Is it safe to treat Breast Cancer during Pregnancy?- A single institution five years retrospective experience

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Abstract

Background: Breast cancer diagnosed during pregnancy poses unique challenges. Application of standard treatment algorithms is limited by lack of level I evidence from randomized trials.

Patients and methods: A retrospective analysis of cases of Pregnancy Associated Breast Cancer (PABC) treated at Kasr Elaini Center of Clinical Oncology and Nuclear Medicine, Faculty of Medicine-Cairo University, Egypt in the period between Jan.2009 and Dec. 2013. Clinico-pathological characters, treatment adopted and treatment outcome were analysed.

Results: Thirty eight files were reviewed, but the cohort involved only 21 patients with available data. The majority presented with early-stage breast cancer. Most of them (66.7%) underwent surgical resection during pregnancy. A total of 18 patients received anthracycline-based chemotherapy during pregnancy; of those, 5 patients also received paclitaxel. Eighteen patients delivered live-born neonates; five cases (27.8%) delivered prematurely. Regarding neonatal outcome, mean neonatal birth weight was 2547 ± 817 grams. In 5 cases (26.3%), neonatal birth weight was <10% for gestational age. Eight neonates (42.1%) had normal Apgar scores (≥7), 6 (31.6%) neonates had fairly low Apgar scores (4-6), and 5 (26.3%) neonates had critically low Apgar scores (≤3). One child (0.05%) was born with a congenital anomaly (cleft lip and tongue tie). No intrauterine fetal demise or neonatal death occurred.

Conclusion: Within a multidisciplinary academic setting, PABC treatment followed contemporary algorithms without apparent increase in maternal or fetal adverse outcomes. Continued attention to maternal and fetal outcomes after PABC is required to determine the benefit of this delivery strategy

Introduction

Cancer complicates about 1 in 1000 pregnancies, with breast cancer as the most common associated malignancy **(1)**. Pregnancy Associated Breast Cancer (PABC) poses a very difficult challenge to the women, her family and the medical staff **(2).** PABC has been defined as breast cancer diagnosed during pregnancy and up to one year postpartum **(3)**. Although much PABC research has considered this group as a whole, it is worth considering two distinct subsets – those diagnosed during pregnancy, and those diagnosed in the postpartum period **(4).**Contemporary management of pregnancy-associated breast cancer (PABC) encourages continuation of pregnancy during treatment. The difficulty in treating the 1st subset is attributed to teratogenic effects of anti-cancer therapy on the developing fetus.

High level evidence base to support oncologic decision is somewhat lacking due to low incidence and ethical consideration regarding involvement in clinical trials. The rising incidence of PABC may be due to trends in delaying pregnancy **(5)**. Compared to non-pregnant it was diagnosed at higher stage and pathology showed higher tumor grade, higher percentage of lymphovscula invasion, more lacking of ER & PR expression and higher Her2u receptor expression. **(6)**.

Age, rather than the pregnancy itself appears to determine the biologic features of the tumor **(7 & 8)**. Survival of PABC appears to be the same like non-pregnant when age & stage adjusted **(9).**

Genetic counseling is to be considered as family history of breast cancer was reported positive in 48% of cases and 9% of cases showed BRCA 1 or BRCA 2 mutation **(10).** The most common presentation of PABC is painless breast lump, but rarely presented with bloody nipple discharge **(11).**

Breast imaging with Ultrasonography is the safest breast imaging during pregnancy. Mammography has low sensitivity, and difficult to interpret **(12)**, but with adequate shielding presents little risk to the fetus. **(7)**. MRI may be used if other forms of diagnostic imaging are inadequate or if the examination provides important information that would otherwise require exposure to ionizing radiation **(13).**

Core needle biopsy has a sensitivity of about 95 %, while Fine Needle Aspiration Cytology (FNAC) is misleading due to hyper-proliferative changes **(14).**

A staging strategy for every individual patient should be discussed and planned at a multidisciplinary setting. Chest x-ray with proper shielding is safe but CT and bone scan carry a high risk. Abdominal Ultrasonography (US) is a good tool for assessment of liver deposits **(15)**.

Treatment of BC during pregnancy depends on the timing of its diagnosis. Induction of abortion should be discussed during 1st trimester. While during 2nd and 3rd trimesters, fetal maturity and anomalies should be looked for before considering termination. Modified Radical Mastectomy (MRM) is safe **(16)**, except for Sentinel Node Dissection (SND) with radio-isotopes, but recently shown to be performed safely **(17)**.

RT is classically contraindicated throughout pregnancy**,** but an expert panel accepted radiotherapy as a relatively safe treatment option during the second trimester of pregnancy. The Panel agreed that the decision should be taken after a thorough discussion of available data between the patient, her family and the multidisciplinary team, taking into account the potential benefits and risks of this treatment. Delaying radiotherapy to the postpartum period should also be considered. They stated that better clinical data are needed **(18).**

Possible outcome depends on the protocol of chemotherapy and the gestational age. Significant exposure to cytotoxic drugs during 1st 4 weeks of pregnancy may result in spontaneous abortions. The risk of birth defects increases if exposure occurred during period of organogenesis (5 – 12 weeks). The most toxic drug during this period is methotrexate. Anomalies may involve eyes, genitals, bone marrow and CNS **(19)**. Exposure to these drugs during 2nd and 3rd trimesters is not associated with teratogenic defects, but may result in intra-uterine growth retardation, prematurity and stillbirth **(20)**.

Late effects of chemotherapy were studied in an observational study of 84 children exposed to chemotherapy in utero. No congenital, neurologic, psychological, cardiac, cytogenetic abnormalities or malignancies were observed. Normal learning and education performance were observed **(21)**. In a parents/guardians survey, regarding outcomes of 40 children exposed to chemotherapy in utero (Age = 2-157 months), no apparent chemotherapy- induced problems were detected **(22).**

Giving chemotherapy during pregnancy necessitates evaluation of fetal morphology, growth and fetal wellbeing by US or even intense fetal monitoring before every cycle of chemotherapy. Preterm delivery may occur. Neutropenia should be avoided (best time for pregnancy termination is 2-4 wk. after the last cycle of chemotherapy) **(7)**

Safety of anthracycline during pregnancy was early studied by Berry et al , in 39 patients with median gestational age at diagnosis of 20 weeks. They received 1-6 anthracycline cycles (median = 4). Mean gestational age at delivery was 38 weeks. No abortions or congenital fetal malformation (CFM) were reported **(23).**

Oligohydramnios or anhydramnios was noted in 8 out of 14 pregnancies exposed to trastuzumab in utero. This may be due to the overexpression of HER-2/neu in fetal renal epithelium **(24)**.

Tamoxifen use should be avoided during pregnancy **(11)**, due to the reported congenital anomalies associated with its use like oculo-auriculo-vertebral dysplasia (Goldenhar syndrome) **(25),** ambiguous genitalia, and Pierre Robin sequence (triad of small mandible, cleft palate and glossoptosis) **(26)**.

Bisphosphonates were given in a small number of patients during pregnancy without negative effects, but potential undesired effects may include maternal and fetal hypocalcaemia & inhibition of fetal osteoclasts **(27)**. Due to the high incidence of pre-term labor, patients should be alert when contractions occur. Vaginal delivery is recommended as it is associated with low risk of therapy delay **(28).**

Patients and Methods

This is a retrospective study conducted at Kasr Elaini Centre of Clinical Oncology and Nuclear Medicine, Department of Obstetrics and Gynaecology, and paediatric neonatology unit, Faculty of Medicine-Cairo University, Egypt. Eligibility criteria included a history of pathologically confirmed breast cancer diagnosed during pregnancy, with adequate data in the oncology and obstetrics files, and referred to the centre in the period between Jan. 2009 and Dec. 2013. Maternal and foetal outcomes, clinico-pathological characters, treatment adopted and treatment outcome were obtained from patients files.

Statistical Methods

Descriptive statistical analysis was performed using the SPSS software program for Windows (v. 10.0; SPSS,Chicago, IL).

Results

PABC represented less than 1% of breast cancer cases referred to breast cancer specialized unit at Kasr Elaini Centre of Clinical Oncology and Nuclear Medicine, Cairo University. Thirty eight files of PABC were reviewed among more than 4000 cases referred in the period between Jan.2009 and Dec. 2013.

Twenty one patients with PABC who met inclusion criteria were included. Detailed demographic and disease characteristics were presented in Table (1). The median age at diagnosis was 36 years (range 25–43). The timing of presentation varied. Patients diagnosed in the first, second, and third trimesters were 7 (33.3%), 8 (38.1 %), and 6 (28.6 %) respectively. Three of the 21 patients (14.3%) were electively terminated during the first trimester (prior to initiating cancer therapy) and eighteen (85.7%) carried their infants to term. The majority of patients (85.7%) were diagnosed with early-stage disease; three (14.3%) patients had metastatic disease at the time of presentation. All were tested to evaluate tumour hormone receptor and HER2 status; 13 (61.9%) were ER/PR positive, and 7 (33.3%) were HER2 positive. Four patients (19%) had triple-negative breast cancer, 4 (19%) had HER2 positive, ER/PR –ve (HER2 enriched), 10(47.6%) had ER/PR +ve, HER2 –ve (luminal subtype), and 3(14.3%) had all receptors +ve (lumina B2). Unfortunately, data about Ki-67 were not adequate.

All patients underwent breast ultrasound, 2 (9.53%) underwent chest x-ray, and two patients (9.53%) underwent MRI of the breast. No mammography or CT-scanning was done during pregnancy.

Table 1: Patient and tumor characteristics

Demographic		Number	(%)
Age	< 30 years	4	26.7%
	≥ 30 years	17	73.3%
Gestational age at diagnosis (weeks)	1st trimester = 0-12 weeks	7	33.3%
	2nd trimester = 13-27 weeks	8	38 .1%
	3rd trimester = 28-40 weeks	6	28.6%
Pregnancy outcome	Termination in the 1st trimester	3	14.3%
	Live birth	18	85.7%
Tumor stage	II	15	71.4%
	III	5	23.8%
	IV	1	4.8%
Receptor status	HR+ve	13	61.9%
	HR-ve	8	28.1%
	Her2u +ve	7	33.3%
	Her2u-ve	14	66.7%
Tumor subtype	TNBC	4	19 %
	Her2u +ve/HR-ve	4	19%
	HR+ve/Her2u-ve	10	47.6%
	Her2u +ve/HR+ve	3	14.3%

TNBC: triple-negative breast cancer

Local Therapy

Twelve (66.7%) out of 18 patients, who carried their pregnancies to term, presented with non-metastatic disease and underwent surgery during pregnancy (Table 2). Only one patient proved to have bone metastases on bone scan done

after labour. Of this group, 3 (25%) underwent breast conservative surgery (BCS) and 9 (75%) underwent modified radical mastectomy. Surgeries performed during 1st, 2nd, and 3rd trimesters were 4 (33.3%), 5 (41.7%), and 3 (25%) cases respectively. Sentinel lymph node biopsy was not performed in all patients.

Table 2: Surgical therapy for pregnancy associated breast cancer

Surgical therapy		Number	(%)
Surgery during pregnancy	Yes	12	66.7%
	No	6	33.3 %
Gestational age at time of surgery	1st trimester	4	33.3 %
	2nd trimester	5	41.7%
	3rd trimester	3	25 %
Type of surgery	MRM	9	75%
	BCS	3	25%

BCS: breast conservative surgery. MRM: modified radical mastectomy.

Systemic Therapy

All patients who carried pregnancy to term (18) received chemotherapy. Ten of them (55.5%) started chemotherapy in the second trimester, and remaining 8 patients (44.4%) started chemotherapy in the third trimester. No chemotherapy was administered in the first trimester. Chemotherapy was palliative for one patient with early liver metastases detected on abdominal ultrasonography, adjuvant for 6 patients (33.3%), and neo-adjuvant for 11 patients (61.1%) (Table 3). Four out of 6 patients, who received adjuvant chemotherapy during pregnancy, had started their chemotherapy in the 2nd trimester. While 6 out of 11 patients (54.54%), who received neo-adjuvant chemotherapy during pregnancy, had started their chemotherapy in the 2nd trimester. Opinion from multidisciplinary tumor board was considered in many cases as well. Most patients received anthracycline based chemotherapy. Both, patient who received palliative chemotherapy and 5 out of 6 (83.3%) patients, who received adjuvant chemotherapy, had their chemotherapy regimen in the form of 5-flurouracil, doxorubicin and cyclophosphamide (FAC). FAC regimen was also used as in the neo-adjuvant settlings in 5 out of 11 patients (45.4%), while the remaining 6 patients (54.5%) treated with AC (doxorubicin and cyclophosphamide) followed by weekly Paclitaxel. Minority of patients planned for neo-adjuvant AC/Paclitaxel had completed more than 4 weeks paclitaxel therapy and two of them received only AC. Minority of patients planned for neo-adjuvant AC/Paclitaxel had completed more than 4 weeks paclitaxel therapy and two of them received only AC. Eight (72.7%) out of the 11 patients treated with neo-adjuvant chemotherapy showed partial response, while 2 (18.3%) patients showed stable disease and the remaining patient (9%) had progressive disease. Response was evaluated using clinical examination and breast ultrasonography. The only patient with liver metastases treated with palliative FAC during pregnancy has stable disease in the liver with partial response in her local disease. Complications of chemotherapy, including anemia, neutropenia, and febrile neutropenia, were rare. One patient required a blood transfusion for anemia. A total of 7 patients (38.8%) treated with chemotherapy developed treatment-related neutropenia; but most cases were mild, with absolute neutrophil counts (ANC) >1000 and no cases of febrile neutropenia was reported. Non-haematological complications included grade I & II vomiting in 3 patients (16.6%), alopecia & mild nausea in most of patients (88.8 &72.2% respectively). No endocrine therapy or trastuzumab were given during pregnancy.

Table 3: Systemic therapy for pregnancy associated breast Cancer

Systemic chemotherapy given during pregnancy		N = 18	(%)
Gestational age at time of chemotherapy initiation	2nd trimester	10	55.5 %
	3rd trimester	8	44.4%
Indication of chemotherapy	Palliative	1	5.6 %
	Adjuvant	6	33.3%
	Neo-adjuvant	11	61.1%
Chemotherapy regimen	FAC	11	61.1%
	AC	2	11.1%
	AC + Weekly Paclitaxel	5	27.5%

FAC: 5-flurouracil, doxorubicin and cyclophosphamide.
AC: doxorubicin and cyclophosphamide.

Maternal and Fetal Outcomes

Nineteen neonates were exposed to chemotherapy in utero (one had twin pregnancy). Mean gestational age at delivery for neonates exposed to chemotherapy was 35.6 ± 2.4 weeks. Five cases (27.8%) delivered prematurely. Ten patients delivered vaginally and eight by cesarean section. Mean birth weight was 2547 ± 817 grams. In 5 cases (26.3%), neonatal birth weight was <10% for gestational age. Eight neonates (42.1%) had normal Apgar scores (≥7), 6 (31.6%) neonates had fairly low Apgar scores (4-6), and 5(26.3%) neonates had critically low Apgar scores (≤3). One child (0.05%) was born with a congenital anomaly (cleft lip and tongue tie). No intrauterine fetal demise or neonatal death occurred.

Table 4 : Maternal and fetal outcomes after treatment for pregnancy-associated breast cancer

Maternal and Fetal outcome		N = 18	(%)
Gestational age at delivery	Preterm (<37weeks)	5	27.8%
	Term (≥37weeks)	13	72.2%
Mode of delivery	Vaginal delivery	10	55.5%
	Caesarean section	8	44.4%
Birth weight for gestational age	Appropriate	14	73.7%
	Small for GA (<10th percentile)	5	26.3%
Apgar score at 5 minutes	≥7 (normal)	8	42.1%
	4 - 6 (fairly low)	6	31.6%
	≤ 3 (critically low)	5	26.3%
Fetal complications	Congenital anomaly	1	0.05%
	Intrauterine fetal demise	0	0%
	Neonatal death	0	0%

Discussion

In this cohort of patients with PABC, contemporary therapies for breast cancer including anthracyclines, taxane chemotherapy and different breast surgeries were utilized without significant adverse maternal or foetal outcomes. There was a low rate of maternal complications, and no fetal abnormalities, even less than consistent with expected population rates (**29**). Consistent with prior reports, and likely due to the young age of the patients, this cohort was enriched for ER negative tumours (**30),** and patients' clinicopathologic details did not differ greatly from those noted in other studies of non-pregnant young women diagnosed with breast cancer (**31**). Almost all patients in the cohort underwent imaging to stage their disease while pregnant. Notably, few patients underwent x-ray imaging of the chest and MRI scanning, with no apparent adverse effect on the foetus. Although, the safety and feasibility of mammography during

pregnancy have been reported (**32**), but it seems that physicians still have some fear from its use during pregnancy.

Reports suggest that mastectomy or lumpectomy can be safely pursued at any point during a pregnancy with minimal risk to the foetus (**33**). However, first trimester surgery is often deferred, out of concern for higher risks of foetal complications (**34**). In this cohort, nearly one third of patients underwent surgery in the first trimester without apparent complications, suggesting the safety of surgical intervention during this time. Although chemotherapy administration during the first trimester has been associated with risk of foetal defects, the use of certain chemotherapeutics in the second and third trimesters is generally considered safe without increase in the rates of foetal abnormalities (**7; 18; 20 & 35**). The chemotherapy data presented in this study support the safety of traditional regimens in this population. Most prior studies evaluating chemotherapy in PABC have examined AC or FAC, but few studies have examined the safety of taxanes, which play an integral role in adjuvant chemotherapy regimens. In this cohort, 27.8 % of patients who received AC also received weekly paclitaxel (less than 12 weeks full course) during pregnancy without undesirable effects. The use of taxanes in PABC has been reported primarily as case reports (**36; 37**). In a review of 42 infants born to 40 patients exposed to taxanes during pregnancy, only one had a malformation possibly related to taxane use (**38**). Further work is required to confirm the safety of taxanes after the first trimester.

Tamoxifen and trastuzumab are traditionally avoided in pregnancy due to teratogenic effects. Case reports have described multiple fetal complications after prenatal exposures to these agents (**39; 40; 41**). Trastuzumab has been associated with oligohydramnios. As a short-term delay in the initiation of endocrine therapy likely does not adversely affect survival outcomes, particularly in early stage breast cancer, it is feasible to consider delayed initiation of tamoxifen until completion of pregnancy. Current adjuvant trastuzumab containing regimens for HER2 positive breast cancer begin with anthracycline-based chemotherapy, facilitating postponement of trastuzumab therapy until after delivery. Most published studies have also reported an increased risk of preterm delivery in patients treated with chemotherapy for PABC (**1; 42; 43**). In this series, more than half of preterm deliveries were planned to facilitate maternal therapy. More than 20% of all labors were unplanned preterm deliveries. Although preterm delivery in this cohort did not appear to result in increased harm to the fetus, data has suggested even late preterm delivery (34–37 weeks) or near term delivery (37–39 weeks) can be associated with adverse outcomes in the fetus (**44 &45**). This study was limited by the small sample size and limited to women treated in university tertiary care center, which introduces the possibility of selection bias. This retrospective study of PABC demonstrates the feasibility of optimal treatment through multidisciplinary care team management.

Conclusion

- Within a multidisciplinary academic setting, PABC treatment followed contemporary treatment without apparent increase in maternal or fetal adverse outcomes.
- The risk of late preterm delivery must be carefully considered when planning the timing of delivery. A careful discussion is encouraged between patient, maternal-fetal medicine specialist and medical oncologist to decide the timing of pregnancy termination to avoid maternal and fetal complication.
- It is necessary to appropriately balance perinatal care of mother and infant. Further data collection and investigation will improve understanding of and treatment paradigms for breast cancer diagnosed during pregnancy

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