Carcinoma breast in pregnancy and lactation

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ABSTRACT
Breast carcinoma is the most common malignancy associated with pregnancy. The incidence is low but increasing due to increasing number of late pregnancies. Symptoms and signs of the disease may be overlooked, resulting in delays in treatment and potentially compromising survival. For this reason, it is imperative that physicians perform careful clinical breast examinations in all pregnant patients—particularly early in gestation, before the breasts become difficult to examine. Upon finding any suspicious breast mass, an open biopsy without delay is indicated. Modified radical mastectomy may be safely performed and is the primary treatment of choice when cancer is diagnosed during pregnancy. Chemotherapy can be given in late pregnancy, and radiotherapy is best avoided. In some cases, especially when disease presents early in gestation, an interruption of the pregnancy may be warranted. Importantly, stage for stage, breast cancer during pregnancy has a similar prognosis to that of breast cancer in young, nonpregnant women; pregnancy itself does not appear to have an adverse effect on the disease process. There is no need for therapeutic abortion. Stage by stage, the prognosis of breast carcinoma in pregnancy is similar to that of non-pregnant controls. With careful counseling, further pregnancy can be planned after 2-3 years in selected cases.

KEY WORDS
Carcinoma, breast, cancer, malignancy, pregnancy, lactation


INTRODUCTION
The most frequent malignancy concurrent with pregnancy is breast cancer.1-5 Pregnancy associated breast carcinoma (PABC) is defined as that being diagnosed during pregnancy, or within one year thereafter.6,7 Approximately 2-3% of all breast cancers coincide with pregnancy or lactation and this tumour affects only one to four out of 10,000 pregnant women, and is thus a rare occurrence.8,9,10 Therefore, most family practitioners, surgeons and obstetricians encounter a pregnant woman with breast cancer only once every several years. Partly because of the rarity of this clinical entity, misconceptions about the natural history and prognosis of this disease have persisted. These misconceptions have adversely affected both the timeliness of diagnosis and the appropriateness of treatment in a pregnant woman who presents with a breast mass.5 It appears that pregnancy and breast cancer are merely coincidental and that pregnancy or lactation does not directly contribute to the development or accelerated progression of breast cancer.11,12 The most common presentation of a malignant tumor is a painless lump, usually discovered by the patient.13

Breast cancer during pregnancy involves a host of psychosocial, ethical, religious, and legal considerations; and historically has placed the welfare of the mother in conflict with that of the fetus. Although the diagnosis of breast cancer during pregnancy may be only a biological coincidence, the emotional impact of this coincidence can be devastating on both patient and family. Informed medical care and compassionate support are both essential for women who simultaneously must confront the diametrically opposed implications and expectations of a life-giving and a life-threatening process. Other special
considerations with pregnancy-associated breast cancer include the timing of delivery, the potential for nursing, and concerns for future fertility.

**DELAYED DIAGNOSIS**

Multiple studies have documented a delay in diagnosis in breast cancer during pregnancy. In contrast, several recent studies have documented lymph node metastasis in 56% to 89% of pregnant women with breast cancer. Since breast cancer during pregnancy is not inherently a different disease from breast cancer in a young patient, the advanced stage of disease at presentation is more likely secondary to delay in diagnosis. There is an average reported delay of 5 to 15 months from the onset of symptoms.

**DIAGNOSTIC TOOLS**

To detect breast cancer, pregnant and lactating women should practice regular judicious self-examination. A thorough and careful clinical breast examination of the pregnant females at the initial visit to the obstetrician, before the breasts become enlarged and difficult to examine, is necessary, and should be continued thereafter. When a physician identifies a clinically suspicious, dominant mass—a mass discrete and distinct from surrounding tissue—in a pregnant woman, proper referral and diagnosis are necessary.

There are 2 significant differences in diagnosing breast cancer in pregnant women compared to nonpregnant women. These involve the use of fine needle aspiration cytology (FNAC) and mammography. When a pregnant woman presents with a palpable, dominant breast mass, fine needle aspiration should be performed at the initial visit, as with a woman who is not pregnant. False-positive results have been reported and are believed to be due to hormonally related cellular atypia during pregnancy. Therefore, it is recommended that open biopsy be performed in a timely manner when a solid mass is identified during pregnancy. USG is a safe and accurate way to differentiate between solid and cystic lesions.

Mammography is widely employed by many physicians to aid in the evaluation of a suspicious breast mass. With proper shielding, mammography poses little risk of radiation exposure to the fetus and the irradiation dose to fetus is minimal (less than 0.50 mrem). However, mammograms should only be used to evaluate dominant masses and to locate occult carcinomas in the presence of other suspicious physical findings. A mammogram during pregnancy is not easy to read and has at least 25% false-negative rate because of the increased water content of the breast tissue and the loss of contrasting fatty tissue that usually defines a mass. In a series by Max and Klamer, mammograms were read as normal in 6 of 8 pregnant women who had palpable breast masses later diagnosed as cancer. Thus, in a pregnant woman with a suspicious breast mass, a mammogram interpreted as normal may mislead the physician into delaying an open biopsy.

In the setting of pregnancy, there simply is no substitute for a properly performed open biopsy. This is particularly true in light of the diagnostic inadequacy of FNAC and mammography during pregnancy. Importantly, there is no evidence to suggest that a breast biopsy poses any significant anesthetic risk to either the fetus or the mother. In a report of 134 breast biopsies performed on pregnant women with general anesthesia, Byrd and coworkers documented only 1 fetal loss. Clearly, breast biopsy during pregnancy is safe and represents the most definitive means of diagnosing a malignancy. To avoid a false-positive diagnosis as a result of misinterpretation of pregnancy-related changes, the pathologist should be advised that...
the patient is pregnant.\textsuperscript{35,41}

**STAGING**

Procedures used for staging of breast cancer should be modified to avoid radiation exposure to the fetus in pregnant women. Nuclear scans cause fetal radiation exposure. If such scans are essential for evaluation, hydration and Foley catheter drainage of the bladder can be used to prevent retention of radioactivity. Timing of the exposure to radiation relative to the gestational age of the fetus may be more critical than the actual dose of radiation delivered.\textsuperscript{37} Radiation exposure during the first trimester can lead to congenital malformations, especially microcephaly. Doses greater than 100 rad may produce congenital abnormalities in 100% of cases. Doses of 10 rad may result in fewer defects. A chest x-ray delivers 0.008 rad,\textsuperscript{42} and bone scan delivers 0.1 rad.\textsuperscript{12} Chest x-rays with abdominal shielding are considered safe, but as with all radiologic procedures, they should be used only when essential for making treatment decisions.\textsuperscript{12,30} For the diagnosis of bone metastases, a bone scan is preferable to a skeletal series because the bone scan delivers a smaller amount of radiation and is more sensitive. Evaluation of the liver can be performed with ultrasound, and brain metastases can be diagnosed with a magnetic resonance imaging (MRI) scan, both of which avoid fetal radiation exposure. Carcinogenesis in the fetus exposed to radiation is another consideration.

Hormone receptor assays are usually negative in pregnant breast cancer patients, but this may be the result of receptor binding by high serum estrogen levels associated with the pregnancy. However, enzyme immunocytochemical receptor assays are more sensitive than competitive binding assays. A study using binding methods indicated similar receptor positivity between pregnant and nonpregnant women with breast cancer.\textsuperscript{43} The study concluded that increased estrogen levels during pregnancy could result in a higher incidence of receptor positivity detected with immunohistochemistry than is detected by radiolabeled ligand binding, due to competitive inhibition by high levels of endogenous estrogen.\textsuperscript{43}

**TREATMENT OVERVIEW**

The management of PABC is very difficult and encompasses many diagnostic and therapeutic dilemmas. The risk to the unborn child plays a major role in the decision process. Ideally the objectives of treatment are to cure the patient of her cancer and deliver a healthy viable infant. Once the appropriate treatment modality is chosen, its implementation must not be delayed because of the pregnancy. The involvement of multiple subspecialties in the management of these patients is highly recommended. The various treatment options are briefly discussed below.

**Surgery:** Modified radical mastectomy is the mainstay of treatment.\textsuperscript{12,30,38,44-46} General anesthesia is safe if the usual precautions are taken to compensate for the physiologic changes induced by pregnancy.\textsuperscript{12} Typical anesthetic agents readily reach the fetus but are not known to be teratogenic.\textsuperscript{45,47} Since the risk of spontaneous abortion during mastectomy is extraordinarily low, pregnancy is not a contraindication to operative treatment. Modified radical mastectomy is the single treatment modality that allows the pregnancy to continue with minimal risk to both the mother and the fetus. A delay in surgical intervention for breast cancer is as detrimental in a pregnant woman as it is in a nonpregnant woman. Breast conservation therapy, with radiation treatments given after delivery or after neoadjuvant chemotherapy, is an option for women with PABC diagnosed late in pregnancy.\textsuperscript{44} Immediate breast reconstruction is not indicated.\textsuperscript{13}

**Radiotherapy:** The standard radiation therapy course consists of whole breast irradiation followed by a boost dose to the tumor bed, for a total of 5000 cGy.\textsuperscript{13} The amount of radiation scattered to the fetus depends predominantly on the distance of the fetus from the field center. In the first trimester of pregnancy, the embryo/fetus situated at a maximal distance from field center may be subjected to 10 cGy to 15 cGy of radiation. Toward the end of pregnancy, however, when the top of the uterus approaches the xiphoid, as much as 200 cGy of radiation may be delivered to the fetus.\textsuperscript{45} Hence radiotherapy is contraindicated in the first trimester of pregnancy and should be avoided in late pregnancy due to increased internal radiation scatter.\textsuperscript{48,49}

It is not known how much radiation can be tolerated by a developing fetus without inducing significant anomalies; precise data are simply not available. Conclusions must be drawn from atomic radiation reports,\textsuperscript{50} in which relatively small doses of radiation resulted in significant central nervous system abnormalities. By extrapolation, during the first trimester, when a developing embryo/fetus may receive as much as 10 cGy to 15 cGy of radiation, significant radiation-induced anomalies may arise. Brent, in an extensive review of literature, defined 0.05
chemotherapeutic agents in utero can be given during the second or third trimester with minimal risks to the fetus and minimal complications of labor and delivery; but should usually be delayed until after delivery.\textsuperscript{53,54}

The therapeutic decision of whether to initiate chemotherapy depends on the stage of pregnancy and the stage of disease. When a woman is diagnosed with breast cancer during the final trimester of pregnancy, it may be reasonable to delay adjuvant therapy until after delivery. However, because adjuvant therapy may have such deleterious effects on the developing fetus during the first 2 trimesters, and delay in initiating chemotherapy may be harmful to the mother, it may be necessary to consider termination of the pregnancy.\textsuperscript{5,12,44} In some cases, this may be the desired option, allowing appropriate therapy without restriction.

Hormonal Therapy: Hormone therapy, such as treatment with tamoxifen, has not been well-studied in pregnant women, either as adjuvant treatment after surgery or as treatment for advanced cancer, so its effects are largely unknown. Tamoxifen should be avoided in the first trimester and possibly beyond.\textsuperscript{38} Prophylactic ovarian ablation does not influence significantly the course of PABC and should be undertaken only in case of progressive or recurrent disease.\textsuperscript{8}


\textbf{NEED FOR ABORTION}

In the past, when it was thought that pregnancy itself detrimentally stimulated tumor growth, therapeutic abortion was an important element of breast cancer treatment. As it has become apparent that breast cancer during pregnancy is not inherently a different disease from breast cancer in a nonpregnant young woman, enthusiasm for abortion as a therapeutic maneuver has waned. Breast cancer in pregnancy is by itself not an indication for abortion.\textsuperscript{6,44,56,57} No damaging effects on the fetus from maternal breast cancer have been demonstrated, and there are no reported cases of maternal-fetal transfer of breast cancer cells.

Whether a woman proceeds with therapeutic abortion depends on the stage of pregnancy, the stage of disease, the desire for breast conservation, and the priorities of the individual patient. In an individual who insists on breast conservation therapy for a cancer discovered during the first trimester, therapeutic abortion may be preferable to exposing the fetus to ionizing radiation.\textsuperscript{11,12,13} Similarly, the dangers of

\textbf{Chemotherapy:} Postoperative chemotherapy is standard treatment for node-positive premenopausal women with breast cancer, and it may also benefit women without nodal metastasis. Although it is not known what length of time is permissible prior to initiating chemotherapy, it is widely believed that delay may ultimately diminish therapeutic benefit.\textsuperscript{5,12} Since exposure of the developing fetus to chemotherapeutic agents may result in teratogenesis and other serious complications, the decision to start adjuvant therapy during pregnancy is a difficult one.

Doll DC et al.\textsuperscript{51} stated that administration of chemotherapy in the first trimester is associated with a high risk (17\%) of birth defects, in terms of probability of IUGR, prematurity, fetal malformation, or death; this risk is less (1.3\%) in the second and third trimesters. Shapira and Chudley\textsuperscript{52} reviewed 71 patients from 8 reports and found a 12.7\% rate of fetal malformation during the first trimester. Unfortunately, the exact risks associated with chemotherapy are by no means clear. Anecdotal reports suggest that cytotoxic agents result in teratogenesis, intra-uterine growth retardation, cardiac anomalies, delayed carcinogenesis and other serious side-effects in infants exposed to these chemotherapeutic agents in utero.\textsuperscript{12,44,30,53,54,55} These reports showed that the risk of teratogenesis was highest during the first trimester. Neoadjuvant or adjuvant combination chemotherapy consisting of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC)
teratogenesis from chemotherapy may convince a woman in her first trimester to terminate the pregnancy, allowing for therapy without hindrance.\textsuperscript{11,12,13} There is no evidence that termination of pregnancy improves the outlook for the patients or alter the natural history of breast cancer, but it does permit standard aggressive therapy in advanced disease.\textsuperscript{5,12} Hence therapeutic abortion should be performed in all women with advanced-stage disease and in whom a significant delay of this treatment would jeopardize maternal health.\textsuperscript{5,11,12}

However, since advanced-stage breast cancer is essentially incurable despite aggressive adjuvant therapy, the well-informed patient may wish to carry the pregnancy to term.\textsuperscript{11}

**EFFECT OF SUBSEQUENT PREGNANCY ON CARCINOMA BREAST**

Breast cancer risk increases with age; therefore, women who delay childbearing gradually move into a higher risk category for the disease. Since many women are delaying childbearing for educational, professional, or personal reasons the number of women who will undergo breast cancer treatment before completing childbearing is increasing.\textsuperscript{58} The earlier literature stated that at least 7\% of women who did not undergo oophorectomy underwent one or more pregnancies, and 70\% of these pregnancies were to be expected in the first five years after cancer treatment.\textsuperscript{3} Adjuvant cytotoxic chemotherapy depletes the number of fertile patients, but as many as 11\% had a deliberate or unplanned pregnancy in a short-term chemotherapy study.\textsuperscript{59}

Breast carcinoma is not in itself a contraindication to subsequent pregnancy.\textsuperscript{45} Pregnancy does not appear to compromise the survival of women with a prior history of breast cancer, based on limited retrospective data. No damaging effects on the fetus from maternal breast cancer have been demonstrated, and there are no reported cases of maternal-fetal transfer of breast cancer cells.

The available literature shows that breast cancer patients who subsequently become pregnant have good survival rates, often the same or sometimes better than patients with no subsequent pregnancy.\textsuperscript{60-72} Kroman et al\textsuperscript{68} studied 173 women who became pregnant after treatment of breast cancer: Women who had a full-term pregnancy after breast-cancer treatment had a non-significantly reduced risk of death (relative risk 0.55 [95\% CI 0.28-1.06]) compared with women who had had no full-term pregnancy after adjustment for age at diagnosis, stage of disease (tumour size, axillary nodal status, and histological grading), and reproductive history before diagnosis. It has been argued that only women with a good prognosis live to become pregnant, thereby skewing the good results found in pregnancy following breast cancer. The individual woman's prognosis, well-being, desire for children, support from spouse and other socio-economic factors must be carefully considered in this difficult decision-making process.\textsuperscript{60}

It is generally recommended that patients wait 2 years after diagnosis before attempting to conceive.\textsuperscript{45,53,69} This allows early recurrence to become manifest, which may influence the decision to become a parent. In women with more advanced disease, the prognosis is poor, and the patient should be advised that she may not survive long enough to raise the child of a subsequent pregnancy.\textsuperscript{11} Little is known about pregnancy after bone marrow transplantation and high-dose chemotherapy with or without total-body irradiation. Sanders et al\textsuperscript{3} studied the data of 1322 patients who had earlier received high dose Cyclophosphamide or total body irradiation (TBI) from 1971-1992 for hematological disorders; and reported 7\% and 37\% incidence of spontaneous abortion; and 18\% and 63\% incidence of preterm deliveries, in cyclophosphamide and TBI recipients respectively. The overall incidence of low birth weight infants in this series was 25\%, which is higher than the expected incidence of 6.5\% for the general population (P = .0001).\textsuperscript{63}

Clark and Chua\textsuperscript{70} found that 72\% of their patients became pregnant within two years of treatment. Those who became pregnant within six months had a comparatively poor prognosis — a 54\% five-year survival rate compared to a 78\% five-year survival rate among those who waited six months to two years to become pregnant after breast cancer diagnosis. Those who waited five years or more to become pregnant had 100\% five-year survival from that point. They concluded that a wait of at least six months from completion of treatment is recommended. The data are consistent with the fact that the longer survival after diagnosis is, per se, an indicator of the patients' better prognosis (whether pregnancy occurs or not). Some pertinent studies on breast carcinoma after pregnancy are summarized as Table 1.

**LACTATION DURING CANCER TREATMENT**

Suppression of lactation does not improve prognosis.
However, if surgery is planned, lactation should be suppressed to decrease the size and vascularity of the breasts and help avoid having breast milk collect in any previous biopsy incisions.

It should also be suppressed if chemotherapy is to be given because many antineoplastics (specifically cyclophosphamide and methotrexate) given systemically may occur in high levels in breast milk and this would affect the nursing baby. In general, women receiving chemotherapy should not breastfeed.5,12

CONCLUSION

Breast carcinoma is the most common malignancy associated with pregnancy. The incidence is low but increasing due to increasing number of late pregnancies. Symptoms and signs of the disease may be overlooked, resulting in delays in treatment and potentially compromising survival. For this reason, it is imperative that physicians perform careful clinical breast examinations in all pregnant patients—particularly early in gestation, before the breasts become difficult to examine. Upon finding any suspicious breast mass, an open biopsy without delay is indicated. Modified radical mastectomy may be safely performed and is the primary treatment of choice when cancer is diagnosed during pregnancy. Chemotherapy can be given in late pregnancy, and radiotherapy is best avoided. In some cases, especially when disease presents early in gestation, an interruption of the pregnancy may be warranted. Importantly, stage for stage, breast cancer during pregnancy has a similar prognosis to that of breast cancer in young, nonpregnant women; pregnancy itself does not appear to have an adverse effect on the disease process. There is no need for therapeutic abortion. Stage by stage, the prognosis of breast carcinoma in pregnancy is similar to that of non-pregnant controls. With careful counseling, further pregnancy can be planned after 2-3 years in selected cases.

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