Chemotherapy for Breast Cancer During Pregnancy: An 18-Year Experience From Five London Teaching Hospitals
Alistair E. Ring, Ian E. Smith, Alison Jones, Catherine Shannon, Eleni Galani, and Paul A. Ellis

ABSTRACT

Purpose
The rare association between breast cancer and pregnancy means that few oncologists gain an expertise in this area. In particular, there are few published data concerning the use of chemotherapy for breast cancer during pregnancy. In this retrospective case series, we describe the experiences of five hospitals in London, United Kingdom, and how they manage this condition.

Patients and Methods
Retrospective searches were performed at five London hospitals in order to identify women who received chemotherapy for breast cancer while pregnant.

Results
Twenty-eight women were identified who had received chemotherapy for breast cancer during pregnancy. Twenty-four women received adjuvant or neoadjuvant chemotherapy for early breast cancer, and four women received palliative chemotherapy for metastatic disease. A total of 116 cycles of chemotherapy were administered during pregnancy. Sixteen women were treated with anthracycline-based chemotherapy and 12 received cyclophosphamide, methotrexate, and fluorouracil. All but one of the women were treated after the first trimester. One spontaneous abortion occurred in the woman treated during her first trimester; otherwise, there were no serious adverse consequences for the mothers or neonates.

Conclusion
These data provide evidence that in terms of peripartum complications and immediate fetal outcome, chemotherapy can be safely administered to women during the second and third trimesters of pregnancy.

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INTRODUCTION

It has been estimated from 32 case series over a period of several decades that 0.2% to 3.8% of breast cancers occur during pregnancy. This incidence may rise as women delay their pregnancies until later in life, and as the number of premenopausal women with breast cancer grows. Pregnancy complicates the management of breast cancer because the need for treatment to maximize chances of survival for the mother have to be balanced against the potential risks to the fetus. This is particularly the case when the use of chemotherapy is proposed in a pregnant woman. Adjuvant chemotherapy has a well-established role in improving survival for women with early breast cancer. Delays or modification of adjuvant treatment to ensure the birth of a healthy infant could potentially compromise maternal survival. It is therefore important to establish what treatments are safe for both mother and the developing fetus during pregnancy. Owing to the rarity of this association and the infrequent use of chemotherapy in pregnancy,
most existing reports are anecdotal. This retrospective series is the largest published thus far and documents data from five hospitals concerning the use of chemotherapy for breast cancer in pregnant women.

**Baseline Characteristics**

Sixty-three women who were pregnant at the time of diagnosis or relapse of breast cancer were identified; 28 of these women went on to receive chemotherapy while pregnant. Of these 28 women, 24 were diagnosed with stage I to IIIB breast cancer while pregnant. Seventeen patients underwent surgery while pregnant; of these 17 patients, 10 had modified radical mastectomies, four received palliative chemotherapy for metastatic disease, and seven patients underwent breast-conserving surgery. The median gestational age at the time of surgery was 16 weeks (range, 5 to 29 weeks). There were no unexpected surgical or anesthetic complications. Four patients had surgery after delivery, following primary chemotherapy received while pregnant. Seven patients did not have surgery; three of these patients received neoadjuvant chemotherapy alone and four received palliative chemotherapy for metastatic disease. All seven of the patients who underwent breast-conserving surgery and seven of the 10 patients who underwent mastectomy while pregnant received postpartum radiation therapy.

**Surgery**

Seventeen patients underwent surgery while pregnant; 10 of the 17 patients had modified radical mastectomies, and seven patients underwent breast-conserving surgery. Fifteen of the 17 patients underwent axillary surgery. The
ductal carcinomas (in 86% of patients for whom this information was available). There were also high incidences of adverse prognostic features, including high tumor grade (74% of patients), lymphovascular invasion (88% of patients), and estrogen–receptor (ER)–negative tumors (42% of patients). Lymph node status was known for 18 patients, of whom 15 (83%) were node positive. Three of the tumors also exhibited inflammatory features.

**Chemotherapy**

Neoadjuvant chemotherapy was initiated during pregnancy in seven patients for large operable, locally advanced, or inflammatory breast cancers. Adjuvant chemotherapy was administered to 17 patients, and four patients received palliative chemotherapy for metastatic disease. A total of 116 cycles of chemotherapy were administered during pregnancy in this cohort; the median number of cycles administered prepartum was four (range, one to six). The median total number of cycles of chemotherapy administered during and after pregnancy was six (range, four to eight cycles). Fourteen of the patients received chemotherapy prepartum only, whereas the remaining 14 received chemotherapy both during and after pregnancy. The types and doses of chemotherapy administered are listed in Table 2. These chemotherapy regimes were tolerated at full doses without major complications. Three episodes of febrile neutropenia were recorded, but all patients responded to antibiotics with no additional complications. The only other grade 3 or 4 toxicities recorded were lethargy (two patients) and alopecia. Two of the patients also received granulocyte colony-stimulating factor while pregnant. No patients received endocrine therapy or radiotherapy during pregnancy.

**Obstetric Characteristics**

Obstetric characteristics related to chemotherapy administration are reported in Table 3. The median gestational age at the commencement of chemotherapy was 20 weeks (range, 15 to 33 weeks). Twenty-two patients started chemotherapy in the second trimester and five during the third trimester. One patient received cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy during the first trimester of her pregnancy. She was not aware that she was pregnant at the time of chemotherapy initiation, but had a positive pregnancy test shortly after the first cycle. Unfortunately, she had a spontaneous abortion before her second cycle of treatment. The median interval between the last cycle of chemotherapy and delivery was 28 days (range, 14 to 70 days). Six patients had cesarean deliveries, and an additional seven patients had their labor induced. The median gestational age at delivery was 37 weeks (range, 30 to 40 weeks). Nine children were born before 37 weeks’ gestation; one case was as a result of spontaneous onset of labor. The patient who delivered at 30 weeks had an early elective cesarean delivery owing to impending spinal cord compression.

**Fetal Outcome**

The median gestational age at delivery was 37 weeks (range, 30 to 40 weeks). One child had a hemangioma on his abdomen, but it was not thought to be causally related to chemotherapy exposure. There were no other recorded fetal abnormalities. Birth weight was available for 17 of the infants; the median birth weight was 3.0 kg (1.4 to 3.5 kg). In the infant born weighing 1.4 kg, placental insufficiency was identified as the cause of intrauterine growth retardation, and an elective cesarean delivery was carried out at 32 weeks. However, none of the infants had a birthweight lower than the 10th percentile for gestational age. Two of the newborns experienced respiratory distress, and in total five newborns needed to be transferred to neonatal high dependency units.

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**Table 2. Chemotherapy**

<table>
<thead>
<tr>
<th></th>
<th>Adjuvant</th>
<th>Neoadjuvant</th>
<th>Palliative</th>
<th>Total</th>
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<tbody>
<tr>
<td>Doxorubicin and cyclophosphamide*</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Epirubicin and cyclophosphamide†</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Cyclophosphamide, methotrexate, and fluorouracil‡</td>
<td>9</td>
<td>3</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>17</td>
<td>7</td>
<td>4</td>
<td>28</td>
</tr>
</tbody>
</table>

Abbreviation: iv, intravenously.

*Doxorubicin 50-60 mg/m² iv day 1, cyclophosphamide 600 mg/m² iv day 1, every 3 weeks.
†Epirubicin 80-100 mg/m² iv day 1, cyclophosphamide 600 mg/m² iv day 1, every 3 weeks.
‡Cyclophosphamide 100-150 mg orally days 1-14, methotrexate 40 mg/m² iv days 1 and 8, fluorouracil 600 mg/m² iv days 1 and 8; every 4 weeks.

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**Table 3. Obstetric Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, years</td>
<td>33</td>
<td>28-42</td>
</tr>
<tr>
<td>Gestational age at diagnosis, weeks</td>
<td>17</td>
<td>4-33</td>
</tr>
<tr>
<td>Gestational age at surgery, weeks</td>
<td>16</td>
<td>5-29</td>
</tr>
<tr>
<td>Interval between delivery and last cycle of chemotherapy, days</td>
<td>28</td>
<td>40-70</td>
</tr>
<tr>
<td>Gestational age at delivery, weeks</td>
<td>37</td>
<td>30-40</td>
</tr>
</tbody>
</table>
Maternal Outcome

As of October 2003, the median follow-up period for the women in this report was 40.5 months (range, 7 to 159 months). Two of the women with stage IV disease died within 3 years of diagnosis, and the other two patients are both alive at 1 year of follow-up. At a median of 40.5 months, the combined survival rate for women with stage I to IIIB breast cancer was 67%, and the disease-free survival rate was 63%.

DISCUSSION

The purpose of conducting this retrospective review was to provide more information to breast cancer specialists and obstetricians faced with a pregnant patient with breast cancer requiring chemotherapy. We are aware of only two case series of a similar size: a French national survey and a series from The University of Texas M.D. Anderson Cancer Center (Houston, TX). The French national survey was a retrospective study based on a postal questionnaire sent to clinicians involved in the management of breast cancer diagnosed during pregnancy. Data were acquired on the histologic and clinical characteristics, treatment, obstetric complications, and pregnancy outcome of 20 women treated with chemotherapy for breast cancer while pregnant. The M.D. Anderson Cancer Center series was a prospectively designed study where patients with primary or recurrent breast cancer diagnosed during pregnancy were managed with locoregional therapy and a standard chemotherapy protocol as clinically indicated. The chemotherapy regimen used was doxorubicin 50 mg/m² continuous infusion over a period of 72 hours, cyclophosphamide 500 mg/m² on day 1, and bolus fluorouracil 500 mg/m² on days 1 and 4. In the initial publication, data were presented on 24 women, two of whom had recurrent disease, and one of whom received chemotherapy during her first trimester. An update of this series including 39 patients has also been presented in abstract form.

The pathologic characteristics of the tumors treated were similar to those reported in other series, in that the majority of tumors were high-grade invasive ductal carcinomas. Twenty-five of 28 patients in this study presented with pathologic lymph node involvement or metastatic disease; similarly, Middleton et al found that only 2 of 39 patients presenting with breast cancer during pregnancy had stage I disease. Patients with breast cancer who are pregnant at the time of diagnosis have previously been shown to present with more advanced disease than matched nonpregnant patients in some, but not all, case-control studies. Of the 19 women with stage I to IIIB breast cancer for whom ER status was available, eight were estrogen-receptor–negative. ER-negative tumors are known to be more common in younger women, but in case control studies, ER-negative tumors have been shown to be more frequent in pregnant patients than in age-matched controls. It has also previously been observed that breast cancer in patients who are pregnant often demonstrate lymphovascular invasion, and are relatively frequently HER2-positive, though whether their frequencies are any different to those in age-matched controls is not known.

The use of cytotoxic drugs during pregnancy is complicated by the potential for teratogenicity as demonstrated in animal studies, together with the risk of other direct toxic effects on the mother and fetus. During the first trimester, the fetus is undergoing organogenesis, and therefore is at its most susceptible. Chemotherapy at this stage may be associated with spontaneous abortions or an increased risk of fetal malformations. One of the patients in this series, and two patients in the French national survey were exposed to chemotherapy during the first trimester, and all underwent spontaneous abortions. However, the one patient exposed to chemotherapy during the first trimester (11 weeks) in the M.D. Anderson series experienced no apparent adverse effects. When live births do occur, historical studies suggest that fetal malformation rates are between 7.5% and 17%,. Because of the high rates of pregnancy loss and fetal malformations, chemotherapy is generally avoided during the first trimester.

Beyond the first trimester, the use of cytotoxic chemotherapy does not appear to increase the risk of malformations. In this series, none of the 27 children exposed to chemotherapy in the second or third trimesters had congenital malformations. Sixteen of these children had been exposed to anthracycline-based chemotherapy. In the M.D. Anderson series, 23 children were exposed to anthracycline-based chemotherapy in the second and third trimesters (doxorubicin, cyclophosphamide, and fluorouracil at the doses previously described) and similarly no malformations were reported. Our series also included 12 patients who received CMF chemotherapy. In the first trimester, methotrexate is particularly associated with birth defects, but we can find no evidence of such an effect later in pregnancy. The French national survey identified 18 patients who received a variety of chemotherapy regimes during the second and third trimesters of pregnancy, and no fetal malformations were identified. Four of these patients received vincristine, which has previously been administered with no fetal complications. Case reports also describe the use of docetaxel and paclitaxel in the second and third trimesters respectively, with no adverse effects. There is no evidence from animal studies that granulocyte colony-stimulating factor is teratogenic, and there are reports of its use during pregnancy (Medical Information Department, personal communication, April 2003). Two patients in the current series also received granulocyte colony-stimulating factor with no significant adverse effects.

The toxic effects of cytotoxic agents are not restricted to fears over teratogenicity. Pre-eclampsia, preterm labor,
intrauterine death, and low birth weights have all been reported in previous series. However, it is not known whether the incidences of these complications are in excess of those in the normal population and what the contribution of chemotherapy is relative to the effects of the underlying disease. Nine of the children were delivered before 37 weeks, and in one case premature delivery occurred as a result of spontaneous onset of preterm labor. In the remainder, early delivery was explained by induced labor or cesarean delivery in order to optimize the timing of delivery relative to chemotherapy, or, in one case, to allow treatment of spinal cord compression. Intrauterine growth retardation is likely to be underestimated in retrospective studies, though one case each was identified in the French national survey and the current study. Of the 17 babies in this series for whom birth weights were available, two had low birth weights (<2.5 kg). Increased neonatal morbidity and mortality are recognized sequelae of intrauterine growth retardation and low birth weight (<2.5 kg) in the normal neonatal population. However, none of the infants in this series and only one infant in the M.D. Anderson series had a birth weight lower than the 10th percentile for gestational age.

Maternal and neonatal sepsis and hemorrhage are potential complications of myelosuppression, which can effect both mother and fetus at the time of delivery. No such complications were observed in this cohort, though the mean interval between delivery and the last cycle of chemotherapy was 30 days, minimizing the risk of neutropenia at the time of delivery.

The potential long-term effects of exposing the fetus to chemotherapy include gonadal dysfunction, impaired physical and neurologic development, and germ cell mutagenesis resulting in carcinogenesis and teratogenicity in subsequent generations. However, follow-up of children is often short and reports concerning long-term development are uncommon. The most comprehensive cohort to date describes 84 children born to mothers who were treated with combination chemotherapy during pregnancy for hematologic malignancies. At a median follow-up of 18.7 years, normal physical, neurologic, and psychological development was observed, with no reports of malignancies in the 84 first-generation children or in the 12 second-generation children.

Given that some transplacental transfer of anthracyclines may occur, fetal cardiotoxicity following maternal exposure to anthracyclines is another long-term concern. No cases of fetal cardiotoxicity were recorded in one large review of the use of anthracyclines in pregnancy, and no echocardiographic changes were observed when a child was monitored in utero. Unfortunately, this case series and many others on this topic are unable to adequately address such late adverse effects owing to a lack of long-term follow-up and the bias introduced by their retrospective nature. For these reasons, the ongoing analysis of the M.D. Anderson data and new prospective databases such as that initiated by the German Breast Group are of utmost importance.

The data presented in this series provide evidence that in consideration of peripartum complications and immediate fetal outcome, chemotherapy can be safely administered to women during the second and third trimesters of pregnancy. The literature reviewed also indicates that there are unlikely to be serious adverse long-term effects on the fetus, though large prospective series are needed to confirm this. Nonetheless, on the basis of the current evidence women should not be denied the potential benefits of chemotherapy because they are pregnant at the time of diagnosis of breast cancer.

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Authors’ Disclosures of Potential Conflicts of Interest
The authors indicated no potential conflicts of interest.

REFERENCES

14. Li CI, Daling JR, Malone KE: Incidence of invasive breast cancer by hormone receptor

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