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What is the Status of Diagnosis and Treatment of Breast Cancer During Pregnancy: Systematic Review

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1. Abstract

Breast cancer during pregnancy (BCP) is clinically rare. Because BCP occurs in a specific physiological period in women, it may cause pregnancy-related complications, seriously affecting women's health. There is a current lack of standards for diagnosis and treatment. We performed a literature search in the pubmed website for articles from 2017 to 2022 using the keywords breast cancer in pregnancy, diagnosis, and treatment ,and then summarized the current situation and the problems in BC diagnosis and treatment during pregnancy, and provided a basis for standards.

2. Introduction

Breast cancer [BC] has surpassed lung cancer to become the most common malignant tumor worldwide, seriously threatening women's physical and mental health [1]. BC during pregnancy [BCP] is a rare malignant tumor with unique features in diagnosis and treatment. The diagnosis of cancer during this particular period of a woman's life is a challenge in clinical management because of the need to ensure psychological safety and pregnancy status. The lack of systematic diagnosis and treatment plan affects the prognosis of patients. By reviewing domestic and foreign literature, we summarized the diagnosis and treatment status and controversial issues of BCP for reference in clinical application.

3. Definition and Epidemiology of BCP

BCP refers to breast cancer diagnosed during pregnancy, which is a part of pregnancy-associated breast cancer [PABC]. BCP has the second highest incidence of malignant tumors in women during pregnancy [2]. PABC accounts for 0.2−3.8% of breast malignancies [3, 4], including BCP and breast cancer occurring within 1 year after delivery [5]. Evolving evidence supports the separation of BCP from postpartum BC[PPBC] due to their differences in incidence, pathological features and treatment. BCP has independent biological properties, so some scholars believe that the concept of PABC should not continue to be used [6]. BCP accounts for about 4% of BC cases in women aged <45 years [7], and there is about 1 case in every 1000 pregnancies [8]. In China, with the opening of the two-child policy and the emergence of delayed childbirth, the number and age of patients are gradually increasing [9].

4. Clinical Features of BCP

Proper assessment of suspected BCP should include physical examination [with special attention to breast and regional lymph nodes], imaging examination, and mass histopathology. BCP patients can usually feel a painless lump in their breast, Due to the underlying anatomical and physiological changes in the breast during pregnancy: Breast gland hyperplasia and volume enlargement,- Thus concealing the findings of some smaller lesions, In addition, the majority of patients are young women, and doctors are prone to subjectively consider benign tumors such as breast fibroadenomas, which causes BCP diagnosis is often delayed [10]. During specialist physical examination, the breast mass is generally hard, with unclear boundaries, irregular shape, hard and fixation [11]. Axillary lymph node enlargement can also be the first symptom.

A small number of patients have irritating cough, hemoptysis and other respiratory disease symptoms as well as dizziness, fatigue, bone joint pain and central nervous system and bone metastasis. BCP has similar clinical features to non-gestational BCP, lack of specific clinical manifestations [12].

5. BCP Imaging Examination

Ultrasound is still the standard first-line imaging examination of the breast, with high sensitivity, specificity and safety for the screening of breast lesions [13]. It has been reported that the sensitivity of ultrasound to detect BC is 100%, and the sensitivity and negative predictive value of breast lesion screening in pregnant patients can also reach 100% [10, 14]. On ultrasound, BCP lesions can present as low or mixed echo masses with irregular shape and unclear boundaries. It has also been reported that some breast cancer foci during pregnancy present with the morphological characteristics of benign tumors with regular margins [15]. The accuracy of ultrasound may be lower , but its advantages such as convenient operation and repeatability provide important clinical information, especially for the determination of breast lesions and axillary conditions, so it is still the preferred screening method at present [16, 17]. Mammography can be used to assess the degree of disease, identify atypical calcification, and assess the contralateral breast. Calcifications that cannot be imaged by ultrasound can be present, especially for dense mammary glands, with sensitivity typically between 78% and 90% [18]. During pregnancy, due to concerns about the impact of radiation on fetal development, many patients resist this examination, but the radiation dose of bilateral mammography is <3 mGy, and the radiation dose to the uterus is <0.03 mGy, exposing the fetus to the minimum dose of radiation [0.001–0.01 mGy] [19, 20]. Mammography is generally safe and feasible during pregnancy [21]. For the lesions not found by breast ultrasound and X-ray examination, magnetic resonance imaging [MRI] is required to avoid the effects of radiation. Breast MRI without contrast agent is safe, but there is still insufficient evidence about the diagnostic value of MRI in BCP. Because gadolinium contrast agents can enter the fetal circulation and amniotic fluid through the blood–placenta barrier, the results in rats indicate that contrast-enhanced MRI is potentially teratogenic [22, 23]. Therefore, routine breast MRI enhancement is not recommended for pregnant patients. However, the latest guidelines of the European Society of Urogenital Radiology for the use of contrast media in pregnant women suggest the use of gadolinium-based contrast media for breast MRI in pregnant women [24]. The author believes that under the current condition of insufficient evidence-based medical evidence, patients with BCP should be cautious when undergoing contrast-enhanced MRI. Unnecessary radiography is not recommended during pregnancy for systemic assessment suspects metastasis. Abdominal ultrasound and chest X-ray examination under the protection of a lead barrier can be performed. If brain or bone metastases are suspected, MRI of the corresponding site can be performe [21]. Nuclear medical examinations including bone scan and positron emission tomography are strictly contraindicated due to significant radionuclide radiation.

6. Pathological Features of BCP

Pathological examination is still the gold standard for diagnosis. Like non-pregnant patients, biopsy and pathological examination should be completed in time for BI-RADS IV/V lesions with high clinical suspicion and imaging examination, so as to provide guidance for the next treatment plan. Under the conditions of excluding contraindications such as bleeding disorders and anesthetic allergies, Ultrasound-guided core needle biopsy [CNB] is the preferred modality [25]. During the puncture operation, attention should be paid to the depth and angle of needle insertion, and the substantial part of the mass should be selected for sampling. For multiple tumors, one lesion should correspond to one set of puncture instruments, and damage to important blood vessels, milk ducts and nerves should be avoided [22]. When submitting the tumor tissue for pathological examination, pathologists should be reminded of the patient's pregnancy, because the presence of proliferative cells may mimic atypia, leading to an increase in false-positive results. The most common histomorphological type is poorly differentiated invasive ductal carcinoma. BCP has been shown to be associated with lower hormone receptor expression rates and with more aggressive subtypes that are characteristic of younger cases, higher grade and proliferation rates, late T stage at diagnosis, lymph node involvement, higher prevalence of triple negative BC [TNBC] and hormone receptor negative [26, 27] subtypes. Unlike non-pregnant women, these tumors usually involve axillary lymph nodes and blood vessels when found. It is noteworthy that approximately 30% of BCP cases are classified as TNBC, and 40% of cases have axillary lymph node infiltration. Small series of studies have suggested there were differences in gene expression between BCP and non-BCP, but no large study supports this theory [28]. In a cohort study of 20 women diagnosed with BCP or in the first year after delivery, the pathogen mutation detection rate was 35% [7/20 cases]. Among them, six patients had pathogenic BRCA1 mutations, and up to 30% of obviously high frequency BRCA1 mutations places BCP patients in a high risk environment [29, 30]. Due to the high incidence of BRCA 1 or 2 mutations in young BC patients, genetic testing should be offered to women with BCP [31].

7. Status and Problems of BCP Treatment

Management of BCP is complex due to the potential risks to the fetus during treatment. The optimal treatment strategy should be planned by a multidisciplinary team consisting of breast surgeons, oncologists, radiotherapists, gynecologists and neonatologists. The strategy should be designed to maximize treatment options for patients while minimizing potential adverse events for the fetus. The guidelines suggest that BCP should be treated according to the same recommendations as for BC in young non-pregnant women [32, 33]. Clinicopathological features, gestational age at

diagnosis, due date, and patient selection are key factors for optimal treatment.

8. Surgical Treatment

Surgery is the main treatment for BCP, and is considered safe throughout pregnancy and should follow the same recommendations as for non-pregnant women when feasible [32]. However, surgery in the first trimester is usually avoided if possible. All pregnant women undergoing surgery should take precautions to avoid uterine hypoperfusion, maternal hypotension, hypoxia, hypoglycemia, pain, fever and infection. Modified radical mastectomy is considered the standard treatment for BCP because it eliminates the need for postoperative radiotherapy and ultimately controls the axillary region, however, this kind of surgery has great physical and mental damage to young women. Therefore, some scholars have tried to perform breast conserving surgery on patients who meet the indications for breast conservation. Although there has not been a large specialized study, similar survival rates have been observed in women who receive breast-conserving or radical surgery. Small studies support the safety of staged reconstruction with tissue dilators placed immediately after mastectomy in BCP, and the benefits of immediate breast reconstruction include improved psychological and aesthetic outcomes [34]. A series of women who received tissue dilators during pregnancy showed no increase in obstetric disease or surgical complications. In addition, anesthesia is an important factor to consider. Many physiological changes during pregnancy can affect anesthesia, and despite several preclinical and clinical observational studies, no significant risk to the fetus has been found from anesthetics, nor has the optimal anesthesia technique been identified. The potential negative effects of anesthetics on fetal development depend on the dose, duration of exposure associated with fetal development, and route of administration [18].

The availability of axillary sentinel lymph node biopsy [SLNB] in pregnant women has been controversial. The American Society of Clinical Oncology [ASCO] recommendation does not support this procedure, while the National Comprehensive Cancer Network [NCCN] guidelines do support this procedure based on several studies showing that it can be performed safely [35, 36]. The main point of contention is the choice of tracer, Technetium 99m colloidal solution as the first choice is considered safe for SLNB by injection during pregnancy. Fetal radiation exposure after injection is within acceptable levels [37]. An international cohort study involving 145 women with BCP reported high recognition rates and low axillary recurrence rates for SLNB [38]. This approach is considered safe in patients with clinically node-negative BCP. Although technetium-99m has been shown to be safe, blue dyes are contraindicated because no studies have tested their safety. In particular, methylene blue has been reported to cause allergic reactions and fetal teratogenicity [39]. Other tracers have not been well reported and are therefore not recommended for routine use.

9. Chemotherapy

Pregnancy has not been shown to be an absolute contraindication to the use of systemic chemotherapy to treat BC. The results of a large retrospective/prospective meta-analysis supporting the use of chemotherapy in pregnancy showed that intrauterine exposure to chemotherapy did not significantly increase the risk of fetal death or major congenital malformations compared with the general population[40]. Therefore, a systematic treatment plan should be formulated according to the stages and biological characteristics of BC. The main concerns of chemotherapy in pregnancy are time, drug selection and measurement. Due to the potential impact of chemotherapy on fetal development, particularly during organogenesis [equivalent to 3–12 weeks of gestation], the risk of congenital malformations and fetal loss due to exposure to chemotherapy may be high. Retrospective data show that the incidence of major fetal malformations is 14–20% when chemotherapy is administered early in pregnancy. The incidence of chemotherapy after the first trimester is 3–5% [33]. Therefore, chemotherapy in the first trimester is contraindicated, but considered safe in the second and third trimesters. Delaying treatment until after delivery is not recommended, as it may lead to worse adverse outcomes [41]. It is recommended to end chemotherapy before 36 weeks of gestation to avoid potential hematological complications during delivery [33]. Regarding the selection of chemotherapy agents, anthracycline, cyclophosphamide and taxane are supported by international guidelines and are the standard for chemotherapy in BC [42, 43]. Physiological changes in pregnancy that affect systemic pharmacokinetics include increased maternal weight, plasma volume, liver and kidney perfusion, cytochrome P450 activity [third trimester], and changes in serum albumin concentration, and those under medication should be avoided. Therefore, the dose of chemotherapy should be calculated according to the actual body weight of the patient, and dose-intensive chemotherapy [same dose given at shorter intervals] can improve the therapeutic effect, especially in high-risk patients [33]. A retrospective cohort study of 109 pregnant women with BC, 10 of whom received dose-intensive chemotherapy, demonstrated the safety of this approach [44]. However, small studies limit the possibility of recommendations for the safety of dose-intensive chemotherapy in patients with BCP. Most prophylactic drugs commonly used in non-pregnant patients can also be safely administered during pregnancy. Histamine type 2 receptor antagonists can be used to prevent allergic reactions without increasing the risk of major malformations [45]. A retrospective cohort study evaluating granulocyte colony-stimulating factor in pregnant women during chemotherapy found no difference in gestational age, congenital abnormalities, and neutropenia in exposed infants [46]. In addition, the use of aprepitan, ondansetron, methylprednisolone and other supportive drugs during pregnancy is also considered safe [47]. Although the use of chemotherapy in the second and third trimesters appears to be mostly safe and tolerated,

a multidisciplinary approach, including rigorous fetal monitoring and maternal blood pressure control, is needed.

10. Radiotherapy

Considering that radiation exposure can cause fetal malformations and other adverse events, it can cause miscarriage in the first trimester, and fetal neurological and reproductive system malformations after 3 weeks of pregnancy [48], and the fetal risk effect is also dose-related. In view of the above reports, radiotherapy for BCP is generally contraindicated. If necessary, it can be done after delivery.

11. Endocrine Therapy

In animal models, tamoxifen has teratogenic effects, involving the urogenital tract more frequently, and increasing the risk of BC in offspring [49]. A systematic review of pregnancy data for 248 BC patients exposed to tamoxifen during pregnancy showed a 17.6% incidence of severe malformation [50]. International guidelines prohibit the use of tamoxifen during pregnancy and it should be discontinued immediately if the pregnancy is expected to continue.

12. Targeted Therapy

In recent years, targeted therapies for BC have been used increasingly [51]. A systematic review and meta-analysis to evaluate the safety of trastuzumab during pregnancy showed that the main adverse events were oligohydramnios and/or dehydration, which were related to gestational age and occurred in 73.3% of fetuses exposed in mid/late stages. This did not occur in fetuses with early exposure, and in subsequent follow-up, and fetuses exposed only in the early stages of pregnancy were also healthy after birth [52]. Therefore, patients with early exposure to trastuzumab in small amounts may be able to continue pregnancy under close monitoring. Current guidelines contraindicate trastuzumab in patients with BCP due to its impact on fetal lung development and the occurrence of hydramnios during pregnancy, as well as unknown long-term consequences for the fetus. Pertuzumab, trastuzumab - entansine [T-DM1] and neratinib are in early use. To date, no studies have demonstrated safety data for use during pregnancy [33].

13. Prognosis

Studies on prognosis of BCP are mostly small retrospective studies and survival analyses of PABC. Azim et al.'s meta-analysis comparing 3,628 patients with PABC and 37,100 controls found that poor prognosis of PABC was mainly driven by patients with postpartum breast cancer rather than BC diagnosed during pregnancy [28]. A national study evaluating the difference in outcome between patients with BCP and PPBC showed no significant difference in 5-year overall survival rate and disease-free survival rate [13]. Amant et al. reported comparable survival rates in patients diagnosed with BCP compared to patients without PABC [53]. Overall, patients with PABC may have a poor prognosis, with a lower 5-year survival rate compared to age-matched general patients with BC. Whether pregnancy has an independent effect on the prognosis of BCP still needs to be investigated in a large-scale retrospective analysis [54].

14. Conclusion

BCP is a rare type of breast malignancy with unique pathological characteristics, and collaboration with obstetrics, neonatal and oncology departments is necessary due to the complexity of maternal treatment and potential impact on the fetus. Surgery is still the main treatment method, and the selection of chemotherapy period is important. Radiotherapy, endocrine therapy and targeted therapy are still contraindicated. After systematic treatment, good outcome and prognosis can be achieved.

15. Declarations

15.1. Data Availability Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

15.2. Ethics Statement

This review does not involve any ethical review of animal experiments, and sources are searchable from PubMed.

15.3. Conflict of Interest

The authors declare that the research has no competing interests as defined by BMC, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

15.4. Author Contributions

Study concept: GL. Project management: ZF,GL. Data collection: GL.Study analysis: GL,JQ. Manuscript preparation:GL. Manuscript editing: GL,JQ. Manuscript review: ZF,GL,JQ,FQ,SL.All authors contributed to the article and approved the submitted version.

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