Review Article

Pregnancy-associated breast cancer - a review analysis

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Summary

The aim of the present review was to assess the relationship between pregnancy and/or lactation and breast cancer, the influence of pregnancy on mortality and prognosis of the disease, the consequences of breast cancer to the current pregnancy and also to discuss the future perspective for women's fertility. *Materials and Methods:* Articles were obtained from Medline (1988 present) using as keywords breast cancer, pregnancy, breastfeeding, lactation, carcinoma and pregnancy. *Results:* Unfortunately, delays in diagnosis and treatment are common during pregnancy and the prognosis is thus worsened. Nulliparity, early menarche and late age at first pregnancy are associated with increased risk for breast cancer. Breastfeeding confers a protective effect on risk of breast cancer, which appears to be related to the duration of breastfeeding. In cases of advanced metastatic disease during the first 14 to 15 weeks of pregnancy when chemotherapy is necessary for prompt treatment, termination of pregnancy may be proposed, particularly if the patient is ER-positive. Modified radical mastectomy is probably the procedure most frequently used today. In general chemotherapy should be delayed until after 14 to 15 weeks of gestation and radiation should be reserved until post delivery. Several authorities generally advise that future pregnancy should be delayed for at least two years after breast cancer treatment. *Conclusion:* Breast cancer has an equivalent prognosis in pregnant and non pregnant patients when matched by age and stage at diagnosis. Women are invariably best treated by multidisciplinary teams.

Key words: Pregnancy; Breast cancer; Chemotherapy; Mammography; Breastfeeding and breast carcinoma.

Introduction

Breast cancer remains the most common cancer in women, with a lifetime risk of almost 11% [1]. It is expected to be increasingly common as childbearing is delayed until later in life. It is actually the most common cancer encountered in pregnant women, occurring from one in 3,000 to one in 10,000 pregnancies [2]. Most researchers define pregnancy associated breast cancer as one that is diagnosed during pregnancy or up to one year postpartum [3]. At least 10% of patients with breast cancer who are younger than 40 years will be pregnant at diagnosis [3]. It is estimated that if one includes the latent time period of breast cancer, then quite probably a lot more women with breast cancer have been pregnant at some time during the disease. When women delay their first pregnancy until the age of 35 years or more, the risk for developing breast cancer increases 3-fold compared to women who conceive at the age of 20 years [4]. Only about 3% of women diagnosed with breast cancer will be pregnant. Unfortunately, delays in diagnosis and treatment during pregnancy are common. Pregnancy induces both proliferation and differentiation of the mammary epithelium. The size, weight, vascularity and density are markedly increased. Thus, the engorgement of the breasts during pregnancy and lactation may hinder detection of masses. There is significant difficulty in detecting pathology within a breast with physiological changes in pregnancy. As a consequence of this delay in diagnosis and treatment prognosis is worse in pregnant than in non-pregnant women, with an increased risk of late-stage disease, particularly in women younger than 30 years old [5]. A delay of one month in primary tumor treatment increases the risk of axillary metastases by 0.9% and a six month delay by 5.1% [6].

This article reviews the currently available literature on diagnosis, risk factors, treatment and prognosis.

Methodology/Sources

Articles were obtained from Medline and PubMed (1988-today) using as keywords "breast cancer, pregnancy, breastfeeding, lactation, carcinoma and pregnancy, breast neoplasms". We summarized the current literature regarding epidemiology, diagnosis, risk factors, treatment and prognosis. Only articles in English were used. Data extraction was performed by the first and corresponding authors.

Clinical presentation and differential diagnosis

Pregnancy-associated breast cancer usually presents as a painless thickening, lump or mass, which is firm, deep-seated and frequently accompanied by nipple discharge. During breastfeeding the woman might note that the infant refuses to breastfeed from the breast that contains the cancer ('milk rejection sign') [7]. Local infiltration may cause fixation of the tumor to the chest wall or edema. Bloody nipple discharge per se does not indicate

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malignancy during pregnancy or lactation, unless it is accompanied by a palpable mass, or if it persists for more than two months. In many cases it may be associated with the initiation of breast-feeding [5]. In any case, cytological study of the bloody discharge is indicated, although the interpretation might be difficult due to physiological proliferative changes associated with pregnancy [2].

Mean breast weight normally doubles during pregnancy, resulting in breast firmness and increased density. All these facts make the clinical and imaging examinations more difficult to interpret. The differential diagnosis of a breast mass in a pregnant woman includes carcinoma, fibroadenoma, lactating adenoma, fibrocystic disease, lobular hyperplasia, lipoma, adenolipoma, galactocele, abscess, sebaceous cysts, fat necrosis, hamartoma and more rarely lymphoma, sarcoma, tuberculosis and neurofibroma [8]. Most of the benign masses diagnosed in pregnancy are the same as those found in non-pregnant women, although they may differ in size, consistency and histological characteristics, due to the hormonal stimulation of pregnancy and lactation. It is noted though that about 30% of these such as lactating adenomas, galactoceles, mastitis and infarcts are unique in pregnancy [9].

Genetic and reproductive risk factors for breast carcinoma

In general, the risk for breast cancer is directly related to the duration of ovarian function. Interruption of the normal cyclic ovarian function by pregnancy appears protective. Pregnancy itself does not appear to influence the outcome of an established breast cancer [8]. Paradoxically, women with a genetic predisposition to breast cancer may be at increased risk during pregnancy and lactation [1, 6]. Various studies in different centers in Japan [10] and Sweden [11] conclude that carriers of BRCA1 and BRCA2 mutations are more likely to develop breast cancer before the age of 40 and during pregnancy than carriers who are nulliparous, and each pregnancy is associated with an increased risk of cancer [1]. Among BRCA mutation carriers, high levels of circulating estrogens during pregnancy may accelerate a malignant transformation that has already begun. Giving birth at a young age does not appear to protect these women against breast cancer [12].

Nulliparity, early menarche and late age at first pregnancy are associated with increased risk for breast cancer [1, 13]. After a full-term delivery a short-term increase in the risk of breast cancer is observed, peaking at three to four years after delivery (relative risk 1.21, 95%CI 1.02-1.44), followed by a subsequent decrease [1]. The mechanism of hormonal influence during pregnancy and lactation is not clear and a pregnancy that ends with preterm delivery has less long term protection [13, 14]. Additionally, studies have concluded that complications of pregnancy like preeclampsia, are associated with a reduction in the risk for subsequent breast cancer [15, 16]. According to a meta-analysis from the Collaborative Group on Hormonal Factors in Breast Cancer breastfeeding confers a protective effect on risk of breast cancer (reduction of about 4%), which appears to be related to the duration of breastfeeding [17]. Termination of pregnancy during the first trimester will lead to a less protective effect against future breast cancer for the women and actually doubles the risk, in comparison with those women who carry a full-term pregnancy [7, 8].

Diagnostic evaluation

Since breast changes become more pronounced in later pregnancy, it is important to perform a thorough breast examination at the initial visit. Diagnostic delays are often attributed to physician reluctance to evaluate breast complaints or abnormal findings in pregnancy. Actually, delay in diagnosis of breast cancer in pregnancy is three to seven months and women are at increased risk of presenting with advanced disease [8]. The increased vascularity and lymphatic drainage of the breast during pregnancy and lactation could be an important factor for metastatic spread, leading to a rather late diagnosis, when the disease is at a more advanced stage. Over 75% of pregnant women diagnosed with breast cancer have nodal metastases when diagnosis is confirmed [8] and women with breast cancer during pregnancy are 2.5 times more likely to have distant metastases than non-pregnant patients.

Physical examination is rather difficult and inaccurate due to the anatomical differences of the breast during pregnancy. A mass might seem to be the same clinically due to the increasing enlargement of the breast, but in reality the mass is surrounded by and buried under the changing breast tissue and is enlarging. A laboratory test that could be useful for monitoring breast cancer in pregnancy is the serum tumor marker CA 15-3.

Mammographic evaluation is controversial with high false-negative rates during pregnancy owing to the high density of the breast. Most authors agree that radiation exposure of the fetus during the mammography is negligible and safety can be established with abdominal shielding [6, 17, 18]. A standard mammography subjects the fetus to only 0.4 mrad (0.004 Gy) [3, 19]. Congenital malformations and spontaneous abortion occur with exposure to more than five rads (0.05 Gy) during the first 24 weeks of pregnancy. There are no reports of untoward effects of mammography on the mother and/or the fetus [20]. The examination though is associated with a low sensitivity. At least 25% of mammograms in pregnancy may be negative in the presence of a cancer. Ishida *et al*. reported successful breast cancer diagnoses in 34 of 50 mammograms of pregnant women [10]. However limited in the evaluation of the pregnant patient, mammography can and must be used as a screening test during pregnancy and lactation when indicated.

Ultrasound is a useful and inexpensive diagnostic modality suitable for diagnosing pregnant women, showing an accuracy of almost 97% in distinguishing between a cystic and a solid lesion and increased accuracy in confirming the presence of palpable masses [18]. It can be used as an adjunct to mammography, increasing the accuracy of diagnosis [21].

Magnetic resonance (MRI) is another diagnostic modality potentially useful in distinguishing and delineating the soft tissue lesions of the breast. Although it does not involve any irradiation, heating and cavitation could be potential risks to the fetus [19, 20, 22]. There is no consensus regarding avoidance of MRI imaging in the first trimester, however it is known that gadolinium crosses the placenta and is associated with fetal abnormalities in rats (FDA category C) [19, 21]. For the diagnosis of metastasis in the brain, liver and bones MRI imaging is the preferred option with quite high sensitivity. Metastases to the placenta are very rare but possible, and usually are discovered post partum. Generally they have been reported in association with widespread metastatic disease. No metastases to the fetus have ever been detected though in cases of breast carcinoma [23], but there are reports for metastases in cases of melanoma, hepatoma, choriocarcinoma and hemotopoietic malignancies.

Fine-needle aspiration (FNA) of the breast mass for cytologic study is a simple procedure. As a diagnostic method, FNA is very reliable for the diagnosis of carcinoma. It is the initial procedure of choice for evaluating a breast mass during pregnancy and lactation. In cases of solid masses excisional biopsy and histological examination of the tissue is recommended when FNA is non diagnostic. Biopsy is usually performed under local anesthesia which is not harmful for the fetus. Consistent to the fact that most patients during pregnancy are young, the majority of breast cancers diagnosed are estrogen receptor (ER) and progesterone receptor (PR) negative. Approximately, 20% of breast biopsies performed during pregnancy reveal breast malignancy [8, 9, 18]. It is very important though to remember the fact that the proliferation seen in normal breasts in pregnancy can be confused with malignant changes and that there are false negative results for ER status because of competitive inhibition by high levels of estrogen with the ligand-binding method. Immunologic assays using monoclonal antibodies which recognize both occupied and unoccupied receptors seem to more accurately reflect the receptor status.

Liquid crystal thermography is a type of brachythermometry where the breast is pressed against a thermosensitive plate lined with cholosteric crystals and a thermographic film representing the thermal pattern of the breast is obtained. Although some authors recommend thermography as an adjunct in diagnosing breast malignancies, others do not agree [24].

Staging studies should be performed and an individualized decision must be made regarding need for subsequent chemotherapy. Among blood tests, measurement of alkaline phosphate levels is unreliable since they normally double or even quadruple during pregnancy. Chest X-ray is considered safe during pregnancy. Ultrasound imaging of the liver is preferable to CT scanning. MRI may be considered in cases of non diagnostic or hard to interpret ultrasound findings. If bone metastases are suspected a bone scan with ^{99m} technetium is advisable.

Treatment of pregnancy associated breast cancer

Pregnancy itself does not appear to influence the outcome of an established breast cancer [8]. Carcinoma of the breast in pregnant women is histologically similar to the ones encountered in non-pregnant patients. There is a similar incidence of inflammatory breast cancer in both groups [6, 24]. Pregnant women tend to have more ER-negative cancers, possibly due to a physiological receptor downregulation in pregnancy [6, 24]. Various studies have reported almost two times higher incidence of ER-negative breast cancers, as many as 80% in pregnant women in comparison with non-pregnant patients [10, 25, 26]. Younger non-pregnant patients tend to have decreased estrogen receptor status when diagnosed with breast cancer. This fact gives little theoretical grounds for suggesting pregnancy termination and oophorectomy as an adjunct to therapy when relevant. There is no evidence that termination of pregnancy after diagnosis of breast cancer is necessary to improve prognosis [1]. A harmful effect of continuing pregnancy has not been demonstrated in most published series, and therapeutic abortion fails to improve survival rates [1, 24, 27]. Spontaneous abortions and premature deliveries are not increased in pregnant breast cancer patients. The only advantage of pregnancy termination seems to be that it removes the need to consider possible detrimental effects on the fetus and complete treatment with chemotherapy, radiotherapy and surgery can be instituted immediately. However, it is difficult to evaluate the potential bias on the published literature, concerning the impact of termination of pregnancy in patients with advanced disease. In general, delays of therapy should be avoided and the recommendation to terminate the pregnancy should be based only on whether the pregnancy itself is an obstacle to effective therapy and on whether the treatment is going to be harmful for the fetus. In cases of advanced metastatic disease diagnosed during the first 14 to 15 weeks of pregnancy when chemotherapy is necessary for prompt treatment, termination of pregnancy may be suggested and considered, particularly if the patient is ER-positive [1, 8, 24, 28]. Termination of pregnancy may also be considered for women with recurrent disease. Breastfeeding women who have completed their treatment can safely breastfeed from the unaffected breast, although radiotherapy may affect or even inhibit lactation due to subsequent fibrosis. Breastfeeding is however discouraged in patients receiving chemotherapy or radiotherapy [29, 30].

Although there are no standard protocols available, the data for immediate treatment are generally reassuring. On the other hand, delay or refusal to undergo appropriate treatment has serious consequences [31]. Because of potential risks to the developing fetus, decisions on therapeutic protocols carry an additional burden. Any treatment must therefore be individualized in accordance with current knowledge and stage of disease as well as the wishes of the patient. Breast surgery during pregnancy appears to be reasonably safe, particularly in the second and third trimester. The relative risk for spontaneous

abortion is 1.58 to 2.0 [8, 24, 32]. There is an increase in infant mortality rate (RR 2.1) and low birth weights (RR 2.0-2.2), but no increase in congenital anomalies or stillbirths and no association between type of anesthesia and pregnancy outcome [8, 32].

Breast surgery is first-line treatment for pregnancy-associated breast cancer with mastectomy and axillary dissection being the preferred option [31, 32]. Modified radical mastectomy is probably the procedure most frequently used today and entails the preservation of the pectoralis major and minor muscles, providing better arm motion and thoracic outline and reducing the incidence of postoperative lymphoedema [24]. Mastectomy and axillary dissection are traditionally considered the best option for Stage I, II and III cancers for women who continue pregnancy. The operation eliminates the need for postoperative irradiation in early-stage disease. Because nodal metastases are common in pregnancy-associated breast cancer and the nodal status affects the choice of adjuvant chemotherapy, axillary dissection is essential. It is prudent to limit breast conserving therapy only for women with early-stage disease, who desire breast conservation and for women diagnosed in the late third trimester [24]. The modality of breast conserving surgery (lumpectomy or quadrantectomy) is discouraged because it generally involves postoperative radiotherapy, which is contraindicated during pregnancy. An external irradiation dose of 5000cGy to the breast exposes the fetus to at least 10-15 cGy with increased risk of teratogenicity, intrauterine growth restriction, mental retardation, childhood malignancies and hematological disorders [24, 32]. Irradiation during the first trimester is more likely to lead to fetal demise. The radiation required to complete therapy can be delayed safely as much as eight weeks from the diagnosis, allowing safe delivery of the infant [33].

For node-positive women or node-negative with a tumor greater than 1 cm, a four to six months course of chemotherapy is the standard care [34]. Generally speaking, all chemotherapeutic agents cross the placenta and are theoretically teratogenic and mutagenic. They may lead to intrauterine restriction, fetal malformation, spontaneous abortion, fetal intrauterine death, preterm delivery, hyaline membrane disease, transient leucopenia, and pancytopenia. However, the greatest teratogenic risk occurs in the first trimester. About 10-20% of infants exposed to cytotoxic agents during the first trimester, when organogenesis is taking place, have major malformations [35, 36]. The risk for malformations is rapidly decreased to 1.6% to 3% if chemotherapy is administered later in pregnancy [8, 35, 36]. In general chemotherapy administration should be delayed, if possible, until after the 14th to 15th week of gestation. Among chemotherapeutic agents used in breast cancer, methotrexate is strongly contraindicated during the first trimester, due to its high abortifacient and malformation action. Also, tamoxifen citrate, a selective ER modulator, is considered inappropriate due to concerns over associated fetal anomalies and lack of efficacy. Most authorities consider sufficiently safe for second and third trimester administration the combination of cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) and the combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) [31, 32, 34-36]. Breastfeeding women should not receive chemotherapy as these agents are secreted to the milk. Chemotherapy dosage is another important issue because of the increased plasma volume, increased hepatorenal function, decreased albumin concentration and decreased gastric motility. Palliative chemotherapy or radiotherapy may be considered for advanced and technically inoperable disease.

Prognosis, subsequent pregnancy and fertility

Breast cancer has an equivalent prognosis in pregnant and non pregnant patients when matched by age and stage of disease at diagnosis [3]. There is no statistically significant difference to the 5-year survival rates for patients matched for age and stage of disease [3, 6, 37]. Pregnancy-associated breast cancer might carry a worse prognosis since it tends to be diagnosed in more advanced stages. The nodal status is of prognostic significance, as well as the number of positive nodes. Pregnancy, probably due to the delay in diagnosis, appears to increase the risk for nodal metastatic disease, with 60 to 85% of women exhibiting auxiliary nodal disease and thus resulting in a worse prognosis [1, 2, 7, 8].

There are no prospective studies evaluating the impact of subsequent pregnancy on breast cancer and even in cases with metastatic disease no adverse effects of subsequent pregnancy have been reported. Unfortunately, most relevant studies are small and retrospective. According to the limited evidence, future pregnancies seem safe for women as long as they have an ER-negative cancer [38, 39], and no statistically significant difference was found in overall or disease-free survival rates for survivors of breast cancer who become pregnant [40-42]. Long-term survival after breast cancer does not appear to be affected by subsequent pregnancy [1]. Additionally, there is some evidence of a 'healthy mother effect', in the sense that a future pregnancy might have a protective effect with a trend towards improved prognosis when compared with women not becoming subsequently pregnant regarding the 5- and 10-year survival rate [1, 6, 39, 43]. However, when the interval is smaller than six months, the 5-year survival has been reported to be 54% in comparison to 78% for women with an interval between treatment of breast cancer and pregnancy of six months to two years [1]. Several authorities generally advise that future pregnancy should be delayed for at least two years after breast cancer treatment and this interval should be extended up to five years for women with metastatic disease [1, 6, 24, 37]. Most women have recurrences within two years and it is likely that this interval will contribute to the identification of those with a better prognosis than those with more aggressive disease. Since younger women have higher relapse rates and significantly lower survival rates, those under 33 years old should consider delaying pregnancy for at least three years to reduce the risk of relapse

[44]. No firm conclusions can be drawn from the available body of evidence up to date. In the end the decision on when it is safe to become pregnant again is realy difficult and should be based on a realistic assessment of the worst case scenario if recurrence of cancer occurs during the subsequent pregnancy.

Chemotherapy significantly affects subsequent fertility, mainly because of increased risk of ovarian failure. Alkylating agents (cyclophosphamide) might cause amenorrhea through ovarian depression [3, 45]. Other chemotherapeutic agents like methotrexate and 5-fluoroucil do not have the same negative effect. Women must be counseled for fertility preservation prior to chemotherapy about the new techniques of egg freezing and ovarian tissue cryopreservation [46]. High levels of circulating estrogens during ovarian stimulation treatments should be considered as a potential risk factor for recurrence especially for women with a history of ER-positive disease [45, 46].

Conclusion

Pregnancy-associated breast cancer incidence will increase as more women postpone childbearing until later in their reproductive life. No aspect of breast cancer is more challenging than diagnosing, counseling and treating pregnant women. The approach should be based on individual patient needs and can not be generalized. Women are invariably best treated by multidisciplinary teams involving surgeons, obstetricians, medical oncologists, neonatologists and psychologists.

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