

ORIGINAL ARTICLE

## Breast Cancer in Pregnancy

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**Abstract:** Pregnancy-related breast cancer (PBC) is one of the most common malignancies during pregnancy (approx. one in 3,000 pregnancies); up to 3% of breast cancers are diagnosed in pregnancy. As maternal age at the time of pregnancy continues to increase as the incidence of breast cancer, the incidence of PBC is expected to increase. A review of the literature was performed in order to identify optimal treatment strategies. Most of the data surrounding the diagnosis and treatment PBC is small cohort studies, and there are no randomized controlled trials. Diagnostic delays are common. Preoperative histologic confirmation is required. Conservative surgery can be proposed at the end of second and third trimester, and radiotherapy is delayed after childbirth. The safety of sentinel lymphnode biopsy has yet to be confirmed, and the axillary dissection is the traditional treatment of choice. The chemotherapeutic agents utilized are the same as those used in non-pregnant patients, but they should not be administered in the first trimester. Radiotherapy and endocrine therapy are recommended to be avoided during pregnancy. The treatment of PBC is multidisciplinary and necessitates active communication among the patient, obstetrician, medical, surgical, and radiation oncologists. Diagnosis is often delayed because of physiologic changes of the breast; obstetricians should perform a thorough breast examination at the first prenatal visit and maintain a high index of suspicion for cancer. Other therapies may need to be considered, although their usage now is not currently recommended owing to the paucity of safety data. ■

**Key Words:** breast cancer, pregnancy-related breast cancer

Pregnancy-related breast cancer (PBC) represents 3% of all breast cancers with an incidence of 10–40 per 100,000 pregnancies; it is the second most common cancer occurring during pregnancy secondary only to cervical cancer.

Because nowadays it is a current trend to delay childbearing until the late fertile age, PBC rate is expected to increase. PBC is becoming a more frequent problem faced by a multidisciplinary team composed by surgeons, oncologists, gynecologists, and obstetricians.

Because of its low incidence similarly to other cancer arising during pregnancy, it is difficult to conduct large prospective studies on PBC in order to examine diagnostic and therapeutic tools and options; no evidence exists concerning the management of this pathological condition.

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### DIAGNOSIS

A controversial issue in PBC is the delay in diagnosis; most recent studies report a delay in diagnosis of 1–2 months (1–3). Therefore, PBC often presents as locally advanced disease. During pregnancy, breasts are involved in severe morphologic changes. There is a marked increase in number and complexity of the terminal ductules resulting in physiologic hyperplasia of the terminal duct and lobular units. In term pregnancy, the ductules are transformed into complex structures with hyperplastic lining cells showing evidence of secretory activity and papillary infolding. In the later stages of pregnancy, there is loss of staining of the terminal duct epithelial cells for estrogen and progesterone receptor protein.

Clinical examination of breasts during pregnancy is difficult because breast presents increased density and firmness. About 80% of women with a palpable painless lump during pregnancy have a benign mass. Any palpable lump persisting for more than 2 weeks should be deeper investigated with further specific workup. Nipple discharge and “milk rejection” sign are not frequently present.

When a breast nodule is clinically detected during pregnancy, the first examination to be performed is ultrasound examination, which is a safe and accurate imaging technique. Moreover, ultrasound examination is also useful to perform fine-needle aspiration or core biopsy that is necessary to reach a definitive diagnosis.

Owing to physiologic changes occurring in breasts during pregnancy, mammography has less sensitivity and is associated with a high false-negative rate; anyway it remains a fundamental imaging tool in the evaluation of PBC. Mammography exposes fetus only to 0.004 Gy, below the threshold for deterministic effect (4).

The use of breast magnetic resonance imaging (MRI) is still controversial because the challenging to discriminate malignant and physiologic hypervascularization occurring during pregnancy and because gadolinium crosses the placenta and is associated with fetal abnormalities in rats (5).

In the diagnostic process, fine-needle aspiration biopsy (FNAB) remains an increasingly important diagnostic tool in the assessment of the nature of various breast lesions. During pregnancy, FNAB provides an opportunity for women to have their breast lesions sampled and examined without significant morbidity for patient and her fetus. The established diagnosis of breast cancer by FNAB allows more flexibility for treatment planning providing prognostic information (6,7). As PBC often occurs as a large mass, core biopsy could be indicated. Moreover, core biopsy could be performed when FNAB is not successful. In rare cases, core biopsy may cause a milk fistula, so it is important to accurately empty the breast with ice packs and binding before biopsy.

When breast cancer is demonstrated, an accurate staging of the disease is needed. Chest X-ray is a safe procedure exposing the fetus at 0.0001 Gy; ultrasound is accurate in evaluating hepatic and abdominal conditions and low-dose bone scan could be used for bone metastases, although no overall consensus among authors has been obtained for this last examination. Unenhanced MRI could be performed in case of suspected liver or bone metastases (8–11).

## PATHOLOGY

In about 80% of patients, PBC is an infiltrating ductal carcinoma. The majority of breast cancers in

pregnancy present high grade and lymphovascular invasion. Microscopically PBC shows high cell yield with granular proteinaceous background; often dispersed cells and loosely arranged cell clusters, large epithelial cells with uniform nuclei and prominent nucleoli; abundant, foamy, vacuolated cytoplasm with fraying of cytoplasmic borders. Many studies showed that around 70% of these tumors are estrogen and progesterone receptors negative in contrast to non-pregnant women (2,3). About two-thirds of cases at diagnosis show a lymphnodal involvement. Studies with limited population also revealed a higher expression of Her2/neu (12,13).

## TREATMENT

The treatment of PBC is a challenging issue because of the lack of standardized guidelines and evidences arising from randomized controlled trials. Planning and timing of different therapeutic procedures is strictly related to the stage of the tumor and to the health of fetus and the mother. The need for prompt treatment presents a clinical dilemma of considerable magnitude as there is always a conflict between optimal maternal therapy and the resultant risks imposed on fetal well-being.

However, the goal for treatment of the pregnant woman with breast cancer is the same as that of the nonpregnant patients with breast cancer: local control of the disease and prevention of systemic metastases. During pregnancy, some treatment modalities need to be modified because of the potential for adverse effects on the fetus.

### Surgery

Surgery remains the mainstay of treatment of breast cancer during pregnancy and is the first step of a multidisciplinary approach to the tumor as in nonpregnant patients. Surgery is a safe procedure; it can be performed in all trimesters of pregnancy with minimal risk for the fetus; after the 12th week of gestation, the risk of abortion is minimal (8–11).

Mastectomy and axillary lymphadenectomy are the surgical procedures most frequently performed because of the large size of the tumor at presentation and the higher rate of axillary nodal involvement. Radical mastectomy can be followed by immediate breast reconstruction with implants and also in pregnant women this is considered an effective step of the treatment of breast cancer.

Breast-conserving surgery could be performed preferably in the last trimester because of the necessity to be followed by radiotherapy that in any case must be delayed after surgery. Moreover, after the first trimester it is possible for the patients to undergo chemotherapy before or after surgery.

Sentinel lymphnode biopsy in pregnant women is little evaluated, and there is not overall consensus among Authors in literature on the safety of this procedure during pregnancy owing to radiation concerns. Gentilini et al. recently showed the results of a study conducted on 12 pregnant women with breast cancer who received low-dose lymphoscintigraphy using  $^{99m}$ -Tc human serum albumin nanocolloids; eleven healthy babies were born with no malformation, one baby had a ventricular septal defect suspected before the lymphoscintigraphy was performed. They support the safety of sentinel lymphnode biopsy in pregnant patients with breast cancer (14).

### Radiotherapy

Radiation therapy is contraindicated during pregnancy owing to its teratogenic effects on fetus. In the first trimester (before the completion of organogenesis), radiotherapy may be related to fetal death, malformations, mental retardation, and induction of childhood neoplasms and hematologic disorders (15).

### Chemotherapy

As PBC often presents as locally advanced disease at diagnosis, chemotherapy could be proposed as adjuvant or neoadjuvant treatment. There are few published data concerning the use of chemotherapy for breast cancer during pregnancy. The risk of major complications using cytotoxic agents is related to the time of application, type of agent, and variations of factors such as plasma volume, hepatorenal function, or albumin concentration. In the first trimester, the risk of congenital malformations ranges from 10–20%, whereas it drops to 1.3% in the third trimester (16). Chemotherapy is generally not administered during the first trimester because of the possible damage to organogenesis, whereas during the second and third trimesters has lower complications. A large retrospective multicenter series from five London Teaching Hospitals reported no major fetal malformations in 27 children whose mothers were treated with chemotherapy regimens based on cyclophosphamide, metothrexate, fluorouracil and anthracycline at second and third trimester (17), providing evidence that in terms of peripartum

complications and immediate fetal outcome, chemotherapy can be safely administered (with same efficacy) to women during the last two trimesters of pregnancy. Similarly, a group of oncologists from the University of Texas M.D. Anderson Cancer Center reported in a series of 57 patients treated with fluorouracil, doxorubicin, and cyclophosphamide chemotherapy no significant short-term complications to the fetus (18).

### Hormonal therapy

As pregnancy-associated breast tumors are usually poor in estrogen receptor, they are believed to be unresponsive to hormonal therapy. There are also few data about the use of anti-hormonal therapy during pregnancy and nowadays it is not recommended (19). There are some reports that describe neonatal abnormalities of the genital tract (20). Although no fetal abnormalities are reported in the study of Clark (21) on 85 women who took tamoxifen for breast carcinoma prevention, further confirmations have to be obtained before proposing clinical use of hormonal therapy during pregnancy.

### Termination of pregnancy

Termination of pregnancy and postpartum delayed treatment are not routinely recommended in the case of PBC and a number of reported series suggested that it does not improve survival (22). In case of advanced disease presented in the first trimester, abortion can be proposed to avoid delay in treatment.

## CONCLUSIONS

Pregnancy-related breast cancer is still a controversial issue. Diagnosis of PBC may be difficult owing to the physiologic modifications of the breast structure during pregnancy. Treatment of PBC is challenging in consideration of the potential risks for the fetus and the possible maternal benefit. Given its different and various implications, biologic, diagnostic, therapeutic, and psychologic, the management of PBC needs a multidisciplinary cooperating team; a close cooperation between all disciplines is mandatory in order to reach an optimal treatment strategy for the patient and her unborn child. Future evidence and ongoing studies are expected to solve problems related to breast cancer management during pregnancy.

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