**MICHALSKA, Maria, KOWALIK, Kinga, ZIELIŃSKA, Aleksandra, TYLCZYŃSKA, Kinga, SKIBA, Jakub, SZYPULSKI, Szymon, IWANIUK, Sebastian, MACIEJEWSKI, Ignacy, SKIBA, Zuzanna and TYLCZYŃSKA, Natalia. Diagnostic and Therapeutic Challenges in Pregnancy-Associated Breast Cancer: A Literature Review. Quality in Sport. 2025;42:60515. eISSN 2450-3118.**
**https://doi.org/10.12775/QS.2025.42.60515**
**https://apcz.umk.pl/QS/article/view/60515**

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). 
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 23.04.2025. Revised: 30.04.2025. Accepted: 14.06.2025. Published: 16.06.2025.

# Diagnostic and Therapeutic Challenges in Pregnancy-Associated Breast Cancer: A Literature Review

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**Abstract**

**Introduction**: Pregnancy-associated breast cancer (PABC) is an increasingly diagnosed malignancy, typically occurring during pregnancy or within one year postpartum. This review summarizes current knowledge on PABC diagnosis, treatment and clinical management, with attention to both maternal outcomes and fetal safety.

**Diagnostic:** The diagnosis of PABC requires careful consideration of both maternal health and fetal safety. Diagnostic process typically begins with the detection of a palpable mass, followed by ultrasound imaging and biopsy. Mammography and MRI may be used selectively, whereas CT and PET-CT are avoided due to radiation exposure. Physiological changes during pregnancy often delay recognition.

**Histopathology:** Histopathological evaluation of PABC follows standard classifications, including the AJCC TNM and WHO systems, with assessment of ER, PR, HER2, Ki-67, and tumor grade. The most common histological type is ductal infiltrating adenocarcinoma.

**Treatment:** Treatment of PABC is complex and multifactorial, often requiring adjustments to standard protocols to balance effective maternal therapy with fetal safety. Surgery is considered safe during all trimesters, while chemotherapy is typically used in the second and third trimesters. Trastuzumab, tamoxifen, and radiotherapy are generally avoided due to fetal risks, though radiotherapy may be considered in selected cases after thorough evaluation.

**Conclusion:** Pregnancy-associated breast cancer requires an individualized, multidisciplinary approach, with diagnosis and treatment tailored to balance effective maternal care and fetal safety.

**Keywords:** PABC, Breast cancer epidemiology, Breast cancer diagnostics, Breast cancer treatment, Cancer treatment adverse effect, Fetal risk

## 1. INTRODUCTION

In female population the most common malignant tumor is breast cancer [1,2]. In 2022 approximately 2,3 million women were diagnosed with this disease [2]. Currently, a number of risk factors for breast cancer are known, including BRCA mutation, hormonal factors, age, personal or family history of breast cancer, no pregnancies, overweight, large breasts, late menopause [3]. Despite that, the number of breast cancer cases is constantly increasing in

every age group, the largest growth was observed in women under 50 years old [4]. Although there has been significant development in diagnosis and treatment, breast cancer is still the leading cause of cancer deaths in the female population around the world [5].

A certain type of breast malignant tumor is pregnancy-associated breast cancer (PABC) [7]. PABC is usually defined as breast cancer, which was diagnosed during pregnancy, lactation or up to one year after childbirth [6,11], but in some studies time criterion was extended to 5-years post-partum. Currently, PABC is rare disease, but the incidence is steadily increasing [8]. One of the reasons for the growing number of cases is probably the higher age at which women become pregnant. In 2020 number of PABC cases was reported from 17.5 to 39.9 per 100,000 births [6], which means among all primary malignant tumor diagnosed during pregnancy or one year post-partum PABC is the most common [9]. The average age of patients is lower than the age of breast cancer cases in general and is 32-34 years old [12]. Diagnosis and treatment of PABC has some differences from that of non-PABC, due to changes in the functioning of the body during pregnancy and safety of the fetus [10]. The aim of this review is to provide comprehensive overview of the available diagnostic methods, and current treatment options for pregnancy-associated breast cancer.

## 2. DIAGNOSTIC

The most frequent clinical manifestation of PABC is palpable breast mass, similarly like in non-pregnant woman [11,12, 13, 14]. Other symptoms may be nipple discharge, erythema, enlarged lymph nodes, skin thickening [11, 12, 13]. However in many cases diagnosis is delayed, due to physiological changes that appear in breast tissue during pregnancy and breastfeeding [11, 12]. For this reason, when a pregnant woman presents any alarming symptoms extended diagnostics should be performed to avoid delayed recognition [11].

### 2.1.Ultrasonography

Ultrasound is the primary imaging technique for evaluatinr women with symptoms of breast cancer [15]. It provides high sensitivity and negative predictive values [11]. Features that may indicate the malignant nature of a lesion are hypoechogenic, irregular mass with posterior shadowing, central necrosis, cystic degeneration or fluid component [11,12]. The main difficulty in the ultrasound diagnosis of PABC are physiological changes that occur in the structure of the mammary gland during pregnancy and lactation. For this reason, any complex cystic lesion newly detected by palpation during pregnancy and lactation requires tissue sampling for definitive diagnosis. The only exception when a lesion can be immediately

diagnosed as an abscess or galactocele is when the symptoms are clearly suggestive of the above diagnosis [11,15].

### 2.2.Mammography

Along with ultrasound, mammography is the second recommended imaging examination for pregnant and breastfeeding women to assess breast abnormalities [15]. However, its sensitivity in this group of patients is reduced, due to higher glandular density [11, 18]. Another feature that speaks against mammography is radiation exposure to the fetus [20]. Recent reports indicate that appropriate abdominal shielding reduce fetal exposure for radiation[15]. Also, currently mammography uses low doses of radiation, which makes the test harmless for the fetus [11]. In some studies we can find information, that mammography should be postponed after first trimester [21]. Organogenesis occurs during this period, so radiation can lead to malformations, but studies have shown that this risk exists when the dose is millions of times higher than the norm [22]. Lactating women are recommended to breastfeed immediately before the examination, as it may decrease tissue density and increase the sensitivity of the test [19]. Mammographic features that may indicate the malignant nature of the lesion are the same in pabc and non-pabc [22]. Main abnormalities found during this examination are abnormal mass, calcification, axillary lymphadenopathy, diffuse trabecular thickening, asymmetric density [23]. For detecting ductal carcinoma in situ mammography is better option, because it’s associated with microcalcifications, so it’s easy to see during this examination, and it is not visible on USG [24].

### 2.3.MRI

MRI uses magnetism and radio waves to generate detailed skans of patients body [25]. However, it’s not routinely recommended during pregnancy, due to its potential teratogenic effect [26]. It seems that it may be related to increased heat deposition in the fetus, high noise levels, potentially leading to abnormal development of the auditory nerves and altered cell migration and proliferation in the first trimester [27]. However, recent studies have shown no statistically significant side effects when it comes to hearing development and fetal growth [28]. Another inconvenience when performing breast mri during pregnancy is the gravitational pressure from the belly due to the prone position during the examination, which may cause discomfort [19]. The main reason against performing mri during pregnancy is the gadolinium contrast used during the test, and its impact on fetus [26]. Chelated gadolinium, used in contrast materials, can cross the placenta and may be metabolized into neurotoxic substance [29]. For this reason DCE-MRI is contraindicated during pregnancy [19]. The only

case of using DCE-MRI during pregnancy involved patients who decided to terminate the pregnancy [30]. Currently research of performing DWI-MRI sequences to circumvent the negative effects of contrast are undergo [26].

The possibilities for using MRI in postpartum and breastfeeding women are definitely greater, due to the lack of adverse effects of gadolinium agents in this group of patients [19]. Less than 0.04% of the injected gadolin substance passes into breast milk, and only 0.8% of at amount is absorbed by the infant [31,32]. For this reason, there are different recommendations for the length of suspension in breastfeeding due to the examination, some specialists say that abstaining from breastfeeding is not required, but if mother has concerns, it is acceptable to pump the milk and continue breastfeeding 6h after the examination [19]. However, interpretation of the images may be difficult due to increased vascularity of the tissue during lactation, increased background parenchymal enhancement, and increased fibroglandular tissue, it may increase the percentage of false-positive or false-negative results [11].

### 2.4.CT and PET/CT

CT and PET CT use ionizing radiation, which at high doses can cause genetic defects, fetal carcinogenesis or spontaneous abortion [33]. In complicated, unresolved cases these examinations may be considered, but only when its results are essential for diagnosis or if it may change the course of treatment [34]. During examination the lowest possible radiation doses should be used, it is important that the cumulative radiation fetal exposure dose shouldn’t exceed 100mGy [35].

### 2.5.Biopsy

The next diagnostic step after imaging examination with suspicious finding is immediate tissue biopsy [26]. There are two procedures that enable tissue sample to be taken: fine needle aspiration and core biopsy [37]. Core needle biopsy has higher specificity in pregnant and lactating women, so it is preferred, but it involves a higher risk of infection and milk fistula formation [37]. However, some studies suggest that there are no statistically significant differences in the type of biopsy performed for the diagnosis of PABC [36]. During pregnancy and lactation, structure of the mammary gland changes, the organ becomes more swollen and vascularized, and therefore risk of complications after a biopsy increases [38]. The most common complications include bleeding, milk fistula, infection, delayed healing [38]. According to the literature, excisional biopsy is not recommended [40].

## 3. HISTOPATHOLOGY

Histological examination of a breast lesion sample makes it possible to confirm or exclude the diagnosis of breast cancer [35]. As in non-PABC, staging should be assessed using the eighth edition of the AJCC TNM classification, while pathological diagnosis should be established using both the WHO and AJCC TNM systems [39,40]. Parameters that are taken into account when assessing tumor staging are tumour grade, estrogen receptor (ER) , progesterone receptor (PR), Ki-67 index, human epidermal growth factor receptor 2 (HER2), and in some cases gene expression data [35]. Based on that parameters, breast cancer can be categorized into the following types: luminal A, luminal B, HER2-enriched (non-luminal), and basal-like [40]. Luminal A tumors are characterized by positive estrogen (ER) and progesterone (PR) receptor status, negative HER2 expression, and Ki-67 low. Luminal B tumors are further divided into two groups: HER2-negative (ER+, PR+, HER2-, Ki-67 high) and HER2-positive (ER+, PR+, HER2+, Ki-67 high). HER2 positive (non-luminal) cancers lack hormone receptors (ER-, PR-) but are HER2+, while basal-like tumors, often referred to as triple-negative, do not express ER, PR, or HER2 [35].

The most common histological type of PABC is ductal infiltrating adenocarcinoma [12]. Some reports claim it is up to 70–80% cases of PABC [41]. According to the findings of a big systematic review, PABC more often are ER- and PR- [42]. Ki-67 index usually is at high level [45]. The most common HER2 expression in PABC remains inconsistent across studies [11]. In one large study, Amant et al. selected 662 pregnant and 2081 non-pregnant women with breast cancer, results showed, that pregnant patients more often had hormone receptor-negative or triple-negative tumor [43]. However, other medical data says that PABC usually are positive for HER2 [44].

## 4. TREATMENT

Due to specific conditions, safety of mother and fetus and future consequences, pregnancy associated breast cancer requires multidisciplinary treatment [46]. After assessing the disease's progress, prognostic factors, and factors related to patient and pregnancy, the most optimal treatment method should be selected, decision should be made after informing the patient about possible impact of the treatment on fetus [35]. If situation allows it, treatment should follow the guidelines for non-pregnant patients [47]. Methods to consider are surgical treatment, chemotherapy, hormonal therapy, targeted therapy and radiotherapy [35].

### 4.1.Surgical treatment

Surgical treatment of breast cancer can be perform during each trimester [48]. Some authors consider this therapeutic option to be the safest [11]. While elected studies says that due to adverse effects of anaesthesia on fetus, surgical excision of the lesion should be performed only in case of definitive treatment [16]. However, several studies have shown that most of the currently used anaesthetic drugs are safe during pregnancy [49]. There are two methods available: mastectomy and breast-conserving surgery, depending on disease stage and other factors [47]. Pregnancy itself is not an indication for mastectomy, but in many cases it is the method of choice due to delayed diagnosis and resulting tumor size [50]. The few studies that have been conducted indicate that using tissue expander to immediate breast reconstruction after PABC radical excision shows promising results [51]. Whereas transplant of autologous tissue for reconstruction is not recommended due to possible complications, significant blood loss and long duration of the procedure[50]. Many studies shows that immediate reconstruction has positive effect on patients mental health, positively influencing the healing process [52]. During second and third trimester conserving surgery can be performed if there are no clear indications for mastectomy, because postoperative radiotherapy can be postponed until after the birth, in the meantime chemotherapy is required [47]. Situation when patients with breast cancer are in first trimester of pregnancy, is more controversial due to the long time between breast-conserving surgery and starting of radiotherapy, which can lead to higher number of recurrences [47].

### 4.2.Chemotherapy

Most cases of PABC are treated with chemotherapy [47]. Chemotherapy is used as the main line of treatment, adjuvant therapy, or neoadjuvant therapy, depending on disease stage, fetal and maternal factors [53]. The protocols for systemic treatment of pregnant and non-pregnant patients are similar, but some modifications are necessary to keep fetal risk as low as possible [47]. Before starting systemic treatment, safety of mother and impact of medications on fetal development should be considered and balanced [54]. Chemotherapy in the first trimester is contraindicated due to increased risk of congenital abnormalities. If the patient's condition allows it, it is recommended to delay starting of chemotherapy until after the 12th week of pregnancy, when the risk of congenital malformations in patients receiving systemic treatment is at a similar level to the population risk [55]. Study conducted in five hospitals in London

involving chemotherapy administration to pregnant women showed that systemic treatment in second and third trimesters is safe for fetal development [56]. However, during these stages, treatment may still lead to complications, the most common are premature labor, low birth weight and IUGR [57]. Systemic treatment should be stopped in the 35th week of pregnancy, as it can cause myelosuppression, increasing the risk of hemorrhage, infection, or sepsis [47]. Therapy can be resumed right after a natural birth or one week after a c-section [11]. Breastfeeding is not recommended during systemic treatment due to the potential transfer of cytotoxic substance to the infant. [57].

### 4.3.Trastuzumab

The main treatment for HER2+ breast cancer is trastuzumab [58]. However, studies show that using this medication during pregnancy, particularly in the second and third trimesters, is associated with significant side effects and should be avoided during this period [59]. Most commonly reported adverse effects include oligohydramnios or anhydramnios [59,60]. A systematic review of 17 studies demonstrated the absence of these adverse effects when the drug was administered during the first trimester [61]. This is probably due to limited transplacental antibody transfer in the first trimester, as trastuzumab is a monoclonal antibody [62]. Therefore, if a patient becomes pregnant while receiving trastuzumab, pregnancy termination is not indicated; however, the drug should be discontinued immediately, and the pregnancy must be closely monitored [35].

### 4.4.Tamoxifen

Tamoxifen is commonly used for treatment of hormone receptor-positive breast cancer [63]. However this medication is not recommended during pregnancy due to its effects on the developing fetus, such as abnormalities of the reproductive system, limb and craniofacial structures. Patients undergoing this therapy and for two months after its completion should use contraception to prevent pregnancy [64,65].

### 4.5.Radiotherapy

The radiation doses administered in radiotherapy are definitely higher than those used in diagnostic imaging [66]. Therefore, radiation therapy is generally avoided during pregnancy [47]. The primary risks of this therapy during pregnancy include congenital malformations such as microcephaly and intellectual disability, along with a higher likelihood of radiation-induced cancer in the fetus [67], and is largely determined by the gestational age at exposure and the administered radiation dose [11]. Evidence from studies suggests that radiation doses

below 0.1–0.2 Gy are generally considered safe for the fetus [68]. Moreover, the use of specialized abdominal and pelvic shielding can significantly reduce the radiation dose absorbed by the fetus [47]. The location of the irradiated area and its distance from the developing fetus also play a significant role in determining risk [35]. Findings from studies condusted in Hiroshima indicate that significant fetal exposure to radiation between the 8th and 25th weeks of gestation may lead to decreased intellectual ability in later life, while exposure before the 8th week or after the 25th week does not appear to impact IQ [69]. Radiotherapy during pregnancy is not an absolute contraindication, in selected cases, it may be considered as a treatment option. The potential risks to the fetus must be carefully weighed against the anticipated therapeutic benefits for the mother. This represents a complex clinical decision that requires multidisciplinary consultation and individualized evaluation [11].

## 5. CONCLUSION

Pregnancy-associated breast cancer (PABC) is a growing clinical problem that needs multidisciplinary and individualized approach. Diagnosis usually requires ultrasound and biopsy, while the mainstay of treatment are surgery and chemotherapy. However, therapeutic strategies must be carefully tailored to each patient, considering both maternal health and fetal safety. Because of the insufficient amount of available data, further research are essential to improve our understanding of PABC and to develop standardized treatment protocols that ensure optimal outcomes for both mother and child.

**Disclosures**

**Author's contribution**

Conceptualization - Maria Michalska and Sebastian Iwaniuk; methodology - Jakub Skiba; software ,- Zuzanna Skiba and Kinga Kowalik; check - Ignacy Maciejewski, Kinga Tylczyńska and Natalia Tylczyńska; formal analysis - Szymon Szypulski and Aleksandra Zielińska; investigation - Natalia Tylczyńska; resources - Ignacy Maciejewski; data curation - Kinga Kowalik and Kinga Tylczyńska; writing - rough preparation - Sebastian Iwaniuk and Zuzanna Skiba; writing - review and editing, Jakub Skiba and Kinga Kowalik; visualization, Aleksandra Zielińska; supervision - Szymon Szypulski; project administration – Maria Michalska; receiving funding not applicable, All authors have read and agreed with the published version of the manuscript.

**Financing Statement:**

This research received no external funding.

**Institutional Review Board Statement:**

Not applicable.

**Informed Consent Statement**

Not applicable.

**Data Availability Statement:**

The authors confirm that the data supporting the findings of this study are available within the article's bibliography.

**Conflict of Interest:**

Authors declare no conflict of interest.

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