CASE REPORT

Transient ventricular hypocinesia after in utero anthracyclines exposure: a case-report and review of the literature

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Abstract
Due to the low occurrence of cancer during pregnancy, limited data are available about outcome of infants exposed to chemotherapy in utero. We report the case of a newborn who developed transient ventricular hypocinesia and late-onset infection after in utero exposure to four epirubicin cycles for pregnancy-associated breast cancer. Moreover, we provide an overview of literature on neonatal outcome after anthracyclines-based chemotherapy regimen during pregnancy. Existing data support use of anthracyclines, as few cases of fetal cardiac toxicity were reported and most of short-term complications were transient. Need for prospective collection of data and longer follow-up is highly recognized.

Keywords: Chemotherapy, anthracyclines, pregnancy, cardiac toxicity, newborn

Background
Due to the low occurrence of cancer during pregnancy, limited data are available in literature about outcome of infants exposed to chemotherapy in utero.

Chemotherapy should be avoided during early pregnancy, as it may increase the risk of spontaneous abortion and congenital abnormalities: exposure to teratogenic agents is critical in the second and third gestational months because organogenesis takes place. Ebert et al. [1] reported 18 newborns with multiple anomalies of different severities and 15 spontaneous abortions among 217 women treated with cytotoxic drugs for malignant and rheumatologic diseases during pregnancy. These data were confirmed by Doll et al. [2] (14–19% of malformations after first versus 1.3% after second and third trimester) and Cardonick and Iacobucci trimester exposure [3] (11 malformations among 376 fetuses, 9 of which exposed during organogenesis).

Even though chemotherapy administration may be safer during the second and third trimesters, intrauterine growth restriction, low birth-weight, preterm delivery, transient infant leucopenia, and other neonatal complications have been described in individual case series.

We report the case of a neonate who developed a transient ventricular hypocinesia and a late-onset infection after exposition to chemotherapy in utero for maternal pregnancy associated breast cancer (PABC). PABC describes the diagnosis of breast cancer during pregnancy or lactation up to 1 year after delivery; the incidence is 0.2% up to 3.8%. Available data on adjuvant therapies for PABC are poor and derived from retrospective studies with few patients and small control groups.

Administration of anthracycline-based chemotherapy regimen in PABC, particularly doxorubicin and epirubicin, is seemingly not detrimental to pregnancy outcome. However, there is still some concern about the fetal safety of this approach, because anthracyclines have a cumulative cardiac toxicity [4], cross the placenta and the long-term effects on the developing fetal heart are not known.

In preparation for this manuscript, search for the published English language literature about the outcome of newborns exposed to anthracyclines in utero was performed via the MEDLINE database and was supplemented with additional cross-references through bibliographies. Available papers are summarized in Table I. [5-20]

Case report
A Tunisian woman, 31-year-old, presented asking medical advice because of a new lump in the breast and mastalgia since a couple of months, following the end of breastfeeding of the first child. At the time of presentation, she was pregnant at 14 weeks of her second pregnancy.

The clinical finding was confirmed by the ultrasound examination: an irregular hypoechogen structure of 2 cm of diameter in the right breast, near the nipple was detected. In the omolateral axilla, some enlarged lymph nodes with a thick cortical were also detected. The fine needle aspiration biopsies performed on the breast lump and the axillary nodes were both positive for breast cancer cells.
Table I. Literature data about the outcome of newborns exposed to anthracyclines in utero.

<table>
<thead>
<tr>
<th>Author, journal, year</th>
<th>Maternal malignancy</th>
<th>Chemotherapeutic treatment</th>
<th>Exposed fetuses, number</th>
<th>Cardiac toxicity</th>
<th>Bone marrow depletion</th>
<th>Other complications in the fetus/newborn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldwasser, Leuk Lymphoma, 1995</td>
<td>NHL</td>
<td>Epirubicin</td>
<td>1</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Giacalone, Cancer, 1999</td>
<td>Breast cancer</td>
<td>Different regimens: Epirubicin n = 10, Doxorubicin n = 4</td>
<td>20</td>
<td>Not reported</td>
<td>1 anemia, 1 neutropenia</td>
<td>1 stillbirth, 1 IUGR, 2 RDS, 1 neonatal death</td>
</tr>
<tr>
<td>Achtari, Am J Obstet Gynecol, 2000</td>
<td>ALL</td>
<td>Idarubicin</td>
<td>1</td>
<td>Acute cardiac failure (II trimester)</td>
<td>Not reported</td>
<td>Prematurity</td>
</tr>
<tr>
<td>Meyer-Wittkopf, Ultrasound Obstet Gynecol, 2001</td>
<td>Breast cancer</td>
<td>Doxorubicin</td>
<td>1</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Aviles, Clin Lymphoma, 2001; Ann Oncol, 2006</td>
<td>Hematologic malignancies</td>
<td>Different regimens: Anthracyclines</td>
<td>84</td>
<td>None. Not late toxicity, too</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Siu, Int J Gynecol Cancer, 2002</td>
<td>AML (M3)</td>
<td>Idarubicin all-trans-retinoic acid (ATRA)</td>
<td>1</td>
<td>Transient dilated cardiomyopathy (II trimester)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Gadducci, Anticancer Res, 2003</td>
<td>Breast cancer</td>
<td>Epirubicin</td>
<td>1</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Germann, Ann Oncol, 2004</td>
<td>Leukemia and solid tumors (breast cancer 21%)</td>
<td>Doxorubicin n = 99; Daunorubicin n = 55</td>
<td>160</td>
<td>2 (2%) in II trimester, 1 (3%) in III trimester</td>
<td>1 (4%) in I trimester, 3 (3%) in II trimester, 3 (10%) in III trimester</td>
<td>Malformations (3%), fetal death (9%), spontaneous abortion (3%), prematurity (6%)</td>
</tr>
<tr>
<td>Peccatori, Lancet Oncol, 2004</td>
<td>Breast cancer</td>
<td>Doxorubicin n = 2, Epirubicin n = 9</td>
<td>11</td>
<td>Not reported</td>
<td>Not reported</td>
<td>1 congenital vesicoureteral reflux</td>
</tr>
<tr>
<td>Andreadis, Gynecol Oncol, 2004</td>
<td>Breast cancer</td>
<td>Epirubicin</td>
<td>1</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ginopoulos, Eur J Gynaecol Oncol, 2004</td>
<td>Breast cancer</td>
<td>Epirubicin</td>
<td>1</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ring, JCO, 2005</td>
<td>Breast cancer</td>
<td>Different regimens: Doxorubicin n = 11, Epirubicin n = 5</td>
<td>28</td>
<td>Not reported</td>
<td>Not reported</td>
<td>1 spontaneous abortion</td>
</tr>
<tr>
<td>Van Calsteren Ganame, JCO, 2006</td>
<td>Leukemia and solid tumors (breast cancer 44%)</td>
<td>Different regimens: Anthracyclines n = 7</td>
<td>10</td>
<td>Reduced wall thickness and left ventricular mass index in all newborn exposed to anthracyclines</td>
<td>Not reported</td>
<td>Neurologic impairment (33%)</td>
</tr>
<tr>
<td>Hahn, Cancer, 2006</td>
<td>Breast cancer</td>
<td>Different regimens: Doxorubicin n = 57</td>
<td>57</td>
<td>Not reported</td>
<td>1 neutropenia and thrombocytopenia</td>
<td>1 Down syndrome, 1 club foot, 1 congenital bilateral ureteral reflux, 1 ADHD, 1 subarachnoid hemorrhage 1 polycystic kidney</td>
</tr>
<tr>
<td>Azim, Ann Oncol, 2008</td>
<td>Breast cancer</td>
<td>Doxorubicin n = 3, Epirubicin n = 23</td>
<td>26</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
Breast-conserving surgery with axillary dissection was performed at 18 weeks of gestational age. The final diagnosis was ductal breast carcinoma of 25 mm (pT2), poorly differentiated (G3) with evidence of lymph vascular and perineural invasion. The surgical margins were minimally involved by cancer; one on 21 axillary lymph nodes showed metastasis of breast cancer (pN1a). The tumor was hormonal positive, with expression of estrogen and progesterone receptors, without an overexpression of erbB2 and with a Ki-67 of 36%.

The administration of anthracycline-based regimen of chemotherapy was started at a gestational age of 25 weeks: the patient received 4 cycles of epirubicin as intravenous infusions on a 21 days outpatient basis, after the assessment of bone marrow, liver, renal functions, and echocardiogram. According to published data [21], the pregnant woman was exposed to similar weight-based doses than non-pregnant women and the doses were adjusted to weight gain. The dose of the fourth and last infusion was decreased for tachycardia.

Fetal well-being was strictly monitored with periodical ultrasound and fetal heart monitoring.

Elective cesarean delivery was planned 3 weeks after the last cycle of chemotherapy in order to avoid maternal and fetal myelosuppression.

The male newborn infant was delivered after 36+6 weeks of gestation. The neonate's weight, length, and cranial circumference at birth were 3080 g, 48 cm, and 34.5 cm (AGA adequate for gestational age), respectively. APGARs were 7 at 1 min and 9 at 5 min.

At first neonatal examination congenital malformations or clinical abnormalities were not detected.

Maternal lactation was suppressed after cesarean delivery because most cytosstatics are released into the milk.

In order to investigate further possible effects of chemotherapy exposure on neonatal outcome, a panel of hematologic and instrumental investigations were performed. No abnormalities were identified at full blood count (hemoglobin, Hb: 21.5 g/dl; white blood cell count, WBC: 11.64 × 10^9/l; neutrophil count: 5.67 × 10^9/l; platelets, PLTs: 269 × 10^9/l); kidney and liver functions were normal. Brain and abdominal ultrasound scan did not show any abnormal finding. Ocular evaluation was silent and screening for hearing impairment with otoemissions resulted negative.

The transthoracic echocardiography performed at fourth day of life showed diffuse hypocinesia of both ventricular cavities with an adequate valvular flussimetria. Electrocardiography (ECG) and blood arterial pressure resulted normal.

As no clinical problems arouse during hospitalization, the baby was discharged at seventh day of life in good clinical conditions and with satisfactory weight gain. An echocardiographic follow-up was arranged 2 weeks later.

The day before the planned control, the baby presented with fever; peripheral blood tests showed WBC 16,640 × 10^9/l, neutrophil count 6.22 × 10^9/l, Hb 14.9 g/dl, PLTs 377 × 10^9/l; C reactive protein (CRP) was increased (0.03 g/l; nv <0.005).

The newborn was readmitted to Neonatal Intensive Care Unit and underwent parenteral antibiotic administration (ampicillin + sulbactam). Colutural analysis on nasal and pharynx specimens resulted positive for saprophic agents (Klebsiella oxytoca, Actinetobacter baumanii, and Staphylococcus aureus). After 5 days of antibiotic therapy, the newborn was discharged with no more fever and in good clinical conditions; C reactive protein concentration remained normal.

Echocardiography performed at 1 month showed a complete reversal of the hypocinesia of both ventricular cavities with evidence of normal function. A further cardiological follow-up was planned at 6 months of life.

Following delivery, the mother continued chemotherapy for a total of four cycles of taxotere, after a cardiological checkup showing a normal heart function. After the end of chemotherapy, the patient underwent mastectomy and plastic reconstruction, as surgical margins of the previous lumpectomy were suboptimal. Endocrine therapy with tamoxifen and GnRH analogues planned for 5 years and for 2 years, respectively, was subsequently started.

Discussion

We report the case of a neonate who developed a transient ventricular hypocinesia and a late-onset infection after in utero exposure to epirubicin for PABC.

Whether the occurrence of late-onset infection was related to cytotoxic drugs remains unclear. Some cases of newborn with bone marrow depletion after treatment with cytotoxic agents during pregnancy are reported in literature (Table I).

The neutrophil count of our patient remained consistent with reference ranges both in the third day of life and at onset of infection (5.670 × 10^9/l and 6.220 × 10^9/l, respectively). Although the WBC was normal, we cannot rule out the previous exposure to chemotherapy might have compromised the neutrophil function and stressed the immaturity of bactericidal mechanisms typical of the neonatal age.

Cardiotoxicity is a recognized complication of chemotherapy with anthracycline-based regimen. Data about outcome of neonates exposed to anthracyclines are very limited; moreover, these data are very difficult to compare due to different combination and dosage of agents and concurrent radiation therapy, in relation to different type of maternal malignancies and different timing of diagnosis.

In the literature selected as described before, few cases of cardiotoxicity have been detected. Achtari [7] reported one case of acute cardiac failure in a newborn exposed to idarubicin during the second trimester. Similary, Siu et al. [11] described one newborn who developed transient dilatative cardiomyopathy after maternal administration of idarubicin in the same period of pregnancy. Germann et al. [13] reported the outcome of 160 patients treated with anthracyclines during pregnancy: only three cases (two after exposure in the second trimester, one in the third) of cardiac toxicity were described.

Van Calsteren et al. [18] reported a trend towards a reduction in left ventricular wall thickness and mass index in children exposed to anthracyclines. However, the authors did not observe congenital heart defects or functional disorders.

Overall, considering all the cases reported in literature and including our report, only 13 patients with cardiac toxicity among 403 fetuses exposed to cytotoxic drugs in utero were described and in the majority of them the cardiac toxicity was transient.

On the whole, these data seem to support the use of anthracyclines during pregnancy, as no significant cardiac short-term complications have been detected for the majority of children exposed.

Nevertheless, current knowledge about long-term effects of in utero exposure to chemotherapy is still poor. Aviles and Neri [10] reported a long-term follow-up of 81 children with actual age of 9.3–29.5 years (mean 17.1), whose mothers were treated during pregnancy with cytotoxic drugs, including anthracyclines. In order to detect cardiac toxicity, all patients
underwent clinical evaluation and echocardiogram every 5 years after birth until 29 years of age; no clinical or echocardiogram features of cardiac dysfunction were detected during the entire follow up.

However, it has been speculated that prenatal exposure to anthracyclines may lead to alterations at the cellular level of the fetal heart, including myocyte cytoplasmatic changes and abnormal architecture of supportive tissue, not detectable with current non-invasive means; indeed, fetuses exposed to anthracycline early during their life might become a new group of patients at risk for premature cardiovascular disease during the adult age.

In order to improve the ability to care for this specific group of children, the need for prospective collection of data and follow-up studies of sufficient length is highly recognized. Due to the low incidence of cancer during pregnancy, the institution of national and international registers is the only option to help the scientific community to collect essential information.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

References