Chapter

Breast Cancer and Pregnancy: Epidemiology, Phenotypes, Presentation during Pregnancy, and Therapeutic Approaches

Massimiliano Berretta, Carlo Oreste Buonomo, Gianluca Vanni and Bianca Arianna Facchini

Abstract

Breast cancer (BC) represents the most frequent cancer worldwide, with almost 2.26 million new diagnoses recorded in 2020, and is the most common malignant neoplasia diagnosed during pregnancy. Pregnancy-related Breast Cancer (PrBC), indeed, is diagnosed in 1 in 2000–4000 pregnant women every year in Europe. PrBC is frequently characterized by unfavorable biological marks that, along with the late diagnosis, the limited imaging applicable, and the often-suboptimal treatments necessary to protect the fetus, could possibly lead to a worse prognosis in this population of patients. Babies born from mothers treated for cancer during pregnancy have been followed during a long-term follow-up and have showed cognitive and physical functions not different from the general population, but more studies are needed. Taking into consideration the complexity of the disease, a multidisciplinary approach is crucial to define the best therapeutical path.

Keywords: breast, cancer, pregnancy, PrBC, BC

1. Introduction

Breast cancer (BC) represents the most frequent cancer worldwide with almost 2.26 million new diagnoses recorded in 2020. Despite the progress made throughout the years to identify new anticancer drugs aiming to improve BC patients' prognosis, it still represents the first cause of cancer-related death in women [1].

BC represents one of the most frequent cancers in women in their reproductive age, with nearly 7% of all BC being diagnosed under 40 years of age [2].

It is well known that, BC being a frequently hormone-related malignancy, its onset may be induced by a higher exposure to estrogens, as may happen with physiological hormones in early menarche, older age at menopause, first pregnancy after the age of 30 and nulliparity, or with the exposure to external sources of hormones, during hormone replacement therapy or due to oral contraceptives.

Other risk factors are represented by personal and family history of BC, dense breast tissue, and lifestyle-based risk factors [3, 4].

Pregnancy represents a protective factor against BC [5], and even the age of the woman at the first pregnancy seems to play a crucial role in preventing the onset of this disease, pregnancy being considered protective if under 30 years of age [6, 7].

2. Pregnancy-related breast cancer epidemiology

Cancer occurs in around one in 1000 pregnancies, with BC being the most frequent, followed by cervical cancer, lymphoma, ovarian cancer, leukemia, colorectal cancer, and melanoma [8], reflecting cancer epidemiology in women in their reproductive years. In Europe, Pregnancy-related Breast Cancer (PrBC), indeed, is diagnosed in 1 in 2000–4000 pregnant women every year [9], representing approximately 0.2–2.6% of all breast cancer cases, and its incidence is probably bound to increase due to the progressively older age of women at the first pregnancy.

The terms PrBC and Pregnancy-associated breast cancer (PABC) have been used for a long time as synonyms, but a recent, more precise definition has allowed to distinguish the two entities: While PrBC includes only BC cases that are diagnosed during pregnancy, PABC also includes cases of BC diagnosed in the post-partum phase, till 1 year after delivery [10].

Risk factors for PrBC seem to be consistent with the general population, and no specific pregnancy-related risk factors have been identified. Women with BRCA mutations have a higher risk of developing PrBC. As these cancer cases are often diagnosed in particularly young women, genetic counseling should be considered [11, 12].

3. Presentation

Clinical presentation of PrBC is similar to BC in non-pregnant women, the palpation of a mammalian lump frequently being the first symptom. Nipple discharge, cutaneous lesions, or palpable lymph-nodes could also occur. The breast tissue physiological modifications that happen during pregnancy, such as engorgement and increased density, along with the young age of the patient and pregnancy itself, often lead to an underestimation of the symptoms and delayed diagnosis. Indeed, women during pregnancy have a 2.5 higher risk of being diagnosed at a higher stage, causing a worse prognosis [13].

4. Biology

Some studies suggest that PrBC biology has no significant difference from non-pregnant patients' BC [14]. Notwithstanding, the hormonal modifications that occur in a pregnant woman with their growth-promoting effect suggest a possible lead to more aggressive forms of BC [15]. In fact, PrBC seems characterized by a lower expression of hormone receptors, with a higher rate of aggressive forms such as triple-negative or HER2-positive forms [16]. Moreover, several studies have shown that these types of tumors seem to be marked by unfavorable molecular characteristics, for instance, a high expression of cancer targets as PD1/PD-L1, RANK ligand, and IGF, and show a lower prevalence of tumor-infiltrating lymphocytes [17]. A recent study has aimed to

identify specific genomic alterations in PrBC, demonstrating through a whole genome sequencing a higher rate of mismatch repair deficiency mutational signature, besides other mutations such as in the mucin gene family [18]. The expression of several other oncogenes could be altered, such as MYC, SRC, FOS, JUN, and KLF1 [19].

These biological marks, along with the late diagnosis, could possibly lead to a worse prognosis in this population of patients, further worsened by the limited staging exams applicable and suboptimal therapies that have to be administered to protect the fetus.

Further studies are needed to clarify the biology of this particular kind of cancer.

5. Diagnosis

Clinical examination represents the first step of the diagnostical process but needs to be always followed by imaging and biopsy. It is well known that ionizing radiations are dangerous during pregnancy due to their teratogen effect on the fetus. This makes the diagnosis and staging more complex, often leading to suboptimal results. **Table 1** summarizes allowed and forbidden diagnostical examinations during pregnancy.

Every breast lump that persists for more than 2 weeks should be investigated, even though around 80% of them result in benign lesions [20].

Breast ultrasound (US) represents the first choice when a mammalian lump during pregnancy is detected, it being non-invasive and safe for the fetus, thanks to the absence of ionizing radiations. It allows, on the one hand, to identify benign lesions that have no need to be studied with further exams and that represent the most common lesions identified during pregnancy and, on the other hand, to detect suspicious lesions that may need a biopsy [21]. US can be used to explore local lymph nodes and identify suspicious nodes that might need fine needle aspiration or biopsy.

Mammography with abdominal shield can be safely administered in these patients at every gestational age [22], but possible limitations related to parenchymal modifications during pregnancy must be considered. Contrast-enhanced breast MRI,

Diagnostical test	1st Trimester	2nd Trimester	3rd Trimester
Breast Ultrasound	✓	✓	✓
Abdomen Ultrasound	✓	✓	✓
*Chest X-Ray**	✓	✓	✓
*Mammography**	✓	✓	✓
Whole body MRI	×	✓**	✓**
Contrast-enhanced breast MRI	×	×	×
CT-scan	×	×	×
PET-scan	×	×	×
Bone scintigraphy	×	×	×
Biopsy	✓	✓	✓

*✓ Allowed; × Forbidden; *Abdominal shield must be used; **In selected cases only*

Table 1.
Allowed and forbidden diagnostical examinations in each pregnancy trimester.

instead, should be avoided due to the capacity of gadolinium to cross the hemato-placentar barrier and to the lack of data assessing its safety for the fetus [23]. The combination of mammography and breast US has a high detection rate, comparable to contrast-enhanced breast MRI, which can safely be avoided during pregnancy [24].

When a suspect lesion is identified, biopsy represents the gold standard. The pathologist should always be informed of the pregnancy status to better analyze the biotic sample.

The stage, according to American Joint Committee on Cancer (AJCC), should always be assessed. Abdominal and pelvis ultrasound and chest X-ray with abdominal shield are the first-choice imaging exams during pregnancy, while computed tomography, bone scintigraphy, and PET scan should be avoided due to the higher rate of ionizing radiation [25]. If strictly necessary, diffusion-weighted whole-body MRI without gadolinium might be an option in case of advanced disease or metastases after the first trimester [26].

6. Therapy

Cancer during pregnancy has for a long time been mistreated because of the lack of evidence about the efficacy and safety of the various available treatments in this peculiar population. By now, it is known that it should be treated as BC in non-pregnant women according to the stage and molecular asset, following some precautions to minimize the risks for the fetus (**Table 2**).

6.1 Surgery

Surgery is feasible at any time during pregnancy, considering that the majority of anesthetics has been demonstrated to be safe during pregnancy [27]. However, there is a slight risk of miscarriage, especially in the first trimester [26]. The preferred approach should be decided following the same guidelines for non-pregnant women, preferably after discussion by a multidisciplinary team due to the complexity of the decisions. Seen as though adjuvant radiotherapy must always be postponed after delivery, mastectomy might be discussed with the patient, especially for diagnosis done in the first trimester. Despite the limited data available on the matter, some studies suggest the feasibility and safety of conservative surgery during pregnancy [28]. Patients with PrBC who desire conservative surgery must be informed of the possible higher risk of local recurrence caused by a delay in the adjuvant radiotherapy treatment [29,30].

Treatment	1st Trimester	2nd Trimester	3rd Trimester
Surgery	✓	✓	✓
Radiotherapy	×	×	×
Chemotherapy	×	✓	✓
Endocrine therapy	×	×	×
Target therapy	×	×	×
Immunotherapy	×*	×*	×*

*✓ Allowed; × Forbidden; *Further studies are needed to assess security during pregnancy.*

Table 2.
Allowed and forbidden treatments in the three pregnancy trimesters.

Concomitant breast reconstruction after mastectomy does not seem to increase the mother-fetus morbidity and can be taken into consideration; the physiological breast tissue modifications during and after pregnancy, although, could lead to a delay in the procedure [28]. There is still no univocal approach regarding sentinel lymph node biopsy during pregnancy: On the one hand, American Society of Clinical Oncology (ASCO) does not suggest this procedure [31]; on the other hand, National Comprehensive Cancer Network (NCCN) guidelines and European Society of Medical Oncology (ESMO) support the procedure when considered necessary. Although further studies are needed, the procedure is considered safe for both mother and fetus if Technetium-99 m (99mTc) colloid solution injection is administered [32], preferably using the one-day protocol, injecting the drug in the morning of the surgery day [33]. Due to the high risk of anaphylactic, a potentially life-threatening reaction, blue dye and isosulfan blue should be avoided [34], while methylene blue should be avoided especially in the first trimester because of its teratogenic effect [35].

6.2 Radiotherapy

As stated above, radiotherapy should always be postponed to after delivery because of the several toxicities that can be caused to the fetus during pregnancy, such as intrauterine growth restriction, mental retardation, risk of childhood cancer, and fetal death [26].

6.3 Chemotherapy

Chemotherapy represents a fundamental weapon in treating BC. Its possible risks for the fetus strictly depend on the gestational age. During the first trimester, chemotherapy is always contraindicated, due to its high risk of miscarriage and congenital malformations (about 14% of cases) [36–38]. If chemotherapy is strictly necessary at this time of pregnancy, its interruption may be discussed with the patient [39]. After the first trimester, the risk of congenital malformations for the fetus drops to 3%, almost equal to the general population. For this reason, chemotherapy can be considered during the second and third trimester [26].

An fetal examination with US should be performed before and periodically during the treatment.

Chemotherapy regimens must be decided according to the tumor stage and biology, as in non-pregnant women. Anthracycline regimens have been known for years to be safe in pregnant women [40–43] and should be preferred. Regimens based on anthracyclines and taxanes appear to be safe during the two last trimesters of pregnancy [44, 45]. When taxanes are indicated, weekly paclitaxel should be preferred to docetaxel every 3 weeks because of its better tolerated toxicity profile and of the no need for steroid premedication or granulocyte colony stimulating factor (GCSF) [26].

The administration of dose dense regimens is still controversial: Although some data show the safety of this approach [46], further studies are needed before it becomes clinical practice.

Chemotherapy dose should be based on body surface area as in non-pregnant women, although some possible pharmacokinetics alterations must be taken into consideration [47].

The interruption of chemotherapy should not be over 35th week of pregnancy, to permit a 3-week washout before delivery [26], reducing possible surgical complications caused by hematological toxicity.

6.4 Endocrine therapy

Endocrine therapy is contraindicated at every trimester of pregnancy. Many studies demonstrated a clear teratogenic effect of tamoxifen in animal models [48, 49] and its relationship with major and minor congenital malformations in humans [50]. Notwithstanding a possible teratogenic effect in animal models, there are still no sufficient data available for aromatase inhibitors during pregnancy [51].

6.5 Target therapy

Trastuzumab, an anti-HER2 monoclonal antibody, has become, during the last few years, the standard of care in Her 2 positive adjuvant, neoadjuvant, and metastatic settings, representing a practice-changing drug. Being a type G Immunoglobulin, it is capable to trespass the blood placenta barrier from the second trimester to the due date. It interferes with the organogenesis process and causes oligo- and/or anhydramnios, as well as unknown long-term consequences on the fetus [33]. For this reason, it is contraindicated during every gestational age. Seen as though these complications have been shown only in the case of trastuzumab administration after the second trimester, incidental trastuzumab administration during the early stage of pregnancy (first trimester) does not necessarily require pregnancy interruption [52].

In the last few years, new anti-HER2 agents have become a part of our clinical practice, as Pertuzumab, trastuzumab-emtasine (T-DM1), or trastuzumab-deruxtecan (TDX). There are no data available on their safety during pregnancy.

6.6 Immunotherapy

Immunotherapy with anti-PD1/PD-L1 monoclonal antibodies has its peculiar role in the treatment of BC, especially in the triple negative forms. Some preclinical studies demonstrated a higher risk of late miscarriage and birth mortality if administered during pregnancy in animal models, probably caused by the non-acquisition of immune tolerance against the fetus [53, 54]. Hence, it is contraindicated till further studies about its security are conducted.

6.7 Supportive care

Most of the supportive care drugs used in non-pregnant women can safely be administrated even during pregnancy. Steroids should be avoided during the first trimester due to the risk of congenital malformations. They can be administered in the second and third trimester, preferably using methylprednisolone and hydrocortisone that are metabolized in the placenta and do not seem to reach the fetus [33]. Ondansetron can be safely administered, as well as H2 antagonists; there are no sufficient data about anti-NK1 agents [16]. Granulocyte-colony stimulating factors (G-CSFs) have shown no significant fetal toxicities in the only retrospective analysis that has analyzed their safety during pregnancy, but further studies may be needed [55].

7. Fetal outcome

As stated above, during the second and third trimester, chemotherapy can be safely administered. Nevertheless, it may be connected to an increased risk of

complications for the fetus, such as intrauterine growth restriction (7–9 up to 22%) or premature rupture of membranes (17–27%) [41, 56].

Mother and fetus should be strictly monitored before, during, and after the oncologic treatment, and after delivery, the placenta should be sent for histological exam, to assess if any BC cells are detected [57]. Moreover, a multidisciplinary approach is fundamental in this population of patients: Only the cooperation between all the figures involved (Oncologist, Surgeon, OBG-YN, Radiologist, Psychologist) can lead to the best approach for each patient.

Babies born from mothers treated for cancer during pregnancy have been followed during a long-term follow-up and have shown cognitive and physical functions not different from the general population, but more studies are needed [17].

8. Conclusions

PrBC incidence is slowly rising; thus, the awareness of its correct management is fundamental for every physician. It should be treated following non-pregnant BC guidelines, applying the abovementioned precautions to limit the possible risks for the fetus. There is no evidence of increased OS after pregnancy interruption; hence, this possibility must be discussed with the patient only in select cases, for instance, when the immediate start of chemotherapy is mandatory. Taking into consideration the complexity of the disease, a multidisciplinary approach is crucial to define the best therapeutical path.

Author details

Massimiliano Berretta[1*], Carlo Oreste Buonomo[2], Gianluca Vanni[2] and Bianca Arianna Facchini[3]

1 Department of Clinical and Experimental Medicine, University of Messina, Messina Italy

2 Breast Unit, Department of Surgical Science, PTV Policlinico Tor Vergata University, Rome, Italy

3 Department of Precision Medicine, University of Campania 'Luigi Vanvitelli', Naples, Italy

*Address all correspondence to: berrettama@gmail.com

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