Breast Cancer in Pregnancy

A Literature Review

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Hypothesis: Breast cancer in pregnancy will increase as more women postpone childbearing until later in life.

Objective: To review the literature on diagnosis, staging, treatment, and prognosis.

Design and Methods: Articles were obtained from MEDLINE (1966-present) using the keywords breast, cancer, carcinoma, and pregnancy. Additional articles were sought using the references of those obtained. A total of 171 articles were found, 125 in English. More than 100 were reviewed, including 7 prospective and 40 retrospective studies, 6 case reports, and at least 47 review articles on various aspects of pregnancy and cancer. Data extraction was performed by 1 reviewer.

Results: Diagnostic delays are shorter than in the past but remain common. Mammography has a high false-negative rate during pregnancy. Biopsy or needle aspiration is needed for diagnosis and cannot be postponed until after delivery. Pregnancy-associated cancers tend to occur at a later stage and be estrogen receptor-negative. However, they carry a similar prognosis to other breast cancers when matched for stage and age. Although modified radical mastectomy is the traditional treatment, breast-conserving therapy is increasingly common. Therapeutic radiation is contraindicated, but chemotherapy is relatively safe after the first trimester. Tamoxifen should be avoided in the first trimester and possibly beyond.

Conclusions: Physicians should perform a thorough breast examination at the first prenatal visit and maintain a high index of suspicion for cancer. Patients who wish to continue their pregnancies have a growing array of treatment options.

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Breast Cancer in pregnancy is expected to be increasingly common as women delay childbearing until later in life, when the incidence of breast cancer tends to rise. The frequency ranges from 1 in 3000 to 1 in 10000 deliveries, making breast cancer the second most common malignancy in pregnancy after cervical cancer. Put another way, at least 10% of patients with breast cancer who are younger than 40 years will be pregnant at diagnosis. This article reviews the literature on diagnosis, staging, treatment, and prognosis.

Most researchers define pregnancy-associated breast cancer as one that is diagnosed during pregnancy or up to 1 year post partum. However, there is considerable variation among authors, with postpartum periods ranging from 6 months to 2 years.

Breast cancer most often presents in pregnancy as a painless mass or thickening and is occasionally associated with nipple discharge: 146 (82%) of 178 women in a British series and 60 (95%) of 63 women in a Mayo Clinic (Rochester, Minn) series presented with a painless mass. If the woman is breastfeeding, she may note a “milk rejection sign” in which the infant refuses the breast that contains the cancer. Mean breast weight normally doubles in pregnancy from 200 g to 400 g, and the resulting breast firmness and density make the clinical examination and mammogram more difficult to interpret.
of the women were symptomatic prenatally. In that study, the median tumor size was 3.5 cm, suggesting either that breast masses were not clinically recognized or that follow-up was delayed.16

A 1-month delay in primary tumor treatment increases the risk of axillary metastases by 0.9%, given a tumor-doubling time of 130 days. A 6-month delay increases the risk by 5.1%.17

The differential diagnosis of a breast mass in a pregnant woman includes not only cancer but also lactating adenoma, fibroadenoma, cystic disease, lobular hyperplasia, galactoceles, abscess, lipoma, and hamartoma and rarely leukemia, lymphoma, sarcoma, neuroma, and tuberculosis.9 Although 80% of breast masses are benign, any mass persisting for 2 to 4 weeks deserves further workup.

**IMAGING**

Mammography is associated with a high false-negative rate during pregnancy owing to the increased density of the breast. In a 1983 study, Max and Klamer18 reported normal mammogram results in 6 of 8 patients. In more recent studies, 34 of 50 mammograms (Ishida et al13) and 5 of 8 mammograms (Samuels et al13) revealed pregnancy-associated carcinoma, whereas in another series, 18 of 23 mammograms showed suspicious abnormalities.14 Thus, mammography appears to have a place, however limited, in the evaluation of the pregnant patient. Mammography during pregnancy is safe: a standard 2-view mammogram subjects the fetus to only 0.4 mrad (0.004 Gy), far less than ultrasonographic background radiation of 2 rad (0.02 Gy) a week.20

Ultrasoundography is a good, inexpensive first imaging choice for the pregnant woman and can distinguish between cystic and solid lesions in 97% of patients. This technique detected 39 (93%) of 42 cancers in a case-control study of pregnant Japanese women13 and detected all pregnancy-associated tumors in 2 small series.14,19 However, 2 of the 4 malignant tumors in 1 of those series appeared benign according to the ultrasonography.19

Currently, studies of breast magnetic resonance imaging (MRI) during pregnancy are not available. Although MRI involves no irradiation, several disadvantages limit its use in the diagnosis of breast cancer in pregnant women. Gadolinium crosses the placenta, is associated with fetal abnormalities in rats, and is classified as a pregnancy category C drug, to be used only if the potential benefit justifies the potential risk to the fetus.20-22 Magnetic resonance imaging itself is associated with 2 kinds of risks to the fetus: heating and cavitation.22 Some radiologists avoid MRI in the first trimester, but there is no consensus on this matter.22,23,25 In nonpregnant women, breast MRI is highly sensitive but only moderately specific.25

For the diagnosis of metastases, MRI is preferred to ultrasonography for hepatic imaging.20 It is also the safest and most sensitive way to scan the brain. For bony metastases, either a low-dose bone scan or MRI of the thoracic and lumbar spine can be used.26 The low-dose bone scan, as described by Baker et al,27 exposes the fetus to 0.08 rad (0.0008 Gy) instead of the standard 0.19 rad (0.0019 Gy). Congenital malformations and spontaneous abortion occur with exposure to more than approximately 5 to 10 rad (0.05-0.1 Gy), especially at less than 25 weeks’ gestation.4,28,29 Microcephaly is the leading risk and appears with doses as low as 10 rad at less than 8 weeks. Mental retardation occurs with doses of 12 to 20 rad (0.12-0.2 Gy) at 8 to 15 weeks. In early pregnancy, 50 to 200 rad (0.5-2 Gy) can place the fetus at risk for permanent growth restriction. Unfortunately, much of our knowledge about x-ray doses comes from World War II findings in Hiroshima and Nagasaki, Japan; these findings may be confounded by malnutrition in that population.29

As with nonpregnant women, staging bone scans and abdominal imaging are unnecessary if the patient is asymptomatic. These tests have a low yield and have not been shown to improve survival rates. Ciatto et al20 determined the staging in 3600 women with clinically operable breast cancer; in their study, 0.3% of chest x-rays films, 0.64% of bone scans, and 0.24% of liver ultrasonographic scans revealed metastases. Metastases to the placenta are also possible, but none of the 10 breast cancer cases in that study included metastases to the fetus. Placental metastases are generally discovered post partum.31

Among blood test results, alkaline phosphatase normally doubles or even quadruples during pregnancy and cannot be used as an indicator of metastases. Alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase usually remain at prepregnancy levels.32 Chest radiography is considered harmless during pregnancy. Lateral and posteroanterior views expose the

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**Table 1. Number of Months From Symptoms to Diagnosis of Breast Cancer**

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size</th>
<th>Pregnant</th>
<th>Sample Size</th>
<th>Nonpregnant</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>King et al9</td>
<td>63</td>
<td>1.4</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Applewhite et al11†</td>
<td>48</td>
<td>13.2</td>
<td>2689</td>
<td>5.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Tretli et al12</td>
<td>20</td>
<td>2.5</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Ishida et al13‡</td>
<td>72</td>
<td>6.2</td>
<td>191</td>
<td>5.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Liberaran et al14§</td>
<td>12</td>
<td>8.2</td>
<td>11</td>
<td>1.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Bonnier et al15¶</td>
<td>114</td>
<td>2.2</td>
<td>280</td>
<td>1.2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Ellipses indicate not applicable.*

†Includes cancer found up to 2 years post partum.

‡Includes cancer found up to 6 months post partum.

§Includes lactating women.

¶Includes 2 cases in which the patient was symptomatic before pregnancy.

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fetus to roughly 0 to 0.01 rad (0-0.0001 Gy). Portable x-ray films expose the fetus to more radiation than standard machines.7,20,33

**DIAGNOSIS**

As with breast cancer in general, biopsy is the “gold standard” for diagnosis. Stopping lactation beforehand will reduce the risk of milk fistula. This is commonly done with ice packs and breast binding; if that fails, bromocriptine (2.5 mg 2 to 3 times daily) can be given for a week before the biopsy. Optimally, the breasts should be emptied of milk before the biopsy. A pressure dressing may be used to decrease the risk of hematoma that arises from the hypervascularity of the breasts during pregnancy.4 Because pregnancy-associated breast cancer often appears as a palpable mass, core needle biopsy may be the most cost-effective initial procedure. Although no studies are available on the use of core needle biopsy during pregnancy, in nonpregnant women the technique can diagnose lesions with high sensitivity and specificity.34-36,37 Alternatively, fine-needle aspiration may be used. In 2 small series, fine-needle aspiration detected all cancers in pregnancy; however, in 1 patient in each study, the results were initially categorized as atypical rather than an indication of carcinoma.38,39 The pathologist must be aware that the patient is pregnant to avoid misdiagnosis of the hyperproliferative changes of pregnancy. The accuracy of fine-needle aspiration is highly dependent on the pathologist’s experience with pregnancy-associated breast cancer.26,38

**GENETICS**

Recent research indicates that women with a genetic predisposition to breast cancer may be overrepresented among pregnant patients with cancer. In a multicenter case-control study in Japan (n = 383),13 a family history of breast cancer was 3 times more common in pregnant and lactating women with breast cancer than in other patients with this disease (12.4% vs 4.2% of controls). Another small study found **BRCA2** (the breast cancer susceptibility gene) mutations in 8 of 9 archival samples from women with pregnancy-associated breast cancer vs 3 of 15 samples from unmatched nonpregnant controls.40 Finally, in a Swedish study of 292 women diagnosed as having breast cancer before age 40 years, known **BRCA1** and **BRCA2** carriers were more likely to develop cancer during pregnancy.41 Among **BRCA** mutation carriers, high levels of circulating estrogens during pregnancy may accelerate a malignant transformation that has already begun.

**PATHOLOGIC CHARACTERISTICS**

Breast cancers in pregnant women are histologically similar to those in nonpregnant women. About 75% to 90% of tumors in both groups are ductal carcinomas.13,15,16 Similarity to those in nonpregnant women. About 75% to 90% of tumors in both groups are ductal carcinomas.13,15,16,42,43 Interestingly, inflammatory carcinomas were thought to be more common in pregnancy.7 However, most studies reported since the 1960s have found a similar incidence of inflammatory breast cancers in pregnant and nonpregnant patients, ranging from 1.5% to 4.2%.9,42,43 Numerous studies have found that women with breast cancer in pregnancy have larger tumors and are more likely to have positive nodes, metastases, and vascular invasion.4,10,13,16,18,44 In a retrospective case-control study, Zemlickis et al45 found that women with breast cancer in pregnancy were 2.5 times more likely to have distant metastatic disease, probably because of a later stage at diagnosis. From 56% to 83% of pregnant women have positive nodes at diagnosis vs 38% to 54% in the nonpregnant population.4,2,13,15,16,42-44 It is unclear if these differences are entirely due to delayed detection or if the increased vascularity of the breast during pregnancy, high circulating levels of hormones, and immune-suppressed state of pregnancy accelerate the course of cancer. Notably, in a study by Anderson et al46 of women whose breast cancer was diagnosed before age 30 years, there was no overall difference in the incidence of positive nodes among pregnant (n = 22) and nonpregnant (n = 205) women. That study excluded women who initially had locally inoperable or metastatic disease.

Many studies have also shown decreased estrogen receptor (ER)–positive status in pregnant patients with breast cancer, possibly owing to receptor down-regulation in pregnancy (Table 2).4,13,15,18,39,43-47,53 Merkel8

### Table 2. Estrogen Receptor/Progesterone Receptor Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size</th>
<th>ER−/PR−</th>
<th>ER−/PR+</th>
<th>ER+/PR−</th>
<th>ER+/PR+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonnier et al15</td>
<td>75</td>
<td>31 (41.9)</td>
<td>10 (12.7)</td>
<td>10 (12.7)</td>
<td>25 (32.7)</td>
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<tr>
<td>Berry et al15</td>
<td>24</td>
<td>16 (65)</td>
<td>2 (10)</td>
<td>2 (10)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Jackisch et al15</td>
<td>14</td>
<td>6 (43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nugent and O’Connell9</td>
<td>14</td>
<td>10 ER− (71)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ishida et al12</td>
<td>23</td>
<td>16 ER− (70)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max and Klamra18</td>
<td>4</td>
<td>3 ER− (75)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mitre et al39</td>
<td>10</td>
<td>9 ER− (80)</td>
<td></td>
<td></td>
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<tr>
<td>Wallack et al40</td>
<td>11</td>
<td>9 ER− (81)</td>
<td></td>
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<tr>
<td>Holdaway et al49</td>
<td>3</td>
<td>3 ER− (100)</td>
<td></td>
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<tr>
<td>Sutton et al50</td>
<td>13</td>
<td>9 ER− (69)</td>
<td></td>
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<tr>
<td>Tobon and Horowitz51</td>
<td>14</td>
<td>7 ER− (50)</td>
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<tr>
<td>Elledge et al52</td>
<td>15</td>
<td>10 ER− (67)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Giacalone et al53</td>
<td>15</td>
<td>9 ER− (60)</td>
<td></td>
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</tbody>
</table>

Abbreviations: ER, estrogen receptor; minus sign, negative; plus sign, positive; PR, progesterone receptor.

*Data are presented as number (percentage). Ellipses indicate not applicable.
hypothesized that high levels of circulating estrogens may even prevent ER-positive cancers. Although younger, nonpregnant women tend to have more ER-negative cancers, that does not fully explain the extent of this trend among pregnant women. The largest study of hormone receptor status, by Bonnier et al, involved 75 patients with breast cancer in pregnancy and a control group of 182 nonpregnant patients with breast cancer. In the pregnant group, 42% of cancers were ER-negative and progesterone receptor (PR)–negative vs 21% in the age-matched controls. Ishida et al reported 70% ER-negative and 71% PR-negative tumors in a group of pregnant and lactating women vs 39% and 32%, respectively, in age-matched controls.

Few studies have looked at HER2/neu expression in pregnancy-associated breast cancer. Elledge et al found that 7 (58%) of 12 breast cancers in pregnant women were HER2/neu positive vs 10% to 25% of breast cancers overall. More recently, Gwyn et al reported 4 (36%) of 11 breast cancers in pregnant women were HER2/neu positive. Notably, the HER2/neu oncogene product p105 is overexpressed not only in ductal carcinomas but also in fetal epithelial cells and the placenta. Serum levels of p105 normally increase in pregnancy, particularly toward the end of the third trimester.

**TREATMENT**

Surgery is the definitive treatment for pregnancy-associated breast cancer. Risks of surgery during pregnancy include spontaneous abortion and preterm labor. About 0.5% to 2.0% of all pregnant women undergo operations ranging from biopsies to major procedures. Duncan et al compared 2565 pregnant women who underwent surgery with controls and found more instances of spontaneous abortion (relative risk [RR], 1.58-2.0) in the surgical group, particularly with general anesthesia and gynecological procedures. There was no increased risk of congenital anomalies. Mazze and Kallen examined 5405 cases of nonobstetric surgery during pregnancy and noted increases in neonatal infant mortality rates (RR, 2.1) and low and very low birth weights (RR, 2.0-2.2), which they linked to a greater incidence of prematurity and intrauterine growth restriction. It was unclear if these problems were associated with the underlying maternal cancer that led to surgery. There was no increase in congenital anomalies or stillbirths and no association between type of anesthesia and outcome. Spontaneous abortions were not addressed.

Breast surgery during pregnancy appears to be reasonably safe. In a 1962 series of 134 patients undergoing breast biopsy with general anesthesia, Byrd et al reported only 1 miscarriage. Berry et al performed 14 modified radical mastectomies during pregnancy, including 4 in the first trimester, without any fetal compromise or preterm labor. Collins et al performed 12 breast biopsies during pregnancy, all in the second or third trimesters, with only 1 complication. Most patients received local anesthesia. Of the 3 general anesthesia recipients, 1 also underwent a modified radical mastectomy at 28 weeks’ gestation. She experienced preterm labor successfully treated with magnesium sulfate and terbutaline sulfate and was delivered of a healthy child by cesarean birth at 32 weeks.

Mastectomy and axillary dissection are traditionally considered the best choice for stage I or II and some stage III tumors when the patient wants to continue the pregnancy. Mastectomy eliminates the need for postoperative irradiation in early-stage breast cancer, with its ensuing risks to the fetus. Axillary dissection is preferred because nodal metastases are commonly found in pregnancy-associated breast cancers, nodal status affects the choice of adjuvant chemotherapy, and sentinel node biopsy in pregnant women poses an unknown risk to the fetus from the radioisotope. Nicklas and Baker suggest that sentinel node biopsy may be safe with a minimal dose of 500 to 600 µCi using double-filtered technetium Tc 99m sulfur colloid. However, no supporting studies for this approach are available at this time.

For patients diagnosed in the late second trimester or beyond, lumpectomy and axillary dissection followed by irradiation after delivery represent a viable treatment option. If the woman is far from term, breast-conserving surgery can be followed by chemotherapy after the first trimester and irradiation after delivery. Depending on the treatment timetable, the patient may undergo cesarean delivery as soon as the fetal lungs mature. Kuerer et al reported no difference in disease-free or overall survival rates with breast-conserving surgery for stage I and II tumors compared with modified radical mastectomy (N=26). Of course, treatment varies based on the individual’s tolerance for risk to herself and her fetus and the aggressiveness of her tumor.

Physiologic changes during pregnancy that can complicate sedation and surgery include hypercoagulability, delayed gastric emptying, increased blood volume and cardiac output, decreased functional residual capacity of the lungs, and decreased serum cholinesterase activity. The pregnant patient should be given preoxygenation, antacids, rapid-sequence induction with cricoid pressure, and a cushion under the right hip to reduce vena caval compression.

**Irradiation**

Radiation therapy generally is not offered because it poses 2 kinds of risks: teratogenicity, and induction of childhood malignancies and hematological disorders. Fetal stage of development as well as dose, intensity, and distribution of radiation are directly related to the toxicity of irradiation during pregnancy. Fetal death is most likely to occur before implantation (days 0-9 after conception), whereas radiation-induced malformations occur between days 15 and 50, during organogenesis. Irradiation-induced growth restriction and mental retardation occur during the first trimester, as does the induction of childhood cancer.

With a standard therapeutic course of 5000 rad (50 Gy), the dose to the fetus ranges from 3.9 to 15 rad (0.039-0.15 Gy) in the first trimester to 200 rad (2 Gy) toward the end of pregnancy, when the uterus rises up near the diaphragm. There are several case reports of normal infants born after their mothers had been irradiated, including 1 fetus exposed to 14 to 18 rad (0.14-0.18 Gy)
in the third trimester and another exposed to 3.9 rad (0.039 Gy) in the first trimester. At least 1 radiologist argues that radiation therapy is not absolutely contraindicated as long as wedges and lead blocks are used. However, given the potential for litigation if malformation or leukemia occurs, irradiation cannot be recommended at this time. The excess cancer risk to the offspring is 6.57 cases per 10000 children per rad per year.

Mothers who have undergone lumpectomy and recent chemotherapy may have a decreased milk supply postpartum. Radiation causes changes to the nipple and milk ducts that also make lactation challenging.

### Chemotherapy

For node-positive patients or node-negative patients with a tumor greater than 1 cm, a 4- to 6-month course of chemotherapy is the standard of care. All chemotherapy agents used in the treatment of breast cancer are pregnancy category D, meaning that teratogenic effects have occurred in humans. However, the greatest teratogenic risk occurs in the first trimester; outside that window, most reports show a surprisingly safe profile (Table 3). Through 1985, the National Cancer Institute’s national registry contained 210 reports of chemotherapy use during pregnancy and 52 associated birth defects. Notably, all but 2 defects were associated with first-trimester chemotherapy. Similarly, Doll et al reported a 16% risk of malformations with first-trimester chemotherapy vs a 1.3% risk later in pregnancy.

In the past, alkylating agents such as cyclophosphamide were associated with frequent malformations. One literature review found a 13% risk of birth defects with the use of alkylating agents in the first trimester and a 4% risk later in pregnancy. However, such reviews are subject to reporting bias in favor of malformations. In addition, the cases reviewed often involve multiple agents and irradiation, making it difficult to distinguish the effects of any 1 drug.

In the only prospective clinical trial so far on chemotherapy for breast cancer in pregnancy, Berry et al administered fluorouracil, cyclophosphamide, and doxorubicin in the second and third trimesters to 24 patients with breast cancer using the same dose given to non-pregnant patients. The only modification was that chemotherapy was not given in the first trimester. None of the infants had birth defects. Complications included preterm delivery (3 cases), transient tachypnea of the newborn (2 cases), and 1 case each of low birth weight, hyaline membrane disease, and transient leukopenia. The median gestational age at delivery was 38 weeks. One patient experienced preeclampsia that led to delivery at 33 weeks. A pilot study is planned to evaluate the health of these children.

Other smaller, retrospective studies have yielded similar findings. Preterm delivery, low birth weight, transient infant leukopenia, transient tachypnea of the newborn, and intraterine growth restriction appear to be the most common complications of breast cancer chemotherapy. However, at least half of infants have no complications when their mothers are treated after the first trimester.

Among the chemotherapeutic agents frequently used in breast cancer, methotrexate is strongly contraindicated; it is an abortifacient and the leading cause of chemotherapy-related birth defects. Although fluorouracil has been associated with 1 case of bony aplasia and hypoplasia, the mother in that case was 41 years old and was exposed to at least 5 rad (0.05 Gy) during diagnostic testing, so the teratogenicity of fluorouracil remains unclear. Anthracyclines are considered safer than alkylating agents during pregnancy. In a literature review of 28 patients, there were 2 maternal-fetal deaths from cancer, 2 spontaneous abortions, and no malformations. There is 1 published report of taxane use during pregnancy in the third trimester, resulting in a normal birth. It has been speculated that liposomal encapsulation may decrease the toxicity of these agents.

Long-term effects of chemotherapy on offspring are unknown. Gwyn and Theriault examined the limited data extending across 2 decades and cautiously concluded that antenatal chemotherapy does not appear to affect a child’s growth and development.

Chemotherapy dosage during pregnancy is complicated by increased plasma volume, increased hepatic function, decreased albumin concentration, and decreased gastric motility as well as the theoretical possibility that the amniotic sac might act as a third space. In addition

### Table 3. Congenital Anomalies After In Utero Exposure to Breast Cancer Chemotherapy

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size</th>
<th>Treatment</th>
<th>Trimester</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berry et al</td>
<td>24</td>
<td>CAF</td>
<td>2, 3</td>
<td>No anomaly</td>
</tr>
<tr>
<td>Zemlickis et al</td>
<td>2</td>
<td>CMF, melphalan</td>
<td>1</td>
<td>2 Spontaneous abortions</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>CAFV, tamoxifen</td>
<td>1</td>
<td>No anomaly</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>CAF, tamoxifen</td>
<td>3</td>
<td>No anomaly</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>CMF</td>
<td>3</td>
<td>No anomaly</td>
</tr>
<tr>
<td>Turchi and Villasis</td>
<td>1</td>
<td>CAMF</td>
<td>1</td>
<td>No anomaly</td>
</tr>
<tr>
<td>Murray et al</td>
<td>1</td>
<td>AC, radiation</td>
<td>1</td>
<td>Imperforate anus, rectovaginal fistula</td>
</tr>
<tr>
<td>Mulvihill et al</td>
<td>1</td>
<td>CMF, melphalan</td>
<td>Unspecified</td>
<td>Spontaneous abortion</td>
</tr>
<tr>
<td>Tobias et al</td>
<td>1</td>
<td>AV, prednisolone</td>
<td>2</td>
<td>No anomaly</td>
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<tr>
<td>Cullins et al</td>
<td>1</td>
<td>Tamoxifen</td>
<td>1, 2, 3</td>
<td>Goldenhar syndrome</td>
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<tr>
<td>Tewari et al</td>
<td>1</td>
<td>Tamoxifen</td>
<td>1, 2</td>
<td>Ambiguous genitalia</td>
</tr>
<tr>
<td>Isaacs et al</td>
<td>1</td>
<td>Tamoxifen, 0.17 rad (0.0017 Gy) radiation</td>
<td>1, 2, 3</td>
<td>Preauricular skin tags</td>
</tr>
</tbody>
</table>

Abbreviations: A, doxorubicin; C, cyclophosphamide; F, fluorouracil; M, methotrexate; V, vincristine.
tion, almost all chemotherapy agents cross the placenta. Because the newborn’s liver and kidneys cannot metabolize or excrete chemotherapy drugs quickly, it may be wise to avoid or reduce chemotherapy for 1 month before delivery.35,74,80 Doxorubicin has been measured in the tissues of a stillborn infant whose mother received the drug shortly before delivery.81 Similarly, 5 of 15 women receiving leukemia chemotherapy within a month of delivery had newborns who were pancytopenic.80 In a French survey of women who, on average, had breast cancer chemotherapy 25.2 days before delivery, 1 of 17 had a newborn with leukemia.81 Cyclophosphamide, methotrexate, and doxorubicin can enter breast milk, and breastfeeding is contraindicated during chemotherapy.

The treatment of cancer-related symptoms during pregnancy is almost identical to that in the nonpregnant woman. Many symptoms, such as dyspnea, nausea, and vomiting, overlap with the normal effects of pregnancy. Ondansetron or haloperidol may be used for nausea and vomiting, methylphenidate hydrochloride for fatigue, selective serotonin reuptake inhibitors for depression, metoclopramide hydrochloride for early satiety, and acetaminophen and morphine sulfate for pain. If morphine is used at term, the neonate may demonstrate an abstinence syndrome that can be treated with paregoric.82

Hormonal Therapy

Tamoxifen citrate, a selective ER modulator frequently used in breast cancer regimens, is associated with fetotoxic abnormalities. One fetus exposed to tamoxifen during all 3 trimesters was born at 26 weeks with oculoauriculovertebral dysplasia (Goldenhar syndrome).71 Another female fetus exposed in utero through 20 weeks had ambiguous genitalia.22 There is 1 case report of a New Zealand woman given tamoxifen as her sole systemic therapy for metastatic stage II breast cancer. The fetus was also exposed to 17 rad (0.17 Gy) of radiation before pregnancy was determined. Her son, delivered at 31 weeks, had a normal weight and preauricular skin tags but no major malformations. He had moderate hyaline membrane disease and necrotizing enterocolitis that could be related to prematurity. At age 2 years, he was meeting all developmental milestones. Notably, the mother initially responded to tamoxifen but then progressed rapidly to chemotherapy-resistant disease in the third trimester. She died 23 months after delivery, and her physicians speculated that the changing expression of ER isoforms in pregnancy may have contributed to tamoxifen resistance. The long-term effects of tamoxifen use and whether it may increase gynecological cancers in daughters (as diethylstilbestrol does) are unknown; in pregnant rats, tamoxifen has been associated with breast cancer in the female offspring.73

Oophorectomy is not recommended in conjunction with pregnancy-associated breast cancer, in part because patients are likely to have ER-negative tumors that are not affected by endogenous hormones. In a 1963 study of 41 pregnant patients with breast cancer who had an oophorectomy, none improved.10 Ishida et al13 noted a decreased 5-year survival rate after oophorectomy of 42%, vs 77% in pregnant women who kept their ovaries. Similarly, abortion is no longer routinely recommended; no improvement in survival rate can be found in the available data.5,6,42 One study even associates abortion with a decreased survival rate.42 It is unclear if this is a true trend or a result of the tendency for abortions to be performed in women with worse prognoses who want first-trimester chemotherapy or irradiation.

PROGNOSIS

The prognosis of breast cancer in pregnancy has changed markedly since 1943, when Haagensen and Stout84 reviewed 20 such cases and concluded that surgery was never indicated because the prognosis was hopeless. They subsequently revised that view in a follow-up study and reported a 5-year survival rate of 32%.9

The outlook is now believed to be similar to that for nonpregnant women when adjusted for stage and age (Table 4).8 When matched for age and stage, the 5-year survival rates were 57% in pregnant women and 56% in nonpregnant women in a 1985 study by Nugent and O’Connell.2 In 1994, Petrek at al16 reported a 5-year survival rate of 82% in both pregnant (n=22) and nonpregnant (n=103) women who were node-negative. Among node-positive patients, the survival rates were 47% in the pregnant group (n=47) and 59% in the nonpregnant group (n=63). Notably, however, most breast cancer in pregnancy is still diagnosed at a later stage. Two studies have found no difference in prognosis of early cancers when matched for stage and age but a poorer prognosis for patients with stage II or IIIa cancers.13,86

A growing body of evidence indicates that the risk of breast cancer peaks for 3 to 15 years post partum in all women, followed by a decrease in the long-term.15,94,86,87 Most of this research was done in women without a history of breast cancer. Patients recovering from pregnancy-associated cancer often seek advice on when and if to have another child. Unfortunately, most relevant studies are small and retrospective and rely on physician recall to find women who become pregnant after cancer treatment.88,89

Table 4. Five-Year Prognosis

<table>
<thead>
<tr>
<th>Source</th>
<th>Node-Negative</th>
<th>Node-Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nugent and O’Connell</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>King et al</td>
<td>22</td>
<td>36</td>
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<tr>
<td>Byrd et al</td>
<td>11</td>
<td>19</td>
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<tr>
<td>Bunker and Peters</td>
<td>20</td>
<td>30</td>
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<tr>
<td>Ishida et al</td>
<td>71</td>
<td>101</td>
</tr>
<tr>
<td>Bonnier et al</td>
<td>50</td>
<td>64</td>
</tr>
<tr>
<td>Petrek et al</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>Kuerer et al</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Rosemond</td>
<td>14</td>
<td>23</td>
</tr>
</tbody>
</table>

*Includes cancer in pregnancy and lactation.
†Figures were extrapolated from a graph.
‡Metastases-free survival.
§Breast-conserving therapy was used.
¶Node-negative group includes at least 2 cases of ductal carcinoma in situ.

References 2, 6, 9, 10, 13, 15, 16, 45, 60, 85.
According to the limited evidence, future pregnancies seem safe for the mother unless she has an ER-positive cancer that has not been cured.\textsuperscript{93,90-91} Velentgas et al\textsuperscript{92} found no statistically significant decrease in overall or disease-free survival rates for survivors of breast cancer who become pregnant. More than half became pregnant within 2 years of their diagnosis (N=53). Several studies of women who had a history of breast cancer and subsequently became pregnant have shown a “healthy mother effect”: the former cancer patients who became pregnant had a better 10-year survival rate than their matched controls.\textsuperscript{93,95} Cooper and Butterfield\textsuperscript{94} also found that breast cancer survivors who subsequently became pregnant had a better 5-year survival rate than controls matched for age and stage. Investigators speculate that only cancer survivors who were initially healthy would continue a pregnancy. However, further research is needed, and a prospective multicenter trial is under way in the United States.\textsuperscript{95} Velentgas and colleagues noted an increased risk of miscarriage after breast cancer treatment (24% vs 18% in controls) and speculated that this could stem either from hormonal changes related to therapy or from an underlying higher risk of miscarriage.

The standard advice to avoid pregnancy for 2 years after breast cancer treatment\textsuperscript{10,96} is somewhat arbitrary given that follow-up must extend for decades. Some oncologists recommend that women with stage III cancer wait 5 years and that women with stage IV disease not consider childbearing.\textsuperscript{98} The decision on when it is safe to get pregnant again must depend on a realistic assessment of the worst-case scenario if the mother should relapse during pregnancy or while her children are young.

CONCLUSIONS

Breast cancer in pregnancy will increase as more women postpone childbearing until middle age. Delays in diagnosis are common. Obstetricians should perform a thorough breast examination at the first prenatal visit and maintain a high index of suspicion for cancer. Mammography poses a low risk for radiation exposure to the fetus in the second and third trimesters. However, mammography has a high false-negative rate and is of limited value because of pregnancy-induced changes of the breast. Ultrasonography is a valuable adjunct to the clinical examination, but fine-needle aspiration or core needle biopsy is needed for diagnosis and cannot be postponed until after delivery. Although pregnancy-associated cancers tend to occur at a later stage and are more often ER-negative, they carry a similar prognosis to other breast cancers when matched for stage and age, particularly if they are detected while still node-negative. Mastectomy and axillary dissection is the traditional treatment of choice. Alternatively, if the cancer is diagnosed later in pregnancy, lumpectomy may be done followed by irradiation after delivery. Therapeutic radiation during pregnancy cannot be recommended because of the risk to the fetus. Chemotherapy is relatively safe after the first trimester and is best given after the middle of the second trimester. Its long-term effects are still unknown. Hormonal therapy should not be used in the first trimester; the risks later in pregnancy and in the long-term remain unclear. According to limited evidence, future pregnancies do not appear to change survival rates.

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REFERENCES

Althought breast cancer is the most common nongynecological malignancy during pregnancy, surgeons diagnose few women with breast cancer while they are pregnant. This article provides a thorough review of all of the issues that surgeons must understand and consider in the pregnant woman with breast cancer. Although not explicitly stated, the review makes it clear that termination of the pregnancy is not necessary to adequately treat these women.

The recommendation for a thorough breast examination in pregnant women should be strengthened to include examinations at the beginning of each trimester, particularly in high-risk women. Women with a genetic predisposition, who have had a previous breast cancer or premalignant abnormality such as atypical ductal hyperplasia and lobular carcinoma in situ, who are older than 40 years, and who have new breast complaints should be considered at higher risk than the average pregnant women. Although implicit in the data, the need to accurately diagnose a localized breast mass in a pregnant woman is essential. Women rarely get cysts during pregnancy. Fine-needle aspiration and, for that matter, core biopsy are of minimal morbidity during pregnancy. Although both ultrasonography and mammography have a role in the assessment of breast masses, a tissue diagnosis is still the gold standard.

The only aspect lacking in this review is a recommendation for the psychological support of the woman in this difficult situation. If the surgeon is unsure or uncomfortable, encourage her to see someone with more experience. Assure her that she and her unborn child will go through this well. Involve her obstetrician in all decisions, and, if the obstetrician is uncomfortable, find one who is familiar with the care of women undergoing surgery and chemotherapy. Arrange for her to meet other women who have gone through this, particularly if she will require chemotherapy, as most will. As is pointed out in this review, the choice and administration of chemotherapy is complicated in pregnant women. Help her find someone with significant experience with this growing group of breast cancer patients. Assurance and reassurance that all those involved in her care are familiar with the risks and benefits of each aspect of her treatment are critically important to her psychological stability and her ability to weather this difficult situation.

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