OncoTargets and Therapy Dovepress

Open Access Full Text Article

SHORT REPORT

Pregnancy and Breast Cancer: A Challenge for the Multidisciplinary Team. A Single Center Experience and Narrative Review

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Purpose: The diagnosis of breast cancer during pregnancy is a rare event, but it is more frequent in our daily clinical practice due to the progressing aging of pregnant women. The management of a woman affected by pregnancy-associated breast cancer (PABC) remains a challenge for the clinician as it is related to ethical and psychological decisions.

Patients and Methods: Here, we retrospectively described 10 cases of PABC in women treated at our Institution. All cases were discussed in the multidisciplinary team. We reviewed available literature data on the topic.

Results: Nine out 10 patients were diagnosed with localized breast cancer. The remaining patients were presented with metastatic de novo disease. Median age was 37.5 years (range 26–42). Seven patients presented with grade 3 tumor and 9 patients had Ki-67 value higher than 30%. All but 2 patients received neoadjuvant chemotherapy consisting of sequential anthracyclines and cyclophosphamide followed by weekly paclitaxel during pregnancy. No safety concerns or complications during delivery for both the mothers and the babies were reported.

Conclusion: Breast cancer during pregnancy is a challenging clinical situation and all the decisions need to consider both the patients and the fetus safety. Data from our series and from literature confirm the safety of standard chemotherapy approach starting from the second trimester of gestation. More research and effort are needed to offer these patients excellent outcomes and it is mandatory that cases should be closely followed up by a multidisciplinary team.

Keywords: pregnancy, breast cancer, chemotherapy, multidisciplinarity

Introduction

Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy (BCDP), lactation or up to one year or more after delivery. PABC is a relatively rare event. Its incidence is approximately 15 to 35 per 100.000 deliveries, with an estimated incidence of 1 case every 1.000 pregnancies.[1,2] However, the number of PABC is expected to increase in the next years as more women tend to delay childbearing.[3] PABC's management decisions are challenging to both the patient and the multidisciplinary team since they are associated with psychosocial and ethical decisions. In addition, data regarding BCDP's treatment are limited to retrospective case series and case reports.[4]

In view of the lack of data in this area, no consensus is present regarding the optimal management of PABC. In this context, we aimed to provide a valuable clinical experience in the management of women diagnosed with breast cancer during pregnancy. Moreover, we aimed to review the available literature regarding the PABC treatment options by focusing particularly on the role of the multidisciplinary team.

Received: 8 June 2024
Accepted: 3 October 2024
Published: 9 October 2024

Materials and Methods

We retrospectively reported 10 cases of BCDP in women treated at our Institution between 2014 and 2023. Nine patients had a pathological diagnosis of breast cancer during pregnancy. One patient was diagnosed with BC in 2019 and developed metastatic liver disease in 2023 during pregnancy. Liver biopsy confirmed the diagnosis.

Data concerning patients and tumour characteristics as well as oncological treatment and delivery were collected from institutional electronic database.

The oncological treatment (chemotherapy and surgery) was agreed in a multidisciplinary way according to stage of breast cancer and gestational age. Main patients' and babies' characteristics are summarised in Table 1.

Moreover, we conducted a literature review related to the treatment of breast cancer during pregnancy using PubMed database, with the latest update performed in December 2023. The keywords included "breast cancer and pregnancy", "breast cancer treatment" and "guidelines". We included available literature and current international guidelines. As concurrent pregnancy and breast cancer is a rare event, no data from large randomized trials are available; therefore, also retrospective studies and case series were included.

Table 1 Patients' and babies' characteristics

	C#1	C#2	C#3	C#4	C#5	C#6	C#7	C#8	C#9	C#10
Age at diagnosis, yrs	39	26	38	39	38	37	35	42	26	35
Previous pregnancies	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Gestational age at diagnosis	33	31	14	22	15	23	27	28	16	22
Histology	IDC	IDC	IDC	IDC	IDC	IDC	IDC	IDC	IDC	IDC
Clinical stage: T N M	 2 1 0	 3 0 0	 2 1 0	 1c 1 0	 2 2 0	 1c 1 0	 2 1 0	 NA 0 0	 1c 0 0	 3 1 1
Prognostic factors: ER/PgR (%) HER2 status Grading Ki-67 (%)	 -/- 3+ 3 40	 40/70 0 3 60	 90/90 2+ (Fish-) 3 65	 70/80 1+ 2 40	 20/10 3+ 2 22	 -/- 0 3 50	 -/- 0 3 75	 -/- 0 3 50	 75/75 0 3 58	 90/- 2+ (Fish+) 2 35
Neoadjuvant CT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Chemotherapy during pregnancy	None	EC	EC+ paclitaxel	EC	EC+ paclitaxel	EC	Carboplatin +paclitaxel	EC	EC+ paclitaxel	Epirubicin
Type of Surgery	MX+DA	Q+SNB	MX+DA	MX+DA	MX+DA	MX+DA	Q +SNB	Q+SNB	Q+SBN	MX+DA
Adjuvant Trastuzumab	Yes	No	No	No	Yes	No	No	No	No	Yes
Adjuvant ET	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes
Adjuvant RT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gestational age at delivery	37	38	38	37	38	37	37	39	40	37
Baby's weight at birth (gr)	3075	2985	2425	3630	3630	2890	2520	2100	2500	2080
APGAR score	9	9	9	9	9	9	9	9	9	9

Abbreviations: C, case; yrs, years; T, primary tumor; N, lymph nodes; M, metastasis; ER, estrogen receptors; PgR, progesterone receptor; HER2, human epidermal growth receptor 2; IDC: invasive ductal carcinoma; neg: negative; FISH, fluorescent in situ hybridization; CT, chemotherapy; EC, epirubicin and cyclophosphamide; ET, endocrine therapy; RT, radiotherapy; MX, mastectomy; Q, quadrantectomy; DA, axillary dissection; SNB, sentinel node biopsy.

Results

Between 2014 and 2023 ten pregnant patients were treated.

Median age at diagnosis was 37.5 years (range 26–42 years).

All patients were diagnosed with breast cancer during the second trimester of pregnancy. Median gestational age at BC diagnosis was 23 weeks (range 14–33 weeks). In three cases, breast cancer was diagnosed during a woman's first pregnancy, while seven women have already had previous pregnancies.

In all cases, the patients noticed a palpable breast lump; therefore, a mammography with a breast ultrasound scan and biopsy with histology confirmation were performed. All women, except one, were diagnosed with localized disease. In one patient, liver and bone metastasis were already present at the onset of the pregnancy.

Regarding histological subtypes, all patients were diagnosed with invasive ductal carcinoma. The majority of cases were luminal breast cancer; three women were diagnosed with triple negative breast cancer, and two women had Her2 positive disease. About 70% of patients had grade 3 tumor and 90% had Ki-67 value higher than 30%. All but 3 patients had clinical stage II breast cancer.

The majority of patients received neoadjuvant chemotherapy during pregnancy. In two cases, childbirth was recommended by the multidisciplinary team as the first therapeutic step, based on the week of pregnancy.

The chemotherapy regimen consisted of sequential anthracyclines and cyclophosphamide times 4 followed by weekly paclitaxel for 12 weeks. Even the patient with metastatic disease was treated with anthracyclines during pregnancy.

Regarding safety, no toxicities other than normally expected in non-pregnant patients were reported. The most common non-hematological toxicity was asthenia, followed by nausea and peripheral neuropathy. Leucopenia and neutropenia were the most frequently reported hematological toxicities. No grade 4 toxicities have been reported.

In all cases treated with neoadjuvant chemotherapy, the delivery was scheduled 4 weeks after the last chemotherapy administration.

Surgery was performed during the pregnancy in six cases. One patient underwent both caesarean section and breast surgery at the same time. The patient with metastatic disease had undergone breast surgery and adjuvant treatments (chemotherapy and radiotherapy) in 2020.

Four patients underwent breast conserving surgery and sentinel node biopsy; in the other cases, mastectomy plus ipsilateral axillary dissection was performed. The choice of the type of surgery was discussed in the multidisciplinary team. Indeed, multiple factors were taken into account for the decision, such as the stage of disease, the need for adjuvant radiotherapy, the trimester of pregnancy and the patient's preference.

After the delivery, patients with HER2 overexpression/amplification received adjuvant trastuzumab for a whole year of treatment. Adjuvant endocrine therapy and radiotherapy were administered as per indication.

To date, nine patients are alive. Seven patients are following regular follow-up, with no evidence of disease relapse. One patient developed bone metastases 3 years after the diagnosis, during adjuvant endocrine therapy. Treatment with ribociclib and fulvestrant was started, with disease response.

One patient developed diffuse neoplastic meningitis during adjuvant chemotherapy. Palliative care has been started but rapidly the clinical conditions worsened. The patient died in May 2023.

The only patient affected by metastatic disease at the onset of the pregnancy is currently being treated with endocrine therapy and anti-Her2 therapy (trastuzumab plus pertuzumab); the last instrumental revaluation reported a stability of disease.

Regarding obstetrical outcomes, the delivery took place without complications for both the mothers and the babies in all ten cases. All the children were born without congenital malformations. So far, regular and age-compliant children's development has been reported.

Discussion and Literature Review

Breast cancer during pregnancy is a particular clinical situation requiring a multidisciplinary coordinated approach. All the decisions need to consider both the patients and the fetus safety. Our ten-case series well highlights the importance and the efforts of the MDT in the management of these patients.

The diagnosis of PABC is challenging due to pregnancy-related changes in the breast, such as increased breast density and nodularity, that make self-exam more difficult. Furthermore, breast changes related to pregnancy may initially be considered physiological manifestations of pregnancy and mask the cancer. This can result in a delayed identification of suspicious masses and in the finding of more locally advanced disease at the time of diagnosis.

On the other side, most women diagnosed with PABC are not included in prevention programmes with mammography because of their age. Moreover, screening mammography during pregnancy is not recommended (even for women aged 40 years or older) because physiological pregnancy-related processes cause a significantly reduced sensitivity of mammography in this setting.[5] Ultrasound is the first-choice exam for the diagnosis of BC during pregnancy due to its safety for the fetus and its sensitivity for dense breasts.[6] On the other side, breast MRI with contrast is not indicated since gadolinium-based contrast has been shown to cross the blood-placental barrier. In addition, no prospective data are available on the effects of gadolinium-based contrast on the fetus.[7]

It must be also highlighted that 80% of breast masses diagnosed during pregnancy are benign.[8]

In the unlucky case of BCDP diagnosis, the patient should be evaluated for metastatic disease according to guidelines for non-pregnant patients. The allowed imaging techniques, in order to protect the foetus, include chest radiograph with fetal shielding, ultrasound of the liver or magnetic MRI of the spine without contrast.[9,10]

Following a BC diagnosis, some women might decide to interrupt pregnancy, especially in case of a disease with an unfavourable prognosis and/or advanced-stage disease. Obviously, patients should miscarry when a cancer diagnosis is made in the first trimester. However, there is no evidence that abortion can improve the outcome of women with gestational BC.[11]

If a patient wishes to go on with the pregnancy, guidelines recommend that pregnant women with BC should be treated according to the same recommendations valid for non-pregnant patients. Clearly, treatment should take into account the absolute need to guarantee the safety of the fetus.[12,13]

As reported before, all patients with gestational BC should be discussed within a multidisciplinary expert team, in order to maximize the curative intent of the patient while minimizing potential adverse events against the fetus. The different treatment approach must take into account the clinicopathological characteristics of BC, gestational age of the woman at diagnosis of BC, expected date of delivery, and patient's preferences.[4] Regarding local treatments, no significant differences between pregnant and non-pregnant women are recommended. The only exception concerns radiation therapy (RT) since it is contraindicated during pregnancy because of the risk associated with fetal radiation exposure.[14] The type of surgery should be discussed within the MDT and with the patient. Mastectomy could be the first-choice option to eliminate the need for breast RT. In fact, patients in the first trimester of pregnancy who are not candidates to receive neoadjuvant chemotherapy and who desire a breast conserving surgery need to delay adjuvant radiotherapy; this can result in an increased risk of local recurrence.[12,15] However, breast conserving surgery could be safely chosen if radiation treatment can be delayed after delivery and after the administration of neoadjuvant chemotherapy, as is in case 2 of our series.

While there is no doubt on the safety of breast and axillary node surgery during any trimester of pregnancy, more controversial appears the use of sentinel node biopsies. Recommendations from the American Society of Clinical Oncology (ASCO) do not support this procedure, while the National Comprehensive Cancer Network (NCCN) guidelines approve this technique.[16,17]

A few data are available, with case series demonstrating increasing evidence of safety in the use of radioactive colloid and a one-day protocol for clinically node-negative pregnant women.[18,19] Nevertheless, waiting for further data, axillary lymph node dissection should be currently considered a standard approach.

Immediate reconstruction with a tissue expander is not contraindicated in pregnant women. However, considering the physiological changes of the breast during pregnancy, a delayed reconstruction after delivery might be preferred.[15]

As for systemic treatment, it is also mandatory to ensure the normal development of the fetus. The majority of antineoplastic drugs belong to the US FOOD and Drug Administration (FDA) pregnancy category D, meaning that teratogenic effects have been recorded in humans. The risks are highest when chemotherapy is administered in the first trimester, which is the period of organogenesis. Therefore, chemotherapy is contraindicated in the first trimester of pregnancy, considering the higher risk of fetal effects, such as congenital malformations, chromosomal abnormalities,

abortion, intrauterine growth retardation.[12,20,21] Outside that window, most chemotherapies can be safely administered. In fact, the risk of fetal malformations is low if chemotherapy is administered in the second or third trimester. However, data suggest that chemotherapy in the second or third trimester could be associated with minor fetal effects such as prematurity and low birth weight in about one-half of exposed infants.[22]

In addition, it is important to remark the lack of prospective studies regarding the effect of antineoplastic drugs administered during pregnancy and that available data are mainly retrospective.[23]

In most cases, the challenging question is whether to start chemotherapy in any case during pregnancy or wait until after delivery. This important decision should be discussed with the patient and must take into consideration the week of gestation and the biologic features of the cancer. As far as possible, BC during pregnancy should be treated according to the same recommendations as in non-pregnant patients.[13] This also implies that a delay in the beginning of chemotherapy, if the patient has reached the second or third trimester of pregnancy, is not justified.

Ideally, the delivery should be planned after demonstration of fetal pulmonary maturity and at 34 or more weeks of gestation. Moreover, chemotherapy should be avoided for three to four weeks before delivery to prevent complications due to maternal cytopenia, such as sepsis and bleeding.

The standard of care for the neoadjuvant and adjuvant BC treatment is represented by regimens based on anthracyclines, cyclophosphamide and taxanes. In a prospective single-arm study,[24] 87 BCDP patients were treated with FAC (fluorouracil, doxorubicin and cyclophosphamide) in the adjuvant or neoadjuvant setting. Anthracycline-based chemotherapy has proven to be safe. The majority of children did not show any significant neonatal complications; no miscarriages, stillbirths or perinatal deaths were reported. Similar results have been reached by smaller retrospective series of anthracycline-based chemotherapy.[25–27] Only limited data are available about late sequelae, such as impaired cardiac function and fertility, suggesting the safety of anthracycline-based chemotherapy also in terms of risks of fetal late sequelae.[28] Limited retrospective data are available on the use of the dose-dense schedule in pregnant women, which is the standard of care for high-risk BC patients. More prospective data are needed to investigate the safety of dose-dense chemotherapy during pregnancy.[22]

While anthracyclines and alkylating agents have been known to be safe during pregnancy for many years, less data are available regarding the use of taxanes. Recently, more reassuring evidence on the safety of taxanes during pregnancy has emerged. A review of literature including 40 case reports of taxane chemotherapy in pregnancy, reported on the safety of this regimen, with minimal maternal and fetal toxicity.[29] In particular, weekly paclitaxel compared to docetaxel has been found to be associated with lower rates of neutropenia and, in general, better tolerance.[30]

Less is known about the use of platinum compounds, partially due to their recent use in the neo-adjuvant setting of triple negative BC. We know that higher levels of cisplatin in the blood, due to low albumin levels in pregnant women and consequent changes in cisplatin protein binding, could be toxic for the patient and the fetus. One study has found platinum-based chemotherapy to be associated with smaller sizes for gestational age.[31] Carboplatin seems to be associated with a better fetal toxicity profile.[30]

The use of trastuzumab during pregnancy is contraindicated due to the risk of oligohydramnios, which can lead to serious fetal consequences (pulmonary hypoplasia, skeletal abnormalities and neonatal death).[31]

Recently, the anti-PD-1 pembrolizumab has been approved in neoadjuvant treatment of triple-negative BC patients based on the results of the Phase III KEYNOTE-522 trial.[32] Data regarding the use of pembrolizumab and other immune checkpoint inhibitors (ICI) during pregnancy are very limited; no data are available regarding the use of ICI during therapy in breast cancer. A case report of a woman diagnosed with malignant melanoma treated with pembrolizumab during pregnancy suggested the possible safety of treatment with IC.[33] However, no conclusions can be drawn since the safety of ICI in such setting will be established in prospective trials.

Endocrine therapies are contraindicated during pregnancy, due to the risk of abnormalities of the fetal reproductive tracts. In addition, to date, no data are available on the use of PARP and CDK4/6 inhibitors during pregnancy.[30]

Regarding maternal health, data show no negative impact on survival of women diagnosed with gestational BC.[34] A meta-analysis of over 3000 women with PABC and 37,100 non-pregnant patients reported an association between gestational BC and poor prognosis; however, the association appeared to be limited to women with BC diagnosis in the postpartum and not to women diagnosed during pregnancy.[35] Similarly, data suggest that the development of children

born from mothers with BC is not different from children of the same gestational age.[36] Long-term data are warranted to better direct the decisions in the management of patients with gestational BC.

Conclusions

Breast cancer during pregnancy remains a challenging clinical situation, even though its frequency is increasing in clinical practice. Essential is the early recognition of BC symptoms in order not to delay the diagnosis. As far as possible, the medical management of BC during pregnancy should be the same as in non-pregnant women. As in non- pregnant women, in pregnant patients the aim of the treatment is to achieve the curability of the disease.

Results from our series and from literature data confirm the safety of the standard chemotherapy approach, starting from the second trimester of gestation, for both the patients and the babies. In particular, our experience underlines the safety and the tolerability of the standard chemotherapy schedule containing both anthracyclines and taxanes. No data are currently available on new immunotherapeutic drugs that have been implemented in clinical practice lately. So far, no children's developmental disorders were reported in our series.

Considering the rarity of this condition, the management of these patients must be centralised in reference centers. Overall, discussion in the multidisciplinary team is mandatory in order to determine modality and timing of treatments and to ensure the most appropriate management for both the patient and the fetus.

Ethics Approval and Informed Consent

The study was approved by the Ethical Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan. The data collected in this study were in accordance with the 1964 Declaration of Helsinki and its later amendments or equivalent ethical standards. Data collection was performed under the normative regulations, indications and restrictions on the matter of retrospective clinical studies.

All patients signed an institutional informed consent for research purposes only and without commercial interest.

Disclosure

Dr Ornella Garrone reports personal fees from MSD, Pfizer, Eisai, Gilead, Lilly, Novartis; travel expenses from Ipsen and Novartis, outside the submitted work. The authors report no other conflicts of interest in this work.

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