Journal of Pre-Clinical and Clinical Research 2024, Vol 18, No 2, 156-161
www.jpccr.eu

REVIEW ARTICLE

Breast cancer associated with pregnancy – a review of therapeutic approaches

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Piekarz J, Picheta N, Burdan O, Szklener K. Breast cancer associated with pregnancy – a review of therapeutic approaches. J Pre-Clin Clin Res. 2024; 18(2): 156–161. doi: 10.26444/jpccr/189445

Abstract

Introduction and Objective. Pregnancy associated breast cancer (PABC) is among the most common malignancies occurring in pregnant and postpartum women. Due to the increasing frequency of diagnoses, it is essential to expand our knowledge of diagnostic and therapeutic methods. Clinicians have to make many difficult decisions regarding the health and life of both the patient and the foetus. The aim of the review is to provide an overview of the disease, and delve into the available safe and controversial methods of treatment for PABC.

Review Methods. A review was conducted of scientific publications available in PubMed, Google Scholar, Clinical Key, Via Medica Journals, and guidelines for the diagnostic and therapeutic management of breast cancer. More than 95% of the publications were published within the last eight years.

Brief description of the state of knowledge. Breast cancer is a widespread and increasing problem affecting women. The question of implementing appropriate imaging studies and subsequent treatment is a set of many difficult questions and decisions made by clinicians. It is mainly recommended to perform surgery, which is allowed at any stage of pregnancy, and chemotherapy after the end of the first trimester of pregnancy. The question of the use of targeted and hormonal therapy ranks among the controversial treatments due to the lack of sufficient studies of the drugs used and their effects on the foetus. Radiation therapy can be considered in necessary situations after calculating the appropriate dose reaching the foetus.

Summary. The review highlights the epidemiology, risk, prognosis and clinical presentation of PABC. Attention was paid to the available and safe diagnostics used in pregnant women. In addition, it delved into the available therapeutic methods and compared their safety of use at different stages of pregnancy and afterwards.

Key words

breast carcinoma, PABC, PrBC, PPBC

INTRODUCTION AND OBJECTIVE

Pregnancy associated breast cancer is a malignant neoplasm that occurs in pregnant women or in the postpartum period, usually up to one year after delivery. Based on new studies of the pathophysiology of the cancer, it has been deduced that PABC should be divided into two distinct disease entities: breast cancer diagnosed during pregnancy (PrBC) and breast cancer diagnosed during the postpartum period (PPBC) [1]. The care of a pregnant patient with a breast tumour is undertaken by a multidisciplinary team of clinicians consisting of a gynaecologist, obstetrician, oncologist, surgeon, geneticist and neonatologist. Decisions made by physicians have consequences not only for the woman, but also for the developing foetus within her [2]. Diagnosis is based on interview, imaging and clinical studies. During pregnancy, many physiological and morphological changes occur in a woman, one of which involves modification in the glandular and ductal tissue of the patient's breast, which makes it difficult to make a proper diagnosis and implement treatment early [3]. PABC therapies are established in a more regimented manner, paying attention to the welfare of mother and child? foetus. It should be mentioned that issues of safe use of drugs in pregnant women have not been adequately researched and proven, which makes it difficult to make decisions and start treatment. Currently, doctors attempt to use the same recommendations in patients with PABC as in non-pregnant women with breast cancer (BC) [4].

REVIEW METHODS

A review of the available literature was conducted based on the PubMed database, Via Medica Journals, Google Scholar, Clinical Key and guidelines for the diagnostic and therapeutic management of breast cancer. Using the key words: breast cancer, PABC, PrBC and PPBC, 162,321 papers were searched for the period 2015–2024. Mainly developed countries were included in the analysis, with papers written in English and Polish being included. After reviewing the papers, a final selection was made and 55 articles.

BRIEF DESCRIPTION OF THE STATE OF KNOWLEDGE

Epidemiology of PABC. PABC is the most commonly diagnosed malignant tumour in patients expecting offspring,

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Received: 27.03.2024; accepted: 28.05.2024; first published: 14.06.2024

and accounts for 21% of all cancers identified in pregnant women [5]. In 4% of patients before the age of 45, breast tumour is diagnosed during pregnancy or one year after the end of pregnancy [6]. In recent years, there has been a significant increase in the number of PrBC and PPBC diagnoses [7]. The incidence rate is determined based on 100,000 births [6]. A general increase in the number of BC cases and the increasingly later age of women becoming pregnant are identified as reasons for the rising incidence trend [7].

Table 1. Frequency of PABC, PrBC, PPBC [6]

Disease	Incidence per 100,000 births
PABC	17.5 – 39.9
PrBC	3.0 – 7.7
PPBC	13.8 – 32.2

Risk of PABC. The young age of a woman with PABC (under 25 years old) negatively affects the course of the disease due to a higher likelihood of metastasis and level of lymphocyte infiltration. In contrast, pregnancy before the age of 25 positively reduces a woman's risk of developing PABC [8]. Longer waiting time for offspring and morphological changes in the breast affect the increased risk of carcinogenesis. In addition, women giving up breastfeeding their child increases the risk of the disease [9].

Prognosis of PABC. The prognosis of PABC depends on a number of factors: age of the pregnant woman, level of maturity of the breast tissue, stage of the tumour, length of time it takes to implement treatment and establish a diagnosis, the presence of gestational immunosuppression and hormone receptor status [10].

When comparing the prognosis of patients with PrBC and PPBC, it was found that pregnant patients had a better prognosis than postpartum women [11]. A clinical – cohort study to compare disease – free time (DFS) and overall survival (OS) included 195 patients (65 with PABC and 130 with BC). Disease recurrence was found in 29% and death in 17% of pregnant women, which was similar to the control group – 20% and 11% [12].

Table 2. Comparison of 2-year survival of patients with PrBC and BC, below and above 35 years of age [13]

Age: \ Disease	PrBC	BC
Before 35	80.6%	86.2%
After 35	89.8%	93.1%

An important consideration in patients with BC is the presence of expression of human epidermal growth factor receptor 2 status (HER-2) [14]. It was found that 10–20% of BC are characterized by the presence of an HER2 positive tumour [15]. These cancers are classified as very fast-growing and aggressive. Before the invention of HER2-targeted therapy, they were referred to as the worst subtype of BC and characterized by low DFS and OS [16]. Because immunotherapy, antibody and hormone therapy are contraindicated in pregnant women, the prognosis of patients with PrBC is likely to worsen, and they will not be able to benefit from modern treatments [17].

Histology. The most common histologic type of PABC diagnosed in 75 – 90% of patients is invasive ductal carcinoma of the breast. Invasive lobular carcinoma is also frequently diagnosed, while the inflammatory subtype is rare [18]. HER2-positive tumours are found in one in three patients, while triple-negative tumours are found in 27.6% of patients, whereas the presence of progesterone receptor (PR) and estrogen receptor (ER) is 42.8% and 43.4%, respectively. The simultaneous presence of PR and ER-positive tumours is 47.9% [19].

Clinical manifestations and diagnosis. PABC manifests as a painless lump accompanied by discharge and retraction of the nipples, as well as redness and ulceration of the skin [20]. Tumour size determines the determination of tumour stage and the selection of an appropriate treatment plan. A distinction is made between tumours ≤2 cm, ≤3 cm, ≤5 cm and >5 cm [21]. The natural physiological changes occurring in a pregnant woman's breast make palpation and assessment of breast structure difficult, often resulting in a delayed diagnosis [22].

Ultrasonography is the first imaging test that is recommended when a lump persisting longer than 2 weeks is detected, and allows the diagnosis of benign lesions which are diagnosed in 80% of patients [23]. Diagnostic mammography is safely performed in pregnant women and, due to its low radiation of 200 – 400 mrad, does not significantly affect foetal development [24]. Nowadays, a new method of breast imaging is contrast-enhanced mammography (CEM), which involves the use of iodine contrast, but its use is contraindicated in pregnant women due to the penetration of the substance through the placenta and into the foetus [20]. Based on studies, the sensitivity of ultrasound in detecting breast cancer in pregnant patients is 95.7%, while that of mammography is 56.5% [25]. Both of the aforementioned tests allow assessment of the extent and focality of the tumour [23].

Biopsy is an essential test to confirm BC. It is performed after clinical and radiological evaluation of the patient's lesion based on the Breast Imaging Reporting and Data System (BI – RADS) scales. BI – RADS 4 and 5 and possibly BI – RADS 3 are among the indications for its performance in patients with PABC [26].

MRI is an excellent diagnostic test for BC, with specificity and sensitivity of 89% and 71.1 – 100%, respectively. In addition, it has no ionizing radiation, which is beneficial for pregnant women [27]. However, due to the use of gadolinium-based contrast agents, which cross the placenta and decompose in the amniotic fluid, they can form toxic substances that will adversely affect foetal development [23]. The decision to perform the test is made after giving the patient the necessary information about the consequences and obtaining informed consent. In addition, it must be based on the reasonable benefits to her and the impossibility of delaying the test until after delivery, as this will adversely affect prognosis and treatment [27].

Metastases in breast cancer most often occur in the liver, lungs and bones. To confirm or exclude them, a chest X – ray with foetal shielding should be performed. CT, PET or bone scintigraphy is contraindicated, while lymphoscintigraphy before sentinel node biopsy is safe for the foetus [28].

Treatment of PABC. Therapy of breast cancer in a pregnant woman requires appropriate tailoring of treatment to the age of the foetus, the patient's preferences, and the stage of the cancer. The woman's care is realized by a team of doctors who approach the patient individually, taking into account the impact of decisions on the health and life on her and the foetus [29]. An obstacle that hinders treatment is the issue of frequent late diagnosis and the extent of the cancer, lymph node involvement and the presence of possible distant metastases [30].

Surgery. Surgical methods used to treat patients with PABC are considered the safest and can be performed at any stage of the pregnancy course. These include mastectomy and breast- sparing surgery. Each of these methods is indicated and preferred in pregnant patients [31]. The former can recommended in every trimester of pregnancy and can be expanded to include breast reconstruction, which will have a positive psychological impact on the pregnant woman [32]. The second option is to perform breast-sparing surgery. Due to the necessary complementary treatment, the surgery is recommended in the second and third trimesters. Radiation therapy should be performed only after the baby is born, so it is usually delayed until the postpartum period [31].

In addition, 50% of patients are found to have metastases in the axillary lymph nodes, in which case surgical excision is performed. In patients without such involvement, a Sentinel Lymph Node Biopsy (SLNB) is performed [32]. Before SLNB, the use of Tc-99m isotope colloid is allowed to visualize the sentinel node, while dyes such as methyl blue are contraindicated due to the high risk of anaphylactic shock [28]. A one-day protocol is recommended which involves the administration of the tracer on the same day the procedure is performed. This makes it possible to shorten the time between lymphoscintigraphy and the procedure during which the node with accumulated colloid will be removed, and the harmful substance will be expelled from the pregnant woman's body [32]. The operation may result in local complications, including haematoma, wound dehiscence, delayed healing, haemorrhage, fat necrosis, or the appearance of bloody nipple discharge. In addition, flap necrosis or cosmetic deformity may occur, leading to the need for plastic surgery [33]. During the course of any operation of a patient with PrBC, uterine contractions and foetal heart rate should be monitored; in the case of its decrease, intravenous fluids should be administered. Phenylephrine could also be considered [34].

Drugs safely used during pregnancy include propofol, desflurane, sufentanil, morphine, corticosteroids, lidocaine and ketamine. Nitrous oxide should not be used to anaesthetize the patient due to its adverse effects on foetal development. In addition, non – steroidal anti-inflammatory drugs (NSAID) or metamizole are not recommended during surgery [18, 29]. It is essential to provide the pregnant woman with adequate post-operative care consisting of post-operative pain management. For this, opioids are used which, despite crossing the placenta, do not cause adverse effects in the foetus. In order to minimize the dose of opioids, combination therapy is used by combining them with acetominophen [34].

Chemotherapy. Chemotherapy is commonly used to treat BC. It can be used as neoadjuvant and adjunctive treatment after surgery or before radiation therapy [35]. In a pregnant woman, there are numerous physiological changes: renal clearance, hepatic metabolism or blood volume, which make it difficult to determine the toxicity profile of the drugs [36]. Chemotherapy in PrBC patients is allowed in the second and third trimesters because the rate of birth defects in this group is relatively low, ranging from 1.5% – 3%. Due to its high teratogenic effect, it is contraindicated in the first trimester, where the risk of defects reaches up to 10 – 20%. It is recommended that the drugs be discontinued after the 35th week of pregnancy and three weeks before the scheduled delivery date, as they affect bone marrow function and, as a consequence, haematological complications may occur at birth [37].

BC chemotherapy uses cytostatic drugs with different mechanisms of action and safety profile. The most commonly used PrBC treatment regimen is based on anthracyclines [37]. Neutropenia, oral ulceration, anaphylaxis and cardiac abnormalities can occur in women taking drugs from this group. It is reported that 7.6% of foetuses have low birth weight and 3.8% have birth defects. The risk of defects is relatively similar to that in pregnant women not receiving chemotherapy [38].

Another group of drugs used in addition to anthracyclines in pregnant women with BC are the taxanes: paclitaxel, docetaxel, although the former is preferred in PrBC [28], [39]. Paclitaxel in weekly administration is used in patients with PABC who are not qualified for anthracycline therapy. Docetaxel, on the other hand, is given every three weeks but is less well tolerated and is associated with a higher risk of neutropenia [40]. A cohort study including 103 PrBC patients between the ages of 21 – 44 who were treated with taxanes, in whom 91.1%, anthracyclines or cyclophosphamide were additionally administered. Adverse symptoms were observed in seven pregnant women: hypersensitivity reactions, nausea, vomiting and neutropenia. An overall live birth rate of 97.9% was determined in the newborns. The most common complications observed were hyperbilirubinemia (12.5%), respiratory distress syndrome (5.7%) and hypoglycaemia (5.7%). Twenty-seven neonates were diagnosed with low birth weight and 17 with small – for gestational age (SGA), while malformations were diagnosed in two [41]. Taxanes, along with platinum, should be used with caution in pregnant women, and decisions about their introduction must be based on the inability to benefit from preferred treatments [36].

Another drug used in BC therapy is methotrexate, but is no longer used in this patients. Methotrexate is contraindicated in patients with PrBC due to its strong teratogenic effects. Pregnant women using the described drug develop congenital malformation syndrome, which manifests as mandibular hypoplasia, auricular deformity, limb deformity, or defects of the nervous system and hearing organ [28].

Other drugs used in the treatment of BC are the alkylating drugs cyclophosphamide and antimetabolite 5-fluorouracil (no longer used in this patients) [24]. The study included 57 women in their second or third trimester who received a standard treatment regimen based on: 5-fluorouracil, doxorubicin and cyclophosphamide. Respiratory problems were noted in 10% of the newborns, while overall birth complications were determined at a similar risk rate to population norms. In addition, no stillbirths or perinatal deaths were observed [42].

In patients with PPBC, chemotherapy is allowed, but note that breastfeeding is contraindicated [28].

Table 3. Drugs used in chemotherapy [24, 27, 35–38, 41, 42]

Group	Drugs	Mechanism	Category
Anthracyclines	Doxorubicin Epirubicin	Builds into the structure of DNA and causes its disruption and fragmentation	D
Taxanes	Paclitaxel Docetaxel	Disrupts microtubule function	D
Alkylating agent	Cyclo-phosphamide	Disrupts DNA, RNA and protein synthesis, consequently prevents cell division	D
Antimetabolite Folic acid antagonist	Methotrexate	Inhibits dihydrofolate reductase activity. Interferes with DNA production and therefore cell division and tumour growth	X
Antimetabolite Fluorinated uracil derivative	5 – fluorouracil	Inhibits thymidyl synthase. Interferes with DNA production and therefore cell division and tumour growth	D

Hormonal treatment. Patients with ER+ breast cancer receive hormonal treatment based on tamoxifen anastrozole and goserelin. The safety of the aforementioned drugs during pregnancy has not been sufficiently studied and confirmed, and with the exception of tamoxifen, all of them fall into category X [43].

Table 4. Mechanism of drugs used in hormonal therapy of BC [45, 46]

Group|	Mechanism	Drugs
Selective Estrogen Receptor Modulators (SERM)	Bind to ER in cancer cells by which it inhibits growth factor synthesis and stimulates PR formation	Tamoxifen
Non-steroidal aromatase inhibitors	Inhibits estrone and estradiol production from androstendione and testosterone	Anastrazole Letrozole
Analogue gonadoliberin (GnRH)	Increases the concentration of LH and FSH	Goserelin

Analyzing the effects of tamoxifen on 108 pregnancies exposed to the drug administered in the first, second and third trimesters, 68 live births were observed. In 12 of these children, congenital malformations were found: genital, craniofacial, external ear, cleft palate, lung hypoplasia, and abnormal karyotype [44]. Exposure to the drug increases the risk of Goldenhar syndrome, characterized by hemifacial underdevelopment and genital malformations [28]. Hormonal drugs are contraindicated during pregnancy due to an increased risk of foetal birth defects, compared to the general population (12.6% vs. 3.9%). Their use should be withheld until delivery [45].

Targeted therapy. Therapy for the treatment of HER2-positive breast cancer is based on the use of trastuzumab (a monoclonal antibody directed against HER2), lapatinib (epithelial growth factor receptor tyrosine kinase and HER2 inhibitors) and pertuzumab (humanized monoclonal antibody IgG1)[36]. In women with PABC, HER + tumours are diagnosed in 28 – 58% of patients. Analysis of 32 foetuses from 30 pregnancies exposed to trastuzumab found that 41.7% of the newborns were born healthy, 58.1% of the babies developed thrombocytopenia or amenorrhea, and 10% had cardiac problems [46]. The implementation of trastuzumab can be delayed for up to 6 months after diagnosis; therefore, due to the teratogenic effect of the drug, it is advisable to hold-off if possible until the postpartum period [47]. Pertuzumab binds to HER-2 subdomain II through which it prevents HER2 heterodimerization and homodimerization. A common adverse reaction to the drug is diarrhea. It has been noted that when pertuzumab is added to chemotherapy, there is no increase in the incidence of cardiotoxicity. The drug is not recommended for use in pregnant women [48].

Immune therapy. Triple-negative breast cancer (TNBC) accounts for about 15% of breast cancers and is associated with a higher risk of recurrence. Therapy for this tumour subtype uses pembrolizumab, which is a humanized monoclonal antibody that blocks the interaction between the programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1). [49]. Patients taking the drug along with chemotherapy experience nausea, alopecia, anaemia, neutropenia, fatigue, diarrhea, vomiting, and insularity. Its use is contraindicated in therapy in pregnant women [50].

Adverse effects following the use of pembrolizumab include immune-mediated disorders of kidney, lung, and liver function. Endocrinopathies, Guillain-Barre syndrome, vasculitis, myositis, encephalitis, colitis, and pneumonitis may also occur. In addition, there are adverse reactions in the skin in the form of exfoliative dermatitis, bullous pemphigoid, Stevens-Johnson syndrome, and toxic epidermal necrolysis [51].

Radiation therapy. Radiation therapy in the treatment of BC is a commonly used adjunct treatment, and can often be withheld until the postpartum period. On the other hand, it should be considered when there are contraindications to other treatments [52].
The biggest obstacle to its inclusion in a PrBC patient is the issue of foetal exposure to radiation and the many consequences that follow. In the developing foetus, the greatest radiation damage occurs during the phase of organogenesis, and include the occurrence of anatomical defects, mental retardation, microcephaly, intrauterine hypotrophy and secondary malignancies [53]. The most important consideration when incorporating radiation therapy into a PrBC treatment regimen is the radiation dose reaching the foetus. The likelihood of foetal harm increases once the dose exceeds 0.1 Gy received by the foetus, but it is stated that this dose can be increased to 0.2 Gy [54]. Some researchers claim that this dose can be increased to 2 Gy at advanced gestational age. It is estimated that 0.05 – 0.15 Gy is delivered to the foetus in therapy when the patient receives 50 Gy [55].

The use of radiation therapy in patients with PPBC does not differ from the treatment of patients with BC [28].

Termination of pregnancy. Termination of pregnancy is not a routinely recommended method, as it does not significantly increase in the survival time of patients. The decision made by the patient must be fully consistent with her beliefs. On the basis of two groups of women with PrBC who differed in the performance of abortion, a slightly longer survival was inferred in patients who carried the pregnancy to term [13].

Supportive care. Treatment of breast cancer is often accompanied by side-effects: nausea, vomiting and neutropenia.

In patients with PABC, the following can be used to minimize them: corticosteroids (GCS, only methylprednisone, prednisone and hydrocortisone, as they do not cross the placenta), ondansetron, promethazine, erythropoietin, and granulocyte colony –stimulating factor (G – CSF) [19].

Table 5. Categories of adjunctive drugs for the treatment of PABC [37]

Drugs	Category
G – CSF	C
Ondansetron	B
Promethazine	C
GKS	C

DISCUSSION

PABC is one of the increasingly common medical problems. Decisions made by a specialized team actually involve two patients: the pregnant woman and her foetus. The faster the diagnosis and implementation of appropriate treatment, the better the chances for the patient. The choice of appropriate treatment is based on many medical aspects and has many consequences. The safest treatments for the foetus are surgical procedures used at any stage of pregnancy and after the end of pregnancy. Chemotherapy is a treatment allowed during the second and third trimesters of pregnancy. The safest and appropriate drugs should be chosen, mainly anthracyclines or taxanes, mainly paclitaxel. Radiation therapy in pregnant women is a contentious issue, but due to its beneficial effects and lack of alternatives, it should be taken into consideration. It is important to determine the appropriate dose reaching the foetus to minimize the risk of birth defects. Newer and modern methods that are being increasingly used in patients with BC, which include: immunotherapies, hormonal or targeted therapy, are contraindicated in pregnant women. Pregnancy termination is not recommended. Supportive care is widely used in PABC patients.

Table 6. Comparison of allowed therapeutic approaches used to treat PPBC and PrBC [28, 32, 42, 52]

Method of treatment	PPBC	PrBC
Mastectomy	Yes	Yes I, II, III trimester
Breast – conserving surgery	Yes	Yes I, II, III trimester
Chemotherapy	Yes	Yes II, III trimester
Hormone therapy	Yes	No
Targeted therapy	Yes	No
Immune therapy	Yes	No
Radiotherapy	Yes	Yes/No

CONCLUSION

PABC is a problem affecting pregnant women and those in the postpartum period. Due to the difficult period of women often associated with numerous psychological disorders, an additional disease such as malignant cancer can further aggravate the mood and lead to depressive states. The lack of adequate and numerous studies on the safety of PrBC therapeutic methods causes difficulties in the decision of the team and the patient to implement treatment due to the protection of the foetus. Efforts must be made to expand our knowledge as well as research into the safety of drugs and radiation therapy in pregnant patients.

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