 20% increase in CO over singleton pregnancies [2].

Key Pulmonary Changes

The maternal system adapts to the increasing requirements for oxygen consumption and CO_2 removal by fetus and the patient herself [1]. The volume of an average breath, i.e., the tidal volume, increases by close to 40%, at the cost of diminishing the expiratory reserve volume (ERV), with a 20% reduction in functional reserve capacity. This is accomplished in part by physical changes in the female chest, with an increasing chest diameter and diaphragmatic changes allowing for a 4-cm rise with full excursion despite the growing uterus. Respiratory muscle function and spirometry parameters are not changed from the nonpregnant state. There is minimal to no change in the respiratory rate with pregnancy. Minute ventilation increases by over 40%, primarily due to the increased tidal volume, which results in an increase in PaO_2 (104–108 mmHg) and helps drive the O_2 gradient toward the fetus, and a decrease in $PaCO_2$ (27–32 mmHg), which drives the CO_2 gradient away from the fetus.

Other Important Changes

Plasma volume increases by 40–50%, and red blood cell volume increases by 18–30%, due in part to an erythropoietin effect [1]. The disproportional increase of plasma to red blood cell ratio results in a dilutional physiologic anemia that starts as early as 6 weeks gestation. The hematocrit often nadirs at about 25–30 weeks, with peak total blood volumes achieved at 30–32 weeks gestation. This anemia may be protective of maternal hemorrhage and aids in maternal-fetal exchange of nutrients, waste, and heat. Body water increases from 6.5 to 8.5 L.

Estrogen influences protein production in the liver, and a number of clotting factors are upregulated in pregnancy, such as factors I, VII, VIII, IX, and X and fibrinogen. Protein S decreases in pregnancy, as do factors XI and XIII. Along with venous stasis and vessel wall injury at the uterine bed at delivery, the combination of these factors produces a hypercoagulable state during pregnancy and the postpartum period. Bleeding and clotting times do not change, however.

In a normal pregnancy, renal function is affected with a 75% increase in renal plasma flow early in gestation (840 ml/min by 16 weeks) and a 50% increase in glomerular filtration rate (GFR) by the end of the first trimester, which result in a drop in creatinine (0.5–0.6 mg/dl) compared with the nonpregnant state. Enhanced tubular reabsorption of sodium occurs secondary to aldosterone, estrogen, and

deoxycorticosterone. Progesterone also impacts the ureters and renal pelves by relaxing smooth muscle, resulting in increased urine retention in these organs.

The uterus also undergoes large and dynamic changes to accommodate the growing fetus, placenta, and amniotic fluid. It can grow close to 20-fold larger than its prepregnancy size by the end of gestation, with a volume that increases 1,000-fold. Uterine blood flow increases by tenfold from the first trimester to the end of pregnancy. By the end of pregnancy, the uterus can receive up to 17% of the CO.

Pregnancy After Cancer Therapy

When assessing a woman with a history of cancer—whether prior to or during pregnancy—it is important to make the patient aware of pregnancy outcomes data in women with similar medical problems. Patients should also be counseled about the risks associated with their specific treatments, since late effects of chemotherapy and radiation may impact a woman's ability to adapt to the physiologic changes in pregnancy. Ideally, women with a history of cancer should seek preconception counseling to determine if pregnancy is safe. If already pregnant, patients should be counseled about the potential fetal and maternal risks of previous cancer treatments and about whether prenatal care should be modified to minimize these risks.

Long-Term Effects of Cancer Therapy that May Alter Normal Maternal Pregnancy Adaptations

Those with the greatest risks of late effects from cancer therapy are women who may have developed long-term cardiovascular or pulmonary damage due to previous treatments. We will review some of the significant chemotherapy agents with known long-term effects, as well as observed radiation effects that may impair the ability to have a normal pregnancy (Table 10.1).

If a patient has abnormal cardiac function, the increased blood volume in pregnancy (maximal volumes achieved at 30–32 weeks gestation) may precipitate heart failure and require either pregnancy termination or premature delivery. Therefore, maternal echocardiograms to determine cardiac functional parameters, such as left ventricular ejection fraction (LVEF), are recommended prior to pregnancy or early in pregnancy and again at 30–32 weeks gestation or earlier if symptoms occur. If there is concern for rhythm abnormalities, electrocardiograms (ECGs) or Holter monitoring may also be recommended.

Poor oxygenation during pregnancy is associated with fetal growth restriction. Pulmonary fibrosis in particular may lead to respiratory distress during pregnancy due to the expected loss of ERV and the enlarging gravid uterus, which may ultimately

Table 10.1 Summary of major organ system changes during pregnancy and long-term cancer therapy effects

Organ system	Pregnancy changes	Long-term treatment effect	Clinical presentation[a]
Cardiovascular	Increased cardiac output	Anthracycline-related cardiomyopathy Radiation-induced restrictive pericardial disease or cardiomyopathy Radiation-induced conduction defects	Heart failure (especially at 32 weeks with maximal blood volume, with labor, and after delivery) Fetal growth restriction Arrhythmias
Pulmonary	Increased tidal volume Decreased expiratory reserve	Bleomycin-associated pulmonary fibrosis Radiation pneumonitis	Respiratory failure Poor oxygenation Fetal growth restriction
Hematologic	Increased plasma volume Hypercoagulability Decreased oncotic pressure	Marrow suppression if recent treatment completion Secondary leukemias due to alkylating agents	Anemia, thrombocytopenia, neutropenia Deep venous thrombosis/pulmonary embolus Enhanced risk for pulmonary edema Cancer diagnosis and treatment Fetal growth restriction
Renal	Increased GFR	Cisplatin or ifosfamide renal damage	Increased risk of preeclampsia Worsening maternal renal function Fetal growth restriction
Uterine	Increased uterine volume	Prepubertal radiation damage with fibrosis and poor vascularization and small volumes	Increased rates of miscarriage Spontaneous preterm labor Increased preeclampsia risk Fetal growth restriction

GFR glomerular filtration rate

[a]Clinically significant, requiring medical treatment, hospitalization, early pregnancy termination, or early delivery

precipitate preterm delivery due to poor fetal growth or maternal symptomatology. Therefore, it is recommended that pulmonary function tests and oxygen diffusion studies be obtained prior to pregnancy or early in gestation.

Impaired renal function in pregnancy is associated with an increased risk of pregnancy complications such as preeclampsia, growth restriction, and resultant (iatrogenic) preterm birth, as well as exacerbation of renal function. Baseline renal function studies (BUN/Cr), and electrolytes should be obtained for counseling purposes and for comparison later in pregnancy.

Cancer Therapies with Cardiovascular Impact

Anthracycline agents (doxorubicin, daunorubicin)—These commonly used chemotherapeutic agents increase the risk of cardiomyopathy, particularly left ventricular dysfunction. With a dose of 450 mg/m^2, the risk of cardiomyopathy is 5%, but if the dose is increased to greater than 600 mg/m^2, the risk increases to 36% [3, 4]. Cofactors such as a history of radiation exposure, hypertension, or coronary artery disease worsen this risk. Given that up to 57% of treated patients will have subclinical cardiotoxicity (abnormal systolic function) and that risk is incurred starting as early as 5 years out of treatment [5], the increased cardiac work required in pregnancy may unmask cancer treatment-related dysfunction. Diastolic dysfunction in particular is a recognized early sign of anthracycline toxicity [5]. Pregnancy may precipitate heart failure and significantly impact maternal and the fetal health. Medical treatments, hospitalization, and sometimes preterm delivery may be necessary in patients with cardiomyopathy during pregnancy. For these patients, the American Society of Clinical Oncology (ASCO) recommends echocardiograms, MUGA scans, or radionuclide imaging for assessment of left ventricular function prior to or echocardiograms during pregnancy. In the few studies of pregnant women with a history of anthracycline exposure, many tolerated pregnancy. However, fractional shortening of the left ventricle less than 30% prior to pregnancy has been found to be associated with worsening maternal status requiring ICU admission in some cases [4, 6]. Treatment of cardiomyopathy in pregnancy includes the use of beta-blockers, hydralazine, nitrate, with avoidance of ACE inhibitors and angiotensin receptor blockers due to teratogenicity and functional renal effects on the fetus.

Trastuzumab—This monoclonal antibody against the Her2/neu receptor for breast cancer treatment has also been associated with cardiomyopathy with left ventricular dysfunction similar to that of anthracycline toxicity. The overall incidence of trastuzumab-related cardiomyopathy ranges from 4% to 10%. The risk of NYHA III and IV class heart failure is higher with concomitant exposure to anthracyclines, an effect that is not as notable with taxanes (incidence of 1–2%) [5]. Trastuzumab exposure can also be associated with asymptomatic decreases in LVEF. Unlike anthracycline cardiomyopathy, however, trastuzumab-related toxicity tends to be reversible. Therefore, prepregnancy cardiac evaluation may be prudent in patients previously exposed to trastuzumab.

Radiation—In studies of survivors of Hodgkin lymphoma, a history of chest irradiation was associated with coronary artery disease and fatal myocardial infarction (MI), restrictive pericarditis, restrictive cardiomyopathy, valvular disease, and conduction abnormalities such as heart block [5, 7]. The latent period to develop cardiac effects from radiation may be up to 20 years posttreatment, with an estimated incidence of 10–30% by 5–10 years after treatment. Patients treated before 1985 were exposed to higher doses of mediastinal radiation. When compared with the general population, Hodgkin lymphoma survivors have a two to sevenfold increased risk of death due to coronary artery disease. Women with a history of Hodgkin lymphoma with exposure to both radiation and chemotherapy with doxorubicin have further increased cardiac

risk with cardiac dysfunction and risk of restrictive myocardial or pericardial disease. When taking a patient's history, it is important to determine NYHA class status in relation to time since last treatment. In addition, it is recommended by the American College of Radiology (ACR) that asymptomatic Hodgkin lymphoma survivors with mediastinal radiation undergo periodic exercise tolerance testing and echocardiograms [8]. The risk of cardiovascular disease appears to be lower in women with exposure to radiotherapy for breast cancer. Changes in radiation therapy for breast cancer over the past several decades have led to a reduction in cardiovascular deaths, from 13% in the mid- to late 1970s to 5.5% in the late 1980s [5].

Cancer Therapies with Pulmonary Impact

Bleomycin—Pulmonary effects of bleomycin are modified by total dose, patient age, renal dysfunction, tobacco use, mediastinal radiation, and administration of oxygen [9]. Pneumonitis can develop during treatment and may continue for 2 years after therapy. If pneumonitis is detected, discontinuing bleomycin or administration of steroids may help. Only a minority will develop pulmonary fibrosis, which in turn can be associated with cor pulmonale and respiratory failure [5].

Radiation—Radiation pneumonitis can occur in 5–15% of patients exposed to external beam chest radiation therapy (EBRT), typically used to treat lung cancer, particularly if the patient has had prior radiation exposure. In the setting of Hodgkin lymphoma, the risk of pneumonitis is 3% in patients receiving radiotherapy alone and 11% in those treated with both chemotherapy and radiotherapy [5]. In breast cancer patients exposed to breast radiotherapy, the risk of pneumonitis is less than 1%.

Therapies with Genitourinary Impact

Cisplatin and carboplatin—Platinum-based chemotherapeutic agents can also affect kidney function, specifically by decreasing GFR and causing tubular dysfunction. Factors that may influence the persistence of altered GFR, even 10 years after treatment, include older childhood age at treatment and higher dosage [10].

Ifosfamide—Studies in young children who received ifosfamide have described long-term nephrotoxicity and glomerular and tubular dysfunction ranging in incidence from 1.4% to 30%. Renal dysfunction may be manifested by clinical hypophosphatemia, renal tubular acidosis, and reduced GFR [11].

Radiation—Women exposed prepubertally to total body irradiation (TBI) for bone marrow transplantation demonstrate a reduced uterine volume and blood flow despite hormone replacement [12]. Studies of Wilms tumor survivors best illustrate the impact on uterine function (presumed uterine wall fibrosis and poor vascularization) with associated adverse pregnancy outcomes (see pregnancy outcomes in cancer survivors below).

Other Sequelae of Treatment

Noncoronary vascular disease—There have been reports of an increased incidence of stroke and carotid artery stenosis in survivors exposed to neck irradiation for Hodgkin lymphoma and other head and neck tumors [5, 7]. Clinicians should be aware that carotid artery stenosis may impair a pregnant woman's ability to Valsalva at delivery. Therefore, prepregnancy carotid Doppler assessment may be helpful, not only to determine the risk of stroke but also to plan the mode of delivery.

Avascular necrosis (*AVN*)**—**Exposure to glucocorticoids predisposes patients to avascular necrosis. One retrospective cohort study showed a sixfold increase in this condition in survivors compared with sibling controls [13]. AVN may limit the ability to bear weight during pregnancy and may increase the risk of cesarean delivery due to limitations in hip flexion required for vaginal delivery.

Obesity—Cranial radiation exposure is associated with increased weight gain later in life, increasing the risk of being overweight or obese by 11–40% [13, 14] and therefore can indirectly modify pregnancy outcomes of cancer survivors. In particular, obesity in pregnancy has been associated with a higher risk of diabetes, preeclampsia, and delivery by cesarean section.

Risk of secondary malignancies—Cancer survivors are at an increased risk of secondary malignancies, particularly in patients with a history of Hodgkin lymphoma. Solid tumors make up 70–80% of second malignancies after Hodgkin lymphoma, with breast, lung, and gastrointestinal tract cancers among the most common [7]. In a case control study comparing those with secondary breast cancer and Hodgkin lymphoma versus those with Hodgkin and no breast cancer, the relative risk of breast cancer with radiation alone (greater than 4 Gy) was 3.2-fold, increasing to 8-fold if the radiation dose was greater than 40 Gy [15]. Interestingly, the use of alkylating agents with radiotherapy decreased the risk to 1.4-fold. The risk also increases over time, with incidences of 10–20% at 20 years from radiation exposure [3]. Acute myeloid leukemia as a secondary malignancy can develop 5–10 years after exposure to alkylating agents and 2–3 years after use of topoisomerase II inhibitors such as etoposide [3]. Therefore, if a woman presents before conceiving for evaluation for pregnancy, she should have the appropriate surveillance for secondary cancers before becoming pregnant to avoid a new cancer diagnosis while pregnant. For example, it is recommended that women with a history of chest irradiation be evaluated with breast imaging prior to conception, beginning at age 25 [16].

Pregnancy Outcomes in Cancer Survivors

Much of the information about pregnancy after cancer has been derived from the Childhood Cancer Survivor Study (CCSS), which included women treated for Hodgkin lymphoma, leukemia, Wilms tumor, sarcomas, central nervous system tumors, and neuroblastomas. Most studies do not support an increase in major

malformations in the offspring of childhood cancer survivors. However, studies are limited by potential recall bias and misclassification bias of outcomes [17]. Questionnaire results from the CCSS showed that exposure to chemotherapy was not associated with an increase in small-for-gestational-age (SGA) infants or preterm birth. However, exposure to radiation therapy was associated with a dose-dependent increase in preterm birth, ranging from 26.1% to 50% [18]. Unfortunately, this study did not report the gestational age at delivery or whether the preterm birth was spontaneous or iatrogenic (i.e., with indicated delivery due to growth restriction, preeclampsia, or abruption). Moreover, the incidence of low-birth-weight (LBW) infants increased with increasing radiation doses, from 25.5% to 36.2% with doses from 250 to 500 cGy, respectively. In reviewing pregnancies reaching over 20 weeks' gestation from the National Wilms Tumor Study group, female patients had a higher risk of hypertensive disease of pregnancy with the incidence ranging from 18.4% to 35.7% with increasing doses of radiation, compared with non-radiation-exposed female survivors (12.3%) and compared with the partners of male survivors, who represent the general population (3–4%) [19]. This finding was not associated with nephrectomy but could be related to poor vascularity (due to radiation changes) at the placental bed, which has been associated with development of preeclampsia. Radiation exposure was also associated with prematurity. Radiation doses of 15–35 Gy were associated with a prematurity rate (20–36 weeks) of 20.7–22.6% compared with 10.2% in nonirradiated females. Spontaneous preterm delivery could be related to poor uterine volume and stretch from fibrosis related to irradiation. It is important to recognize that multiple gestation also predisposed to preterm birth and likely further exacerbated the risk.

Surveillance for Recurrence of Disease

Cancer surveillance can be challenging in women who become pregnant soon after cancer therapy is completed. One can use breast cancer and Hodgkin lymphoma as examples. Current ASCO recommendations of surveillance after breast cancer treatment include (a) regular exams every 3–6 months in the first 3 years after treatment with assessments every 6–12 months for two more years to complete a 5-year course, and (b) if the breast has been conserved, serial mammograms yearly after the first year (with the first mammogram 6 months after treatment if radiation was given) [20]. Genetic counseling and testing (i.e., BRCA1 and BRCA2) are usually obtained if familial risk is a concern. Pregnancy may make breast surveillance more difficult since breast tissue during pregnancy undergoes hypertrophy and increased vascularity. However, pregnancy should not preclude the use of mammograms for surveillance

Recommendations for initial follow-up after Hodgkin lymphoma remission often focus upon the immediate 2 years out from treatment with complete differential blood counts (CBC), physical exams every 3–4 months, and whole-body CT surveillance every 6 months. The frequency of CT scans then occurs once a year for 5 years

[8, 21]. Cardiac monitoring with echocardiograms and exercise tolerance tests may be recommended in patients with a history of mediastinal radiation or anthracycline exposure. The role of positron emission tomography (PET) for surveillance is not yet standard. Pregnancy cancer survivors should be counseled about the potential risks and benefits of radiation exposure to the developing fetus versus delaying CT surveillance. Given the potential of the PET radionuclide tracer fluorodeoxyglucose (FDG, a fluorinated glucose analogue) to cross the placenta, this test should be avoided in pregnancy [22]. Early breast cancer surveillance is particularly recommended in patients with a history of chest irradiation, and thyroid function monitoring is recommended in patients with a history of neck irradiation [8, 21].

When Cancer Is Diagnosed During Pregnancy

It is estimated that the incidence of cancer during pregnancy is 1 in 1,000 pregnancies, though one retrospective review from 2001 suggests that the number of primary neoplasms may be lower (0.7/10,000 live births) based on California birth/death records [23]. However, the first number includes those women who miscarry and choose termination, while the latter does not. We also acknowledge that with the delay of childbearing, older mothers who have a different risk profile for cancer are now becoming pregnant, spontaneously or with artificial reproductive techniques. Historically, cancer in pregnancy has been identified in later stages or has been associated with delayed diagnosis since presenting complaints associated with cancer may be similar to pregnancy-related symptoms. For example, symptoms of fatigue, nausea, anemia, and breast discharge are commonplace during pregnancy but could actually be related to a cancer diagnosis. Therefore, such symptoms may not be evaluated in a timely fashion unless severe. In contrast, due to access to care and surveillance for cervical cancer with pap smears, cervical cancer is often detected earlier in pregnant women compared with nonpregnant women [24].

Once a woman receives a diagnosis of cancer during pregnancy, this should trigger a multidisciplinary approach to her care. The team should include obstetricians, maternal-fetal medicine (MFM) specialists, surgeons, oncologists, neonatologists, nursing professionals, mental health professionals, clergy, and the patient's family. Clinical care should take into consideration the risks to the mother in terms of her cancer treatment and prognosis (e.g., for an aggressive cancer or advanced stage at diagnosis) while also considering the attendant risks to the fetus. The patient should be counseled regarding whether pregnancy will impact her cancer prognosis, particularly if the standard treatment regimen will be altered by pregnancy. Depending on the gestational age at the time of diagnosis, pregnancy termination and/or early delivery should be discussed. Furthermore, a woman should be aware of her potential for future pregnancies. The other considerations in counseling are gestational age at time of diagnosis—diagnosis late in pregnancy may be dealt with by delivery whereas diagnosis in the first or second trimester, when delivery is not a viable option, termination may be considered. In addition, the type of imaging and radiation exposure dose—for surveillance and treatment—need to be selected such that

they are safe but effective and able to provide the best clinical information. Magnetic resonance imaging (MRI) and ultrasound are considered safe; multiple abdominopelvic CTs may not. Abdominal CT may expose a fetus to 3.5 cGy, and the safe limit of radiation to a fetus is 5 cGy, in terms of risk of malformations or growth restriction. Lower exposures of 1–2 cGy increase the risk of future childhood leukemia from 1:3,000 to 1:2,000 children [25]. Discussions should focus on the timing of surgery and other treatments if needed and how treatment may impact the fetus, how it may impact the ability to carry to term, and the potential for premature delivery and the inherent infant outcomes associated with prematurity.

Ideally, the process of diagnosis and treatment should be guided by the patient's beliefs and goals. The patient's partner or spouse and family should be involved, and recommendations for advance directives should be made. The MFM specialist coordinates appropriate fetal surveillance with surgery and chemotherapy, optimal delivery time in the context of treatment regimens, as well as route of delivery decisions. These clinicians work together with the oncologists to determine if any delay in treatment incurred due to the gestational age of the fetus would lead to a significantly poorer prognosis for the mother.

First-Trimester Diagnosis

If possible, therapy is avoided in the first trimester due to organogenesis of the fetus. The first 4 weeks of gestation—the time from conception to implantation—is considered that "all-or-none" period such that if an exposure is to affect the pregnancy, the result would be pregnancy loss. From 4 weeks to approximately 11 weeks gestation, organogenesis is occurring, making this the most vulnerable time for teratogenesis. First-trimester exposure to chemotherapy agents and/or radiation has been associated with miscarriage or fetal malformation compared with second-/third-trimester exposures, which are associated with growth restriction, bone marrow suppression, and a decreased incidence of structural malformations [26]. Reports of malformations associated with first-trimester exposure range from 14% to 19% [27]. By comparison, the incidence of malformation in the second and third trimester is comparable to that of the general population. A patient's decision to terminate a pregnancy is always a personal one but may be medically recommended if pregnancy worsens the prognosis of cancer or if the cancer is so advanced or aggressive that immediate treatment is recommended as the patient may not survive the duration of the pregnancy.

Use of Chemotherapy

Guidance for use of chemotherapeutic agents during pregnancy is determined by the standard of care used in the nonpregnant patient and the available safety profile of the drugs in pregnancy. Most data about chemotherapy usage and outcomes are

derived from case series or case reports, not prospective studies. Methotrexate, a chemotherapy agent used against trophoblastic tissue with ectopic pregnancies and gestational trophoblastic malignancies, is contraindicated in pregnancy. Methotrexate has been associated with embryopathy with poor ossification, hypertelorism, micrognathia, and ear abnormalities. Alkylating agents in the first trimester have been associated with abnormalities such as low set ears and limb malformations, while relatively safe use of these agents in the second and third trimesters has been reported, with fewer malformations [28]. Weight adjustments for dosages, increased blood volume, and increased renal blood flow and GFR can be considered; however, actual pharmacokinetic studies of chemotherapy agents in pregnant women have not been performed. Use of chemotherapy in the second and third trimesters has been most associated with fetal growth restriction and low birth weight. One recent study reviewed 376 fetuses exposed to chemotherapy (mostly second- and third-trimester exposures) and found a 6% rate of fetal or neonatal mortality and a 7% rate of growth restriction [28].

Use of Radiation as Treatment

If possible, radiation therapy is avoided, but not absolutely contraindicated, as there have been published case reports of safe use. Case reports of local radiotherapy for breast cancer, Hodgkin lymphoma, brain cancer, and head and neck tumors with appropriate shielding describe healthy pregnancy outcomes showing fetal exposures to be approximately 3–10 cGy from first and second trimesters when tumor site dosing ranged from 30 to 80 Gy in the mother [29]. However, it is clear that malformations increase with first-trimester exposure to higher doses such as 10–20 cGy. Exposures of higher doses of radiation may not necessarily result in structural abnormalities but may be related to mental retardation, particularly at higher doses. Reportedly, the threshold dose in a fetus from 8 to 15 weeks for mental retardation is 6 cGy, increasing to 25 cGy at 16–25 weeks of gestation [29]. Second- and third-trimester exposures are associated with a slight increase in the development of childhood cancers (leukemia, solid tumors) as previously mentioned.

Timing of Delivery

Decisions are based on reducing the fetal outcomes of prematurity (i.e., respiratory distress syndrome [RDS], intraventricular hemorrhage) while trying to optimize maternal response and prognosis. Delivery should be planned to avoid the maternal bone marrow suppression seen in the early days after chemotherapy in the mother and 2–3 weeks later in the neonate, understanding that a preterm infants with immature

systems may not metabolize drugs very well. Placentas should be sent to pathology to evaluate for metastasis, particularly for melanoma, lymphoma, and leukemia patients.

Effects on the Offspring

Patients will worry about whether their baby can acquire cancer from them and will want to know about the short- and long-term impacts of the different cancer treatments upon the neonate. In 2003, a collection of all known case series and reports (with the first reported case in 1866) was published, including 87 cases of placental metastasis and six cases of infant melanoma, of which three had documented placental involvement [30]. Clearly, the difficulty with these data is that there is no denominator of births for these 87 cases to generate a true incidence. We can presume that cancers in infants born to cancer patients are a truly rare phenomenon, with possibly higher incidence in survivors of melanoma.

Patients should be informed of the fact that certain drugs can cross the placenta to the fetus and that the placenta as well as the fetus has the capacity to metabolize drugs. However, direct literature about transplacental passage of chemotherapeutic agent is minimal. Most studies that attempt to assess the long-term effects of treatment are limited by their retrospective nature and are often done by questionnaire, which has inherent limitations of recall bias. The most cited prospective study is from Aviles and Neri, who followed 84 children from mothers treated with chemotherapy for leukemia and lymphoma (over 40% in the first trimester) and who underwent physical exams, hematologic exams, and neurologic and developmental assessments with a median evaluation time of 18.7 years [31]. These offspring had no significant developmental delay, no increased incidence of structural defects, normal sexual development, and no increased incidence of cancer.

Anthracyclines (typically used in the second and third trimesters) have poor transfer rates across the placenta, due in part to regulation by P-glycoprotein transport. There are reports that anthracyclines can lead to cardiotoxicity in the offspring, with one case series showing three infants with cardiotoxicity out of 160 treated women [32]. In that series, one infant died having been recently exposed to third-trimester daunorubicin. It is not clear what the actual gestational age was of this case, since prematurity may modify the impact of the drug as well. In contrast, Aviles et al. assessed a cohort of 81 children (ranging from 9.3 to 29.5 years) who were exposed to maternal anthracyclines and underwent surveillance with echocardiograms; none had cardiac dysfunction [33]. In another study of a fetus exposed to doxorubicin and cyclophosphamide, serial fetal echocardiograms and postnatal echocardiograms until age two showed no evidence of cardiac damage [34].

Patients should be aware that their offspring could also be at risk for the sequelae of prematurity and very low birth weight, given that women with malignancies who continue their pregnancies are in general at a twofold increased risk of premature birth and a threefold increased risk of very low birth weight [23].

Future Fertility

Women undergoing cancer treatment regardless of the pregnant state may be at higher risk of infertility and gonadal injury due to chemotherapy or later radiation (see Chap. 1 in this volume). Planning for future pregnancies should be addressed with reproductive specialists in oncofertility and with MFM specialists.

Other Considerations

Because both pregnancy and cancer increase the risk of clots, the decision to offer prophylactic anticoagulation during or after the pregnancy should be assessed by the MFM specialists and oncologists. With regard to long-term effects of cancer treatment, lessons learned from cancer therapies of the past have led to continuing modifications in radiation and chemotherapy regimens to minimize the incidence of long-term sequelae experienced by reproductive-aged women who underwent cancer treatment two to three decades ago.

Pregnancy and Breast Cancer

Breast cancer is the most common cancer diagnosed in pregnancy, with an incidence of approximately 1 in 3,000 pregnancies or 1 in 2,600 to 1 in 10,000 live births [35, 36]. Diagnosis and treatment are modified by the presence of the fetus in the context of gestational age—if the diagnosis is made early enough, the patient has the option to terminate the pregnancy with the understanding that the best available evidence does not suggest benefit to the cancer outcome by termination but that the termination would eliminate the concern for a fetus affected by the diagnostic and therapeutic modalities needed to treat the cancer. Delays of diagnosis or treatment (in order to avoid risk to the fetus) may lead to an increased risk of axillary node metastasis. This possibility impacts maternal survival: Based on mathematical modeling, a delay of treatment by 1 month may lead to a 0.9% increase in node involvement in a pregnant woman with early-stage breast cancer and increases to 2.6% with a 3-month delay [37]. These numbers also have relevance in terms of the delay of diagnosis that often occurs with pregnancy, as tumors in pregnancy are more likely to be larger when diagnosed during or immediately after pregnancy, averaging 3.5 cm in size versus 2 cm in those not associated with pregnancy [36]. Pregnancy does not appear to worsen the prognosis of breast cancer when compared with nonpregnant breast cancer patients of similar age and cancer stage.

Diagnosis should be pursued if a suspicious mass is noted in pregnancy for 2 weeks or more, often a painless mass the patient has palpated. Pregnancy should not prevent the routine diagnostic tests for breast cancer, including mammogram with abdominal shielding (exposing the fetus to less than 0.5 cGy) and ultrasound, nor should evaluation wait until after delivery. While breast discharge is not

uncommon in pregnancy, it tends to be clear or milky. Bloody or purulent discharge or involvement of a solitary duct is concerning. Breast MRI is not conventionally used in pregnancy since gadolinium crosses the placenta. Fine needle aspiration can be done, but the pathologist must be informed of the patient's pregnancy state since cytology can be altered and core needle biopsies are usually recommended. Excisional biopsies should be performed when indicated.

Estrogen and progesterone receptors and Her2 receptor statuses should be determined. The breast cancers identified during pregnancy are more likely to be poorly differentiated and have negative hormone receptor status when compared with cancers in nonpregnant women [35]. A baseline echocardiogram may be obtained in case anthracycline chemotherapy is needed. Serial fetal ultrasound and assessments should be obtained as recommended by MFM specialists. Evaluation of genetic mutations, such as in the BRCA genes, should also be considered as this may impact future fertility planning and prophylactic oophorectomy may be an option for these patients in terms of risk management.

Staging in pregnancy includes a complete history, physical, chest X-ray (CXR) with abdominal shielding, liver ultrasound, and noncontrast MRI to assess the spine. While CT scans can be done, radiation exposure to the fetus can be avoided if MRI is able to reveal information on metastasis. Surgery can and should take place for either lumpectomy or mastectomy after appropriate counseling by the surgery team. Depending on the gestational age (particularly second or third trimester), fetal monitoring will be recommended before and after surgery, with particular awareness of preterm labor. Fetal monitoring during the surgery must be performed with the understanding that fetal intervention (delivery) will occur in third-trimester patients if the monitoring is not reassuring, based on extensive discussion with MFM and neonatology.

Sentinel node biopsy has been reported in pregnancy with and without isosulfan blue (which can be associated with anaphylaxis) with varying outcomes, including miscarriage after the procedure in the first trimester [38]. Given the inherent risks of increased miscarriage in the first trimester, some may delay this surgery until the second trimester, but this is not mandated.

Treatment of breast cancer during pregnancy must weigh the issues of improving maternal survival against concerns about teratogenic effects or miscarriage in the first trimester. As a result, chemotherapy is often delayed until the second trimester. A protocol using 5-fluorouracil, doxorubicin, and cyclophosphamide is frequently utilized and has been well described in a large series of patients from MD Anderson Cancer Center [39]. Combination anthracycline and cyclophosphamide regimens have also been used [38, 40, 41]. The experience with taxanes is limited in pregnancy, and these agents tend not to be used, in part since the P450 system is significantly upregulated in pregnancy and may result in higher metabolism of the drug resulting in potentially lower concentrations [40]. In addition, because taxanes impact microtubules, which are involved in cell division and intracellular/intercellular functions, potential fetal toxicities may extend beyond cell division [28]. A recent review of the literature identified 42 neonates born to women who received taxanes, with incomplete data on maternal toxicity and neonatal status; 2 of 21 women exposed to paclitaxel had RDS, likely due to prematurity, and one infant had

pyloric stenosis possibly associated with the taxane exposure [42]. Breastfeeding is not recommended while a patient is receiving chemotherapy since the concentration of chemotherapies in breast milk has not been well studied [43].

Radiation therapy for breast cancer is frequently delayed until after delivery of the fetus to avoid fetal exposure to potential radiation doses of 50–60 cGy, but cases must be individualized. Delaying radiotherapy in some cases may increase the risk for local recurrences; a recent international consensus paper suggests that local radiation can be considered, using appropriate shielding of the abdominopelvic region to reduce radiation exposure by 50–75%, in the first and second trimester when the uterus is further away from the chest [41].

The use of trastuzumab is generally avoided in pregnancy given case reports associated with oligohydramnios and concern for fetal renal dysfunction [40]. Tamoxifen has been associated with anomalies in a drug registry and in animal models and is usually started after delivery.

It is not uncommon to plan a late premature delivery (34–36 weeks) or early-term delivery (37 weeks) to allow for Taxol chemotherapy to start, particularly if the breast cancer is of a more advanced or aggressive nature. Neonatology will have discussed with the patient the risks of prematurity, and the patient will have received steroids to enhance fetal lung maturity prior to delivery. A large population-based study from the Swedish Birth registry suggested that women with breast cancer in pregnancy had an odds ratio (OR) of 3.2 (95% CI 1.7–6.0) for prematurity (spontaneous and iatrogenic), an OR of 2.9 (95% CI 1.4–5.8) for LBW infants, and an OR of 2.1 (95% CI 1.2–3.7) for malformations [44]. Use of this information to counsel women is limited because these data did not specify the specific breast cancer stages and treatment modalities used; if there were more first-trimester exposures, it may explain an increase in anomalies, while the preterm birth increase may be due to more planned deliveries to allow for further maternal therapy.

A recent review suggests that since chemotherapy usage during the pregnancy has become more prevalent [26], survival rates are similar to those of nonpregnant women when matched by age and cancer stage, implying that the pregnancy itself does not inherently confer a poorer prognosis, as has been historically noted [35]. Since more aggressive disease tends to recur in the first 2 years, some have recommended that subsequent pregnancies be delayed until after this time frame.

Pregnancy and Hodgkin Lymphoma

The incidence of Hodgkin lymphoma in pregnancy has been estimated at 1 in 1,000 to 1 in 6,000 pregnancies, with this malignancy frequently affecting women in their teens to their 20s [45]. Age at the time of diagnosis and cancer stage based on the Ann Arbor system—number and location of affected nodes, extralymphatic involvement, and the presence or absence of constitutional symptoms such as weight loss, night sweats, and fever—impact prognosis. Literature reviews suggest that pregnancy does not alter prognosis [22, 26, 45], and pregnancy termination does not

improve survival. In fact, in one study, 70% of pregnant Hodgkin lymphoma patients have early-stage disease and 8-year survival rates were over 80% [45].

Diagnosis of lymphoma is based on lymph node biopsy. Pregnancy should not prevent performance of the biopsy. Hodgkin lymphoma histology in pregnancy is similar to the nonpregnant state. Staging involves complete history and physical, lab studies including complete blood differential count, platelets, liver and renal function assays, lactate dehydrogenase (LDH) and alkaline phosphatase levels (acknowledging that alkaline phosphatase is increased in pregnancy due to the placenta), CT of the chest, abdomen, and pelvis, and CXR. The risk/benefit of fetal radiation exposure should be discussed with the patient; the primary fetal risk in terms of future childhood malignancies is higher when exposure occurs outside the first trimester. Bone marrow biopsy can also be done during pregnancy. While radionuclide tracers are used with PET in the nonpregnant state for staging, PET scans are avoided in pregnancy due to the concern that FDG can cross the placenta and lead to higher radiation doses to the fetus [22].

Treatment should take into account the changes of physiology during pregnancy, such as increased third space volume and renal clearance. Chemotherapy is avoided in the first trimester to avoid teratogenic effects. Often, if diagnosed in the first trimester, Hodgkin lymphoma is followed and the treatment started in the second trimester if the pregnancy is desired and to avoid miscarriage and decrease fetal malformation risk. If the lymphoma is aggressive or more advanced, termination can be considered by the family. If unacceptable, then single agent therapy with anthracycline can be considered, followed by multiagent therapy once in the second trimester [22]. As noted with breast cancer, certain agents are frequently administered in the second and third trimesters, with an understanding of the increased risk of growth restriction and prematurity. The regimen commonly used for Hodgkin lymphoma is ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) [22, 26]. MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) use has also been reported. Avoidance of delivery until 2–3 weeks after the last chemotherapy exposure will reduce the bone marrow impact on the neonate.

In light of the fact that combined chemotherapy with low-dose radiation can lead to survival rates as high as 93% [45], radiotherapy of the neck or axilla can be considered with shielding of the abdomen and has been described in a series of 16 pregnant women [46]. In that study, the fetus was estimated to receive 10–13.6 cGy after abdominal shielding with normal pregnancy outcomes. If necessary for the sake of treatment, late preterm delivery can be considered after appropriate neonatal counseling and steroid administration for fetal lung maturity.

Pregnancy and Other Cancers

Other cancers such as non-Hodgkin lymphoma, melanoma, cervical cancer, thyroid cancer, and ovarian cancer are also seen reproductive-age women. The basic tenets explored by the sections on breast cancer and Hodgkin lymphoma relating to

aggressiveness of the cancer, chemotherapy effects, and radiation effects in the context of gestational age should be applied to other cancers as well. It is understood that aggressive leukemias (acute) and lymphomas (large B-cell lymphomas, mature T-cell and NK-cell neoplasms) often mandate immediate treatment, usually chemotherapy, as well as the recommendation for termination if the gestation is early [22, 47]. Metastasis to the placenta is rare but has been occasionally reported with melanoma, lymphoma, and leukemia. In melanoma, fetal involvement in the face of placental involvement could be as high as 22% [30]. Slower growing cancers, e.g., chronic leukemias and follicular or early-stage papillary thyroid cancer, can be treated after delivery as the time course would not necessarily affect the patient's prognosis [26, 45].

While other cancer diagnoses may be delayed by pregnancy, cervical cancer is being diagnosed at earlier stages of pregnancy due to prenatal care and pap smears. Swedish data from 1914 to 2004 showed improved survival from cervical cancer and that in those women under 50 years of age, stage I diagnosis was reported in 75.6% of cases from 1960 to 2004 versus 24.8% in those from 1914 to 1943 [24]. Indeed, with the advent of human papilloma virus (HPV) vaccinations, one hopes that this form of cancer will become rarer still. Cancer of the cervix and ovary should be managed in conjunction with gynecologic oncology, since surgery is a critical aspect of treatment. Treatment of cervical cancer mandates either delivery or termination, with either radical hysterectomy which is done in the third trimester with cesarean delivery or in the first trimester with fetus in the uterus or radiation treatment [48].

Ovarian cancer occurs rarely during pregnancy, with an incidence of approximately 1 in 20,000 live births [49]. If clinical assessment suggests that disease is isolated to one ovary and the pregnancy is desired, serial evaluation with ultrasound and possible early delivery with definitive surgery and staging postpartum is recommended. Unilateral salpingo-oophorectomy can be performed in those patients with low malignant potential or stage IA cancer, particularly if fertility is desired [26, 48]. However, evidence of advanced disease may mandate the recommendation for termination if the gestational age is early enough, followed by surgical staging and debulking with appropriate chemotherapy to follow. These patients will need to be counseled on the potential impact of delay of surgery to allow for the fetus to achieve a reasonable gestational age for survival.

Conclusions

Hopefully, the complexity of managing pregnancies in women with a past or current history of malignancy has been illustrated here. Importantly, no single caregiver should bear the burden to provide care: A multidisciplinary approach involving the patient and her support network, the oncology and surgery teams, and the obstetrical and MFM team is required to give the patient the best medical counseling and care and to manage her expectations during the pregnancy regarding her future child in the context of treatment and prognosis.

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