Maternal and fetal outcomes of taxane chemotherapy in breast and ovarian cancer during pregnancy: case series and review of the literature

E. Cardonick¹*, A. Bhat², D. Gilmandyar³ & R. Somer²

¹Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Cooper Medical School at Rowan University, Camden; ²Division of Hematology and Medical Oncology, Department of Medicine, Cooper Medical School at Rowan University, Camden; ³Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, University of Rochester Medical Center, Rochester, USA

Received 15 March 2012; revised 20 April 2012; accepted 24 April 2012

Background: The purpose of this study was to evaluate the use of taxane chemotherapy during pregnancy and compare maternal and neonatal outcomes with those in women who did not receive taxanes during pregnancy, and review current existing data.

Study design: This is a retrospective cohort study in which women were identified from the Cancer and Pregnancy Registry at Robert Wood Johnson Medical Center. A retrospective chart analysis and an independent t-test were carried out comparing patient outcomes. A literature search in Ovid, Medline and PubMed was then carried out using the terms ‘breast or ovarian cancer’, ‘pregnancy’, ‘paclitaxel’, ‘docetaxel’, ‘taxanes’ and ‘chemotherapy’.

Results: Twelve of 129 women with breast cancer were exposed to taxanes during pregnancy. Three of nine women with ovarian cancer received taxane-based treatment during pregnancy. Birth weight, gestational age at delivery, rate of growth restriction, congenital anomalies and incidence of maternal and neonatal neutropenia were not statistically different between the two groups.

Conclusions: Taxane-based chemotherapy does not appear to increase the risk of fetal or maternal complications when compared with conventional chemotherapy in the small cohort of women in our Registry.

Key words: cancer, docetaxel, neonatal outcomes, paclitaxel, pregnancy, taxanes

*Correspondence to: E. Cardonick, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Cooper Medical School, One Cooper Plaza, Dorrance 623, Camden, NJ 08103, USA. Tel: +1-856-342-2491; Fax: +1-856-342-7023; E-mail: cardonick-elyce@cooperhealth.edu

© The Author 2012. Published by Oxford University Press on behalf of the European Society for Medical Oncology. All rights reserved. For permissions, please email journals.permissions@oup.com.
introduction

Approximately 1 in 2000 pregnancies are complicated by cancer [1]. In a recent population-based cohort study, matching patients from the Cancer Registry and Medical Birth Registry of Norway, breast cancer appeared to place the most risk in the age group studied [1]. Given the recent trend for women to delay childbearing, we expect more cases of breast cancer to be diagnosed during pregnancy. The lack of large randomized trials and cohort studies makes it difficult for clinicians to know how best to treat pregnant women with cancer.

Loibl et al. [2] in 2006 published recommendations on the treatment of breast cancer during pregnancy. Regarding the use of taxanes, the authors suggested, ‘Because of the lack of evidence, the expert opinion was not to recommend the routine use of newer cytotoxic drugs like the taxanes during pregnancy.’ Amant et al. [3] at an international consensus meeting concerning breast cancer concluded that ‘since the safety of taxanes is less documented when compared to anthracyclines, an additional cycle of anthracycline-based chemotherapy during pregnancy and completion of taxane-based chemotherapy after delivery can be considered.’ Authors from an additional international consensus meeting decided that in cervical and ovarian cancer, chemotherapy and an alternative surgical approach need to be considered. Administration of chemotherapy for gynecologic cancers during the second or third trimester does not increase the incidence of congenital malformations [4].

The medical literature on chemotherapy during pregnancy contains few prospective trials on the treatment of pregnant women with cancer and the effects if any of chemotherapy on their offspring [5–8]. The majority of the literature are case reports and small retrospective series which have been reviewed and summarized in the Lancet Oncology in 2000 (343 exposures) and later expanded to 447 cases in 2008 [9, 10]. The combination regimen of doxorubicin and cyclophosphamide, with or without 5-FU (with taxanes delayed until postpartum), has been the most common approach to treating breast cancer during the second and third trimesters with a relatively safe toxicity profile for the mother and fetus [5, 11–17]. The taxane class of chemotherapy recently emerged for therapy in the neoadjuvant, adjuvant and metastatic settings. In a recent meta-analysis, the addition of taxanes to an anthracycline-based regimen resulted in a statistically significant reduction in the risk of relapse (17% relative reduction) and death (15% relative reduction) for high-risk early breast cancer patients. This disease-free survival (DFS) benefit was shown to be independent of ER expression, degree of nodal involvement and type of taxane [18]. Earlier studies have shown the benefit of paclitaxel and docetaxel mostly in operable node-positive disease [19]. More recently, Sparano et al. [20] and Jones et al. [21] have shown that taxanes improve both DFS and overall survival in node-negative breast cancer patients. Taxanes are widely used as standard first-line treatment of high-risk early-stage and advanced/metastatic breast cancer in non-pregnant women, resulting in a better response rate and longer time to progression than standard anthracycline-based regimens [18–21]. There is little data regarding the safety of taxane use for breast cancer during pregnancy. For patients who complete anthracycline-based therapy for breast cancer before 28-week gestation, knowledge of the safety of taxane exposure for the fetus could allow them to conform to the same standard of care as a non-pregnant woman with breast cancer and not delay this treatment until the postpartum period.

Platinum-based therapy in combination with a taxane is the standard of care for non-pregnant patients with ovarian cancer [4, 22]. Case reports using platinum-based chemotherapy for ovarian cancer during pregnancy have suggested relatively good maternal and fetal outcomes [23–30]. We report a cohort of 15 women: 12 diagnosed with breast cancer prospectively followed after enrolling in the Pregnancy Registry before the knowledge of their pregnancy outcome. Three women diagnosed with ovarian cancer are also reported, two of whom reported their exposure to the Registry after delivery. All were exposed to taxane-based therapy before delivery. To our knowledge, this is the largest cohort of pregnant patients treated with taxanes from a single database describing maternal and fetal outcomes.

patients and methods

The Cancer and Pregnancy Registry is a voluntary registry created in 1995 to collect cases of pregnant women at various institutions diagnosed with cancer (primary or recurrent) during pregnancy. To decrease the bias of a prior knowledge of pregnancy outcome, enrollment was encouraged at the time of cancer diagnosis, not delivery. Inclusion criteria were defined as a cancer diagnosis between the first day of a last menstrual period and the end of pregnancy by loss, elective termination or delivery. Patients provided written permission to have medical records requested from their oncologist, obstetrician and pediatrician. IRB approval was obtained from Robert Wood Johnson Medical School. Information collected from oncology records was reviewed to obtain details about cancer diagnosis and treatment. When it pertained to breast cancer, tumor characteristics such as size, stage including lymph node status, hormone receptor status and HER-2 protein expression were collected. Chemotherapy regimen, interval and doses, incidence of neutropenia, maternal survival and incidence of postpartum recurrences were also collected. Obstetrical and pediatric records were reviewed to document neonatal birth weight and gestational age at delivery, incidence of intrauterine growth restriction (IUGR) and congenital anomalies and complete blood counts with differential at birth. Only malformations meeting the CDC Metropolitan Atlanta Congenital Defects Program criteria were included [31]. The mode of delivery and the rates of spontaneous preterm delivery in each group were also analyzed. IUGR was defined as a birth weight <10% for gestational age norms. Pediatricians were requested to provide documentation of birth weight, birth defect/complication information and yearly medical follow-up. Maternal, perinatal and neonatal outcomes were reported and neonatal and maternal follow-up was sought yearly. The timing, doses and regimens of chemotherapy were decided by each patient’s oncologist. The database was searched for all cases of taxane use in pregnancy. Neonatal outcome was collected. Comparisons of birth weight and gestational age at delivery, congenital anomalies, incidence of birth or long-term
medical complications for the neonate were compared between the patients treated with chemotherapy for breast or ovarian cancer with or without taxanes.

**results**

The Registry includes 160 women diagnosed with breast cancer during pregnancy: 147 with primary disease, 11 with recurrence and 2 who had been previously diagnosed in the past and confirmed to have a new contralateral primary cancer. Of these, 129 were offered chemotherapy during pregnancy. Twelve of these (all primary disease) received either paclitaxel or docetaxel during pregnancy after completing anthracycline-based therapy. All women had contacted the Registry before knowing the outcome of their pregnancy and were prospectively followed during treatment, delivery and yearly postpartum. Details of maternal age and gestational ages at diagnosis and tumor characteristics of the patients with breast cancer are detailed in Tables 1 and 2, respectively.

Seven women underwent surgery during pregnancy, five in the first trimester and two in the second trimester. Lymph node status was positive in six patients (50%). Six women received chemotherapy in the neo-adjuvant setting and six in the adjuvant setting. There was no radiation therapy given during pregnancy. Chemotherapy was initiated after 12 completed weeks of pregnancy in all patients. Six patients received paclitaxel, following either adriamycin and cyclophosphamide (AC) \((n = 5)\) or 5-fluorouracil, adriamycin and cyclophosphamide (FAC) \((n = 1)\). Four patients received docetaxel following AC \((n = 2)\), epirubicin and cyclophosphamide \((n = 1)\) or epirubicin alone \((n = 1)\). After AC chemotherapy, two patients first received paclitaxel and then docetaxel due to side-effects of tachycardia and hot flashes with paclitaxel. Taxane treatment was started at a mean gestational age of 23.8 ± 2.8 weeks. Only one patient received taxane therapy weekly; intervals in other patients varied from 2–3 weeks. The use of growth factor support with granulocyte colony stimulating factor \((GCSF)\) was reported in three patients, administered at 15 weeks of gestation. Maternal side-effects during taxane therapy included complaints of mucositis, dyspnea, tachycardia, vasomotor symptoms and an allergic reaction.

Two patients complained of uterine irritability and mild contractions after taxane therapy. No other maternal toxic effects were documented (Table 3).

Fourteen women were diagnosed with ovarian cancer (13 primary, 1 recurrent) during pregnancy. See Table 1 for maternal and gestational ages at diagnosis. Nine women received chemotherapy during pregnancy, and in three cases the regimen included a taxane. All women had early detection of stage I ovarian cancer at diagnosis. Oophorectomy was carried out during the first trimester in one patient who presented with ovarian torsion, and between 12 and 18 weeks in the other two patients. All surgeries during pregnancy were done via laparotomy. Chemotherapy was initiated at 8 weeks in one patient and after 22 weeks in two patients. Chemotherapy regimens included paclitaxel with either cisplatin \((n = 1)\) or carboplatin \((n = 2)\). All three women tolerated chemotherapy well during their pregnancy and no complications or side-effects were reported (Table 4).

**pregnancy and neonatal outcomes**

Chemotherapy regimens, birth and neonatal complications are listed in Table 3. Including a set of twins, 16 fetuses were exposed to taxane-based treatment in utero. The median and interquartile range for gestational age at delivery was 36.9 (36.4–37.8) weeks. The median and interquartile range for birth weight was 2452 (2155–2619) g. Two patients were induced for pre-eclampsia at 30 and 34 weeks, respectively. Three infants were born with birth weights <10% for gestational age. Complications at birth and neonatal hospital course included apnea of pre-maturity, gastroesophageal reflux disease, neutropenia in one infant, hyperbilirubinemia and, due to prematurity, respiratory distress syndrome in the neonate iatrogenically delivered at 30 weeks—he is reported by the pediatrician to be healthy at 87 months of age. A single neonate was diagnosed with a congenital anomaly: hyperthrophic pyloric stenosis at 4 weeks of age. The infant had surgery at 6 weeks of age and was doing well at the follow-up 2 months later. No other fetal malformations were reported in the cohort exposed to taxanes (Table 5).

Long-term follow-up for the infants in the Registry was provided by pediatricians for 12 of the 16 cases, with the median age and interquartile range at the time of the follow-up being 46 (18.3–96) months; mean weight and height percentiles are 49% and 40%, respectively. Minor medical issues included recurrent otitis media, IgA deficiency and mild speech delay. In the ovarian cancer cohort, follow-up was provided for three of the four infants, with the mean age of follow-up being 120 ± 71 months (median 91). Mean weight and height percentiles are 37% and 47%, respectively. No birth defects were reported for these four neonates and one child was born with birth weight <10% for gestational age. One member of a twin gestation had hyperbilirubinemia and jaundice at birth. This twin had been diagnosed with Asperger’s syndrome and speech delay, dyslexia and Tourette’s syndrome. His twin was exposed to the same chemotherapy in utero and is developmentally normal and excelling in school. One woman became pregnant again while undergoing taxane therapy and experienced a spontaneous first trimester miscarriage.

---

**Table 1. Maternal age and gestational age at diagnosis**

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>N</th>
<th>Median (mean interquartile range) Age, median (mean interquartile GA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>160</td>
<td>31.5 (30.0–38.0) years 10.5 (3.25–16.5) weeks</td>
</tr>
<tr>
<td>Ovarian</td>
<td>14</td>
<td>33 (31.5–35.25) years 17.0 (7.0–20) weeks</td>
</tr>
</tbody>
</table>

GA, gestational age.

**Table 2. Breast cancer stage and tumor characteristics in women exposed to taxanes**

<table>
<thead>
<tr>
<th>Stage</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

n = 12; ER-positive n = 4 (33%), HER 2 neu-positive n = 3 (25%).
<table>
<thead>
<tr>
<th>GA dx (weeks)</th>
<th>Stage</th>
<th>GA chemo (weeks)</th>
<th>Neo/adj regimen</th>
<th>Toxicity</th>
<th>GA delivery (weeks)</th>
<th>BW (g)</th>
<th>Complications at birth: mother; infant</th>
<th>BD</th>
<th>Age at follow-up (months)</th>
<th>Medical issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>III</td>
<td>AC-13; D-24</td>
<td>Neo AC→D</td>
<td>Mouth sores</td>
<td>36</td>
<td>2438</td>
<td>None</td>
<td>No</td>
<td>54</td>
<td>Recurrent otitis media, myringotomy tubes</td>
</tr>
<tr>
<td>5</td>
<td>II</td>
<td>AC-14; P-25</td>
<td>Adj AC→P</td>
<td>None</td>
<td>34</td>
<td>2155</td>
<td>Preeclampsia; hyper-bilirubinemia</td>
<td>No</td>
<td>117</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>IIB</td>
<td>AC-12; P-21</td>
<td>Adj AC→P</td>
<td>None</td>
<td>30</td>
<td>1417</td>
<td>Preeclampsia; Apnea of prematurity, RDS, GERD</td>
<td>No</td>
<td>87</td>
<td>IgA deficiency, mild constipation</td>
</tr>
<tr>
<td>7.8</td>
<td>IIA</td>
<td>AC14; P-21</td>
<td>Adj AC→P</td>
<td>Neutropenia and PCP pneumonia</td>
<td>36</td>
<td>2580</td>
<td>Preterm labor and delivery</td>
<td>No</td>
<td>17</td>
<td>None</td>
</tr>
<tr>
<td>3.5</td>
<td>I</td>
<td>AC-13; P-20</td>
<td>Adj AC→P</td>
<td>Contractions</td>
<td>36</td>
<td>2835</td>
<td>PPROM</td>
<td>No</td>
<td>34</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>III</td>
<td>EC-18; D-30</td>
<td>EC→D</td>
<td>None</td>
<td>37</td>
<td>2410</td>
<td>None</td>
<td>No</td>
<td>16</td>
<td>Delayed speech</td>
</tr>
<tr>
<td>13</td>
<td>III</td>
<td>AC-14; D-23</td>
<td>Neo AC→D</td>
<td>Cellulitis of arm</td>
<td>37</td>
<td>2155</td>
<td>Meconium-stained fluid</td>
<td>No</td>
<td>61</td>
<td>None</td>
</tr>
<tr>
<td>22.5</td>
<td>III</td>
<td>ED-24</td>
<td>Neo ED</td>
<td>None</td>
<td>37</td>
<td>2523</td>
<td>None</td>
<td>No</td>
<td>18</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>III</td>
<td>AC-16; P-23; D-26</td>
<td>Neo AC→P→D</td>
<td>Allergic reaction to paclitaxel</td>
<td>36</td>
<td>2410</td>
<td>Neonatal neutropenia</td>
<td>No</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>17</td>
<td>III</td>
<td>AC-19; P-26; D-28</td>
<td>Neo AC→P→D</td>
<td>Hot flashes, nausea, tachycardia with paclitaxel</td>
<td>36</td>
<td>2892</td>
<td>None</td>
<td>No</td>
<td>22</td>
<td>None</td>
</tr>
<tr>
<td>15.5</td>
<td>I</td>
<td>FAC-20; P-27</td>
<td>Neo FAC→P</td>
<td>Contractions</td>
<td>36</td>
<td>1956</td>
<td>IUGR</td>
<td>No</td>
<td>22</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>III</td>
<td>AC-14; P-22</td>
<td>Adj AC→P</td>
<td>None</td>
<td>37</td>
<td>2466</td>
<td>IUGR</td>
<td>No</td>
<td>22</td>
<td>None</td>
</tr>
</tbody>
</table>

GA, gestational age; GA dx, gestational age at diagnosis in pregnancy; PPROM, premature rupture of membranes; RDS, respiratory distress syndrome; IUGR, intrauterine growth restriction (<10% for gestational age at birth); GERD, gastroesophageal reflux; AC, adriamycin/cytoxan; P, paclitaxel; D, docetaxel; E, epirubicin; Adj, adjuvant chemotherapy; neo, neoadjuvant.
Combining the two cancer cohorts together, a congenital anomaly occurred in one infant (6.25%). At 4 weeks of age, an infant was diagnosed with pyloric stenosis, which was surgically corrected and the infant developed normally. The percentage of malformations in the taxane-exposed cohort was not statistically different from the percentage in the non-taxane exposed group, although the patient numbers are quite low to determine a difference. IUGR was reported in 18.75% of cases, 2 in the breast cancer cohort and 1 in the ovarian cancer cohort, all were treated with paclitaxel. One was found to be healthy at 22 months of follow-up and the other neonates were lost to the follow-up. The rate of IUGR reported in our cohort of patients treated with taxanes is not statistically significant compared with patients treated with other chemotherapy regimens (non-taxane group) for breast or ovarian cancer. The two chemotherapy cohorts were also compared for gestational age and birth weight at delivery, incidence of spontaneous preterm delivery, complications at birth or at the time of neonatal follow-up. There were no preterm deliveries nor birth defects in the group with ovarian cancer (Table 5).

**discussion**

A literature search in Ovid, Medline and PubMed was carried out using the terms ‘breast or ovarian cancer’, ‘pregnancy’, ‘paclitaxel’, ‘docetaxel’, ‘taxanes’ and ‘chemotherapy’. Pregnant women with breast cancer have stage-specific survival, which is similar to that of non-pregnant women when treatment courses mimic how non-pregnant women are treated [11–17]. Treatment of breast cancer is multidisciplinary and includes surgery, systemic chemotherapy, radiation and hormonal therapy, the latter two of which are held during pregnancy. Non-pregnant women are treated with taxane therapy simultaneously or sequentially with anthracycline-based therapy but this is not routinely offered to pregnant women with breast cancer despite demonstrating a decrease in the risk of relapse in operable node-positive and -negative disease [18–21].

There are rare reports on the use of paclitaxel during pregnancy. In animal models, taxanes have been shown to be embryotoxic and fetotoxic, resulting in increased intrauterine deaths, decreased fetal weight and delayed fetal ossification [32, 33]. Van Calsteren et al. [32, 33] conducted a preclinical study on transplacental transfer of taxanes in pregnant baboon models and found a very low concentration of taxanes in fetal plasma and tissues after maternal administration of chemotherapy. The tissue concentration remained detectable until 72 h after infusion. The high-lipid solubility and high protein and tissue binding of taxanes explain their large distribution volume, low plasma levels and slow elimination. Differences among the two tested taxanes were noted as well. Docetaxel appeared to have a 1.9-fold higher affinity for tubulin-binding site than paclitaxel and a stronger tissue binding. Van Calsteren also conducted a preclinical and a clinical case–control trial to determine the impact of physiologic changes of pregnancy on pharmacokinetics of chemotherapeutic agents, including taxanes. For all drugs tested, a decreased AUC and maximal plasma concentration and an increased distribution volume and clearance were observed in pregnancy. These data support the hypothesis that physiologic changes of pregnancy may result in a decreased plasma drug exposure of standard-dosed chemotherapy [33].

Because of the low molecular weight and lipophilic properties, taxanes are expected to cross the placenta, yet are substrates for the P-glycoprotein (Pgp), an efflux transporter for various xenobiotics which is highly expressed in the human placenta. In murine models, the lack of or the pharmacologic blocking of Pgp significantly increases fetal exposure to taxanes. The strong expression of Pgp in human placenta raises the hypothesis of a protective role of this protein against these drugs, reducing placental transfer [34]. Paclitaxel and docetaxel are inhibitors of microtubule depolimerization and are metabolized by cytochrome P450 isoforms CYP3A4/5 and CYP2C8 (docetaxel more so than paclitaxel). Fetuses do not express CYP3A4 in their liver tissue and production by the neonatal liver reaches only to ∼40% of adult levels in the fourth month of life and 72% at 12 months [35, 36]. A 3-week delay after chemotherapy in pregnancy is suggested before delivery to allow bone marrow recovery. Iatrogenic preterm deliveries before 34 weeks are best avoided in cases of cancer treatment during pregnancy. Although the fetal liver does not yet express CYP3A4, the maternal liver markedly increases production during the third trimester and may be responsible to fetal tolerance to these agents. Although they may have different pharmacokinetics, toxicity profile and efficacy, our numbers were too small to analyze the pregnancy and neonatal outcomes of paclitaxel exposure separately from docetaxel.

**Table 4. Use of taxanes for ovarian cancer during pregnancy**

<table>
<thead>
<tr>
<th>GA dx (weeks)</th>
<th>Stage GA chemo (weeks)</th>
<th>Neo/adj regimen</th>
<th>Toxicity</th>
<th>GA delivery (weeks)</th>
<th>BW (g)</th>
<th>Complications at birth, mother; infant</th>
<th>BD</th>
<th>Age at follow-up (months)</th>
<th>Medical issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>I</td>
<td>8</td>
<td>Ca + P</td>
<td>36</td>
<td>1886</td>
<td>IUGR</td>
<td>No</td>
<td>160</td>
<td>Twin A: none; Twin B: Tourette’s syndrome, dyslexia, Asperger’s syndrome and speech delay</td>
</tr>
<tr>
<td>16</td>
<td>I</td>
<td>22</td>
<td>Cit + P</td>
<td>38</td>
<td>2608; 2623</td>
<td>Twin B: jaundice; hyperbilirubinemia</td>
<td>No</td>
<td>38</td>
<td>None</td>
</tr>
<tr>
<td>18</td>
<td>I</td>
<td>24</td>
<td>Ca + P</td>
<td>39</td>
<td>3629</td>
<td></td>
<td>No</td>
<td>38</td>
<td>None</td>
</tr>
</tbody>
</table>

GA, gestational age; GA dx, gestational age at diagnosis in pregnancy; Ca, carboplatin; P, paclitaxel; IUGR, intrauterine growth restriction; Adj, adjuvant chemotherapy; neo, neoadjuvant.
Two patients reported vasomotor reactions such as flushing, tachycardia and nausea after paclitaxel, which they did not report after receiving docetaxel.

Upon review of the literature, we identified few case reports and reviews on the use of taxanes in human pregnancy. Mir et al. in 2008 reviewed 15 case reports for ovarian (5 cases) and breast cancer (10 cases) during pregnancy. Paclitaxel was administered as a single agent in two of nine cases and in combination with various agents including carboplatin, cisplatin, epirubicin, adriamycin, cyclophosphamide and trastuzumab in others. Docetaxel was administered in the remaining six breast cancer patients. Chemotherapy was administered in the second and third trimesters in all patients and no fetal malformations were reported. The offspring were reportedly normal at birth and at 10 months of age. Chun et al. [37] reported three cases of pregnant women with stage Ib1–Ia cervical cancer who were treated with paclitaxel plus platinum neoadjuvant chemotherapy followed by radical surgery. All were treated during the third trimester, two received cisplatin and paclitaxel, one received carboplatin and paclitaxel. At the latest follow up, the children who were all appropriately grown and normal at the time of delivery were developmentally normal at 48–60 months of age.

Three cases of treatment with paclitaxel for lung cancer during pregnancy were found in the literature [38–40]. Garcia-Gonzalez et al. [38] reported a case of paclitaxel use in metastatic lung cancer during pregnancy with normal neonatal growth and development at the 15-month follow-up. Kim et al. [39] reported a patient with stage IV non-small-cell lung cancer with brain metastasis who underwent a craniotomy with tumor removal, followed by whole brain irradiation. She then received palliative chemotherapy with docetaxel and

| Table 5. Neonatal and birth complications in neonates treated with chemotherapy including or without taxanes |
|---------------------------------|----------------|----------------|----------------|----------------|
| GA at delivery (weeks)          | Taxane         | Non-taxane     | P-value        |
| Breast                          | 12             | 116            | 0.92           |
| Gram weight                     | 12             | 2353.1         | 0.18           |
| Ovarian                         | 3              | 37.7           | 0.67           |
| Gram weight                     | 4              | 2686.5         | 0.76           |

Two patients reported vasomotor reactions such as flushing, tachycardia and nausea after paclitaxel, which they did not report after receiving docetaxel.

Upon review of the literature, we identified few case reports and reviews on the use of taxanes in human pregnancy. Mir et al. in 2008 reviewed 15 case reports for ovarian (5 cases) and breast cancer (10 cases) during pregnancy. Paclitaxel was administered as a single agent in two of nine cases and in combination with various agents including carboplatin, cisplatin, epirubicin, adriamycin, cyclophosphamide and trastuzumab in others. Docetaxel was administered in the remaining six breast cancer patients. Chemotherapy was administered in the second and third trimesters in all patients and no fetal malformations were reported. The offspring were reportedly normal at birth and at 10 months of age. Chun et al. [37] reported three cases of pregnant women with stage Ib1–Ia cervical cancer who were treated with paclitaxel plus platinum neoadjuvant chemotherapy followed by radical surgery. All were treated during the third trimester, two received cisplatin and paclitaxel, one received carboplatin and paclitaxel. At the latest follow up, the children who were all appropriately grown and normal at the time of delivery were developmentally normal at 48–60 months of age.

Two patients reported vasomotor reactions such as flushing, tachycardia and nausea after paclitaxel, which they did not report after receiving docetaxel.

Upon review of the literature, we identified few case reports and reviews on the use of taxanes in human pregnancy. Mir et al. in 2008 reviewed 15 case reports for ovarian (5 cases) and breast cancer (10 cases) during pregnancy. Paclitaxel was administered as a single agent in two of nine cases and in combination with various agents including carboplatin, cisplatin, epirubicin, adriamycin, cyclophosphamide and trastuzumab in others. Docetaxel was administered in the remaining six breast cancer patients. Chemotherapy was administered in the second and third trimesters in all patients and no fetal malformations were reported. The offspring were reportedly normal at birth and at 10 months of age. Chun et al. [37] reported three cases of pregnant women with stage Ib1–Ia cervical cancer who were treated with paclitaxel plus platinum neoadjuvant chemotherapy followed by radical surgery. All were treated during the third trimester, two received cisplatin and paclitaxel, one received carboplatin and paclitaxel. At the latest follow up, the children who were all appropriately grown and normal at the time of delivery were developmentally normal at 48–60 months of age.

Two patients reported vasomotor reactions such as flushing, tachycardia and nausea after paclitaxel, which they did not report after receiving docetaxel.

Upon review of the literature, we identified few case reports and reviews on the use of taxanes in human pregnancy. Mir et al. in 2008 reviewed 15 case reports for ovarian (5 cases) and breast cancer (10 cases) during pregnancy. Paclitaxel was administered as a single agent in two of nine cases and in combination with various agents including carboplatin, cisplatin, epirubicin, adriamycin, cyclophosphamide and trastuzumab in others. Docetaxel was administered in the remaining six breast cancer patients. Chemotherapy was administered in the second and third trimesters in all patients and no fetal malformations were reported. The offspring were reportedly normal at birth and at 10 months of age. Chun et al. [37] reported three cases of pregnant women with stage Ib1–Ia cervical cancer who were treated with paclitaxel plus platinum neoadjuvant chemotherapy followed by radical surgery. All were treated during the third trimester, two received cisplatin and paclitaxel, one received carboplatin and paclitaxel. At the latest follow up, the children who were all appropriately grown and normal at the time of delivery were developmentally normal at 48–60 months of age.

Two patients reported vasomotor reactions such as flushing, tachycardia and nausea after paclitaxel, which they did not report after receiving docetaxel.

Upon review of the literature, we identified few case reports and reviews on the use of taxanes in human pregnancy. Mir et al. in 2008 reviewed 15 case reports for ovarian (5 cases) and breast cancer (10 cases) during pregnancy. Paclitaxel was administered as a single agent in two of nine cases and in combination with various agents including carboplatin, cisplatin, epirubicin, adriamycin, cyclophosphamide and trastuzumab in others. Docetaxel was administered in the remaining six breast cancer patients. Chemotherapy was administered in the second and third trimesters in all patients and no fetal malformations were reported. The offspring were reportedly normal at birth and at 10 months of age. Chun et al. [37] reported three cases of pregnant women with stage Ib1–Ia cervical cancer who were treated with paclitaxel plus platinum neoadjuvant chemotherapy followed by radical surgery. All were treated during the third trimester, two received cisplatin and paclitaxel, one received carboplatin and paclitaxel. At the latest follow up, the children who were all appropriately grown and normal at the time of delivery were developmentally normal at 48–60 months of age.
cisplatin followed by gemcitabine and cisplatin as the second-line chemotherapeutic agents between weeks 9 and 22 of gestation. An infant weighing 1490 g was born by cesarean section at 33 weeks. Fetal karyotype was 46 XX, with no cytogenetic abnormalities. Pediatric evaluation revealed no evidence of hearing, thyroid, adrenal, hepatorenal and hematologic dysfunction, or gross congenital malformations in the infant. At 10 months, the child was developmentally normal. Azim et al. reported a patient treated with weekly paclitaxel and carboplatin for non-small-cell lung cancer beginning at 19–20 weeks. At 30 weeks, she went into spontaneous preterm labor and delivered a normal infant who was developmentally normal at 5 months but no information was provided regarding birth weight.

More recently, in 2010, Mir et al. published a systematic review of taxane use in pregnancy where he described 23 publications describing 40 case reports (27 breast, 10 ovarian, 3 lung cancer) in which a taxane was used during pregnancy. Paclitaxel was administered in 21 cases, docetaxel in 16 and both drugs in 3 cases. The only malformation reported was pyloric stenosis in a neonate whose mother received multiagent chemotherapy along with taxanes (this is the identical infant reported here). Neonatal complications including respiratory distress were likely related to prematurity. The authors concluded that taxane chemotherapy remains a feasible treatment option for pregnant cancer patients, with a favorable toxicity profile, when given in the second and third trimesters of pregnancy.

Although our paper describes a smaller cohort of 15 patients with breast and ovarian cancer treated with taxanes during pregnancy, to our knowledge, it is the first to study taxane use in pregnancy that assesses maternal and neonatal outcomes from a single database in a prospective manner in the majority of cases and compares the outcomes with women treated with non-taxane-containing chemotherapy regimens during pregnancy. Relatively few toxic effects were noted in our cohort, possibly related to our small sample size. Maternal side-effects were limited to complaints of mouth sores, dyspnea, neutropenia, infections, tachycardia, hot flashes, an allergic reaction and uterine irritability.

Limitations of this study include the small size of this cohort and the inherent risks in collecting information through a voluntary registry. The strength of the registry is that enrollment is encouraged at diagnosis, not at the time of delivery, so neonatal information is obtained prospectively. Otherwise, there is a tendency that women delivering an infant with a malformation may be more likely to report an exposure during pregnancy or join a registry. The small sample size exists due to the hesitancy of practitioners and patients to adopt new treatments during pregnancy despite advances in the non-pregnant population. Given the voluntary nature of Registry enrollment, there is tremendous variability of data pertaining to treatment rendered, and the completeness and detail of records received. It is not possible to determine whether birth or neonatal complications are attributable to the taxane class or the other chemotherapeutics that were previously given concurrently or sequentially. The rate of IUGR is slightly higher (18.5%) than the background rate described in pregnancy, which depending on the population varies from 8% to 10%. This requires further study as more cases of taxane exposure are reviewed. We could not find a statistical difference in the incidence of IUGR when compared with neonates exposed to chemotherapy not including taxanes. Our maternal and neonatal follow-up is ongoing. In the interest of women currently diagnosed during pregnancy, we publish our findings to date even though our mean follow-up is currently 4.5 years. It is our intention to help guide physicians to make critical treatment decisions and patients to make more informed choices regarding their cancer treatment during pregnancy.

conclusions

Our experience with this case series of 15 patients (16 fetuses) adds to the reassuring data regarding the feasibility and relative safety of giving taxanes during the second and third trimesters of pregnancy when indicated. If AC or FAC is completed before 30 weeks of gestation, there may be too long a delay before postpartum taxane treatment is initiated. As such, our study confirms prospectively that taxanes need not necessarily be delayed in pregnant women with breast cancer. This was also well tolerated in the three patients with ovarian cancer; however, two exposures were reported after neonatal outcome was known.

As in all cases of chemotherapy use in pregnancy, an extensive discussion must be undertaken with the patient and her family and multidisciplinary team of physicians, including oncologists, maternal fetal medicine specialists and neonatologists. Discussion should include the benefits and the risks involved based on the paucity of safety and efficacy data of taxane use during pregnancy. While small, our study reassures that taxane use shows no significant neonatal or maternal effects, and may be considered a viable option for pregnant patients. More reports of taxane use during pregnancy with details and long-term data on maternal and fetal toxicity are needed.

acknowledgements

This article was presented as a poster at the SMFM 30th Annual Scientific Meeting in Chicago, IL, USA.

funding

Funding for database support to collect and record this data was provided by Teal Tea Foundation, a non-profit organization to support women with ovarian cancer.

disclosure

The authors have declared no conflicts of interest.

references


