Maternal and Neonatal Outcomes of Dose-Dense Chemotherapy for Breast Cancer in Pregnancy

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OBJECTIVE: To estimate the effect of dose-dense chemotherapy during pregnancy on maternal and neonatal outcomes.

METHODS: This is a retrospective cohort study in which women were identified from the international Cancer and Pregnancy Registry at Cooper Medical School at Rowan University in Camden, New Jersey. A chart analysis was completed and Fisher's exact test and independent *t* test were used in comparing patient outcomes.

RESULTS: Ten women received dose-dense chemotherapy, received every 2 weeks, and 99 women received conventional chemotherapy, received with at least 3-week intervals, for breast cancer 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.

CONCLUSION: In the small cohort of women in our registry, dose-dense chemotherapy does not appear to increase the risk of fetal or maternal complications.

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LEVEL OF EVIDENCE: II

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With the exception of skin cancer, breast cancer is the most common malignancy in women and the most frequent solid cancer diagnosed in pregnancy.[1,2] Smith et al[2] reported, from the California Obstetrics registry for 1992–1997, that the incidence of breast cancer is 13 per 100,000 of live births. This may have been an underestimation because the registry did not include women who chose to terminate their pregnancies after diagnosis. Because more women delay childbirth into their third and fourth decades, the incidence of breast cancer diagnosed during pregnancy and in the immediate postpartum period appears to be increasing.[3–5] Stensheim et al[3] reported over the course of a recent population-based cohort study in Norway, in which patients were matched from the Cancer Registry and Medical Birth Registry, that the incidence of cancer diagnosed during pregnancy did in fact increase.

It is well established that adjuvant chemotherapy improves the survival of women diagnosed with breast cancer.[6,7] Delaying treatment as a result of pregnancy may adversely affect maternal survival. Beadle et al[8] published a review of the treatment of 104 women younger than 35 years of age with pregnancy-associated breast cancer: 51 cancers developed during pregnancy and 53 within 1 year after pregnancy. For those patients who developed breast cancer during pregnancy, any treatment intervention during pregnancy provided a trend toward improved overall survival compared with delaying evaluation and treatment until after delivery. The authors noted a 78.7% overall survival rate in those women who received treatment during pregnancy compared with 44.7% of those who did not (P=.068).[8] The question of whether pregnant women should be denied chemotherapy seems to have been answered in the current medical literature.[9,10] If such a delay would compromise the maternal chance of cure and the fetal risk appears acceptable, based on gestational age of the

fetus at the time of diagnosis, the treatment of maternal cancer should not be delayed.

In recent studies in nonpregnant women, dose-dense chemotherapy regimens, which decrease the time interval between cycles, have been shown to possibly be more effective than conventional older schedules and, at minimum, shorten the time needed to complete chemotherapy.[11,12] The fear of neutropenia during pregnancy, increasing the infectious risks for mother and fetal susceptibility to opportunistic infections such as cytomegalovirus as well as the limited data on the use of dose-dense chemotherapy and the stem cell mobilizers (granulocyte cell-stimulating factor), usually accompanying this more intense regiment, leave health care practitioners cautious to use these more aggressive dose-dense regimens antepartum.

A recently published study reports on fetal exposure to granulocyte cell-stimulating factor in 34 women.[13] The authors found no statistically significant difference in pregnancy and neonatal outcomes of those exposed in utero to both chemotherapy and granulocyte cell-stimulating factor as compared with those who were only exposed to chemotherapy.[13] In view of the possible greater effectiveness of dose-dense chemotherapy for nonpregnant women and reassuring reports on the use of accompanying granulocyte cell-stimulating factor, it would be beneficial to have data regarding maternal and fetal tolerance of this more modern and potentially more efficacious dosing schedule. We attempt to answer whether the advances of treatment such as a dose-dense chemotherapy schedule can be safely offered to pregnant women with breast cancer. We report the outcomes of a large group of pregnant women with breast cancer who were exposed to dose-dense timing of doxorubicin and cyclophosphamide during their gestation.

MATERIALS AND METHODS

This is a retrospective cohort study of pregnant women who were enrolled in the international Cancer and Pregnancy Registry at Cooper University Hospital, Cooper Medical School at Rowan University, in Camden, New Jersey, after a diagnosis of breast cancer. This is a voluntary registry (patients called to enroll on their own after finding out about the registry), which was created to collect the data from multiple institutions to improve the understanding of the effect of cancer and chemotherapy exposure on women and their neonates.

Pregnancy-associated breast cancer is defined as breast cancers occurring during pregnancy or within 1 year postpartum. The purpose of the Registry is to help oncologists and obstetricians decide the best course of action when cancer is diagnosed during a pregnancy as well as to learn about how pregnancy may affect the presentation of breast cancer. For this reason, diagnoses up to 1 year postpartum are not included here.

Women included in our registry are diagnosed with breast cancer between their last menstrual period and either a spontaneous or induced loss or up to 6 weeks postpartum. All women included in this study received chemotherapy during their pregnancy. Women with spontaneous or induced pregnancy losses before chemotherapy treatment and those with incomplete records were excluded.

The majority of women were enrolled before their delivery or spontaneous or induced loss (prospective enrollment). However, women who learned of the Registry postpartum and wished to enroll after their delivery were identified as retrospective enrollments. In the dose-dense group, 9 of 10 (90%) patients enrolled prospectively, one patient calling to register 4 days after her delivery. In the conventional group, 77 women (78%) contacted the registry before their delivery. Patients were interviewed at enrollment to provide initial medical information and then with their written consent, this information was confirmed with medical records obtained from obstetricians, oncologists, and pediatricians and reviewed by the authors.

Information collected from oncology records was reviewed to document maternal stage, lymph node status at diagnosis, and estrogen, progesterone, and Her2/neu receptor status; chemotherapy regimen; interval and doses; incidence of neutropenia; maternal survival; and incidence of postpartum recurrences. Obstetric and pediatric records were reviewed to document neonatal birth weight and gestational age at delivery, incidence of intrauterine growth restriction and congenital anomalies, and complete blood counts with differential at birth. Only malformations meeting the Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program criteria were included. The mode of delivery and the rates of spontaneous preterm delivery in each group were also analyzed. The timing, doses, and regimens of chemotherapy were decided by each patient's oncologist based on the judgment of the prescribing physician and standard of care.

Independent t test was used to compare means and Fisher's exact test was used to compare patient outcomes with $P<.05$ deemed statistically significant. Kaplan-Meier curves were used to illustrate survival and log-rank test was used for comparison of survival. Institutional review board approval was obtained from Robert Wood Johnson Medical School.

RESULTS

Data on women diagnosed with breast cancer and enrolled in the registry between July of 1997 and December of 2010 are reported here. Pregnant women receiving chemotherapy every 2 weeks (dose-dense) are compared with women who received chemotherapy with at least 3-week intervals (conventional chemotherapy). All patients in the dose-dense group completed their planned chemotherapy regimen before delivery. Ninety-eight percent of women in the conventional chemotherapy group completed all of their cycles during pregnancy (one patient received five of six planned treatments as a result of cardiac symptoms). A total of 109 women were diagnosed with breast cancer during pregnancy. Ten women received dose-dense chemotherapy and 99 women received conventional chemotherapy. Maternal characteristics including stage at diagnosis, lymph node status at diagnosis, and estrogen, progesterone, and Her2/neu receptor status were similar for both groups and are reported in Tables 1 and 2. All chemotherapy was initiated after the first trimester. All 10 patients in the dose-dense group received their proposed schedule in a 2-week fashion during their pregnancy. In the conventional chemotherapy group, chemotherapy was given no more frequently than every 3 weeks. None of the patients in the dose-dense group received higher doses of chemotherapeutic agents than in the conventional group.

The dose-dense group received 600 mg/m^2 cyclophosphamide and 60 mg/m^2 doxorubicin in standard fashion every 2 weeks for a total of four cycles followed in five patients by either 175 mg/m^2 paclitaxel or 75–100 mg/m^2 docetaxel every 2 weeks for a total of one to four cycles depending on gestational age and timing of delivery. Two patients in the dose-dense group developed severe nausea and vomiting in response to paclitaxel and were switched to docetaxel for the remainder of the cycles. Both had received two doses of paclitaxel and were switched to docetaxel for the last two planned cycles as a result of intolerance.

The doses used for the conventional chemotherapy cohort included various chemotherapy regimens with the most common being 600 mg/m^2 cyclophosphamide and 60 mg/m^2 doxorubicin given once every 3 weeks for a total of four cycles in standard fashion followed in five patients by either 175 mg/m^2 paclitaxel or 75–100 mg/m^2 docetaxel at 3-week intervals. The various chemotherapy regimens used are outlined in Table 3. Pegfilgrastim or filgrastim was used in six of the 10 women in the dose-dense group and 16 of 99 women in the conventional group.

Table 1. Maternal Characteristics

Chemotherapy Interval	Conventional Chemotherapy	Dose-Dense Chemotherapy	*P*
Lymph node status	63.2	42.9	.42
ER status	40	33.3	>.99
PR status	37	44	.73
HER2 or Neu status	30.3	22.2	>.99
BRCA1/2	2	0	>.99

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.
Data are percent positive unless otherwise specified.

Table 2. Stage at Diagnosis

Chemotherapy Interval	Conventional Chemotherapy	Dose-Dense Chemotherapy
Stage 1	16	30
Stage 2	56	40
Stage 3	24	30
Stage 4	4	0

Data are %. Overall *P*=.42.

Table 3. Chemotherapy Regimens

Regimen	Conventional Chemotherapy	Dose-Dense Chemotherapy
Doxorubicin and cyclophosphamide	70	4
5-fluorouracil and doxorubicin and cyclophosphamide	16	0
Doxorubicin and cyclophosphamide followed by paclitaxel	3	2
5-fluorouracil, epirubicin, and cyclophosphamide	2	0
Doxorubicin and cyclophosphamide followed by docetaxel	2	1
Doxorubicin, cyclophosphamide, and dactinomycin	2	1
Epirubicin and cyclophosphamide	2	0
Epirubicin and docetaxel	2	0
Doxorubicin and cyclophosphamide followed by paclitaxel for 2 doses and switched to docetaxel for remaining 2 doses	0	2
Total	99	10

Data are n.

The mean gestational age at delivery was 35.7 weeks (standard deviation 1.6) and 36.6 (standard deviation 2.3) for dose-dense and conventional chemotherapy groups, respectively (P=.6). We analyzed the incidence of women with preterm delivery (defined as less than 37 weeks of gestation) as a result of either spontaneous preterm birth or preterm premature rupture of membranes. Elective inductions or deliveries were excluded. The rate of spontaneous preterm birth or preterm premature rupture of membranes was 30% for the dose-dense and 17% for conventional chemotherapy groups. This difference was not statistically different (P=.188). Mean birth weight was 2,560 g in the dose-dense group and 2,576 g in the conventional chemotherapy group (P=.642). There were no fetuses with growth restriction in the dose-dense group compared with 7.1% (7 of 99) in the conventional chemotherapy group (P>.99). Of the 10 neonates in the dose-dense group, 10% (1 of 10) experienced transient neutropenia without long-term sequelae, whereas none had neutropenia in the conventional chemotherapy group (P=.09). That same neonate was diagnosed with congenital pyloric stenosis, which was surgically repaired 6 weeks postpartum. Compared with this one congenital anomaly in the dose-dense group, there were three in the conventional chemotherapy group. These included holoprosencephaly, asymptomatic main pulmonary artery fistula incidentally found on echocardiogram, and hemangioma of an eye. The incidence of birth defects was not statistically different between groups (P=.30). The overall incidence of birth defects in both groups (3.6%) was not higher than the 3% overall prevalence of birth defects in the noncancer population in the United States.[1] There was one (1%) neonatal death in the conventional chemotherapy group resulting from a severe autoimmune disorder. This neonate was not born with neutropenia nor born to a mother who experienced neutropenia. The neonate was born with thrombocytopenia, a rash, and increased erythrocyte sedimentation rate. She had multiple biopsies, which excluded neonatal systemic lupus erythematosus, leukemia, and leukemia cutis. The bone marrow biopsy was also normal and, according to rheumatology records, this autoimmune disorder was thought to be unrelated to in utero chemotherapy exposure. Comparatively, there were no neonatal deaths in the dose-dense group. Neonatal outcomes are outlined in Table 4.

There was one case of maternal neutropenia (10%) in the dose-dense group and five (5.1%) in the conventional chemotherapy group (P=.437). The patient in the dose-dense group with neutropenia received doxorubicin and cyclophosphamide and then a paclitaxel regimen, whereas the patients in the conventional chemotherapy group with neutropenia received the following regimens: doxorubicin, cyclophosphamide, and 5-fluorouracil (n=1); doxorubicin and cyclophosphamide (n=3); and epirubicin and cyclophosphamide (n=1). None of the women in the dose-dense group reported neuropathy, and one woman reported myalgia only. Median for maternal follow-up was 3.9 years (range 2.2–6.5 years). The incidence of recurrence in the dose-dense group was 20% (2 of 10), which was not significantly different than the incidence in the conventional chemotherapy group at 24% (24 of 99; P>.99). The median time to recurrence was statistically insignificant with 17.55 months (range 13.07–22.03 months) in the dose-dense group and 16.17 months (range 7.51–24.26 months) in the conventional chemotherapy group (P>.99).

Table 4. Neonatal Outcomes

Chemotherapy Interval	Conventional Chemotherapy	Dose-Dense Chemotherapy	P
Gestational age (wk)	36 4/7	35 5/7	.60
Birth weight (g)	2,576	2,560	.64
IUGR (%)	7	0	>.99
Congenital anomalies (n)	3	1	.30
Neutropenia (%)	0	10	.09
Spontaneous preterm birth or preterm PROM (%)	17	30	.19

IUGR, intrauterine growth restriction; PROM, premature rupture of membranes.

Overall 3.5-year survival in the dose-dense group was 90%, whereas in the conventional chemotherapy group, it was 86% (P>.99). These results are summarized in Table 5. Figures 1 and 2 are survival curves, illustrating time to death from birth and time to death from diagnosis for each group, respectively.

DISCUSSION

As a result of a delicate balance among maternal well-being, fetal safety, and limited data, cancer diagnosis during pregnancy presents a challenge to the health care practitioners and patients. For patients who choose to continue their pregnancy after the cancer diagnosis, the delay in initiating treatment to prevent fetal exposure until the postpartum period may be detrimental to their health and long-term survival. There is evidence in the nonpregnant population that dose-dense chemotherapy may improve survival compared with conventional dosing or, at minimum, is certainly not inferior and may allow faster

Table 5. Maternal Outcomes

Chemotherapy Interval	Conventional Chemotherapy	Dose-Dense Chemotherapy	*P*
Neutropenia	5.1	10	.44
Recurrence	24	20	>.99
Time to recurrence (mo)	16.2	17.6	>.99
Survival	86	90	>.99

Data are % unless otherwise specified.

completion of chemotherapy.[11–14] The latter is especially salient in pregnant patients in whom timing is of utmost importance to complete the cycles within several weeks of delivery so that sufficient time is allowed for maternal recovery before delivery. In our cohort, 50% of women in the dose-dense group received taxane therapy as compared with only 5% of those in conventional chemotherapy group. Although all regimens were chosen by the patients' oncologists, we theorize that this large discrepancy is again the result of timing limitation of conventional chemotherapy. To complete dose-dense therapy during pregnancy, approximately 16 weeks are needed (four cycles of doxorubicin and cyclophosphamide followed by taxane every 2 weeks for four cycles). For conventional chemotherapy completion, 12 weeks are needed only for doxorubicin and cyclophosphamide completion (four cycles every 3 weeks) and adding taxane every 2 or 3 weeks would bring the completion time very close to delivery, if not past the date. This limits the completion of full conventional chemotherapy cycles with the use of taxane, if deemed necessary by the patient's oncologist, to only those women who are diagnosed very early in their pregnancy and initiate treatment as soon as they enter the second trimester.

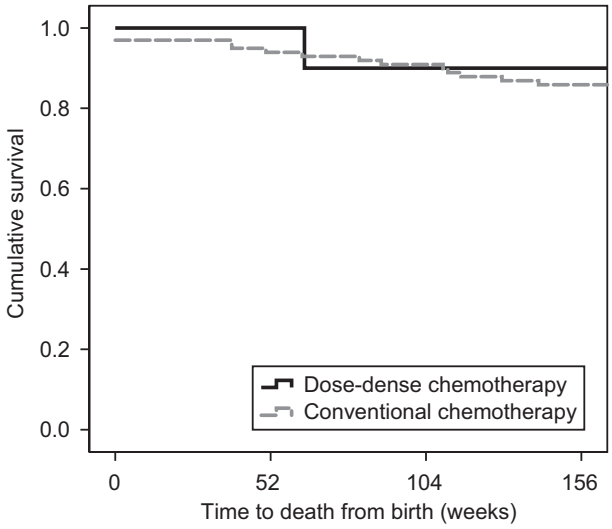

Fig. 1. Time from date of delivery to time of death. *P*=.723.
Cardonick. Dose-Dense Chemotherapy in Pregnancy. Obstet Gynecol 2012.

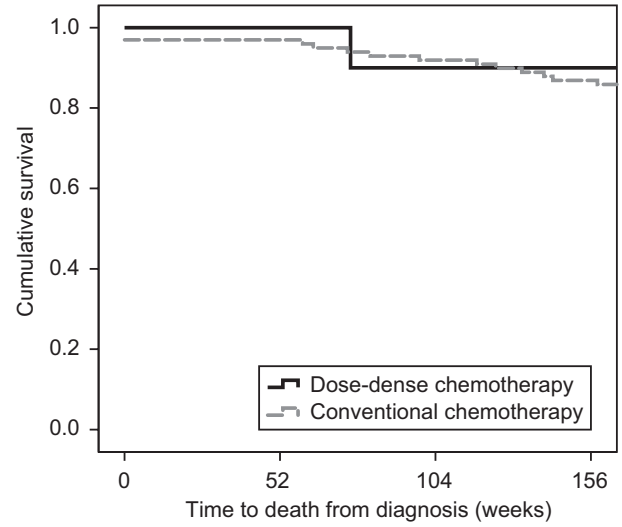

Fig. 2. Time from cancer diagnosis to death. *P*=.728.
Cardonick. Dose-Dense Chemotherapy in Pregnancy. Obstet Gynecol 2012.

Our study reports on 10 women exposed to a dose-dense regimen of doxorubicin and cyclophosphamide. Although the small number of patients, lack of randomization, and the lack of power are major limitations of our study, we believe this report may be a reassuring beginning to further enhance our knowledge of fetal effects (or possibly the lack thereof) of in utero exposure to a range of chemotherapeutic regimens and dosing intervals.

The major limitation of our study is the small number of women receiving dose-dense chemotherapy. This is not surprising as a result of the hesitancy of health care practitioners and patients to readily adopt new treatments during pregnancy despite advances in the nonpregnant population. Conservative approaches to the treatment of cancer during pregnancy are warranted such as not using new chemotherapeutic agents if there is no experience during pregnancy. Literature in the case of cancer during pregnancy is destined to be primarily in case report formats. As advances in chemotherapeutic dosing strategies and biologic treatments are made, it is beneficial for obstetric literature to keep up with reporting of cases exposed to these new protocols to improve care for pregnant women. It is very difficult to study this population prospectively, which is

a major advantage of a registry enrolling women at diagnosis during pregnancy. Although patients are enrolled in the Cancer and Pregnancy Registry prospectively, these data are analyzed as a retrospective cohort. Based on a power calculation performed for this study, 1,158 women would need to have been recruited to detect a significant difference in gestational age at delivery between groups, 1,950 women would be required to detect variation in birth weight at delivery, 896 for maternal time to recurrence after delivery, and 2,160 women would have been required to reach power for survival comparisons.

Being diagnosed with breast cancer during pregnancy poses great challenges for patients and their physicians. The fear of harming the fetus can prevent the pregnant woman with breast cancer from receiving the optimal treatment for her disease. Exposure of the fetus to chemotherapy in utero has been reported in approximately 400 cases.[15] To date, no study has reported on maternal and neonatal outcomes of fetal exposure to dose-dense chemotherapy. Our study supports that the dose-dense schedule may be considered for pregnant women with breast cancer. Although our study is small, it showed no significant neonatal or maternal effects using the more frequent dose-dense interval. Larger studies and longer follow-up is required, but our study may be reassuring in counseling patients faced with the difficult decisions of receiving the optimal chemotherapeutic regimens and schedules during pregnancy.

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