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Pregnancy-associated breast cancer - diagnosis, treatment and outcomes for women and their offspring

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ABSTRACT

Introduction: Pregnancy-associated breast cancer (PABC) is the most common malignancy in pregnant women with an incidence of 1 in 3-10 thousand pregnancies. It is mostly defined as breast cancer diagnosed during pregnancy or within 1 year postpartum. The number of PABCs is going to raise due to the trend of delaying childbearing.

Purpose: This review summarizes data on the occurrence and characteristics of PABC. The analysis comprises diagnosis and proper treatment of BC during pregnancy. Prognosis of women and their offspring are emphasized.

Material and methods: The review is based on publications mainly from 2010 to 2019 and 5 articles from 1994-2008 collected on the PubMed.

Results: The sensitivity of breast ultrasonography (USG) in pregnancy is 70-100% and it is considered as safe for the fetus. Staging evaluation in pregnant women consists of chest x-ray, liver USG and non-contrast bone MRI. 71-88% of PABCs are invasive ductal carcinomas. Treatment consists of breast surgery regardless of time and optionally, chemotherapy from the 2nd trimester. Radiotherapy, tamoxifen and trastuzumab are contraindicated in PABC. Therapeutic abortion does not improve oncological outcome. Overall prognosis is similar for both pregnant and non-pregnant patients with similar type and stage of BC. The rate of congenital malformations is 1,3% for both children of PABC patients treated with chemotherapy and born from women without chemotherapeutic treatment. The most frequent obstetrical complication of PABC treatment is preterm delivery.

Conclusions: Pregnancy does not impact oncologic outcome, if the treatment is appropriate. PABC patients have survival rates consistent with the stage of disease. Proper treatment of PABC does not increase the risk of congenital malformations and is relatively safe for the fetus.

Key words: pregnancy-associated breast cancer; breast cancer; prognosis; pregnancy; breast cancer treatment

INTRODUCTION

Pregnancy-associated breast cancer (PABC) is an increasing problem worldwide. The classical definition includes cases of breast cancer (BC) diagnosed in any time of pregnancy and those diagnosed during the first year postpartum. However, some authors suggest extension of this definition to cases diagnosed within 5 or even up to 15 years after delivery [1]. Pregnancy is deemed to have twofold impact on BC risk, which was outlined for the first time by Lambe in 1994. According to the report, first 15 years after delivery increase the risk of developing BC, while subsequent years are associated with protective impact [2]. PABC is rare, although it is the most common malignancy in pregnant women with estimated frequency of 1 in 3-10 thousand pregnancies. PABCs account for almost 16% of all BC cases in women under the age of 35 [3]. The median age of diagnosis is 33 years and 21 weeks of gestational age. Due to the trend of delaying childbearing the appearance of BCs in pregnancies is going to raise in following years [4].

PURPOSE

The aim of this review is to summarize available data on diagnosis, treatment and outcomes in women suffering from pregnancy-associated breast cancer. The influence of BC therapy on fetal and neonatal outcomes will be emphasized. While preparing this review, publications mainly from 2010-2019 and 5 articles from 1994-2008 were included in the analysis. The data was collected in the PubMed.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Diagnosis

During the time of pregnancy, breast tissue undergoes physiological changes. Glandular tissue proliferates and it results in density and volume increase of breast. These changes impede precise self-examination and clinical examination of breasts. This may be the main reason of delayed diagnosis of PABC. It is estimated that the time of delay is 5-10 months in pregnant women in comparison to 1-4 months in non-pregnant ones [4]. The most common clinical presentation of PABC in the moment of diagnosis is suspicious, painless palpable mass in breast [5]. Every mass palpable for more than 2 weeks needs further examination [4].

First diagnostic step in PABC is breast ultrasonography (USG). It enables differentiation of benign and malignant tumors in pregnant women [6]. The sensitivity of USG in pregnancy is 70-100% and it is higher than sensitivity of mammography, due to increased density of breasts during pregnancy [5]. Moreover, ultrasonography allows for core biopsy under local anesthesia without endangering fetus [4].

If a mass is more suspicious, it is recommended to perform mammography [5]. This examination allows to evaluate whether any additional tumors are existing. It should be performed with proper abdominal protection in order to protect fetus, although a fetal radiation exposure is limited [4]. The sensitivity of mammography among pregnant women is about 70% with a range from 25 to even 90% in various studies [4,7,8].

Breast magnetic resonance (MRI) with gadolinium should be avoided in diagnosis of PABC. A gadolinium has a detrimental effect on fetal development. However, MRI without contrast can be performed instead of scintigraphy in patients requiring skeletal system assessment [9].

Novel paramagnetic contrast agents such as gadobenate dimeglumine and gadoterate meglumine are approved in Europe for use in particular cases of pregnant women [7]. Nevertheless, novel agents require further investigation on their safety and efficacy.

The final diagnosis is based on a result of histopathological examination of a specimen obtained during biopsy [5]. It is estimated that around 80% of breast biopsies results are not malignant in pregnant women [4].

Staging evaluation of breast cancer is modified in pregnant women. Standard procedures in non-PABC include computed tomography (CT) of chest and abdomen and scintigraphy. In PABC a fetal risk is taken into account. Standard staging procedures are associated with high radiation dose for the fetus. In this regard CT and scintigraphy should be avoided in PABC [5]. If staging is necessary, other methods should be performed. It is recommended to perform chest x-ray with uterine shielding, liver ultrasonography and bone MRI without contrast [10].

An accurate assessment of nodal status is crucial due to higher risk of nodal metastasis in PABC patients and proper selection of the best possible treatment. Nodal evaluation should start with an ultrasound followed by fine needle aspiration biopsy (if required) [5]. Sentinel lymph node biopsy (SLNB) is an approved method of axillary evaluation in PABC patients with negative nodal status. Some researchers tested an influence of technetium (99-Tc) used during SLNB on fetus. No explicit danger for the fetus was observed. Using blue dyes (lymphazurin, isosulfan blue) should be avoided due to the risk of anaphylaxis. SLNB is generally safe during pregnancy and can be performed [7,11].

Tumor characteristics

The main histological type among PABC patients is invasive ductal carcinoma with a rate of 71-88% [3,4]. The mean age of diagnosis is 30-38 years [3]. Women with PABC are younger than non-PABC patients (average age 34,9 years vs. 38,5 years) [12]. PABC is more frequently diagnosed postpartum than during pregnancy [3,13]. In comparison to age-matched non-pregnant women with BC, PABC tumors are characterized by more advanced stages, larger size, higher rate of G3 tumors and nodal involvement. Patients with PABC have also less frequent expression of estrogen receptors (ER) and progesterone receptors (PR) [1,3-5,13]. It is also estimated that inflammatory breast cancer is more often diagnosed in PABC cases than in non-PABC [3].

Treatment of PABC

Treatment of PABC should be carried out with the standards of therapy of this cancer in the general patient population, taking into account the specificity of anticancer therapy during pregnancy. The essential therapeutic option in patients suffering from pregnancy-associated breast cancer in the first trimester is surgery. Radical surgery should be performed, if possible. Various authors agree that breast and axillary surgery can be safely performed in each trimester of pregnancy [4,5,7]. However, due to the increased risk of spontaneous abortion during the first trimester, it is reasonable to postpone surgery to the second trimester. After 12 weeks of pregnancy, the risk of miscarriage is minimal [14,15]. The decision on a type of operation should be considered individually. PABC is associated with high risk of local recurrence therefore radical mastectomy prevails over breast conserving surgery [13]. Radical modified mastectomy is recommended in first and second trimester of pregnancy [16].

Breast conserving surgery requires further radiotherapy, which is contraindicated during pregnancy [4,5]. It can be performed in the third trimester with radiotherapy deferred until delivery. If lumpectomy is planned at a distant time from delivery, it should be complemented by neoadjuvant or adjuvant chemotherapy. It is advised against performing lumpectomy in the first trimester if systemic therapy is not planned, due to negative impact on outcomes [14].

Breast reconstruction after mastectomy during pregnancy is considered feasible both immediately and delayed to postpartum period. It is preferred to use implants for immediate reconstruction. Due to possible difficulties of achieving symmetry between breasts because of breast engorgement during pregnancy, a deferment of reconstruction should be taken into consideration [5,7]. Nevertheless, the results of the study conducted by Lohsiriwat *et al.* suggest that intrapartum reconstruction is available. No serious adverse events such as hematoma or flap necrosis were reported. Moreover, 12 of 13 women who underwent immediate reconstruction using tissue expander or implant, continued their pregnancy [17].

Radiotherapy is strongly contraindicated during pregnancy, because of increased risk of disruption to organogenesis and fetal malformations [18]. It is recommended not to exceed 12 weeks pause between surgery and radiotherapy. A longer interval results in an increased risk of local relapse [19]. Some authors suggest that using proper abdominal shielding may reduce a radiation dose to fetus and avoid detrimental effects on the fetus [4,7]. Relevant research is required to evaluate whether benefits of breast irradiation during pregnancy are worth the risk. Chemotherapy is another therapeutic option for PABC patients. The use of cytostatic agents depends on the trimester of gestation. It is recommended to avoid chemotherapy in the first trimester, due to high teratogenic potential of chemotherapeutic drugs in this period of time. When a gestational age reaches 14 weeks, chemotherapy is assumed to be safe for the developing fetus [5]. The risk of fetal malformation is the highest in the first trimester with a range of 14-19% in contrary to 1,3% risk during the second and third trimesters [20]. In view of the foregoing, chemotherapy is recommended from the second trimester onwards. It is thought that chemotherapy treatment should be based on the same protocols in both PABC and not pregnant patients. In patients with pregnancy-associated breast cancer the scheme consisting of 5-fluorouracil, doxorubicin and cyclophosphamide is confirmed to be safe [21,22]. If tumors do not respond to anthracyclines-based regimens, the second option are taxanes, especially paclitaxel. However, the routine use of taxanes is not recommended in PABC treatment because of the insufficient data on safety profile of these agents [4,23]. There is no evidence that chemotherapy dose reduction is beneficial or harmful for the fetus. In turn, dose reduction may have a negative impact on oncological outcomes of women [5]. It is advisable to discontinue administering chemotherapeutic agents after 35th week of gestation or at least for 2 weeks before the due date in order to avoid hematological complications during labor in mother and child [4,6].

Endocrine therapy with tamoxifen during pregnancy is associated with 20% risk of congenital defects [14]. Other severe incidents such as spontaneous abortions and fetal demise have been noted [24]. Tamoxifen is contraindicated in breast cancer treatment in pregnant women and should be delayed until birth [4,5].

A study on trastuzumab administration during gestation showed that most of newborns of PABC patients treated with anti-HER2 therapy had mild to severe renal disease, pulmonary disease or infections at birth [14].

Poor neonatal outcomes arise out of oligohydramnios, anhydramnios, fetal heart failure, renal failure and respiratory insufficiency [4-6]. Trastuzumab is believed to be as effective when given 6 months after chemotherapy intrapartum. In this regard, trastuzumab should not be administered during pregnancy [14].

Pregnancy termination

It is considered that therapeutic abortion does not improve oncological outcomes. Maternal survival is not dependent upon pregnancy termination and depends solely on appropriate anticancer therapy. The decision on abortion has to be individual and based on the risk of possible progression of malignancy or fetal harm related to oncologic therapy [25].

Neonatal outcomes

Minimal detrimental impact on the fetus related to the use of chemotherapeutic agents is related to lowered level of these agents within the fetal system as opposed to maternal system [5,21]. The long-term follow-up conducted by Aviles *et al.* on children born from women treated with chemotherapy due to hematological malignancies showed no neurocognitive, physical nor psychological effects among these children [26]. The most frequent obstetrical complication of PABC treatment is preterm delivery. It is estimated that breast cancer is a factor of an even 5-fold increased risk of premature labor in comparison to pregnancies in healthy women (30,05% vs. 7,21%, $p < 0.0001$). However, it is under consideration whether this increased ratio of preterm labors is associated only with the anticancer treatment, the cancer itself or with the iatrogenic induction of preterm deliveries in order to undergo more aggressive treatment [27]. Another research showed the premature deliveries incidence rate of 54,6% in comparison to 50% in general population based on The European Registry. The average time of delivery was 35,7 +/- 3,2 weeks [23]. Pregnancies in women suffering from breast cancer have also a twofold greater risk of preterm premature rupture of membranes [27]. There is no difference in the rate of congenital malformations between the offspring born from women who underwent chemotherapy in pregnancy and women not treated with chemotherapeutic agents and it amounts to 1,3% [6]. The offspring of PABC patients treated appropriately are not under a higher risk of congenital anomalies, intrauterine growth restriction and intrauterine fetal demise [27]. Nevertheless, it should be pointed out that obstetric complications observed in several studies are not only preterm labor and preterm rupture of membranes, but also severe intrauterine growth restriction, oligohydramnios, anemia, dyspnea, pneumonia, preeclampsia, respiratory distress syndrome and necrotizing enterocolitis in newborn [6, 23, 27].

Prognosis

Prognosis of PABC patients is very important issue discussed by various researchers. The data on this subject is inconclusive. Most recent data suggest that overall prognosis does not differ between age-matched pregnant and non-pregnant patients with similar type and stage of breast cancer [5,28]. The results of a study carried out by Genin *et al.* showed no significant differences in overall survival (OS), disease free survival (DFS) and distant relapse rates between PABC patients and non-pregnant controls [13].

Another study showed similar 5-year survival rate between both pregnant and non-pregnant patients treated with 5-fluorouracil, adriamycin and cyclophosphamide (77% vs. 71%, $p = 0.046$) [29]. Other authors suggest worse prognosis of PABC patients due to young age and delayed diagnosis [30]. One more poor prognostic factor is more frequent occurrence of T3-T4 tumors and negative hormonal status. It is also believed that tumors in pregnant women have the same poor prognosis regardless of their advance stage as not pregnant women with T3-T4 tumors [13]. It has been proven that local recurrence occurs more often in pregnancy-associated breast cancer patients rather than non-pregnant controls [13,28]. Moreover, patients diagnosed with BC postpartum have inferior outcomes, especially when diagnosed within 1 year after delivery. In a study conducted by Van Den Rul *et al.* BC patients diagnosed within 1 year after labor had decreased 5-year DFS (53%) and OS (60%) rates in comparison to not pregnant controls (DFS = 68%, OS = 84%) [31]. Lowest survival rate of 38% is found in BC patients diagnosed during 12 months postpartum and increases in a later period reaching 51-60% in 13-48 months postpartum, in comparison to nulliparous women with a survival rate of 65% [12]. Increased rates of distant metastases in liver and brain were also observed in postpartum breast cancer [32]. There are no contraindications for becoming pregnant after surviving breast cancer in young patients. It is recommended to discontinue taking tamoxifen for at least 2 months before attempting pregnancy [5].

SUMMARY

Pregnancy-associated breast cancer is a significant challenge in oncology nowadays. Besides maternal benefits from anticancer treatment, fetal well-being should be carefully evaluated. The therapy plan should be based on the decision of the multidisciplinary team. Treatment of breast cancer is trimester-dependent in pregnant women. To the best of our knowledge, gestation does not impact oncologic outcome, if the treatment is appropriate. Breast surgery remains the essential therapeutic option in pregnant patients, with possible chemotherapy from the second trimester. Radiotherapy, anti-HER2 therapy and hormonal therapy should be avoided until labor. There is no significant risk of serious detrimental effects on fetus. The prognosis of the offspring of PABC patients is good and pregnancy termination is not recommended as it does not improve maternal outcomes. Pregnant women suffering from BC have survival rates consistent with the stage of disease.

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