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REVIEW

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Biology, staging, and treatment of breast cancer during pregnancy: reassessing the evidences

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ABSTRACT Breast cancer is one of the most frequently diagnosed malignancies during pregnancy. Here, we review the management of women with breast cancer during pregnancy (BCP), focusing on biology, diagnosis and staging, local and systemic treatments, obstetric care and long-term follow-up of children with prenatal exposure to anticancer treatments.Breast cancer is one of the most frequently diagnosed malignancies during pregnancy. Here, we review the management of women with breast cancer during pregnancy (BCP), focusing on biology, diagnosis and staging, local and systemic treatments, obstetric care, and long-term follow-up of children with prenatal exposure to anticancer treatments.

KEYWORDS Breast cancer; pregnancy; chemotherapy; endocrine therapy; targeted therapy

Introduction

Breast cancer represents the most common tumor diagnosed in women and the most frequent malignancy in women of reproductive age[1]. Approximately 7% of all breast carcinomas are diagnosed annually in patients below 40 years, and the incidence is even higher in developing countries[2]. The overall incidence of breast cancer during pregnancy (BCP) varies between 2.4 and 7.3 per 100,000 pregnancies[3-8]; however, breast cancer is predicted to become more common due to the current trend of postponing pregnancy to later in life[9] and evidence suggesting that both the incidence of breast cancer in young women and the occurrence of BCP are increasing[10,11].

Biology and prognosis

Breast cancer arising at a young age has potentially unique biologic features[12]: as shown by gene-expression profiling, the complexity of this condition seems to go beyond breast cancer subtype distribution[13]. The hormonal milieu during pregnancy with its growth-promoting effects might theoretically result in a more aggressive biology of breast cancer[14]. Although some studies have suggested no major differences in the expression of hormone receptors and HER2 between pregnant and non-pregnant age-matched breast cancer patients[15-17], several studies have shown that BCP seems to be more commonly associated with unfavorable tumor biology such as predominance of triple-negative breast carcinomas (TNBC)[18-20], high expression of potentially relevant cancer targets (e.g., PD1/PDL1, SRC, insulin growth factor and Wnt/β-catenin, RANK ligand), and low prevalence of tumor-infiltrating lymphocytes[21-23].

The unique biologic features of BCP and the more frequent delay in diagnosis might explain the poor prognosis reported by some authors, even if the immediate postpartum period showed a clear trend toward inferior outcomes compared with outcomes during pregnancy or in women with non-pregnancy-related breast cancer[24]. Moreover, patients with BCP could be offered "nonstandard" and potentially suboptimal systemic therapies, with a possible negative impact on their prognosis. On the contrary, patients with BCP treated at a single center who received the same standard anthracycline-based chemotherapy regimen during pregnancy had similar clinical outcomes than non-pregnant

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patients with breast cancer[16]. Similar findings were observed in the largest cohort study available[17].

Diagnosis and staging

BCP generally presents at a more advanced stage at diagnosis than breast cancer in the general population[25,26]. The possible delay in diagnosis is related to the fact that pregnancy increases breast density and nodularity, making clinical and radiologic examinations more difficult[27-29]. Physicians should thus be aware that a breast lump in a pregnant patient may be associated with a cancer diagnosis; in these cases, imaging and biopsies should be performed without delay[25]. Histopathological diagnosis based on core biopsy represents the gold standard for BCP and should follow standard procedures as in non-pregnant patients, but the pathologist needs to be informed about the pregnancy status to properly consider alterations that may be caused by the physiological modifications of breast tissue during pregnancy[11,25].

Imaging procedures for diagnosis and staging should aim to limit exposure to ionizing radiation[11,25]. Breast ultrasound and mammography with abdominal shielding can be safely and effectively performed in pregnant patients[30,31] at all gestational ages; however, contrast-enhanced breast magnetic resonance imaging (MRI) is not recommended due to inadequate data concerning fetal safety with contrast media[11,25]. Ultrasound represents the preferred imaging modality for staging the abdomen and pelvis, and chest X-ray with abdominal shielding can be performed to stage the chest[25]. In case of advanced disease or suspected metastasis, diffusion-weighted whole-body MRI without gadolinium can be considered after the first trimester[25]. Computed tomography, bone scan, and positron emission tomography should be avoided during pregnancy[11,25].

Genetic counseling should be offered to pregnant breast cancer patients, especially if there is a family history of breast carcinoma or a TNBC diagnosis, similarly to what is recommended for all young patients with breast cancer[32-34].

Local treatment

Surgical management

Surgery can be safely performed at any time during gestation by making careful risk/benefit assessment because of the need for anesthesia. The surgical approach should follow the same guidelines as for non-pregnant cases[11,25]. Mastectomy is not mandatory for patients with BCP solely on the basis of possible delay in the delivery of radiotherapy[11,25]. Although the available published data on breast conservation are limited, they support the safety and feasibility of this procedure in pregnant patients[35]. However, patients diagnosed in the first trimester who desire to conserve the breast should be informed about a possible increased risk of local recurrence due to the long delay in postoperative radiotherapy[35].

According to the American Society of Clinical Oncology (ASCO), clinicians should not recommend sentinel lymph node biopsy (SLNB) in patients with BCP[36]. However, the use of lymphoscintigraphy with technetium-99 SLNB has been shown to be safe and feasible during pregnancy[37-40]. The 1-day protocol is associated with a negligible dose to the fetus (i.e., $\leq$0.014 mGy), much lower than the limit established by the United States (US) National Council on Radiation Protection and Measurements[41]. Hence, specific guidelines for patients with BCP suggest that SLNB rather than axillary clearance should be offered whenever indicated[11,25].

Blue dye for mapping should be discouraged in pregnant patients due to the low but potentially harmful risk of anaphylactic reaction[11,25] and the capacity of radiolabeled colloid alone to identify sentinel lymph nodes in 99% of patients.

For breast cancer patients who undergo mastectomy, breast reconstruction with an expander is more feasible and safer than autologous flap-based procedures and should be offered to all patients except those with inflammatory breast cancer[11,32,42].

Radiotherapy

Exposure of the fetus to radiotherapy can cause several adverse effects (e.g., intrauterine growth restriction, mental retardation, risk of childhood cancer, fetal death)[25]. Although some successful cases of radiotherapy for BCP with the subsequent birth of healthy children have been reported, the available data are too limited to draw solid conclusions and it is preferable to postpone its use until the postpartum period[11,25,35,43].

Systemic treatment

Chemotherapy

The indication for using chemotherapy in patients with BCP should follow standard recommendation as in the non-pregnant setting and should be based on both tumor biology and tumor stage; however, in this setting, some specific issues should be considered, including gestational age at diagnosis,

expected date of delivery, and the preferences of the patient and her family[11,25].

In patients with BCP, chemotherapy is contraindicated during the first trimester of gestation, while it can be safely administered in the second and third trimesters[11,25].

The first trimester is the period of organogenesis, which is characterized by high vulnerability to drugs and possible occurrence of spontaneous abortions and major congenital fetal malformations[11,25]. According to the US National Toxicology Program Monograph, the overall rate of major malformations following exposure to chemotherapy during the first trimester was 14%, with some chemotherapeutic agents (i.e., cyclophosphamide and 5-fluorouracil) being associated with a higher risk of major malformations (18% and 31%, respectively)[44]. Termination of pregnancy is not associated with improved maternal outcome[45]; however, for women with stage IV disease and for those with high-risk early-stage breast cancer diagnosed during the first trimester, termination of pregnancy can be considered to avoid delay in the initiation of cytotoxic therapy. During the second and third trimesters, the administration of chemotherapy is associated with an overall 3% rate of major malformations[44], similar to the prevalence in the US general population[46,47].

Nonetheless, the use of chemotherapy during the second and third trimesters can be associated with an increased number of obstetric and fetal complications, including intrauterine growth restriction, hypertensive disorders of pregnancy, and early delivery in approximately 10-20% of cases[11,25]. This relatively higher risk of pregnancy complications calls for a multidisciplinary evaluation of patients undergoing chemotherapy during pregnancy, including careful monitoring of fetal growth and maternal blood pressure (see also next paragraph). Meanwhile, iatrogenic prematurity is associated with impaired cognitive development[48,49] and should be avoided whenever possible[11,25].

Anthracycline-based or anthracycline/taxane-based chemotherapy regimens are standard of care for treating breast cancer[50,51] and should be recommended also in patients with BCP during the second and third trimesters[11,25].

Anthracyclines are the most studied chemotherapy compounds during pregnancy, with more than 400 women with BCP treated with these regimens[52]. Hence, anthracycline-based chemotherapy should be considered as the first choice[11,25]. In non-pregnant breast cancer patients, the addition of 5-fluorouracil to anthracycline and cyclophosphamide has been shown to be associated with no survival benefit but increased toxicity[53]; therefore, the combination of doxorubicin or epirubicin and cyclophosphamide (i.e., AC or EC, respectively) should be considered the preferred option also in women with BCP[11,25].

Clinical experience with the use of taxanes in patients with BCP is more limited. Docetaxel and paclitaxel are substrates for the placental P-glycoprotein transporter that seems to reduce the amount of drug passing from the placenta into the fetus; even in experimental models, paclitaxel and docetaxel were shown to persist at low levels in fetal tissues for a long time[55]. A systematic review of women with BCP, including 50 pregnancies with exposure to paclitaxel and docetaxel, showed that taxanes were well tolerated during pregnancy with manageable toxicities[56]. Thus, when clinically indicated, the use of taxanes can be considered during pregnancy[11,25]. Due to the better toxicity profile and no need for granulocyte colony-stimulating factors (G-CSF) nor premedication with high-dose steroids, weekly paclitaxel should be preferred in women with BCP[11,25].

Dose-dense chemotherapy is used in high-risk non-pregnant patients[57,58], and one small retrospective cohort study evaluated the feasibility of this treatment during pregnancy[59]. Although the study showed no increased risk of fetal or maternal complications, dose-dense chemotherapy should not be used in women with BCP due to the limited data available and the need for G-CSF support.

Clinicians should be aware that the pharmacokinetics of some cytotoxic drugs (e.g., doxorubicin, epirubicin, docetaxel, and paclitaxel) might be altered during pregnancy[60,61]. Nonetheless, dose reduction as well as increased doses and treatment intervals should be avoided[11,25].

A 3-week interval between the last dose of chemotherapy and the expected date of delivery should be allowed to avoid delivery during the nadir period[11,25]. Due to the possible occurrence of spontaneous delivery after week 34 of gestation, chemotherapy should be discontinued at week 34 of gestation[11,25]. Weekly chemotherapy regimens (e.g., weekly epirubicin and weekly paclitaxel) have a lower risk of hematological toxicity and shorter nadir periods; hence, they might be considered as a valid treatment option in pregnant patients, particularly as single-drug treatment in the metastatic setting[11,25].

Anti-HER2 agents

Trastuzumab is approved for the treatment of patients with HER2-positive breast cancer in the neoadjuvant, adjuvant, and metastatic settings. However, the HER2 pathway has a crucial role in fetal organogenesis and is also involved in the early conception and implantation phases[62].

Immunoglobulin G antibodies can cross the placenta starting from the second trimester of pregnancy, with a continued increase of passage from then on up to term[63,64].

In humans, around 34 breast cancer patients who have been exposed to trastuzumab during pregnancy have been described[65]. When trastuzumab was administered during the second or third trimester, the pregnancy was complicated with oligohydramnios, resulting in preterm delivery in 5 cases reported[66]. The remaining 29 cases became accidentally pregnant during trastuzumab treatment with consequent exposure during the first trimester[66,67]. First-trimester exposure was not associated with pregnancy complications or fetal malformations, and no cases of oligohydramnios were described[66,67].

Therefore, in contrast to chemotherapy, trastuzumab exposure during the first trimester seems to be not associated with congenital malformations, while exposure beyond the second trimester is likely to produce "on-target" effects, with a high number of cases developing oligohydramnios[65]. Thus, elective administration of trastuzumab should be avoided during pregnancy and postponed until after delivery[11,25]. No cases of women treated with pertuzumab or T-DM1 during pregnancy have been reported so far[65], and only one case of lapatinib exposure has been published[68]. Thus, these drugs should not be used in pregnant patients[65].

Endocrine therapy

In women with BCP, endocrine therapy is contraindicated[11,25]. Fetal malformations (i.e., craniofacial malformations and ambiguous genitalia) have been described in children with in utero exposure to tamoxifen[70,71]. Hence, the use of endocrine agents should be postponed until after delivery[11,25,69].

Supportive care

Among 5-HT3 receptor antagonists, ondansetron was shown to be not associated with an increased risk of developing adverse fetal outcomes[74]. Granisetron does not seem to cross the placenta[75], while no data are available about NK1 receptor antagonists and palonosetron[72,73]. Steroids are contraindicated during the first trimester because of the risk of cleft palate, while they can be administered during the second and third trimesters[11], with a preference for methylprednisolone and hydrocortisone, which are extensively metabolized in the placenta and do not reach the fetus[11,76].

The safety of G-CSF during pregnancy is limited to a small retrospective series[77-79,59], and they should be used only if strictly indicated[11,26].

Obstetric care

As mentioned, cytotoxic chemotherapy can be safely administered in the second and third trimesters, but can be associated with an increased risk of obstetric and fetal complications. The most common complication associated with chemotherapy exposure is intrauterine growth restriction, with an incidence of 7–9% up to 22% in the largest case series[45,80,81]. Other possible obstetric complications, including premature rupture of membranes, can occur in 17–27% of cases[45,80,81].

Pregnancy in cancer patients should be considered and monitored as "high risk"[11,25]. A multidisciplinary team should be involved in the care of women with BCP from the earliest phase possible. An ultrasound confirming dates with detailed fetal anatomic evaluation before treatment initiation is recommended to rule out preexisting fetal anomalies[26]. During treatment, fetal ultrasound monitoring is recommended at regular intervals[11], and the mother should be accurately evaluated at each chemotherapy cycle, including assessment of arterial blood pressure and proteinuria. The mode of delivery should not differ from usual obstetric indications, and delivery should occur in a tertiary center[82]. Furthermore, the placenta should be sent for histological evaluation to assess possible breast cancer cell contamination[83].

Long-term outcomes of children after in utero exposure to anticancer therapies

Reassuring data about the long-term follow-up of babies born from mothers treated for cancer during pregnancy have been reported[48]. With an observation period between 18 months and 20 years, the children's general health, growth, behavior, and hearing did not differ to those of the general population; moreover, cardiac dimensions and functions were within normal ranges[48]. Cognitive development scores were overall within normal ranges but lower for children who were born preterm than for those born at full term[48]. Another multicenter case-control study confirmed these results[49]. No significant difference in cognitive development was observed between cases and controls; however, the gestational age at birth was correlated with the cognitive outcome in both study groups, confirming that prematurity

is correlated with a worse cognitive outcome independent of cancer treatment[49].

Preterm delivery can lead to several complications also in the general population, and the risk of occurrence of complications increases with decreasing gestational age at birth[84]. Thus, delivery after 37 weeks of gestation is recommended whenever possible, and iatrogenic preterm delivery should be avoided[11,25]. Although these findings are encouraging, more data and longer follow-up are necessary to identify possible adverse effects that may not be apparent until later in life, including cardiac function impairment and infertility[85].

Conclusions

The diagnosis of BCP represents a unique challenge for the patient, her caregivers, and the treating physicians and often raises several religious, moral, or social issues that should be taken into account[86]. The complex medical situation in BCP requires the involvement of a multidisciplinary team from the early phases of its management[11,25].

Current guidelines on this topic rely on limited evidence. Hence, further research is required to obtain more conclusive data. Prospective studies for the management of BCP are ongoing in the US and Europe. Since running randomized trials is impossible in this setting, the participation of patients in international registries, such as the one organized in Europe by the International Network on Cancer, Infertility and Pregnancy (https://www.esgo.org/network/incip/), will help accrue adequate numbers to provide more robust evidence on the management of women with BCP.

Conflict of interest statement

No potential conflicts of interest are disclosed.

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