Breast Cancer in Pregnancy: A Retrospective Cohort Study

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Abstract

Gestational breast cancer (GBC) is the second most commonly occurring malignancy affecting pregnant women. Management is complex due to potential foetal risks in the setting of maternal treatment. We report on the maternal, foetal, short-term neonatal and placental histopathologic findings of a retrospective cohort of pregnant women with either pre-gestational (group 1) or GBC (group 2) from a tertiary-level maternity care centre. Of the 69 women identified over 12 years, there were 47 in group 1 and 22 in group 2. Demographics, stage of breast cancer at diagnosis were similar in the 2 groups. Women with GBC (group 2) were more likely to receive surgery and chemotherapy or surgery alone as compared to those in group 1. No women with GBC received radiation during pregnancy, but 2 received this treatment postpartum. With regard to pregnancy outcomes, in-

duction of labour was more common in women with GBC, as was preterm birth. Most preterm birth in women with GBC was late preterm, iatrogenic in nature to facilitate postpartum treatment. We conclude comparable pregnancy outcomes for women with GBC as compared to those with pre-gestational breast cancer.

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Introduction

Breast cancer is the most frequent cancer among women in the world with 1.7 million new cancer cases diagnosed in 2012 (25% of all cancers in women) [1]. It is the most common cause of cancer death among women and the second most common cancer death in developed countries after lung cancer [1]. Gestational breast cancer (GBC) is defined as carcinoma that is diagnosed during pregnancy or within 1 year postpartum. Breast cancer is the second most common malignancy associated with pregnancy after cervical cancer, complicating approximately 1 in 3,000–10,000 pregnancies [2]. Several publica-

tions over recent years have improved our understanding of the interaction of breast cancer and pregnancy. For example, we now know that GBC tends to be diagnosed at more advanced stages of the disease due to delay in detection and diagnosis [3], yet the survival rate for GBC is comparable to non-GBC, stage for stage, if treated appropriately [4, 5]. Birth outcomes for newborns born to women with GBC are generally favourable, yet recent publications have shown higher rates of preterm birth and foetal growth restriction as compared to healthy mothers [6, 7]. Due to the complexities of maternal treatment and potential impact on the foetus, collaboration with obstetrics, neonatology and oncology are necessary to coordinate and time management and delivery of the infant. Little information is available regarding the chemotherapy administered during pregnancy and subsequent placental findings. One study reporting on placentas from 13 patients who received chemotherapy in pregnancy for various carcinomas suggested that chemotherapy exposure in the first trimester induces excessive polyploidization of the trophoblast, likely representing an adaptive response to intra-amniotic toxins. Exposure to cytotoxic agents during the second and third trimesters may predispose to placental underdevelopment. Without control groups, specific effects of chemotherapy are difficult to ascertain [8].

At our tertiary maternal care centre, a specialized team of maternal foetal medicine, neonatology and medical oncology manages patients with gestational malignancies. The objective of the study is to report the maternal, foetal and short-term neonatal outcomes as well as placental histopathologic findings in women with a current or prior diagnosis of breast cancer in our centre over a 12-year period.

Methods

We conducted a retrospective cohort study including pregnant women with either current (gestational) or prior diagnosis of breast cancer from 2004 to 2015. Patients were identified from the hospital database and data was extracted from patient records. The extracted data included demographic data such as age, ethnic group, and parity. Histopathological details as well as tumour grade and stage, clinical presentation and disease course, type of treatment received (chemotherapy, radiation and surgery) as well as details of treatment regimens, pregnancy course, maternal and foetal/neonatal complications, labour and delivery details, and data on the neonate until discharge from hospital. We also included data on placental histopathology where available. Patients were divided into 2 groups: those with a prior history of breast cancer (group 1) and those with breast cancer during pregnancy (group 2). Summary statistics and frequencies were calculated for all vari-

ables. Outcomes were compared between groups using Chi-square tests for categorical variables and Student's *t* test or Fisher's exact test for continuous variables. A *p* value of 0.05 was considered significant. The study was approved by the hospital Research Ethics Board (REB number 16-0181-C).

Results

We identified 69 pregnant women with breast cancer. Of those, 47 had prior history of breast cancer (group 1) and 22 patients had GBC during pregnancy (group 2). The maternal characteristics for both groups are shown in Table 1. There were no significant differences between groups with respect to maternal age, ethnicity, and parity, other medical comorbidities, smoking status and alcohol consumption, a prior foetus with a congenital anomaly, multiple gestations or gestational diabetes. In both groups, invasive carcinoma (68 and 86%) was more common than carcinoma in situ (17 and 14%). Where documentation was available, the commonest stage of cancer at diagnosis was Stage II for women in group 1. For women in group 2, the stage of diagnosis of breast cancer was almost equally divided between Stages I–IV. In both groups, the tumour grade at the time of diagnosis was most likely to be Grade III (43 and 50% respectively). Women in group 1 were most likely to have received a combination of surgery, radiotherapy and chemotherapy (70%) prior to the current pregnancy. In contrast, women in group 2 (those currently pregnant) were most likely to receive surgery and chemotherapy (50%) or surgery alone (32%).

Details of the treatment strategies received by women in group 2 are outlined in Table 2. Treatment was initiated in the antepartum period in 21 out of 22 cases and deferred until the postpartum period only in one. A total of 16 out of 22 women underwent surgery in the antepartum period, the commonest surgery being mastectomy with lymph node dissection followed by lumpectomy/resection with sentinel node biopsy, at a mean gestational age of 22–23 weeks. Of the 15 women that received chemotherapy in group 2, thirteen received this in the antepartum period commencing at a mean gestational age of 26 weeks. Only 2 patients in group 2 received radiotherapy (along with surgery and chemotherapy) and in both cases, this was commenced in the postpartum period.

Pregnancy outcomes are described in Table 3. There was a significant difference between groups 1 and 2 with regard to rates of labour induction (32.6 vs. 50%, *p* = 0.045). However, there were no differences in rates of elective caesarean deliveries (17.4 vs. 27.3%, *p* = 0.5) or

Table 1. Characteristics of patients

	Prior history of breast cancer (<i>n</i> = 47)	Current history of breast cancer (<i>n</i> = 22)
Age, years, mean $\pm$ SD	37.32 $\pm$ 3.53	35.64 $\pm$ 4.78
Ethnicity, <i>n</i> (%)		
Caucasian	24 (51.1)	9 (40.9)
Black	2 (4.3)	2 (9.1)
Asian	11 (23.4)	4 (18.2)
Other	5 (10.6)	3 (13.6)
Unknown	5 (10.6)	4 (18.2)
Current smokers, <i>n</i> (%)	2 (4.3)	1 (4.5)
Alcohol consumption during pregnancy, <i>n</i> (%)	6 (12.8)	3 (13.6)
Other medical comorbidities, <i>n</i> (%)	29 (61.7)	11 (50)
Nulliparity, <i>n</i> (%)	26 (55.3)	10 (45.5)
Twin gestation, <i>n</i> (%)	1 (2.1)	0 (0)
Prior history of congenital anomaly, <i>n</i> (%)	2 (4.3)	1 (4.5)
Gestational diabetes, <i>n</i> (%)	7 (14.9)	3 (13.6)
Type of malignancy, <i>n</i> (%)	27 left; 20 right	10 left; 11 right; 1 bilateral
In situ carcinoma	8 (17)	3 (13.6)
Invasive carcinoma	32 (68.1)	19 (86.4)
Phylloides tumour	1 (2.1)	0 (0)
Unknown/not documented	6 (12.8)	0 (0)
Stage of malignancy, <i>n</i> (%)		
Stage I	12 (25.5)	3 (6.4)
Stage II	15 (31.9)	4 (8.5)
Stage III	1 (2.1)	4 (8.5)
Stage IV	1 (2.1)	3 (6.4)
Unknown/not documented	18 (38.3)	8 (17)
Tumor grade, <i>n</i> (%)		
Grade I	9 (19.2)	1 (4.5)
Grade II	8 (17)	2 (9.1)
Grade III	20 (42.6)	11 (50)
Unknown	10 (21.3)	8 (17)
Treatment, <i>n</i> (%)		
Surgery	6 (12.8)	7 (31.8)
Surgery + chemotherapy	4 (8.5)	11 (50)
Surgery + radiotherapy	2 (4.3)	0 (0)
Surgery + radiotherapy + chemotherapy	33 (70.2)	2 (9.1)
Chemotherapy only	0 (0)	2 (9.1)
Surgery + radiotherapy + other treatments	1 (2.1)	0 (0)
Unknown	1 (2.1)	0 (0)
Chemotherapy in pregnancy, <i>n</i> (%)	Not applicable	15 (68.2)
Surgery type, <i>n</i> (%)		
Resection/lumpectomy $\pm$ sentinel node biopsy	23 (48.9)	7 (31.8)
Lumpectomy with lymph node dissection	7 (14.9)	4 (18.2)
Mastectomy $\pm$ lymph node dissection	14 (29.8)	9 (40.9)
Unknown/no surgery	3 (6.4)	2 (9.1)

spontaneous vaginal deliveries (41.3 vs. 59.1%), antepartum or postpartum hospital admissions, or the length of hospital stay during admission. In group 1, 2 women went into spontaneous preterm labour (23 and 36 weeks); 1 woman had preterm pre-labour rupture of membrane at 20 weeks followed by spontaneous labour at 24 weeks; 1

woman had a caesarean delivery at 25 weeks for foetal wellbeing concerns. Of the 15 women who went into spontaneous labour, details on mode of delivery were available in 14. Of these, 11 delivered vaginally and 3 by caesarean birth (one due to failure to progress and 2 due to fetal distress).

Table 2. Treatment strategies in women with gestational breast cancer

Initiation of treatment (<i>n</i> = 22)	
During pregnancy	21
Deferred until after delivery	1
Surgical treatment (<i>n</i> = 20)	
Resection/lumpectomy ± sentinel node biopsy	7
Lumpectomy with lymph node dissection	4
Mastectomy ± lymph node dissection	9
Timing of surgery	
Antepartum	16
Postpartum	4
Gestational age at surgery, if antepartum, weeks, mean (SD); range	22.4 (7.9); 11–35
Chemotherapy (<i>n</i> = 15)	
FEC (5-fluorouracil + epirubicin + cyclophosphamide)	10
FEC ± docetaxel ± herceptin	3
A-CT (adriamycin + cyclophosphamide + paclitaxel) + tamoxifen	1
Unknown/not reported	1
Timing of initiation of chemotherapy	
Antepartum	13
Postpartum	2
Gestational age at initiation of chemotherapy if antepartum, weeks, mean (SD); range	25.7 (5.4); 20–35
Radiation (<i>n</i> = 2)	Both postpartum

Of the 15 where labour was induced, 9 delivered vaginally and 6 by caesarean section (4 due to failure to progress in labour and 2 due to foetal distress). Indications for the 8 elective caesarean sections in this group were repeat caesarean section in 4, prior myomectomy in 2 and breech presentations in 2.

Twenty-nine (61.7%) patients required antepartum admissions for various indications and the length of stay ranged from 1 to 17 days. Only 2 patients had post-delivery hospital longer than 3 days (four and eight days) and 3 required postpartum readmissions for retained products of conception and delayed postpartum haemorrhage. Only 1 woman in group 1 required admission to the ICU, and this eventually resulted in the maternal death of one woman in our cohort. The patient had prior history of breast cancer (treated with lumpectomy, chemotherapy and radiation); she subsequently developed radiation-associated metastatic angiosarcoma. Despite her poor prognosis, the patient opted to continue the pregnancy and receive palliative care as an inpatient. The patient was admitted to the intensive care unit at 21 weeks gestation with respiratory distress and paraplegia as a result of a large metastatic lesion in the left mediastinum, spine and multiple lesions in both lungs. She died at the 22nd week of her pregnancy as a result of respiratory failure due to metastases of mediastinum and lung.

In group 2, elective caesarean delivery was performed in 6 out of 22 women (4 were elective repeat procedures,

and one each for breech presentation and foetal well-being concerns respectively). Of the 16 vaginal births, one occurred following spontaneous onset of labour, while labour was induced in all others cases. Three patients had hospital admissions more than 3 days (2 were due to hypertension and 1 due to a wound hematoma requiring surgical evacuation). There was 1 postpartum readmission for blood pressure control.

With regard to foetal and neonatal outcomes, although there was a significant difference between groups 1 and 2 in the rates of preterm birth (8.7 vs. 63.6%, $p < 0.0001$), the mean gestational age at delivery between the 2 groups was similar (37.8 ± 4.4 vs. 36.3 ± 2.0 weeks, $p = 0.95$), as was the mean birth weight ($3,095.2 \pm 871.2$ vs. $2,727 \pm 663.4$, $p = 0.43$). This is because most deliveries in group 2 were in the late preterm period (34–37 weeks), to facilitate ongoing treatment. There were no other significant differences with regard to foetal and neonatal outcomes between groups. Adverse outcomes in group 1 included 1 spontaneous miscarriage, 5 cases (10.9%) of foetal growth restriction, 3 cases of Apgar scores <7 (6.5%) and 1 early neonatal death. The neonatal death was as a result of extreme prematurity in the case of a twin gestation with delivery at 23 weeks. The only adverse outcome in group 2 was 1 case of foetal growth restriction, which occurred in a pregnancy where the woman was treated with chemotherapy cycles after 21 weeks and she delivered at 37 weeks. The placental pa-

Table 3. Pregnancy outcomes

	Prior history of breast cancer (<i>n</i> = 47)	Current history of breast cancer (<i>n</i> = 22)	<i>p</i> value
<i>Maternal outcomes</i>			
Maternal death, <i>n</i> (%)	1 (2.1)	0 (0)	ns
Onset of labour (<i>n</i> = 46)*			
Spontaneous	15 (32.6)	2 (9.1) ^{\$}	0.045
Induced	15 (32.6)	11 (50.0)	
Elective caesarean section	8 (17.4)	6 (27.3)	0.5 (ns)
Unknown	9 (19.6)	3 (13.6)	
Mode of delivery (<i>n</i> = 46)*, <i>n</i> (%)			ns
Spontaneous vaginal delivery	19 (41.3)	13 (59.1)	
Instrumental vaginal delivery	3 (6.5)	1 (4.5)	
Caesarean section	17 (37)	6 (27.3)	
Unknown	8 (17.4)	2	
Hospital admissions, <i>n</i> (%)			
Antepartum	29 (61.7)	18 (81.8)	0.16 (ns)
Postpartum**	3 (6.5)	1 (4.5)	1 (ns)
Duration of admission in days, mean (SD); range	4.7 (3.9); 1–17	2.2 (2.2); 1–10	0.74 (ns)
Antepartum, mean ± SD; range	2±1.49; 0–8	2.1 (1.9); 1–7	0.58 (ns)
Intensive care unit admission, <i>n</i> (%)			ns
Antepartum	1 (2.1)	0 (0)	
Postpartum	0 (0)	0 (0)	
<i>Fetal/neonatal outcomes, n (%)</i>			
Gestational age at delivery in weeks, mean ± SD; range	37.8±4.4; 33+3 – 41+3	36.3±2.0; 25+6 – 40	0.95 (ns)
Miscarriage	1 (2.1)	0 (0)	ns
Fetal/neonatal death	1 early neonatal death	0 (0)	ns
Congenital anomalies	0 (0)	0 (0)	ns
Preterm birth, <i>n</i> (%)*	4 (8.7)	14 (63.64) ^{\$}	<0.0001
Fetal growth (<i>n</i> = 46)*			
Appropriate for gestational age	34 (73.9)	18 (81.82)	ns
Fetal growth restriction	5 (10.9)	1 (4.54)	
Unknown	7 (15.2)	3 (13.64)	
Average fetal weight in grams, mean (SD); range	3,095.2 (871.2); 560–4,480	2,727 (663.4); 750–3,965	0.43 (ns)
Apgar scores at five minutes (<i>n</i> = 46)*, <i>n</i> (%)			ns
>7	33 (71.7)	17 (77.3)	
<7	3 (6.5)	0	
Unknown	11 (23.9)	5 (22.7)	
NICU admission (<i>n</i> = 46)*, <i>n</i> (%)			ns
Not admitted	32 (69.6)	13 (59.1)	
Admitted	6 (13)	4 (18.2)	
Unknown	7 (15.2)	5 (22.7)	
<i>Placental/histopathology, n (%)</i>			
Normal/non-significant pathology	8/14 (57.1)	5/9 (55.6)	ns
Abnormal pathology	6/14 (42.9)	4/9 (44.4)	
Acute chorioamnionitis	3	1	
Impaired placental development	1	1	
Chronic inflammation	0	1	
Fetal vascular thrombosis	2	1	

* *n* = 46 excludes 1 miscarriage at 11 weeks, ** *n* = 46 excludes 1 maternal death.

^{\$} Significant difference between groups.

ns, not significant.

thology showed appropriate villous maturation; however, there was perivillous fibrinoid deposition and adjacent infarction; the placenta was small size for gestational age (less than 3rd %ile) and the umbilical cord showed normal coiling. No other cases of growth restriction occurred in patients receiving chemotherapy in our study. There were no congenital anomalies in either group.

Placental histopathology was performed in 14 cases in group 1 and 9 in group 2. In group 1, out of 14 (42.9%) 6 had abnormal placental histopathology results. This included 3 cases of acute chorioamnionitis: 1 case in a woman who had preterm premature rupture of membranes at 20 weeks and went on to deliver at 24 weeks; another who delivered twins at 23 weeks, and the third who underwent a caesarean birth at 40 weeks for failure to progress. In addition, there was 1 case of impaired placental development in a woman with a vaginal delivery of a healthy infant at 37 weeks and 2 cases of foetal vascular thrombosis in women who had uncomplicated vaginal deliveries at 39 weeks. In group 2, 44.4% of patients had abnormal placental histopathology. Acute chorioamnionitis was found in 1 patient who had preterm vaginal delivery at 34 weeks. One patient had a repeat caesarean section at 36 weeks and placenta pathology showed impaired placental development and chronic inflammation. One patient had preterm vaginal delivery at 34 weeks and placenta showed foetal vascular thrombosis. The remaining patient had a spontaneous vaginal delivery at 37 weeks and pathology showed impaired placental development.

Discussion

In this study, we collected maternal and neonatal data from patients who had current and prior history of breast cancer. Late preterm birth was a significant finding in both groups, but more common in patients who had chemotherapy, which may relate to the planned early induction of labour in order to start treatment after delivery. Previous studies report a mean gestational age at delivery of 36–37 weeks, indicating that a significant proportion of patients deliver (iatrogenically) preterm [6, 9].

The incidence of breast cancer during pregnancy is increasing, likely due to women in high-income countries having children at an increasingly older age, with the probability of developing breast cancer increasing with age [10, 11]. The majority of breast cancers in pregnant women are infiltrating ductal adenocarcinomas, as in

non-pregnant women and this finding is similar to our findings. However, GBCs are predominantly poorly differentiated and diagnosed at an advanced stage, particularly in those diagnosed while lactating [12–14]. Women with GBC were more likely to have an induction of labour but had similar rates of gestational diabetes, preeclampsia, instrumental deliveries, and placental abruption [15]. Our findings show that patients with breast cancer who had chemotherapy had higher rate of induction of labour and late preterm labour, but this neither increased the caesarean rates nor reduced the birth weights, average gestational at delivery or NICU admission rates. A study of 129 children born to mothers diagnosed with cancer during pregnancy (over half of whom had breast cancer) showed prenatal exposure to maternal cancer with or without treatment did not impair the cognitive, cardiac, or general development of children in early childhood. Prematurity was correlated with a worse cognitive outcome, but this effect was independent of cancer treatment [7].

In our study, data showed no adverse effect on maternal survival or indirect maternal deaths during in both groups as shown in previous studies [4, 16]. As mentioned, there was 1 maternal death in group 1, due to a secondary metastatic sarcoma. With regard to foetal and neonatal survival, chemotherapeutic agents are known to cross the placenta and may adversely affect embryogenesis by affecting cell division. Exposure to such agents after the first trimester of pregnancy has not been associated with increased risk of malformations [17], yet in contrast to other studies we did not observe an increase in low birth weight in exposed pregnancies [7], likely due to our low numbers. Typical regimens of chemotherapy administered to patients in our program include are FEC (5-fluorouracil, epirubicin, cyclophosphamide), docetaxel and ACT (Adriamycin, cyclophosphamide and paclitaxel) with Herceptin and tamoxifen reserved for postpartum therapy.

Given our small numbers, we cannot conclude that abnormal placenta pathology or foetal congenital anomalies are more apparent in patients who received chemotherapy in pregnancy.

Limitations of our study include its small size and retrospective nature as well as variation in treatment approaches for GBC. Furthermore, placenta pathology was not available in all cases of GBC.

The strength of our study is confirmation that these pregnancies complicated by GBC can continue in an uncomplicated fashion from both maternal and foetal point of view and that early induction of labour results in rates

of mean birth weight and mean gestational age to pregnancies in women with pregestational breast cancer. Given our small numbers we cannot infer the impact of early induction on rates of caesarean section in GBC patients. In our institution, caesarean rates run over 30% for our general population, in keeping with trends across North America.

Conclusion

In conclusion, our study suggests that pregnancy outcome in women with GBC is similar to those with a history of breast cancer prior to pregnancy. With multidisciplinary treatment, women with a prior or current history of breast cancer can anticipate good maternal and

foetal/neonatal outcomes. In contrast to larger similar studies, our study does show increased rates of preterm birth or small for gestational age, likely to due to low numbers. Prospective registries outlining pregnancy outcomes in women with breast cancer are needed to confirm these findings and aid in the counselling of these women.

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Disclosure statement

The authors have no conflict of interest to declare.

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