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Management of breast cancer during pregnancy

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ABSTRACT

Introduction: Pregnancy-associated breast cancer (PABC) is one of the most common malignancies during pregnancy. Since maternal age at the time of pregnancy is increasing, PABC rate is expected to increase. Diagnostic delays are common.
Methods: Retrospective observational study analysing twelve pregnant patients with breast cancer who underwent surgical treatment during the period of February 2006 to June 2013 at the Department of Surgery I, University of Insubria Varese.
Results: The median age of pregnant patients was 34 y (range 28–44 y). Three patients were affected by BRCA1 mutation. In six patients diagnosis was made during gestation, in the other six patients breast cancer was discovered during breastfeeding. Ten patients underwent breast-conserving surgery. Sentinel lymph node biopsy was performed in six patients; in one of them it was positive so axillary dissection was simultaneuosly performed. Six patients underwent axillary dissection ab initio. In all cases the histological type was invasive ductal carcinoma; grade 3 in ten patients and grade 2 in two patients. Eleven of twelve patients received adjuvant chemotherapy, one patient both adjuvant and neoadjuvant. In three cases also radiation therapy was performed after delivery. In all cases healthy babies were born. Nine of twelve patients are still alive and disease free, after a median follow-up of 20 months (range 3–52 months). Three patients died from systemic progression of the disease.
Conclusion: There are no significant series of patients in worldwide literature to develop standard protocols. Pregnant women must be followed by a multidisciplinary team.

1. Introduction

Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy or within one or two years after delivery. [1,2]

Breast cancer is the second most common malignancy diagnosed during pregnancy, ranging from 1 in 1,000 to 1 in 3,000 pregnancies [3,4]; up to 3% of breast cancers are diagnosed in pregnant women [5] between the ages of 23 and 47 years (median age, 33 years). [6] However, the incidence is expected to increase as more women delay childbearing.

1.1. Diagnosis

The delay in diagnosis is still a controversial issue in PABC; recent studies report a delay in diagnosis of 1–3 months. [7] During pregnancy and lactation, the breast undergoes dramatic changes in response to an increase in the circulating hormones estrogen, progesterone, and prolactin, which all have a proliferative effect on glandular and ductal tissue. [8] The breast changes can obscure detection of breast mass for patients and physicians, leading to more advanced stages at diagnosis than in the general population. [9,10] Clinical examination of breasts during pregnancy is difficult because the breast presents increased density and firmness. Breast ultrasonography is the first diagnostic instrument used by clinicians when a breast mass and the axillary area need to be assessed in a pregnant woman, since it is non-ionizing and has high sensitivity and specificity. [6,11] Mammography has less sensitivity and is associated with a high false-negative rate; but it remains a fundamental imaging tool in the evaluation of PABC. Mammography exposes a fetus to only 0.004 Gy, below the threshold for a deterministic effect. [12] The use of breast magnetic resonance

imaging (MRI) is still controversial because the of the challenge to discriminate malignant and physiologic hypervascularization occurring during pregnancy and because gadolinium crosses the placenta and is associated with fetal abnormalities in rats. [2] Magnetic resonance imaging itself is associated with risks to the fetus. [13–17] The standard examination to obtain a histological diagnosis is a core biopsy under local anesthesia, which can be done safely during pregnancy with a sensitivity of around 90%. [11,18] Milk fistulas are rare. Gestational and puerperal hormones induce physiological hyperproliferative changes of the breast, which could lead to a false positive or false negative result with fine-needle aspiration cytology. Therefore, this procedure is not recommended during pregnancy. [19] Diagnostic over-interpretation is avoided when the pathologist is aware that the patient is pregnant.

When breast cancer is diagnosed, an accurate staging of the disease is needed. Chest X-ray is a safe procedure when appropriate abdominal shielding is used, and exposes the fetus to 0.0001 Gy. Computed tomography (CT) scans of the abdomen are avoided at all stages of pregnancy due to the dangerous levels of radiation exposure; abdominal ultrasonography is a safe alternative in evaluating hepatic and abdominal conditions; no overall consensus among authors has been obtained for low-dose bone scan. Unenhanced MRI could be performed in case of suspected liver or bone metastases. [5,6,20–22]

1.2. Pathology

Invasive ductal carcinomas are the most common histological subtype. [3,23,24] Tumors are usually high grade and lymphovascular invasion is commonly seen. [3,9,22–25] Hormone receptor status is commonly negative because pregnant women are even less likely to be estrogen-receptor positive. [26] Numerous studies have found that women with breast cancer in pregnancy have larger tumors and are more frequently to have positive nodes, metastases and vascular invasion. [1,2,9,23] Studies with limited population also revealed a higher expression of Her2/neu. [27,28]

1.3. Genetics

Recent research indicates that women with a genetic predisposition to breast cancer may be over-represented among pregnant patients with cancer. Women diagnosed as having breast cancer before age 40 years, known BRCA1 and BRCA2 carriers were more likely to develop cancer during pregnancy. Among BRCA mutation carriers, high levels of circulating estrogens during pregnancy may accelerate a malignant transformation that has already begun. [29,30]

1.4. Treatment

The aim of treatment of PABC is the same as that for non-pregnant 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.

1.4.1. Surgery

Surgery is the definitive treatment for PABC, and is the first step of a multidisciplinary approach to the tumor as in non-pregnant patients. Surgery is safe and it can be performed in all trimesters of pregnancy with minimal risk for the fetus. There are two main possible strategies for breast surgery: radical modified mastectomy (RMM) and conserving surgery, and for axilla lymph node (ALN) dissection or sentinel lymph node biopsy (SLNB). The difference between these two options is that after breast-conserving surgery, radiotherapy is mandatory in order to decrease local recurrence; so a conservative procedure is mainly considered in the last trimester. The survival rates of both are similar. [6,31] SLNB in pregnant women is safe; recently Gentilini showed the results of a study demonstrating the safety and feasibility of this technique to be similar to that for non-pregnant women. [32] RMM can be followed by an immediate reconstruction of the breast with implants. Several reports concur that surgical treatment is usually well accepted by patients without significant complications, either for the mother or for the fetus. [22,23] An increased risk of low birth weight infants is reported as a result of premature labor or intrauterine growth retardation. [33]

1.4.2. Radiotherapy

Radiation therapy is contraindicated during pregnancy; the exposure of the fetus to ionizing radiation in utero, due to its teratogenic effects, is not considered a safe therapeutic option. [34] Mental retardation is the main risk after the 8th week of pregnancy, and children born after having been exposed to radiation in utero have an increased risk of childhood cancer. [35,36]

1.4.3. Chemotherapy

Chemotherapy could be proposed as adjuvant or neoadjuvant treatment. Cytotoxic chemotherapy should be avoided in the first trimester of pregnancy due to its high potential for teratogenicity during organogenesis, possibility of spontaneous abortion or fetal malformations (ranging from 10–20%). [7,37–39] Beyond the first trimester, however, chemotherapy does not appear to significantly increase the risk of malformations. During later trimesters, the possibility of such phenomena decreases to an acceptable level (up to 1.5%), allowing adjuvant or neo-adjuvant regimens to be used. [40]

Among the chemotherapeutic agents frequently used in breast cancer, methotrexate is strongly contraindicated. [41,42] The teratogenicity of fluorouracil remains unclear. [43] Anthracyclines are considered safer than alkylating agents. [44] Alkylating factors and antimetabolites must also be avoided due to an increased rate of fetal malformations. [45,46] Taxanes seem to be safe in the third trimester, but are not recommended since there are no more data. [41] Long-term effects of chemotherapy on offspring are unknown. [47] Chemotherapy dosage during pregnancy is complicated by increased plasma volume, increased hepatorenal 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, almost all chemotherapy agents cross the placenta.

1.4.4. Hormonal therapy

Tamoxifen is not recommended during pregnancy. [5,26] There are no reports of women with PABC receiving aromatase inhibitors although teratogenic effects have been described in animal models. [48] Several studies report up to 20% fetal abnormalities, including craniofacial malformations and ambiguous genitalia. [5]

1.4.5. Termination of pregnancy

Termination of pregnancy and postpartum delayed treatment are not routinely recommended because they do not improve survival. [37]

2. Patients and methods

From February 2006 to June 2013, twelve patients with PABC from a single Clinical Center (Department of Surgery I, University of Insubria Varese, Italy) were included in this retrospective observational study. Data regarding epidemiology, patients and tumor characteristics, lymphnodal status, lymphovascular invasion, treatment and follow-up were collected in a database.

Immunohistochemical evaluation of proliferative fraction (Ki-67 labelling index), estrogen (ER) and progesterone receptor (PgR) expression and HER2/neu overexpression were performed according to our standard technique. [49]

All patients came to our attention after the discovery of newly formed mammary mass or the presence of other clinical suspicions at breast self-examination. These lesions were then investigated with ultrasound, and subsequently with mammography, followed by microhistology. The treatment and follow-up of these patients were recorded, and all patients underwent check-ups every 4–6 months after treatment.

All patients have been proposed various therapeutic strategies and were informed that currently in the literature there is no evidence that the interruption of pregnancy is able to increase overall survival.

Prior to surgery systemic staging was carried out including chest X-ray and ultrasound of the abdomen together with anesthetic assessment and a careful obstetric-gynecological examination.

The main follow-up of patients was obtained by serial outpatient visits.

3. Results

Twelve women with breast cancer were included in the study; the diagnosis was made in 6 cases during pregnancy (group 1) and in the other 6 cases during lactation (group 2). In group 1, 2 patients were in the first trimester, 1 in the second trimester and 3 in the third trimester, with mean gestational ages of 8, 23 and 33 weeks. The only patient whose pregnant state was discovered concurrently with the diagnosis of breast cancer chose voluntary interruption of pregnancy, although all therapeutic possibilities were explained at length.

The median age of the pregnant patients was 34 y (range 28–44 y). All patients underwent preoperative breast ultrasound and bilateral mammography; in all cases the histological diagnosis was obtained by core biopsy under local anesthesia. Chest radiograph and abdomen ultrasound were also performed in all patients to investigate metastatic disease and in any of these distant metastases were found. The mean size of the primary tumor at the time of diagnosis was 3.3 cm (range 0.5–8.2 cm).

Conservative surgical therapy was performed in 4 cases in group 1 and in only 2 cases in group 2. In four pregnant patients sentinel node biopsy was performed without any consequence to the fetus; in all cases the lymph node was negative. In a lactating woman, however, it was necessary to perform axillary lymph node dissection for the presence of micrometastases in the sentinel node. Six patients underwent axillary dissection ab initio for metastatic axillary disease discovered by physical examination and ultrasonography; 2 in group 1 and 4 in group 2. Hormone status receptors were negative for 3 patients in group 1 and 4 in group 2.

In our study 3 patients were affected by genetic mutation of the BRCA1 gene.

All patients included in the study had invasive ductal carcinoma, grade 3 in 10 patients and grade 2 in 2 patients. In 4 cases of group 1 the diagnosis was made after the discovery of a palpable mass during breast self-examination, while in 2 patients the tumor was diagnosed during regular check-up.

The 4 patients who underwent surgery during pregnancy have healthy babies without any complication.

One patients did not receive any chemotherapy. After completion of pregnancy, nine patients received full-dose combination adjuvant chemotherapy, including alkylators, anthracyclines and taxanes; two patients received both neoadjuvant and adjuvant chemotherapy.

Breast external radiotherapy was implemented in three patients after delivery.

Delivery was cesarian in most of patients, one patient delivered spontaneusly at 39 weeks of gestation and one patient underwent induction.

All patients underwent suppression of breastfeeding with cabergoline to prevent accumulation of lipophilic agents such as taxanes in the milk.

In 3 patients distant metastases occurred: two had liver metastases and another had both liver and lung metastases. These 3 patients died of metastatic breast cancer 12, 27 and 30 months after surgery, respectively.

At the moment of writing, after a mean follow-up of 20 months, the other patients are well without signs of local or distant recurrence.

4. Discussion

The incidence of breast cancer in pregnancy is likely to increase due to the trend of women, mainly in modern society, to postpone pregnancy to older age, between 35 and 45 years, a period of fertile age in which there is an increasing incidence of breast cancer.

The precise definition of the extent of disease, the patient's desire to complete gestation, and information on the maturity and integrity of the fetus, are only some of the factors to be taken into account in the planning of the therapeutic program during pregnancy; it is therefore essential to exactly know the clinical behavior and the biology of breast cancer in pregnant patients in order to reach the best treatment for each patient.

There is no evidence that the interruption of pregnancy modifies the prognosis of these patients in terms of recurrence or survival. [50]

Surgery may be conservative or radical. The review by Woo et al. [2] concluded that modified radical mastectomy with axillary dissection is considered the best choice for patients diagnosed with breast cancer in the first quarter, who decide to continue pregnancy, in order to eliminate the necessity of radiation therapy, which can only be administered after delivery. [51] Conservative surgery can be proposed if technically possible; there are some ongoing studies evaluating the feasibility and the potential side effects on the fetus of intraoperative radiotherapy (ELIOT – electron beam intraoperative radiotherapy) in the first and second quarter. [52]

There are conflicting opinions on the use of sentinel lymph node biopsy in pregnancy with radioactive technetium; Kaufmann et al. [53] do not recommend its use for the supposed teratogenic effect, while Gentilini et al. published data demonstrating the safety of this procedure. [32]

In the literature there are very few data on hormone therapy conducted in pregnant patients, but the use of these drugs is contraindicated during pregnancy. [54] Chemotherapy given in the first trimester is associated with an increased risk of miscarriage and congenital malformations of the fetus, and it is therefore contraindicated.

Encouraging data are published on the administration of chemotherapy during the second and third trimester. [55] There are no reported cases of increased malformation in infants of mothers who received chemotherapy during pregnancy. Cases of low birthweight are reported as a result of intrauterine growth retardation and premature delivery. [10]

Delivery must be completed not earlier than 3 weeks after the last cycle of chemotherapy, to reduce maternal and fetal hematological toxicity. The short-term follow-up of infants is reassuring, but results have yet to be published on neonatal follow-up in the long term.

Some authors argue that pregnancy is not considered a risk factor for breast cancer, at the same stage and age [1]; on the other hand some authors considered that prognosis of patients with breast cancer

diagnosed in pregnancy is worse than for the control population, in terms of both recurrence and survival.[9,56] In a report on a large series of breast cancer cases during pregnancy (797 cases) versus 4,177 controls, from the California Cancer Registry, the authors also argue that controlled for stage, race, tumor size, type of surgery and hormonal status, pregnancy worsens the prognosis of the tumor, with a relative risk of 1.14.[57]

Generally cancers diagnosed at a young age are more aggressive than those affecting women of older age, and for this reason breast cancer in pregnancy is generally more aggressive and often occurs in more advanced stage than in non-pregnant women.

Some authors suggest that the morphological and immunohistochemical characteristics may change related to the period: pregnancy, breast-feeding or after delivery.[58]

5. Conclusions

The management of patients with cancer during pregnancy requires the effort of a multidisciplinary team that is able to offer to these patients the best options and the necessary psychological support in an extremely delicate period of their life.

The worst prognosis of these patients is probably related more to the biological characteristics of the tumor than to pregnancy itself.

Taking into account that the diagnosis of cancer during pregnancy remains an infrequent event and that the effects of therapy on the unborn child are not yet fully known, it would be desirable for all cases to be referred to specialized centers, in order to establish national and international registries that ultimately will provide deeper knowledge of the problem and a more adequate counseling of patients. A project is ongoing, in collaboration with the Breast International Group (BIG), to create a European registry that will help us to increase our knowledge in this field.

The diagnosis of breast cancer during pregnancy has high psychological impact on the patient's life, her family, and even the multidisciplinary team. The conflict between giving life and questioning it creates a tension that needs great clinical wisdom and respect for the deepest feelings of the patient, but also awareness of its limitations in the face of decisions that are never simple. The right balance between maximum benefit to the patient and minimal harm to the fetus is not always achievable; the difficult management of this situation needs the uncommon ability to listen and the humility to make comparisons with other colleagues to find the best solution. The decision of the patient should always be respected, there is no place for superficial evaluations.[5,59]

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