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Children Exposed to Treatments in Utero in Pregnant Patients with Breast Cancer: Experience from Two Large Egyptian Hospitals

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Background: Pregnancy-associated breast cancer (PABC) is one of the common malignancies during pregnancy. Limited data is present about the effect of anticancer therapy on children born to mothers exposed to in utero treatments.
Aim: To describe the outcome of pregnancy in a cohort of Egyptian patients treated for PABC.
Methods: We reviewed all breast cancer cases diagnosed during pregnancy at two large Egyptian institutions between January 2009 and December 2016. Thirty-eight patients with complete obstetric and fetal data were included.
Results: All patients received anthracycline-based chemotherapy in the 2nd and 3rd trimesters and 9 of them received paclitaxel. The mean gestational age at delivery was 35.7 ± 3.4 weeks. The mean birth weight was 2736 ± 768 grams. Congenital anomaly (cleft lip and tongue tie) was reported in only one (4%) child. Perinatal death occurred in one (4%) baby due to prematurity. One (4%) child was exposed to trastuzumab in utero in the 1st trimester and he was completely healthy. Two (8%) other children were exposed to tamoxifen with no complications either neonatal or postnatal.
Conclusion: Chemotherapy during pregnancy may be used with minimal maternal and fetal complications. Multidisciplinary approach is crucial for better management. Continued long-term follow-up of the children in this cohort is required.

Keywords: Chemotherapy, Neonatal outcome, Pregnancy associated breast cancer
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INTRODUCTION

Pregnancy-associated breast cancer (PABC) is defined as breast cancer occurring during pregnancy or in the 1st year postpartum. It is the commonest form of invasive cancer in pregnant women [1-4]. It makes up about 7% of all breast cancers in women < 45 years of age in western nations with the incidence expected to rise due to women's delay in childbearing [5, 6].

PABC has a clinic-biological picture characterized by presenting commonly at a younger age in an advanced-stage with aggressive biology associated with higher tumor grades, less expression of estrogen and progesterone receptors and more expression of Her2 receptor. These may be associated with poor prognosis as reported in multiple large retrospective studies [2, 7]. However, some studies didn't find worse prognosis after adjustment for age and tumor characteristics [5, 8, 9].

The optimal management of PABC is not established well; careful diagnosis, staging, and therapeutic interventions within a multidisciplinary approach is needed for the proper balance of benefits and hazards for the mother and her fetus.

Chemotherapy is often required in most cases presenting with advanced-stage and/or aggressive biology. There is growing evidence that the administration of chemotherapy during pregnancy is probably safe. Data from long-term follow-up (up to 19 years) indicates only minimal deleterious effects on the fetus except for prematurity [10]. However, chemotherapy administration during the 1st trimester must be avoided due to the high risk of teratogenicity that may occur during this period of organogenesis (5–12 weeks) [11]. Furthermore, the possibility of spontaneous abortion or fetal malformations ranges from 10–20% with chemotherapy administrated during that period [12-14]. Current standard chemotherapeutic agents that can be used in the adjuvant or neoadjuvant settings include an anthracycline, which is considered safer than alkylating agents such as cyclophosphamide [15]. The teratogenicity of fluorouracil remains unclear [16]. About taxanes, data is accumulating regarding its safety for use during pregnancy [17].

Trastuzumab is considered a standard-of-care in the treatment of HER2-positive breast cancer, either in the adjuvant or advanced-disease setting, as it reduces the risk of relapse and improves overall survival [18-22]. The administration of trastuzumab in pregnant patients is reported to be associated with a high incidence of oligo- and/or anhydramnios as well as renal failure associated with poor neonatal outcome. That is why it is not recommended during pregnancy [23].

Hormonal treatments, like tamoxifen, should be postponed until delivery as they are associated with documented teratogenic effects [24].

Data confirming the safety of chemotherapy administration during pregnancy with no major maternal or fetal complications is accumulating. However, data of long-term outcomes of children exposed in utero to chemotherapy is still limited [25].

The objective of this study was to describe the pregnancy outcome in a cohort of Egyptian patients who had been treated for breast cancer with systemic anti-cancer therapy during pregnancy.

METHODS

Between January 2009 and December 2016, 57 patients presented with PABC in the two Egyptian cancer centers participating in this study, the Kasr Al-Ainy Centre of Clinical Oncology and Nuclear Medicine (NEMROCK), Cairo University in Cairo and Aswan Cancer Center in Aswan. Data about the pregnancy and neonatal outcomes were obtained from the Department of Obstetrics and Gynecology and the Pediatric Neonatology Unit. The study was approved by the ethical committees of the two institutes. The following information was obtained from medical records: age of the patient at diagnosis, gestational age at diagnosis during which the patient received chemotherapy and any complications that occurred during pregnancy together with neonatal data as birth weight and any neonatal malformations.

Once the patient was diagnosed with breast cancer, consultation with the obstetrician within the multidisciplinary team was performed for careful assessment of the fetal health. The patient was informed about the potential side effects of chemotherapy on the fetus. Also, the limited data on long-term hazards to the infant was discussed carefully with the patient.

For operable disease, surgical consultation was obtained within the multidisciplinary team. Chemotherapy during pregnancy consisted of standard FAC (cyclophosphamide 500 mg/m^2, adriamycin 50 mg/m^2 and 5-fluorouracil 500 mg/m^2 on day 1; repeated every 21 days), AC (adriamycin 60 mg/m^2 and cyclophosphamide 500 mg/m^2 on day 1; repeated every 21 days) or AC sequentially with paclitaxel (80 mg/m^2).

The descriptive statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 10.0 software program for Windows (SPSS, Chicago, IL).

RESULTS

The analysis included 38 PABC patients with adequate data in the oncology and obstetric departments. Thirty-eight children were born after exposure to varying numbers and types of anticancer treatments in utero.

Details of systemic anti-cancer treatment are illustrated in table 1. All of our cohort of children were exposed to anthracycline-based chemotherapy with 76.3% (n= 29) had exposure to at least four cycles. FAC regimen was the most commonly administered chemotherapy in pregnant patients (n=21, 55.3%). The remaining 17 patients were treated with AC regimen. Of the planned AC/paclitaxel treatment, more than 4 weeks of paclitaxel therapy was completed in 9 patients. Chemotherapy was given during the 2nd trimester in 20 (52.6%) patients and the 3rd trimester in 18 (47.4%).

Delivery data and neonatal complications are shown in table 2. Mean gestational age for babies after exposure to chemotherapy at delivery was 35.7 ± 3.4 weeks. Nine (23.7%) of the patients had a premature delivery. Eighteen patients delivered by normal vaginal delivery and 16 patients by cesarean section. Four patients had no data about the mode of delivery. Data on the birth weight was available for 27 babies. The mean birth weight was 2736 ± 768 grams. Neonatal birth weight was <10% for gestational age in 9 cases (9/27, 33.33%). It was noted that 77.7% of babies born with birth weight small for gestational age, occurred in mothers who received paclitaxel. Perinatal death occurred in one baby born prematurely.

Of the 38 babies born, data on the complications that occurred during and/or after delivery was present in 25 babies. The commonest complication that occurred in the neonatal period was neonatal jaundice (5 babies). Of the entire cohort, one child had a congenital anomaly in the form of a cleft lip and tongue tie. Another baby was born with undescended testis.

In our cohort of children, two were exposed to tamoxifen in utero. In the 1st case, the mother became pregnant while on a 4-year adjuvant tamoxifen therapy. The patient delivered a healthy baby who is now 5 years old and has no congenital abnormalities or developmental problems. The 2nd child was exposed

Table 1: Systemic anti-cancer treatment in 38 patients with pregnancy-associate breast cancer

Systemic anti-cancer treatment		**n (%)**
Chemotherapy		
Gestational age at time of chemotherapy	2nd trimester	20 (52.6)
	3rd trimester	18 (47.4)
Chemotherapy regimen	FAC (5-fluorouracil, doxorubicin, and cyclophosphamide)	21 (55.3)
	AC (Adriamycin and cyclophosphamide)	8 (21)
	AC + paclitaxel	9 (23.7)
Number of cycles	>4 cycles of anthracycline based chemotherapy	29 (76.3)
	≤3 cycles of anthracycline based chemotherapy	9 (23.7)
Hormonal therapy (tamoxifen)		
Gestational age at time of tamoxifen	1st trimester	2 (5.2)
Anti-her2 neu receptors (trastuzumab)		
Gestational age at time of trastuzumab	1st trimester	1 (2.6)

Table 2: Neonatal outcome of children exposed in utero to systemic anti-cancer treatment for breast cancer

	All	FAC / AC	AC + paclitaxel
	n (%)	n (%)	n (%)
Gestational age at delivery (n= 38)			
Preterm (<37weeks)	9 (23.7)	4 (44.4)	5 (55.6)
Term (≥37weeks)	29 (76.4)	25 (86.2)	4 (13.8)
Mode of delivery (n=34)			
Normal Vaginal delivery	18 (52.9)	14 (77.7)	4 (22.3)
Caesarean section	16 (47.1)	11 (68.7)	5 (31.3)
Birth weight for gestational age (n=27)			
Appropriate	18 (66.66)	16 (88.9)	2 (11.1)
Small for gestational age (<10th percentile)	9 (33.33)	2 (22.3)	7 (77.7)
Fetal complications (n=25)			
Jaundice	5 (20)	2 (40)	3 (60)
Neonatal ICU hospitalization (n=15)	1 (6.7)	1 (100)	0
Congenital anomaly	1 (4)	1 (100)	0
Undescended testis	1 (4)	1 (100)	0
Intrauterine fetal demise	0	0	0
Neonatal death	1 (4)	1 (100)	0

FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide; **AC**: Adriamycin and cyclophosphamide

to 2 months of tamoxifen and he is in complete health.

Another child was born to a mother exposed to trastuzumab in utero. The patient received 4 cycles of trastuzumab. Despite having an intrauterine device, she became pregnant without knowing and completed 4 cycles of trastuzumab before the discovery of her pregnancy. The child born was completely normal and healthy. He is now 3 years old.

DISCUSSION

In this multi-institutional, retrospective study involving 38 children exposed to in utero anticancer treatments, we documented the possible safety of chemotherapy administration including anthracyclines and taxane during pregnancy without significant adverse fetal or postnatal outcomes.

The main neonatal problem observed in our study was low birth weight, the incidence of which was 33.3%. This percent is higher than that in the general population of the United States which is 12.2% [26].

One (4%) of the children in our series was born with a congenital anomaly (cleft palate). The rate of congenital abnormalities in our cohort is little bit higher than the United States average rate of approximately 3% [27]. Exposure to cytotoxic drugs during the 1st 12 weeks of pregnancy may result in spontaneous abortions and increase the risk of birth defects [11]. On the other hand, the safe use of certain chemotherapeutics in the 2nd and 3rd trimesters is confirmed in multiple studies [28-30].

Our data is comparable to a prospective clinical trial by Hahn et al, who reported the short-term safety of FAC chemotherapy given during the 2nd and/or 3rd trimesters in PABC [31]. Follow-up with the same children (median age of 7 years) was reported by Murthy et al. They found that the majority of the children were healthy with no significant complications observed related to chemotherapy exposure. Congenital abnormalities were reported in 3 cases in that study [32].

In another study conducted by Amant et al, prenatal exposure to chemotherapy was not associated with increased complications. They did not find an association between prenatal exposure to chemotherapy and central nervous system, cardiac or auditory toxicities [10].

Anthracyclines based chemotherapy regimens (AC or FAC) are the most commonly used chemotherapy regimens in PABC [33]. As for taxanes, despite their integral role in the treatment of breast cancer, limited data is present on their use during pregnancy [34]. In our series, about 23% of PABC patients who received AC also received one or more cycles of weekly paclitaxel with no observed undesirable effects. We observed higher incidence (77.7%) of low birth weight babies born to mothers received weekly paclitaxel compared to FAC chemotherapy.

Trastuzumab administration is contraindicated for PABC as it may result in serious complications as oligohydramnios and renal failure. However, some reported that in utero exposure to trastuzumab during the 1st trimester was followed by the delivery of healthy babies without congenital malformations [35]. Fortunately, adjuvant regimens containing trastuzumab for the treatment of her2 positive disease start with anthracyclines based chemotherapy, so give the time for a pregnant patient to give birth before starting trastuzumab. The start of treatment can be delayed until completion of pregnancy without adversely affecting the survival outcomes [36]. In our series, one child was exposed during 1st trimester to 4 cycles of trastuzumab without neonatal or postnatal adverse effects.

The use of tamoxifen is known to be teratogenic. Some case reports indicated healthy babies born after exposure to tamoxifen [24, 37]. In contrast, a study by Braems et al, reported a higher incidence of congenital malformations after in utero exposure to tamoxifen as reported by the AstraZeneca Safety Database. Eleven babies were born with congenital malformations out of 44 live births, which means that every four live births, one infant was born with malformations [38]. We report 2 children born to patients who became pregnant while taking tamoxifen therapy. The 1st child is now 4 years old and completely healthy with no abnormalities. The

2nd baby is now 4 months and he is a normal healthy baby.

This study was limited by its small sample size and short follow-up period. More prolonged follow up is needed to determine the effect of extensive in utero chemotherapy exposure on health outcomes of the children.

In conclusion, anthracycline-based chemotherapy ± paclitaxel may be used for PABC without major maternal or fetal complications. Follow-up of these children is needed to assess any future problems especially when they become adults.

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This study was a continuation of Abdelrahman et al [25] report on the initial outcome of children born after exposure to in utero chemotherapy.

Conflict of interest

The authors have no conflict of interest to declare.

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