Review Article

Breast cancer in pregnancy: a comprehensive review of diagnosis, management, and outcomes

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Abstract: In the past decades the incidence of pregnancy-associated breast cancer (PABC) increased. Earlier diagnoses through breast awareness and screening, have led to increases in survival and a decline in breast cancer (BC) recurrence. Managing BC during pregnancy presents a unique challenge for healthcare providers. This article comprehensively examines various treatment strategies and diagnostic challenges, with a focus on balancing maternal health and fetal well-being. The collision between pregnancy and BC puts women in a fear-invoking paradox of their own health, their pregnancy, and the outcomes for both. Case-based approaches and multidisciplinary meetings are essential for navigating these complex scenarios. Early detection, tailored treatment plans, and careful consideration of fetal safety are paramount in effectively managing BC during pregnancy. Some evidence suggests that women with PABC have a worse outcome compared with historical controls. However, young age is a worse prognostic factor independently, and women with pregnancy tend to be young. Increased awareness and detection, rationally aggressive treatment, and enhanced understanding of the mechanisms are imperative steps toward improving the prognosis. The aim is to give optimal treatment to the mother to maximize the chances of survival, whilst minimizing the risks of harm to the fetus.

Keywords: Breast cancer (BC); pregnancy-associated breast cancer (PABC); management; diagnosis

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Introduction

Pregnancy-associated breast cancer (PABC) is one of the debatable topics of oncology. PABC is defined as cancer diagnosed during pregnancy or 1-year post-partum (1) or during lactation. PABC treatment is challenging as not only maternal health is under consideration but also the impact of different treatment strategies on developing fetuses is a crucial part of the decision-making process.

PABC is a complex topic in oncology, encompassing cancers diagnosed during pregnancy or within a year post-partum (1), including during lactation. Treatment of PABC requires careful consideration of both maternal and fetal health. Risk factors for breast cancer (BC) in pregnancy are like those for non-pregnant women, with maternal age at pregnancy becoming increasingly significant. Although pregnancy generally protects against BC, advanced maternal age at conception increases hormonal exposure, thereby elevating the risk.

Important considerations

The occurrence of PABC is steadily rising due to the increasing maternal age over decades (2). The World Health

Organization (WHO) has projected that the incidence of PABC will continue to increase as more women delay childbearing (3). Studies worldwide have reported variable data on the incidence of BC. Some research indicates a prevalence of BC ranging from 1 in 3,000 to 10,000 BC diagnoses (4).

The risk factors of BC in pregnancy are not different from non-pregnant women. Early menarche, late menopause, no childbearing, effects of diet, sedentary lifestyle, increased body mass index (BMI), ethnic background, and family history are all considered risk factors associated with BC (5). Late maternal age is one of the important risk factors added to the list. Breast cells are continuously under the influence of fluctuating hormones throughout different phases of female life. At puberty, breast size increases, during reproduction and lactation breast tissue undergo multiplication to serve the purpose. Pregnancy hormonal influence leads to the maturity of breast cells and makes them resistant to being influenced by hormones. In short, pregnancy is protective for BC development, however, increased maternal age at pregnancy increases the exposure of breast cells to hormones, leading to BC (6).

Diagnostic challenges

Diagnosing PABC presents challenges. The breast undergoes physiological changes during pregnancy, making imaging modalities less effective. Patients typically present with a palpable mass, and less commonly with focal pain, diffuse breast enlargement, and nipple discharge (7). Pre-existing benign lumps may also grow during pregnancy due to hormonal effects. It's noteworthy that over 80% of palpable masses biopsied in pregnant and lactating patients are benign (8). Pathologists should be notified when performing a core biopsy from the breast in pregnant women because pregnancy increases the cellularity of breast tissue.

Diagnosis of PABC is challenging as the risk of radiation exposure to the fetus is weighed against the benefits to maternal health. We discuss each imaging modality and its diagnostic value:

Ultrasound (US) is the primary imaging method for assessing breast abnormalities during pregnancy. It boasts an excellent safety profile for both obstetric and non-obstetric purposes (9). Unlike other methods, it doesn't expose the fetus to ionizing radiation. Ultrasonography is the preferred choice for imaging during pregnancy and lactation, with a sensitivity for carcinoma nearing 100% (10). It can distinguish between cystic and solid masses, helping to identify potentially concerning lesions that may need further evaluation. Although pregnancy leads to increased fibro-glandular tissue, which appears mildly hypoechoic, malignant findings on US resemble those in non-pregnant patients.

Mammography is a highly valuable imaging tool, widely used for screening, diagnosing, and monitoring BC. However, its use during pregnancy raises concerns about radiation exposure and its potential harm to the developing fetus. Typically, mammography isn't the first choice for imaging during pregnancy due to these concerns, but it may be considered in specific cases where the benefits outweigh the risks. Radiation exposure can lead to harmful effects on fetal development. When mammography is necessary after confirming malignancy, it's performed with a shield over the abdomen to minimize radiation effects on the fetus (11). Shielding with a lead apron can reduce radiation exposure to the uterus by up to 50% (12). Physiological changes in breast tissue during pregnancy lead to decreased sensitivity of this modality (13). However, mammography is still performed to assess breasts in pregnancy after which if deemed necessary other imaging techniques can be utilized.

Magnetic resonance imaging (MRI) is a significant imaging tool for evaluating breast health. While it's not typically the first choice for investigating breast symptoms, it is the most sensitive imaging modality available (14). Unlike other methods, MRI does not use ionizing radiation. It is usually recommended when breast tissue is dense and cannot be adequately assessed on a mammogram, or to determine the extent of disease and confirm the presence of solitary lesions.

During pregnancy, breast changes lead to increased vascularity, which can affect MRI interpretations. However, the use of contrast in MRI during pregnancy remains controversial (15). Gadolinium, a contrast agent, is categorized as a pregnancy category C drug, with adverse effects reported in animal studies (16). When a pregnancy continues, intravenous gadolinium-based contrast material should be avoided due to the risk of crossing the placenta and accumulating in amniotic fluid.

Staging BC patients in pregnancy is formidable. If necessary, exposure to ionizing radiation should be limited to safe levels. Individualized approach enabled by long axial field-of-view (LAFOV) positron emission tomography (PET)/computed tomography (CT) during pregnancy with an administered radioactivity dose 10 times lower than the usual may help in safe staging in pregnancy. LAFOV

PET/CT-scanner combines ultralow-dose PET scan with an ultralow-dose CT scan; however, more research is needed to accurately recommend this as a safe staging investigation (17).

The choice of diagnostic imaging method during pregnancy depends on specific clinical circumstances, the stage of pregnancy, and the need for accurate diagnosis and assessment of breast abnormalities. Close collaboration among the medical team, the patient, and the obstetrician is essential to ensure that the selected imaging techniques are safe and appropriate for both the mother and the developing fetus.

Management

The management of BC during pregnancy is influenced by various factors such as the stage and type of cancer, gestational age, and maternal preferences. Treatment options may involve surgery, chemotherapy, radiation therapy, and hormone therapy. The timing of treatment initiation requires careful consideration to balance the necessity of controlling the cancer with minimizing risks to the fetus.

The timing of treatment is crucial and depends on both the gestational age and the stage of cancer. Considering the potential risks of anesthetic medications and chemotherapy to developing fetuses, treatment may be delayed until the second trimester if cancer is diagnosed in the first trimester, as the literature indicates a decreased risk of abortions and fetal malformations in the second trimester compared to the first trimester. However, more aggressive cancers may require earlier intervention.

Multidisciplinary collaboration plays a vital role in the management of pregnant patients with cancer. Close cooperation between oncologists, obstetricians, surgeons, and other specialists is essential to develop a comprehensive treatment plan that considers both the cancer and the needs of the pregnant patient. Regardless of the gestational period, thorough pre-operative evaluation is crucial for surgical management. This process requires close coordination among the anesthesiologist, obstetrician, and pediatrician to prioritize the safety of both the mother and the fetus (18).

Surgical treatment

Addressing BC during pregnancy is a complex situation that necessitates a multidisciplinary approach to ensure optimal outcomes for both the mother and the developing fetus. It involves striking a balance between effective cancer treatment and the safety of pregnancy, which requires careful consideration of several factors.

When considering BC treatment in pregnant patients, the following key points are considered:

Surgical management may involve various approaches, including lumpectomy, mastectomy, reconstruction, and oncoplastic techniques. The choice of procedure depends on factors such as the stage of cancer, tumor size, and the gestational age of the fetus, aiming to achieve both oncological control and preservation of the pregnancy.

Sentinel node biopsy is the standard procedure during BC surgery. A dual technique is often used to stage sentinel nodes, enhancing the sensitivity of this method. Most centers utilize blue dye or radioisotope for sentinel node biopsy. However, blue dye should be avoided during pregnancy due to the potential risk of allergic or anaphylactic maternal reactions, which could harm the fetus (19). Despite this, sentinel node biopsy is considered safe during pregnancy. Performing sentinel lymph node biopsy in pregnancy resulted in extremely high overall live birth rate (95.8%) without any reported case of maternal anaphylactic reaction, maternal death, neonatal death and stillbirth, thereafter demonstrating safety of method for mother and foetus (20).

Anesthesia considerations in pregnant patients involve several factors, including gestational age, maternal age, the significance of the pregnancy, and the stage of BC. Anesthesia protocols are customized to minimize risks to the fetus, with anesthesiologists employing techniques that ensure the safety and stability of both the mother and the unborn child during surgical procedures. The primary goal during surgery is to ensure adequate maternal oxygenation and optimize uteroplacental perfusion. Strategies to prevent hypoxemia, hyperoxia, hypotension, acidosis (hypercarbia), intraoperative awareness, and hyperventilation (respiratory alkalosis) are crucial elements of anesthetic management (21). The timing of general anesthesia is crucial during pregnancy, particularly in relation to fetal age. Surgery is best avoided between the 3rd and 5th week after conception, during gastrulation, due to the potential association with neural tube defects. However, anesthesia and surgery are generally safe if indicated during the first trimester (22).

Post-surgical management requires vigilant monitoring of both the mother and the fetus, as well as the administration of suitable adjuvant therapy while considering the possible effects on the developing fetus. There have been no teratogenic effects associated with current anesthetic agents when used at standard

concentrations, nor is there evidence that in-utero exposure to anesthetic or sedative drugs has any effect on the developing fetal brain (23).

When mastectomy is performed, discussions about breast reconstruction are typically postponed until after delivery to prioritize the safety of the fetus. During pregnancy, breasts can double in weight, experience increased ptosis, and change in size and pigmentation of the nipple-areolar complex. These peripartum changes are often unpredictable and can complicate decision-making regarding surgical techniques (23). However, in certain situations, immediate reconstruction may be considered after a thorough assessment of the risks and benefits. Caragacianu *et al.* demonstrated safety and favorable outcomes following immediate reconstruction with tissue expanders in ten patients with PABC (24).

The primary concern with breast reconstructive surgery during pregnancy is the prolonged duration of surgery, which increases exposure to anesthetic drugs for both the mother and fetus. Prolonged surgery may also result in prolonged maternal hypoxemia and hypercapnia. Prolonged maternal hypoxemia causes uteroplacental vasoconstriction, reducing uteroplacental perfusion and resulting in fetal hypoxemia, acidosis, and potentially fetal death. Maternal hypercapnia should also be avoided as it is associated with uterine artery vasoconstriction and reduced uterine blood flow (25).

Systemic treatment

The administration of chemotherapy in pregnant patients is a complex decision that involves a multidisciplinary team of specialists, including oncologists, obstetricians, and neonatologists, who collaborate to determine the best course of action.

It requires a careful balance between effectively treating the cancer and safeguarding the health of both the mother and the developing fetus.

Chemotherapy is generally administered during the second and third trimesters when the risk to the fetus is relatively lower. Chemotherapy is contraindicated in the first trimester of gestation to avoid interference with organogenesis, as early exposure has been associated with up to 20% risk of major malformations (26). However, the timing may vary depending on the type and stage of the BC and the gestational age of the fetus as need to weigh fetal benefits with maternal risks. Chemotherapy is associated with an increased risk of congenital malformations only in the first 12 weeks of pregnancy (27).

The key considerations for administering chemotherapy during pregnancy include the choice of chemotherapeutic agent and dosage. Oncologists opt for chemotherapy drugs with minimal risk to the developing fetus, favoring certain agents considered safer during pregnancy.

From around 12–14 weeks of gestation, many chemotherapy drugs can be safely given. Standard anthracycline-taxane-based regimens, commonly used in non-pregnant patients, can be administered. The selection of the regimen depends on tumor characteristics and potential fetal risks (28).

Studies indicate that chemotherapy pharmacokinetics change during pregnancy, resulting in relatively lower drug exposure compared to non-pregnant women. Placental metabolism contributes to this, leading to lower peak plasma concentration and faster clearance of chemotherapy drugs (29,30).

This decrease in exposure is more noticeable for taxanes than anthracyclines. While the impact on treatment benefits is uncertain, it's believed to be minimal. Evidence from the neoadjuvant setting suggests that pregnant and non-pregnant BC patients have comparable rates of pathological complete response (pCR) (31,32).

Chemotherapy doses should not be adjusted during pregnancy, and women should receive standard doses based on their actual weight, as in non-pregnant patients.

After 35 weeks of gestation, a 3-weekly chemotherapy schedule is discouraged to allow a recovery window for maternal and fetal bone marrow between the last cycle of chemotherapy and delivery (33). Alternatively, a weekly regimen can be used, or chemotherapy can be avoided at nearly 34 weeks of gestation.

The multidisciplinary team carefully evaluates the potential risks and benefits of administering chemotherapy, considering its impact on the mother's health, potential effects on the fetus, and overall prognosis for both.

Maternal health monitoring: close monitoring of the mother's health during chemotherapy is crucial to manage potential side effects and ensure treatment effectiveness. This includes regular assessments of the mother's overall well-being and any adverse reactions to chemotherapy.

Regular fetal monitoring is essential to assess the well-being and development of the fetus during and after chemotherapy. This typically involves US examinations and other surveillance methods to ensure optimal fetal growth and health.

A study by Amant *et al.* (34) assessed 129 children whose

mothers' received chemotherapy during pregnancy (all cycles after the first trimester) compared to 129 matched children born from women without cancer. Despite a higher incidence of preterm birth and small gestational age in the exposed group, the children's development was normal, with no clear adverse effects on growth, cognitive function, or cardiac function in early childhood. The study suggested that cancer diagnosis during pregnancy should not lead to pregnancy termination. The only factor associated with worse cognitive outcomes was prematurity, regardless of anticancer treatments (35,36).

After completing chemotherapy, postpartum care focuses on monitoring the mother for potential long-term effects of treatment and ensuring appropriate follow-up for BC management.

Chemotherapy during pregnancy for BC involves weighing risks and benefits for both mother and fetus. Close collaboration between the medical team and the patient ensures a personalized and optimized treatment plan for the best outcomes.

While breastfeeding has significant benefits for newborns, it's not recommended during systemic chemotherapy, endocrine therapy, targeted therapy, or immunotherapy due to potential drug excretion in breast milk (34).

BC cells sometimes exhibit the expression of the HER2/neu protein. Targeted therapy directed at this protein is typically recommended as it disrupts the multiplication of these cancer cells.

A meta-analysis examining metastatic tumours or PABC in the adjuvant setting, which included 18 patients, revealed various outcomes based on exposure during different trimesters (37).

- First trimester: no adverse effects on newborns were observed when the drug was administered solely during the first trimester.
- Second/third trimester: a higher prevalence of adverse birth events (57%) was noted, with stillbirths and oligohydramnios/hydramnios being the most frequently reported events (73.3% of patients).

To date, there are no large studies published to prove the safety of endocrine therapy for BC in pregnancy. All data has been gathered retrospectively when patients were exposed to endocrine therapy and were unaware of their pregnancy status. A total of 249 fetuses exposed to tamoxifen during the first trimester or later have been identified in a systematic review by as mentioned, due to the lack of long-term data on pediatric outcomes associated with the use of tamoxifen during pregnancy, it is not possible to draw definitive conclusions on its use; therefore, pregnancy remains contraindicated during treatment and up to 3 months after its interruption (38).

The potential risks to the fetus during BC treatment must be carefully evaluated. While some chemotherapy agents can be administered safely during pregnancy, others may pose risks to fetal development. Unfortunately, after using cyclophosphamide during the first trimester, malformations of the toes, eyes, lower ears, and cleft palate were found. Anthracyclines are well known for their cardiotoxic effects, which depend on multiple mechanisms, including oxidative damage, changes in calcium metabolism, and activation of apoptotic pathways, which lead to a progressive deterioration of heart function (34).

Limited experience is available in taxanes in PABC. Placental P-glycoprotein transporter seems to reduce the drug passing to the fetus. According to a systematic review, 50 patients with PABC exposed to taxanes tolerated well the drugs and showed manageable toxicities; therefore, their use can be considered in combination with cisplatin/carboplatin, when clinically indicated (39).

Radiotherapy treatment

The administration of radiotherapy for BC during pregnancy is a complex decision that requires careful consideration of the potential risks to the developing fetus. The influence of radiation on pregnancy in general may include fetal death in the first 2 weeks after conception, malformations up to 2 months, and intelligence quotient (IQ) decrease between the 3rd and 6th month (40). While radiotherapy is generally avoided during pregnancy due to the potential risks of harm to the fetus, there are certain situations where it may be considered if the benefits to the mother outweigh the risks to the unborn child.

The timing of radiotherapy is crucial, and it is typically avoided during the first trimester when the developing fetus is most vulnerable to the potential harmful effects of radiation. Regarding gestational age, excessive exposure during the first 2 weeks after conception may result in implantation failure or death (all-or-nothing law). During the 2nd–8th week after conception, malformations may occur, especially during the organogenesis stage. From the 8th to the 25th weeks, the central nervous system is extremely sensitive to radiation; thus, excessive exposure during this period may result in mental disability (41).

In non-pregnant patients, proton-radiation therapy is increasingly administered because of its favorable dosimetric

properties compared with photon-radiation therapy. Although data on the use of pencil beam scanning proton-radiation therapy during pregnancy are scarce, different case reports and dosimetric studies have indicated a more than 10-fold reduction in fetal radiation exposure compared with photon-radiation therapy (17).

The multidisciplinary team of healthcare providers carefully evaluates the potential risks and benefits of administering radiotherapy during pregnancy, taking into account the specific characteristics of BC, the overall health of the mother, and the potential impact on the developing fetus.

If radiotherapy is deemed necessary during pregnancy, shielding techniques may be used to protect the fetus from unnecessary radiation exposure. These techniques involve the use of specialized shielding devices to minimize the radiation dose to the surrounding healthy tissues and the fetus. However, prospective studies are required to establish the safety of radiotherapy during pregnancy.

Radiotherapy can be delayed until delivery by carefully assessing the risk of delayed treatment on maternal outcome. If radiotherapy is delayed until after delivery, postpartum care focuses on closely monitoring the mother's health and providing appropriate follow-up treatment to manage BC effectively.

Ultimately, the decision to administer radiotherapy during pregnancy for BC is made on a case-by-case basis, considering the specific circumstances and the risks and benefits for both the mother and the developing fetus. Close collaboration between the oncology team, obstetricians, and other specialists is essential to ensure that the treatment plan is personalized and optimized to achieve the best possible outcomes for the mother and the child (42).

Radiation therapy is generally avoided due to the potential harm to the fetus. The long-term effects of radiation have not yet been fully enlightened. Therefore, this procedure is generally not recommended in routine medical practice during pregnancy (43).

Prognosis and outcomes

The outlook for BC during pregnancy depends on factors such as the stage of diagnosis, tumour characteristics, and the effectiveness of treatment. Timely detection and personalized treatment strategies can result in positive outcomes for both the mother and the child. Long-term monitoring is essential to detect any recurrence and to track the child's developmental progress.

The management of BC during pregnancy requires a multidisciplinary approach involving oncologists, obstetricians, radiologists, and counsellors. This collaborative effort ensures comprehensive care, addressing the physical and emotional needs of both the mother and the developing fetus.

Deciding whether to defer radiotherapy is challenging, especially during the first trimester when chemotherapy is also not recommended. Therefore, each case should be discussed by a multidisciplinary team, including gynecologists and obstetricians, considering the patient's prognosis and gestational age. Ultimately, after thorough counselling, the patient must make her own decision, and the clinician should respect her right to self-determination (44).

Medical experts can seek advice when treating pregnant women with cancer from advisory boards created to guide medical professionals in this dilemma. In 2021 the International Advisory Board on Cancer in Pregnancy was established, and in continuation, the Danish Advisory Board on Cancer in Pregnancy (DABCIP) has now been founded. DABCIP consists of 22 members from 13 different medical disciplines (45,46).

Conclusions

BC during pregnancy presents a complex challenge, requiring personalized diagnosis and treatment. Multidisciplinary care and timely interventions are essential for optimal outcomes for both mother and child. Ongoing research offers hope for improved strategies and outcomes in the future.

Surgical management of BC during pregnancy requires a delicate balance between effective cancer treatment and maternal-fetal health. Decisions are made case by case, considering cancer stage, gestational age, and patient preferences, especially in precious pregnancies, with input from a multidisciplinary medical team.

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