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Breast cancer diagnosis during pregnancy

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Abstract

Breast cancer diagnosed during pregnancy is a challenging situation for the patient and her medical team. As women are delaying childbirth, the incidence is expected to increase. Most of the data surrounding the diagnosis and treatment of cancer during pregnancy is in case reports and small cohort studies. However, the data continues to expand regarding the safety of systemic treatments during the second and third trimesters for both the mother and the fetus. In this article, the use of diagnostic imaging, procedures, surgery and chemotherapy are reviewed as well as prognosis and future pregnancies after the treatment for breast cancer.

Keywords

breast cancer; chemotherapy; pregnancy

Breast cancer & pregnancy

Breast cancer is one of the most common cancers during pregnancy with the frequency approaching one in 3000 pregnancies [1]. Given that more women are delaying childbirth into their thirties, the incidence is expected to increase [2]. As the breast changes with pregnancy, these changes pose some challenges to the diagnosis, monitoring and treatment of breast cancer. No randomized, controlled trials with pregnancy are available and most of the data guiding our treatments come from case reports or retrospective cohort descriptions or case-control studies. In this article, we review the literature of breast cancer during pregnancy, including the incidence, diagnosis, evaluation and treatment. In addition, we review available data for

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pregnancy after the diagnosis of breast cancer, which is a significant survivorship issue for young breast cancer patients.

Epidemiology

Breast cancer is one of the most commonly diagnosed malignancies during pregnancy. In a large, retrospective, population-based study in California between 1991 and 1997, there were 1.3 cases per 10,000 live births [3]. However, when breast cancer is diagnosed in women aged 30 years and younger, almost 10-20% of cancers are detected during pregnancy or within the first postpartum year [1,4].

Prior pregnancy & breast cancer risk

In the first 3-10 years after delivery, there is a transient increase in the risk of developing breast cancer, despite the long-term protective benefits of pregnancy. Three separate population-based studies have evaluated this [5-7]. Of note, one of the studies did look at family history as one of the risk factors [5], which added to this increased risk. This increased risk may be associated with a *BRCA* mutation; however, information on this is limited. Patients with a *BRCA2* deleterious mutation appear to have an increased risk of developing a breast cancer, especially within the first 2 years postpartum [8]. Given the age of diagnosis of pregnant women with breast cancer, genetic counseling should be considered.

Not only is there a transient increase in the risk of developing breast cancer after a pregnancy, but women who do develop breast cancer after a recent pregnancy may have a worse prognosis [9,10]. Guinee *et al.* described an increase in mortality from a new diagnosis of breast cancer, which decreased with each subsequent year after a pregnancy [9]. Kroman *et al.* have demonstrated that if a recent pregnancy was within 2 years of a new diagnosis of breast cancer, the relative risk of dying when compared with women without a recent pregnancy was 1.58 (95% CI: 1.24-22.02) [11].

Diagnosis

Pregnant woman may present with similar physical examination findings to nonpregnant breast cancer patients such as a mass or palpable thickening of the breast tissue. Often, a delay in cancer diagnosis in pregnant breast cancer patients is secondary to pregnancy and lactation, including increased size and density of the breast tissue. Thus, pregnant breast cancer patients often present with an advanced disease stage and with axillary lymph node involvement. Given the concern for a delayed diagnosis, palpable masses persisting over 2 weeks during pregnancy should be investigated, although it is reported that approximately 80% of breast biopsies during pregnancy will be benign [12,13].

Mammography

Mammography should be ordered in pregnancy with proper abdominal shielding. Radiation exposure for the fetus is estimated at 0.4 cGy [14]. Owing to the increased water content in the pregnant breast and loss of contrasting fat, which may be even more pronounced in the very young breast cancer patient, the sensitivity of mammography may be decreased. Reported sensitivity of mammography for detecting breast cancers in the pregnant breast ranges from 63 to 78% [15-17].

Ultrasonography

Ultrasound is used to distinguish between cystic and solid breast masses and does not carry with it any risk for fetal radiation exposure. Most breast cancers diagnosed during pregnancy are found to be a solid mass, although one report described two of four malignant tumors having

benign characteristics, further stressing the importance to monitor and consider biopsy of suspicious breast masses in pregnant women [15,17,18]. One study demonstrated that in 20 women who underwent preoperative mammography, the mass was identified in 18 of 20 women, but 100% of the masses were found by ultrasound. In addition, ultrasound correctly identified axillary metastases in 15 of 18 women who underwent ultrasound nodal assessment [19].

Breast MRI

MRI has not yet been prospectively studied for the diagnosis of breast masses in pregnant or lactating women. The use of gadolinium during pregnancy is not widely accepted. Gadolinium has been shown to cross the placenta and be associated with fetal abnormalities in animal models [20,21]. However, there is growing evidence that gadolinium during pregnancy may be safe [22,23]. From our literature search, we found only one case report using MRI for breast imaging during pregnancy [24].

Biopsy

Any clinically suspicious mass should be biopsied, even if the ultrasound and mammogram are nondiagnostic. Fine needle aspirate (FNA) in the pregnant breast is a well-established technique; however, it is important for the pathologist to be aware that it is from a breast of a pregnant patient [25,26]. In addition, core and excisional biopsies can be performed safely under local anesthesia, with a single report of the development of a milk-fistula after biopsy found in the literature [27].

Pathology

The majority of breast cancer cases are infiltrating ductal adenocarcinomas. The prospective cohort from The University of Texas MD Anderson Cancer Center (MDACC) reported 84% of the tumors to be poorly differentiated [28]. Pregnant women with breast cancer tend to have a lower frequency of estrogen receptor and/or progesterone receptor expression compared with historical controls [28-31]. Amplification of HER-2/*neu* is normally observed in approximately 20-30% of breast cancers in pregnant patients. In one series [32], HER-2/*neu* amplification was reported to be disproportionately amplified in pregnant patients (up to 58 vs 16% in nonpregnant patients); however, other series show similar HER-2/*neu* amplification (28%) in pregnant breast cancer patients [28].

Staging evaluations during pregnancy

Initial staging should include a complete history and physical examination; chest x-ray with proper abdominal shielding; ultrasound of the liver and a screening noncontrast MRI of the thoracic and lumbar spine to exclude bone metastases. If there are further concerns of liver metastases after ultrasound, an abdominal nongadolinium-enhanced MRI can be considered, since the liver may have fatty replacement during pregnancy. CT scans and bone scans are not recommended owing to concerns over fetal radiation exposures [33].

Locoregional therapy

Surgery

Breast surgery can be safely performed in all trimesters; however, many patients and surgeons will choose to wait until after week 12 of gestation when the risk of spontaneous abortion decreases [33]. Often, patients may opt for mastectomy, but preoperative chemotherapy during pregnancy with an option for lumpectomy and radiation after delivery may also be an option. Safety and efficacy of sentinel lymph node biopsies has been reported, but is not routinely performed during pregnancy [34]. Although the estimated fetal radiation is low, the isosulfan

blue-dye mapping is not recommended because of the risk of anaphylaxis as well as the unknown effects of the dye on the fetus.

Radiation therapy

External beam breast or postmastectomy radiation should be postponed until after delivery. The fetus is at highest risk of damage to organogenesis in the first trimester and with each successive trimester would sustain a higher proportion of the standard 50-60 Gy used [35]. There are a few case reports of radiation administered during pregnancy with proper abdominal shielding [36,37]; however, given the ability to treat the cancer with surgery and chemotherapy until delivery, radiation should be administered after delivery for breast cancer.

Systemic therapy

Chemotherapy

Although little is known regarding the pharmacokinetics of chemotherapeutic agents in pregnancy owing to natural physiologic changes (e.g., increased plasma volume, impaired renal and hepatic function and third spacing potential), successful administration of chemotherapy to pregnant breast cancer patients has been documented. Since published reports demonstrate that first trimester chemotherapy exposure is associated with a 14-19% risk of fetal malformations and second trimester is significantly safer with a fetal malformation risk of 1.3%, chemotherapy should not be administered in the first trimester [38]. In addition, antifolates, such as methotrexate, a commonly used agent for breast cancer, are known abortifactants and have been found to have higher rates of fetal abnormalities [38].

The University of Texas MDACC has the largest prospective cohort of pregnant breast cancer patients treated on a standardized protocol. In the last published update of this cohort, 57 women were treated with 5-fluorouracil 500 mg/m^2 intravenously on days 1 and 4, doxorubicin 50 mg/m^2 administered by continuous infusion over 72 h and cyclophosphamide 500 mg/m^2 administered intravenously on day 1 (FAC). A median of four cycles were administered during pregnancy. Dosing was adminstered relative to the patient's actual weight and was not capped as the pregnancy progressed [31]. The mean gestational age at delivery was 37 weeks.

As case reports continue to be published, there is accumulating evidence that taxanes may also be safe in the second and third trimesters [39-41]. However, currently taxanes are often used only after delivery of the child; this likely to remain so until further safety data is available. Taxanes may be an excellent option for those patients receiving preoperative chemotherapy whose tumors are not responding to anthracyclines and are amenable to surgery. Other chemotherapies that have been reported to be used include case reports of vinorelbine, carboplatin and cisplatin, especially for the treatment of ovarian cancer [39,42].

Biologic agents

There have been several reports of trastuzumab administered during pregnancy. Anhydramnios or oligohydramnios has been a common reported toxicity [43-45]. Although no fetal abnormalities have been reported, one child developed respiratory failure with a capillary leak syndrome and necrotizing enterocolitis and died 21 days after delivery [46]. Another patient developed reversible heart failure [45] and one fetus had renal failure that reversed [44]. The use of lapatinib, a new HER-2-directed tyrosine kinase inhibitor, has been reported in one patient who conceived while on lapatinib and had approximately 11 weeks of exposure, the pregnancy was otherwise uncomplicated with delivery of a healthy baby [47]. Given the very limited data of biologic agents during pregnancy, they are still not recommended for routine administration. Biologics should be considered after delivery or in e mergency case by case situations.

Endocrine therapy

Endocrine therapy, when indicated, should be initiated after delivery and after the completion of chemotherapy. There are some case reports of fetal exposure to tamoxifen without damage to the child, but other reports describe birth defects, including Goldenhar syndrome and ambiguous genitalia, as well as reports of vaginal bleeding, and spontaneous abortion [48-52].

Monitoring the pregnancy

Evaluation of fetal viability and confirmation of the age of the fetus must be carried out before the administration of chemotherapy. The patient should be referred to and examined by a maternal-fetal medicine specialist. Frequent visits and well-coordinated communication among the patient, medical oncologist, surgical oncologist and obstetrician is imperative. The timing of delivery and any risks of preterm labor should be discussed. Chemotherapy should not be administered 2 weeks prior to an anticipated delivery in order to avoid neutropenia in the mother as well as potentially in the fetus. In an otherwise uncomplicated pregnancy, often chemotherapy will be held after week 35 in order to avoid these potential complications. Potential pregnancy-related complications can include pre-ecclampsia and preterm labor. These should be treated according to standard care guidelines. Planned induction or cesarean deliveries may also be performed to avoid these hematologic complications.

Breastfeeding

Many chemotherapeutic agents are excreted in breast milk. Neutropenia in an infant breastfed while the mother was receiving therapy with cyclophosphamide has been described [53,54]. Therefore, breastfeeding during administration of chemotherapy, biologic therapy, endocrine therapy and radiation therapy is not recommended.

Prognosis

Prognosis in pregnant breast cancer patients is often difficult to assess. Although many women have an advanced stage at diagnosis, this may contribute to conflicting reports in the literature, especially when comparing pregnant versus nonpregnant patients. In a series from Toronto, Canada, there was no statistically significant difference in survival when matched for age, stage and year of diagnosis [55]. Several other series also have had similar results [17,56]. Alternatively, other case-control studies describe pregnancy as an independently poor prognostic factor. However, the addition and timing of chemotherapy administration in these series is unclear [29,57,58]. Recently, Beadle *et al.* described 652 women diagnosed with breast cancer who were aged 35 years or younger. Women who were either pregnant at the time of diagnosis or diagnosed within 1 year postpartum, did not have a worse rate of locoregional recurrence, distant metastases or overall survival [59].

Short- & long-term complications for the child

Immediately after delivery, there is the potential for early and reversible chemotherapyrelated toxicities for both the mother and the fetus. These can include anemia, neutropenia and alopecia. There are little data regarding the children born to women treated with chemotherapy during pregnancy. In the prospective series recently updated from University of Texas MDACC, there were no miscarriages, stillbirths or perinatal deaths [31]. The majority of the children did not have significant neonatal complications. With the age of children at the time of this survey ranging from 2 to 157 months, the most common complication was difficulty breathing (10%) and one child, born at 38 weeks' gestation, had a subarachnoid hemorrhage

2 days postpartum. One child had Down's syndrome and two children had congenital abnormalities (club foot and bilateral ureteral reflux).

There is no other large cohort of breast cancer patients evaluating the long-term complications including cardiac, neurocognitive or reproductive complications. Aviles *et al.*, described 84 children with 18.7 years of follow-up [60], who were born to women who received chemo therapy during pregnancy for hematologic malignancies. These children were also reported not to have any significant physical, neurologic or psychological abnormalities.

Future pregnancies after treatment for breast cancer

The potential for future pregnancies is often a very important concern for young breast cancer survivors. If the woman did not experience premature ovarian failure (POF) or suffer from chemotherapy-induced infertility, when to pursue a pregnancy is often a very burning question for young breast cancer survivors. The majority of studies, including four large, registry-based series that, although limited by the methodology, provide evidence that women who become pregnant after successful treatment for breast cancer do not appear to have a worse prognosis than women who do not have subsequent pregnancies [11,61-63]. In fact, future pregnancies may have a protective effect, as described by Mueller *et al.* [64], with a decreased risk ratio of 0.54 for women who gave birth after 10 months of a diagnosis of breast cancer compared with women who did not have a subsequent pregnancy (95% CI: 0.41-40.71). A woman must carefully consider her personal risk of recurrence, based upon her tumor biology, consider her desire for children and discuss fully with her oncologist and obstetrician. Although some physicians will advise a wait of 2 years after diagnosis, this is most often due to the fact that if an aggressive recurrence is to happen, many of the recurrences will occur in the first 2 years and a new pregnancy may complicate treatment options.

Conclusion & future perspective

The treatment of breast cancer during pregnancy is multidisciplinary and necessitates active communication among the patient, obstetrician, medical, surgical and radiation oncologists. Appropriate diagnosis, biopsy and imaging is required for proper surgical and medical management of the breast tumor. Fertility options and future pregnancy plans should be discussed with the patient prior to starting systemic therapies. As more women may present with breast cancer during pregnancy and as women delay childbirth, the medical community will need to continue to add to this growing body of literature. Other therapies, such as taxanes and new biologics, may need to be considered, although their usage now is not currently recommended owing to the paucity of safety data. In addition, evaluating and following the children who were exposed to chemotherapy *in utero* will be paramount to providing women with better informed consent as well as providing pediatricians who care for these children with better guidelines for any changes in their healthcare, if needed.

Executive summary

Epidemiology

- Women are delaying childbirth and we expect the rate of breast cancer during pregnancy to increase. Currently, it is estimated that approximately one in every 3000 births occur during breast cancer.

Diagnosis & imaging

- Women should have breast masses properly evaluated during pregnancy. Mammography with fetal shielding, ultrasonography and MRIs should be considered. Fine needle aspiration, core biopsies and breast surgeries appear to

have no significant increase in risk and should be performed in a timely fashion for a breast lump diagnosed during pregnancy.

Treatment

- Chemotherapy should be considered after the first trimester in coordination with a multidisciplinary approach with monitoring by an obstetrician. Anthracycline-based chemotherapy has the most published safety data during pregnancy and should be considered in the first line. Several other agents have also been reported. Radiation should be completed after delivery of the child.

Future pregnancies

- Epidemiologic data do not appear to support an increased risk of recurrence for women who have a subsequent pregnancy after a diagnosis of breast cancer. Long-term follow-up of the children exposed to chemotherapy during pregnancy is warranted.

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