

Ductal Carcinoma *In Situ* in Pregnant Women

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Rezumat

Cancerul mamar este a doua cea mai frecventă neoplazie care afectează femeile gravide. În literatura actuală există date limitate cu privire la opțiunile terapeutice pentru carcinomul ductal *in situ* (CDIS) în sarcină. Deoarece incidența cancerului mamar în sarcină este în creștere, această temă este de interes. În Statele Unite ale Americii una din 3000 de femei însărcinate este diagnosticată cu cancer mamar. Majoritatea femeilor cu CDIS sunt diagnosticate prin screening, deoarece acestea sunt asimptomatice. Întrucât screening-ul de rutină prin mamografie nu este recomandat în timpul sarcinii, diagnosticul de CDIS fără patologie invazivă este rar la femeile gravide. Cancerul mamar în sarcină reprezintă 0.2-3.8% din toate cazurile de cancer mamar nou diagnosticate. Această raportare nu diferențiază cazurile de CDIS de cele cu cancer mamar invaziv, astfel este dificil de stabilit adevărata incidență a CDIS în sarcină. Acest review sintetizează recomandările multidisciplinare actuale privind tratamentul optim al CDIS diagnosticat în timpul sarcinii.

Cuvinte cheie: carcinomul ductal *in situ*, sarcina, diagnostic, tratament

Abstract

Breast cancer is the second most common malignancy affecting pregnant women. Ductal carcinoma *in situ* (DCIS) during pregnancy has not been well described with limited literature addressing the optimal treatment options. This is important topic

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as the incidence of pregnancy-associated breast cancer (PABC) has been increasing. In the United States, 1 in 3000 pregnancies are complicated by breast cancer diagnosis. Most DCIS are screen detected as most patients are asymptomatic. Since routine screening mammogram is not recommended during pregnancy, diagnosis of DCIS without invasive disease is uncommon diagnosis. Although PABC is reported to account for 0.2-3.8% of all newly diagnosed breast cancer, it has not been defined between the diagnosis of DCIS or invasive breast cancer making true incidence of DCIS in pregnancy difficult to report. This review summarizes multidisciplinary recommendations for optimal treatment for DCIS diagnosed during pregnancy.

Key words: ductal carcinoma *in situ*, pregnancy, diagnosis, treatment

Introduction

Breast cancer is the second most common malignancy affecting pregnant women following cervical cancer (1-3). Pregnancy-associated breast cancer (PABC) was understood as carcinoma of the breast in pregnant and breastfeeding patients. The commonly used definition is breast cancer diagnosis during gestation and or within one year of childbirth (4,5), however, some would consider up to 2 years postpartum as PABC (6,7). Ductal carcinoma *in situ* (DCIS) during pregnancy has not been well described and there was limited literature addressing the optimal management and treatment options. For the purpose of this review, we are focused on the management of the pregnant patient with DCIS. The goal of this review is to summarize the care of the pregnant patient with DCIS including diagnostic, surgical, and adjuvant therapeutic perspectives of radiation and systemic therapy in this unique population. Herein, we provide practical guidance to the optional treatment approach to patients diagnosed with DCIS during pregnancy.

Incidence

The incidence of PABC has been increasing. In the United States, 1 in 3000 pregnancies are complicated by breast cancer (8) The average age of women with PABC ranges from age 32 to 38 years (9,10). A large population study conducted in Sweden showed the number of

PABC cases doubled from 16.0 to 37.4 cases per 100,000 deliveries between 1963 to 20026. This increase is likely due to many women postpone their first delivery to obtaining advanced education and being focused on their career path. The age at first gestation has increased from 24.9 years in 2000 to 26.3 years in 2014 (11). Having first gestation after age 30 has been established as increased risk of breast cancer and has been acknowledged as a risk factor for PABC (9,12,13). Therefore leading to delay in childbearing and increasing the incidence of PABC. Although PABC is reported to account for 0.2-3.8% of all newly diagnosed breast cancer, (14) it has not been defined between the diagnosis of DCIS or invasive breast cancer making true incidence of DCIS in pregnancy difficult to report. Result from Colon et al reported DCIS constituted 12.4% of all carcinoma in young women less than 40 and 18.3% of all carcinoma in women aged 40 and over (15), however, they did not report if any of these patients under 40 were diagnosed during their pregnancy. Incidence of DCIS during pregnancy has not been reported.

Diagnosis

Breast cancer during pregnancy is usually diagnosed by patients or physicians due to having symptoms such as palpable mass, pain or nipple discharge 9 as pregnant patients are usually not receiving screening breast imaging. The diagnosis of PABC is often

delayed by up to 13 months after the appearance of symptoms (16). Delays in the diagnosis are likely due to pregnancy-induced breast changes such as breast engorgement, which makes concerning symptoms difficult to differentiate from normal physiologic changes of the breast tissue. Those with PABC were twice as likely to be diagnosed with a higher stage with T3 to T4 disease (17) making diagnosis of DCIS rare event. Most DCIS are screen detected as most patients are asymptomatic. Since routine screening mammogram is not recommended during pregnancy, diagnosis of DCIS without invasive disease is uncommon diagnosis. Women older than 40 are recommended to return to screening mammogram 3 months after completion of breast feeding to allow their breast to return to baseline density.

Workup of Breast Abnormality

Breast ultrasound is the recommended first-line modality for workup of breast symptoms in a pregnant patient due to its lack of ionizing radiation and a high sensitivity (18). The utility of ultrasound in detecting malignancy in pregnant patients has been reported to be 100% sensitive (19-21) and 100% negative predictive value (19). In addition, ultrasound can be used to differentiate benign palpable breast masses in these patients. If the ultrasound demonstrates suspicious findings, diagnostic mammogram should be performed followed by core needle biopsy for pathologic evaluation (*Fig. 1*). Mammography is considered to be safe during pregnancy with appropriate abdominal shielding. Bilateral two-view digital mammogram exposes less than 3 mGy radiation which is equivalent to the average background radiation over 7 weeks of background radiation (22). The estimated dose to the uterus exposure is less than 0.03 μ Gy, (23) which is significantly below the acceptable fetal exposure which is <50,000 μ Gy (24). The sensitivity of mammogram is low in women under the age of 40 due to increased parenchymal density of the breast tissue (25). However, mammography is helpful in evaluat-

ing the contralateral breast as well as detection of microcalcifications which may not be visualized on ultrasound. Since microcalcification is the most common imaging abnormality found in patients with DCIS, imaging evaluation with mammography is recommended (26). Contrast-enhanced MRI during pregnancy is contra-indicated due to the use of gadolinium-based contrast. Gadolinium contrasts are classified as pregnancy category C by the U.S. Food and Drug Administration (FDA) as it will cross the placenta.

Pathologic tissue diagnosis is recommended when suspicious abnormality has been identified by ultrasound or with mammogram. Ultrasound guided core needle biopsy is preferred to

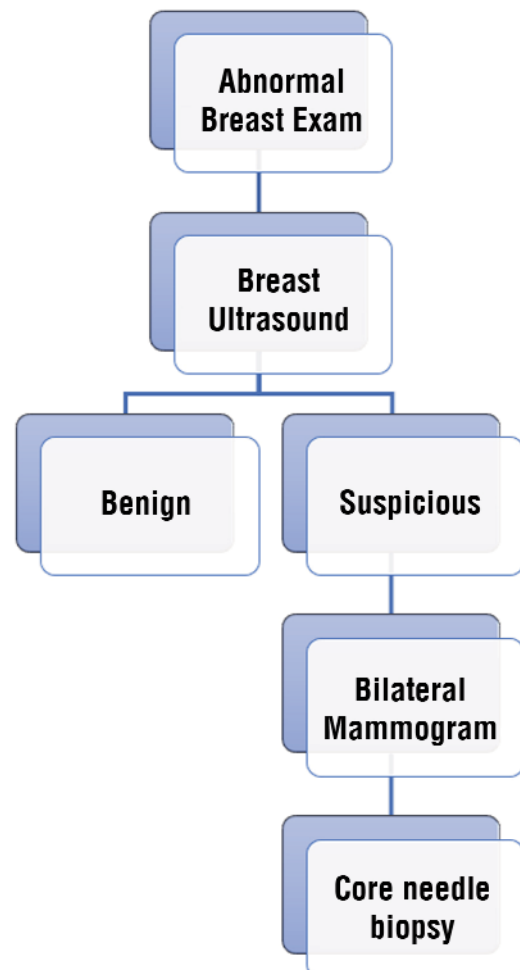


Figure 1. Work-up of breast abnormality during pregnancy

stereotactic biopsy due to no added risk of ionizing radiation, however, stereotactic biopsy and mammographic guided wire localization are safe during pregnancy. The use of local anesthetic with lidocaine as no increased risk to the fetus. The risk of milk fistula rate has been reported to be rare complication of large bore core needle biopsy (27).

Treatment

The aims of treatment of breast cancer should be the same for pregnant and nonpregnant women. However, once a diagnosis of DCIS has been made, it is important to consider where the patient is in her pregnancy to determine treatment options. If the patient is near term, it is reasonable to proceed with delivery prior to starting treatment. If the patient is early in her pregnancy (first or second trimester), treatment may be initiated in the second trimester after evaluating imaging findings. There has been no evidence to suggest termination of pregnancy affects survival outcome (28). The majority of PABCs and pregnancies occur in women under age 45, therefore the possibility of genetic mutation carrier should be considered. All women younger than 45 years with newly diagnosed breast cancer should be offered genetic testing.

Despite being considered non-invasive disease, and often defined as Stage 0 breast cancer, conventional management include breast-conserving surgery followed by radiation or mastectomy in addition. In addition, adjuvant endocrine therapy may be recommended. There has been concerns regarding overtreatment of DCIS in the recent years (29,30). Several recent studies suggest that patients with low-grade DCIS may have similar overall survival outcome with or without surgery (31,32). There are three active clinical trials (LORIS ((LORIS (United Kingdom, NCT02766881), COMET (United States, NCT02926911)33 and LORD (The Netherlands, NCT02492607)) randomizing patients to active surveillance and standard of treatment. These trials likely would not apply

to pregnant patients with DCIS as the eligibility age for these studies is over 40-46 and only low to intermediate grade DCIS are included. Based on these ongoing clinical trials, delay in treatment until delivery may be an option for selected patients.

Surgical Treatment

The surgical recommendation for pregnant women is similar to women who are not pregnant. Surgical recommendations are based on the extent of the disease. Since treatment of DCIS do not include the need for chemotherapy, surgical intervention is the main stay of the treatment. Based on the extent of disease, patient may be candidate for breast-conserving surgery. In the case of extensive calcifications patients may be recommended mastectomy. The role of radiation therapy following breast-conserving surgery in DCIS remains controversial. Breast-conserving surgery is limited in first and second trimester for invasive breast cancer due to timing of radiation therapy as radiation is contraindicated during pregnancy. Despite adjuvant radiation decreasing local recurrence rate, it does not affect overall survival or breast-cancer-specific survival for DCIS, therefore the discussion with radiation oncology provider is important as omission of adjuvant radiation may be considered. There has been recent trials evaluating the use of a bio-signature to evaluate recurrence risk to identify patients who may be low risk for recurrence and adjuvant radiation may be omitted (34).

Performing sentinel lymph node biopsy with lymphoscintigraphy with ^{99m}Tc sulfur colloid is safe during pregnancy. Radiation dose to the uterus was calculated to be $1.67 \mu\text{Gy}$ which is significantly below the threshold of acceptable fetal exposure which is $<50,000 \mu\text{Gy}$ (35-37). The use of isosulfan blue dye is not recommended as this dye is classified as category C by the FDA. Sentinel lymph node biopsy is considered standard of care for patients undergoing mastectomy for DCIS in the clinically negative axilla due to potential upstage to invasive disease. If

Table 1. Suggested Surgical Management DCIS in Pregnancy

Time of Diagnosis	Surgical Treatment
1 st trimester	<ul style="list-style-type: none"> Consider waiting till second trimester, unless imaging concern of upstaging to invasive disease
2 nd trimester	<ul style="list-style-type: none"> Consider surgery using rapid sequence induction and fetal monitoring
3 rd trimester	<ul style="list-style-type: none"> Consider surgery using rapid sequence induction and fetal monitoring Consider waiting till delivery depending on imaging concern and week of gestation

breast-conserving surgery is being considered, sentinel lymph node biopsy is not necessary in the setting of DCIS without invasive component as sentinel lymph node biopsy can be performed later if invasive breast cancer were to be identified.

It has been reported that immediate reconstruction with tissue expander placement after mastectomy maybe feasible and safe. Several studies reported no increased maternal morbidity, obstetrical complications or adverse fetal outcome in patients who underwent immediate reconstruction even with increased operating time with addition of reconstruction (38,39).

Another consideration for surgical treatment is for the patients to undergo breast-conserving surgery during pregnancy for the benefit is shorter operating time and allows for breast feeding. Performing mastectomy could be delayed until after delivery especially if the patient wishes to undergo bilateral mastectomy as definitive surgical treatment to avoid radiation or in the setting of pathogenic genetic mutation. There's no contraindication to breastfeeding from the treated breast if breast conservation was performed (40). However, breastfeeding is contraindicated during radiation therapy and tamoxifen.

Anesthetic Considerations for Surgery

Anesthetic considerations should include the safety of the mother and the fetus. Surgery may be performed at any time during pregnancy, however, it is safest in the second trimester (weeks 12-24 of gestation). It is recommended that mean arterial pressure remain 60 for optimal uterine perfusion. After 20 weeks of gestational age, patient should be

positioned with left lateral uterine displacement tilt to avoid aortocaval compression. After 24 weeks of gestation, intraoperative fetal monitoring is recommended (41).

Adjuvant Therapy

Radiation therapy is contraindicated in pregnancy due to risk of fetal malformations. There maybe a role for adjuvant radiation following breast conservation after delivery depending on the timing of surgery. Radiation is generally recommended to be given within 6 weeks for surgical excision. If mastectomy was performed, most patients will not meet the criteria for post mastectomy radiation.

Tamoxifen is contraindicated during pregnancy and classified as Category D by the FDA. Tamoxifen has been associated with spontaneous abortions, preterm labor, intrauterine growth restriction, genital tract anomalies similar to those who was exposed to diethylstilbestrol (42). Given these findings, tamoxifen is recommended after delivery. Due to lack of safety data regarding excretion of tamoxifen in breast milk, tamoxifen is also not recommended during lactation. The decision to delay endocrine treatment to allow for breastfeeding maybe discussed on individual bases with medical oncologist.

Conclusion

DCIS during pregnancy is rare diagnosis posing clinically challenging situation for the patients and their physicians. The work up for breast abnormality found during pregnancy should be pursued with ultrasound as the primary modality prior to mammogram. Biopsy and surgery should proceed as if the

patient is not pregnant with minor modifications depending on the gestational age. The surgical recommendation for pregnant women is similar to women who are not pregnant, however, breast-conserving surgery maybe limited in first and second trimester due to timing of radiation therapy as radiation is contraindicated during pregnancy. A multidisciplinary team approach is recommended for optimal treatment planning. Recommendation should be personalized based on the gestational age, concern for upstage to invasive disease, extent of DCIS, and patient preferences.

Conflict of Interest

The authors declare no conflicts of interests.

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