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Minireview

Pregnancy-associated breast cancer

Giuseppe Floris[1,2], Sileny Han[2,3], Frederic Amant[2,3]

[1]Department of Pathology, [2]Multidisciplinary Breast Cancer Centre and [3]Department of Gynaecology of the University Hospitals Leuven, Catholic University of Leuven. Leuven, Belgium

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Abstract

Traditionally pregnancy-associated breast cancer (PABC) is defined as any breast carcinoma diagnosed during pregnancy or within the first year after delivery. PABC is a rare event, representing overall between 0.2-3.8% of all breast cancers. The incidence of PABC is about 1 in 3000 pregnancies. The physiological changes occurring in the breast during pregnancy may obscure the presence of a palpable mass in a pregnant woman. Core needle biopsy (CNB) or excisional biopsy are the preferred method to provide definitive diagnosis. The histologic spectrum of PABC does not differ from breast carcinomas diagnosed in non-pregnant women of similar age. Metastatic spread to the placenta is an exceedingly rare event that can occur to PABC patients, mostly in women who have disseminated metastatic tumors. Therapeutic strategies are determined by tumor biology, tumor stage, gestational age and the patient's and her family's wishes. The choice for breast cancer surgery and systemic therapy for PABC should follow the same guide-lines as for non-pregnant women. Preterm birth is associated more often with complications regardless of chemotherapy exposure, therefore iatrogenic preterm delivery should be avoided when possible. Overall prognosis of patients diagnosed with PABC is similar to that observed in non-pregnant women of the same age. The institution of international collaborative registries will further help in assessing more accurately the outcomes of the mothers and their children.

Keywords

Pregnancy, breast cancer, pathology, fetal outcomes.

Corresponding author

Giuseppe Floris, Department of Pathology of the University Hospitals Leuven, Catholic University of Leuven. Leuven, Belgium; email: giuseppe.floris@uzleuven.be.

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Introduction

Traditionally pregnancy-associated breast cancer (PABC) is defined as any breast carcinoma diagnosed during pregnancy or within the first year after delivery. PABC is a rare event, representing overall between 0.2-3.8% of all breast cancers [1]. Diagnosis of PABC occurs in pregnant women between the ages of 23 and 47; the median gestational age at diagnosis being 21 weeks [2]. PABC is the second most frequent malignancy during pregnancy after cervical carcinoma [3]. The incidence of PABC is about 1 in 3,000 pregnancies, however it is anticipated that the incidence of PABC will increase as more women delay childbearing. PABC often presents as an advanced disease which poses great challenges in the clinical and therapeutical management of patients with PABC depending on the gestational age [4]. The main goal of therapy is to provide optimal treatment to the mother while minimizing the risk to the fetus, and eventually preserving fertility in young women.

Diagnosis

The physiological changes occurring in the breast during pregnancy may obscure the presence of a palpable mass in a pregnant woman. Although the great majority of palpable mass are benign in this period, a persisting hard lesion should lead to prompt medical clarification [4]. During lactation nipple discharge may be difficult to recognize. Breast ultrasound imaging is safe and has high sensitivity and specificity in diagnosing PABC. Ultrasonography is considered the standard method of choice for the evaluation of suspicious breast masses during pregnancy. The use of X-rays in pregnant women require a strong indication given the potential risk of fetal malformation and mental retardation that are associated with exposure to ionizing radiations. With the new imaging equipment like digital mammography and appropriate shielding, the radiation for the fetus can be sensibly reduced to below 0.05 Gy [2]. Deterministic effects of radiation, such as fetal death, malformations or impaired fetal development, can arise when the dose of radiation exceed 0.1-0.2 Gy during pregnancy [4]. The increase in size, vascularization and glandular density in a pregnant woman reduce the sensibility in detecting malignant lesions with mammography to less than 70% [1]. Nevertheless, mammography remains important for detecting multicentric tumors, bilateral tumors or suspicious calcifications in pregnant woman. Metastatic investigations for breast cancer include chest radiography, liver ultrasonography and non-contrast skeletal MRI. When the estimated risk of distant metastasis is low, postponement of staging until after delivery may be considered [4]. The role of MRI with contrast is controversial in pregnancy, given the fact that gadolinium-based contrast passes the placenta and causes fetal abnormalities in animal models [4].

Pathology

A diagnosis of carcinoma during pregnancy and lactation can be made by fine needle aspiration cytology (FNAC). However the interpretation of such cytology specimen poses great challenges, because physiologically altered non-neoplastic mammary epithelial cells may appear atypical in this setting resulting often in false positive results without accurate clinical information. For this reason core needle biopsy (CNB) or excisional biopsy are the preferred method to provide definitive diagnosis [4]. The histologic spectrum of PABC does not differ from breast carcinomas diagnosed in non-pregnant women of similar age. Invasive carcinoma of no special type is diagnosed in the large majority of the patients (71-100% of the cases). Less frequently are encountered lobular carcinomas, mucinous carcinomas, carcinomas with medullary features or inflammatory carcinoma. PABCs are significantly larger than tumors found in non-pregnant women showing higher grade, more frequent lymph-vascular invasion as well as higher incidence of nodal involvement (in 60-70% of the patients) [4-6]. PABCs are found to be more frequently negative for estrogen (ER) and progesterone receptor (PgR) by immunohistochemistry, however remain unclear whether hormonal receptor status is significantly different in non-pregnant breast cancer patients of the same age given the fact that patients below

40 years usually show negative ER/PgR status. Epidermal growth factor receptor 2 (HER-2) is found to be amplified in about 15-20% of breast cancer patients and in about 39% of patients under 35 years of age [2]. PABCs carry HER-2 amplification in about 36-42% of the cases according to data collected from international observational studies, showing thus no significant differences as compared to non-pregnant women of the same age [4]. These observations suggest that pathological features of PABC are most likely influenced only by the age of the patients rather than by the pregnancy itself [4]. Metastatic spread to the placenta is an exceedingly rare event that can occur to PABC patients, therefore a thorough examination of the placenta is recommended in these cases. This is most likely to occur in women who have disseminated metastatic tumors. Gross evidence of metastatic carcinoma is usually apparent on the placental surface. Microscopically the tumor cells are generally located in the intervillous spaces; rarely is observed villous invasion [6]. Distant metastasis to the fetus have never been described.

Treatment and prognosis

As illustrated by many studies therapeutic abortions do not improve the survival of women with PABC [2]. The choice for breast cancer surgery for PABC should follow the same guide-lines as for non-pregnant women. Therefore mastectomy is not always mandatory, if radiotherapy following conserving breast surgery can be postponed after delivery [4]. The axillary staging by sentinel lymph node biopsy is considered to be safe during pregnancy. In non-pregnant women injection of radioactive colloid into the breast results in an estimated dose to the abdomen of about 0.00045 Gy, which is below the 0.1-0.2 Gy fetal threshold absorbed dose [4]. The use of chemotherapy is considered to be relatively safe during the second or third trimester of pregnancy. Exposure to chemotherapy during the first 10 days of pregnancy may eventually results in spontaneous abortion; while during organogenesis (10 days to 8 weeks after conception) is likely to generate congenital malformations. Therefore, to ensure fetal protection, chemotherapy is generally started after the 14-16th week of gestation when the risk of miscarriage and congenital malformations decrease to less than 1.5% [1, 4, 5]. Pharmacokinetics and pharmacodynamics of cytotoxic agents can change in pregnancy, moreover the amniotic fluid acts as a third space reservoir potentially prolonging the exposure of the fetus to the active forms of the used drugs [2, 3]. The chemotherapeutic agent utilized are the same as those used in non-pregnant women in adjuvant or neo-adjuvant regimens. The use in pregnant women of monoclonal antibodies against HER-2 such as trastuzumab is not recommended. HER-2 is strongly expressed in the fetal renal epithelium and can lead to oligohydramnios or anydramnios depending on duration of the exposure [7]. Other anti-HER-2 molecules should also not be used in pregnancy because of lack of safety data [4]. The delay in diagnosis of PABC as well as to the higher proportion of patients with lymph nodes involvement contribute to an advanced stage at diagnosis. Therefore, the general 5-year metastasis free survival and overall survival of PABC is considered to be relatively worse as compared to non-pregnant women of same age [1]. However breast cancers diagnosed during pregnancy are not analyzed separately in most of the cases because of their rarity, not allowing a control on all prognostic factors [4]. Indeed more recent evidence coming from an international collaborative study suggests that overall survival of patients diagnosed with PABC is similar to that of non-pregnant patients [8].

Fetal outcomes after chemotherapy

Pre-term deliveries after fetal pulmonary maturation is common and is often performed after pulmonary maturation of the fetus. A significant lower mean birth weight is frequently encountered in babies who were exposed to chemotherapy, despite a normal Apgar score [3, 4]. Pre-term delivery is associated to increased risk of side-effects, malformations or newborn complications. However, as recently described in a large international observational study, these complications seem to be more related to the pre-term birth rather than to chemotherapy exposure, given the fact none of the children included in the study were exposed to chemotherapy during the first trimester [9]. Data on long term outcomes after partial exposure to chemotherapy are scarce. Nevertheless data collected from small studies support the observation that in these children the general health and growth, neurological, cardiac and auditory functions do not differ from the healthy population. Prematurity may be associated with impairment in cognitive development [3, 4, 10, 11].

Conclusions

PABC is a rare clinical event, which is supposed to increase with the trend of delaying childbearing to the late 30s and 40s in some sociocultural context. Pathobiological features of PABC seem to be related to young age rather than to the pregnancy itself. Therapeutic strategies are determined by tumor biology, tumor stage, gestational age and the patient's and her family's wishes. Preterm birth is associated more often with complications regardless of chemotherapy exposure. The institution of international collaborative registries where PABC are systematically investigated, such as in the Belgian and German registry, will help in assessing more accurately the outcomes of mothers and their infants.

Declaration of interest

The Authors declare that there is no conflict of interest.

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