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Breast Cancer During Pregnancy

Maternal and Fetal Outcomes

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Abstract: Purpose: Breast cancer is the most common malignancy occurring during pregnancy. Because more women delay childbearing, the diagnosis of cancer during pregnancy will likely increase. Case reports exist in the literature regarding the treatment of pregnant women with breast cancer, but few are prospective and few provide long-term follow-up on the neonate exposed to chemotherapy. In this report, 130 women diagnosed with breast cancer were reported to our voluntary national registry and followed up prospectively.

Patient and Methods: The Cancer and Pregnancy Registry is a voluntary registry that monitors the clinical course, treatment, and disease outcome of women diagnosed with cancer during pregnancy and the perinatal and neonatal outcomes of their children.

Results: Of the 130 diagnosed, 120 were diagnosed with a primary tumor, 8 with a recurrence, and 2 with a new primary cancer. Mean maternal age at diagnosis was 34.8 ± 4.2 years. Mean gestational age at diagnosis was 13.2 ± 8.1weeks. Gestational age was 12.8 ± 7.8 weeks for patients with primary disease and 16.25 ± 11 weeks for those with recurrent cancer. One hundred thirteen women were followed up for mean of 3.14 ± 2.5 years. Of those followed up, 103 were diagnosed with primary breast cancer during pregnancy, 8 with a recurrence, and 2 with a new primary. Recurrence was reported in 30 patients at an average of 16.2 ± 10.8 months from delivery to recurrence. Twenty-one patients are deceased with an average of 24.71 ± 15.32 months from delivery to death. Only 42% were diagnosed with an estrogen-positive tumor and 35% of cases had a progesterone receptor-positive tumor. Human epidermal growth factor receptor 2 was positive in 25% of patients. Chemotherapy was given during pregnancy in 104 cases; the first treatment was given at a mean gestational age of 20.4 ± 5.4 weeks. The malformation rate of exposed neonates was 3 not greater than the general population. Survival by stage for a primary diagnosis in pregnancy is as follows: stage I, 100%; stage II, 86%; stage III, 86%; and stage IV, 0%.

Discussion: Pregnant women diagnosed with breast cancer can receive treatment comparable with nonpregnant women leading to a similar survival when matched for stage at diagnosis. The majority of children who were exposed to chemotherapy in utero did not demonstrate significant complications. We report the single largest cohort of women diagnosed with breast cancer during pregnancy.

Key Words: pregnancy, breast cancer, chemotherapy, children

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Cancer can complicate pregnancy, occurring in 1 per 1000 pregnancies, with 3500 cases estimated annually. Breast cancer is the most common malignancy occurring during pregnancy. Because more women delay childbearing to later maternal ages, the diagnosis of cancer during pregnancy will likely increase. In addition, delayed first birth is itself a risk factor for breast cancer. Newly found breast masses discovered during pregnancy should not be attributed to normal physiologic changes of pregnancy or delay in diagnosis may occur. Ultrasound and mammography can be safely used to investigate any palpable mass in the breast or axilla,[1] and at any gestational age, biopsies can be safely performed.

Once a pregnant woman is diagnosed with breast cancer, decisions need to be made promptly regarding the pregnancy and cancer treatment. Studies of pregnant women diagnosed with breast cancer fail to show a survival benefit with termination of the pregnancy, and this is a personal choice to be made on a case by case basis.[2–6] Although it may be perceived that administering life-saving chemotherapy to the mother is in conflict with the interests of the developing fetus in utero, the goals of breast cancer treatment are the same for pregnant and nonpregnant women: control the cancer locally and prevent systemic spread. Case reports exist in the literature regarding the treatment of pregnant women with breast cancer, but few are prospective and few provide long-term follow-up on the neonate exposed to chemotherapy. In this report, one of the largest series reported to date, 130 women diagnosed with breast cancer were reported to our voluntary national registry. The majority were followed up prospectively during pregnancy. Maternal and neonatal follow-up is provided and is ongoing.

PATIENTS AND METHODS

The Cancer and Pregnancy Registry is a voluntary registry established in 1996 to monitor the clinical course, treatment, and disease outcome of women diagnosed with cancer during pregnancy and the perinatal and neonatal outcomes of their children. Establishment and maintenance of the database have been approved by the institutional review board. The Registry has a total of 234 patients from North America, Europe, and Australia diagnosed during pregnancy with cancer, including ovarian, cervical, lung, colon, rectal cancer, Non-Hodgkin lymphoma, Hodgkin lymphoma, and acute leukemia. Breast cancer is the most common cancer diagnosed in pregnant women in the registry, comprising 130 of the enrollees. To be enrolled, patients completed an institutional review board consent form and signed medical release forms giving us permission to obtain records from their obstetrician, oncologist, radiation oncologist, and their child's pediatrician.

Pregnant women are offered enrollment at the diagnosis of cancer and followed up prospectively. Some women did request enrollment after learning of the registry after delivery. These patients are enrolled but noted in the registry as a retrospective

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enrollment. Ninety-nine patients were prospectively enrolled, and 31 were retrospectively enrolled.

Records were requested with regard to cancer diagnosis, treatment, and yearly oncology follow-up after delivery. Medical records were the source of information entered in the database. Obstetric records were reviewed for pregnancy outcome and pediatric records for yearly follow-up on the child. Oncology records were reviewed for details about presentation, diagnosis, staging, and treatment during pregnancy including chemotherapy agents, doses, and dates of administration, and gestational age at treatment. Neonatal data were collected at delivery and yearly from the child's pediatrician. Placental pathology was requested and performed at the hospital where the patient delivered. Maternal disease and health status were requested on a yearly basis from the patient's oncologist. Data were entered into a database after medical record review. Follow-up is conducted on a yearly basis with oncology and pediatrics.

RESULTS

One hundred thirty women with breast cancer diagnosed during pregnancy are included in the database. Unlike previous reports of "gestational breast cancer," cases diagnosed up to a year postpartum are not included in this report. Patients are included if their diagnosis occurred between the last menstrual period, LMP, and termination, miscarriage, or delivery. Patients were also included if their diagnosis was within 6 weeks of their delivery because they were assumed to have had breast cancer during the pregnancy, which was undiagnosed until postpartum. Medical records for all patients were requested and reviewed.

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Of those 130 diagnosed, 120 were diagnosed with a primary tumor, 8 with a recurrence, and 2 with a new primary cancer. Ninety-eight women contacted the registry before knowing the outcome of their pregnancy and were prospectively followed up during pregnancy. Twenty-nine women contributed their information after miscarriage or delivery, and their records were reviewed as well. Mean maternal age at diagnosis was 34.8 ± 4.2 years, with ages ranging from 23 to 47. The mean gestational age at diagnosis was 13.2 ± 8.1weeks. Gestational age was 12.8 ± 7.8 weeks for patients with primary disease and 16.25 ± 11 weeks for those with recurrent cancer. Of the 130 diagnosed, 80% were white, 7.7% were African American, 7.7% were Hispanic/Latino, 1.5% were American Indian, and 1.5% were Pacific Islander; ethnicity was not listed in 1.6%. Maternal demographics are displayed in Table 1.

T1

Fifty women (39%) reported a family history of breast cancer. Eighteen women (16%) reported a first degree relative with breast cancer (16 mother and 2 sister), and 2 women (1.7%) report a first degree relative with ovarian cancer. Thirty-two women (23%) reported more distant relatives with breast cancer.

In 32 women, this was their first pregnancy, thus the majority of patients were multiparous. Thirty patients were advised to terminate, 20 by a physician; oncologist, surgeon, or obstetrician. Termination was recommended to 16 patients at a gestational age of less than 12 weeks, 5 patients with a gestational age range of 13 to 23 weeks, 1 patient with a gestational age of 24 weeks, and gestational age was unknown in 6 patients. The number of women advised to terminate their pregnancies did not change between 1996 and 2003 but declined only slightly in the last 5 years. Ten underwent elective termination, and 6 had a spontaneous miscarriage before 13 weeks gestation. Chemotherapy had not been given before spontaneous loss. One patient who underwent elective termination received chemotherapy before she recognized she was pregnant.

Of those with primary disease, 23 women were diagnosed with stage I, 55 with stage II, 25 with stage III, and 4 with stage IV. In 13 women, stage at diagnosis was not documented. For those with recurrent disease, stage at diagnosis was as follows: 1 patient with stage I, 0 patients with stage II, 1 patient with stage III, and 5 patients with stage IV; 1 patient with unknown stage. One woman diagnosed with a new primary was stage I and the other stage IV. Invasive ductal carcinoma was the most common subtype of breast cancer diagnosed during pregnancy. As expected with premenopausal breast cancer, the majority of women diagnosed during pregnancy had estrogen receptor-negative tumors. Only 42% were diagnosed with an estrogen-positive tumor. Thirty-five percent of cases had a progesterone receptor-positive tumor. Human epidermal growth factor receptor 2 (HER-2/neu) was positive in 25% of patients. Breast cancer gene 1 or 2 was tested in only 37 patients and was positive in 3 patients. Table 2 lists stages at diagnosis, cancer subtypes, and receptor status.

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Ninety-five patients underwent surgery during pregnancy, 38 in the first, 48 in the second, and 9 in the third trimester. Fifty-four women under went mastectomy, 34 lumpectomy, and 15 excisional biopsy that did not require further surgery. None of the patients received radiation until postpartum. Two patients underwent bilateral mastectomy. Lymph node status was positive in 50 patients (53%). Three patients miscarried within 1 month of their surgery in the first trimester. This miscarriage rate of 7% is not higher than that in the general population in which 15% of pregnancies miscarry by 12 weeks gestation. The mean time between diagnosis and surgery during pregnancy was 52.2 days, regardless in which trimester the patient was diagnosed. Mean gestational age at surgery was 14.7 ± 7.7 weeks. Sentinel node biopsy, the majority using radioactive material without blue dye injection, was performed in 30 patients. Within this group, 2 spontaneous miscarriages occurred in the first trimester. (Of 17 patients undergoing sentinel biopsy during the first trimester, two (12%) miscarriages occurred.) Three children (10%) had a birth weight less than the 10% for gestational age at delivery. Two children are followed up for recurrent otitis media, and 2 had complications in the neonatal intensive care nursery due to prematurity. Two children were born with malformations in the sentinel node biopsy group-asymptomatic pulmonary artery fistula and hydrocephalus not requiring a shunt. One child was born with thrombocytopenia and was diagnosed with an autoimmune disorder, resulting in her demise at 13 months of age. No other long-term medical issues were reported in neonates exposed to the sentinel node procedure.

Of the 113 patients with an ongoing pregnancy, 9 patients underwent surgery only, 77 patients received surgery and adju-

TABLE 1. Demographics

Patient Characteristics	Percentile
Mean age at diagnosis (yr)	34.8 ± 4.3
Mean gestational age at diagnosis (wk)	13.14 ± 8.1
Primagravid	25%
Race/ethnicity (%)	
White	80
Hispanic	7.7
African American	7.7
American Indian	1.5
Pacific islander	1.5
Unknown	1.6
Family history: breast or ovarian cancer (%)	
No history of breast cancer	59.3
First degree relative: breast cancer	16
First degree relative: ovarian cancer	1.7
Second degree/distant: breast cancer	23

TABLE 2. Breast Cancer Types, Mean Tumor Size, Receptors and Stages

	Type	Mean Tumor Size	ER +	ER −	PR +	PR −	HER-2/ Neu +	HER-2/ Neu −	BRCA
Primary disease									
Stage unknown (N = 13)	Unknown (N = 6)	1.2	1 (16%)	2 (33%)	0 (0%)	1 (16%)	1 (16%)	0 (0%)	Not tested = 2
	Ductal (N = 6)	1.1	2 (29%)	3 (43%)	1 (14%)	3 (43%)	1 (14%)	4 (57%)	Negative = 3
									Not tested = 2
	Lobular (N = 1)	1.1	1 (100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)	Not tested = 1
Stage I (N = 23)	Unknown (N = 2)		2 (100%)	0 (0%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)	Negative = 1
	Ductal (N = 20)	1.1	11 (55%)	9 (45%)	7 (22%)	12 (60%)	4 (20%)	16 (80%)	Negative = 6
									Not tested = 11
	Medullary (N = 1)		0 (0%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)	Positive = 1
Stage II (N = 55)	Unknown (N = 5)	1.2	3 (60%)	2 (40%)	3 (60%)	2 (40%)	1 (20%)	2 (40%)	Not tested = 3
	Ductal (N = 46)	2.1	14 (30%)	32 (70%)	10 (22%)	33 (72%)	12 (26%)	31 (67%)	Negative = 16
									Positive = 1
									Not tested = 24
	Medullary (N = 1)	2.5	0 (0%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)	Not tested = 1
	Inflammatory (N = 1)		0 (0%)	1 (100%)	0 (0%)	1 (0%)			Not tested = 1
	Lobular (N = 2)	1.5	1 (50%)	1 (50%)	2 (100%)	0 (0%)	1 (50%)	1 (50%)	Not tested = 2
Stage III (N = 25)	Unknown (N = 2)		1 (50%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)		Negative = 1
	Ductal (N = 16)	3.8	9 (56%)	6 (38%)	9 (56%)	6 (38%)	7 (44%)	7 (44%)	Negative = 3
									Not tested = 8
	Inflammatory (N = 4)	2.0	0 (0%)	4 (4%)	1 (25%)	3 (75%)	1 (25%)	2 (50%)	Negative = 1
									Not tested = 3
	Lobular (N = 3)	3.3	2 (67%)	1 (33%)	3 (100%)	0 (0%)	1 (33%)	2 (67%)	Negative = 2
Stage IV (N = 4)	Ductal (N = 3)		2 (67%)	1 (33%)	2 (67%)	1 (33%)	1 (33%)	1 (33%)	Not tested = 2
	Lobular (N = 1)		0 (0%)	1 (100%)	0 (0%)	1 (100%)			Not tested = 1
Total	120		49 (41%)	66 (55%)	41 (34%)	67 (56%)	32 (27%)	70 (58%)	Positive=2
									Negative=32
									Not tested= 60
Recurrent disease									
Stage Unknown (N = 1)	Inflammatory (N = 1)		0 (0%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)	Not tested = 1
Stage I (N = 1)	Ductal (N = 1)	0.3	1 (100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)	Negative = 1
Stage III (N = 1)			1 (100%)	0 (0%)					
Stage IV (N = 5)			3 (60%)	1 (20%)	2 (40%)	1 (20%)	0 (0%)	3 (60%)	Positive = 1
Total	8		5 (63%)	2 (25%)	3 (38%)	2 (25%)	0 (0%)	5 (63%)	Positive = 1
									Negative = 1
									Not tested = 1
New primary									
Stage unknown (N = 1)	Ductal		0 (0%)	1 (100%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)	Not tested = 1
Stage IV (N = 1)	Ductal		1 (100%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)	Not tested = 1
Total	2		1 (50%)	1 (50%)	1 (50%)	1 (50%)	0 (100%)	1 (50%)	Not tested = 2
All patients									
Grand total	130		55 (42%)	69 (53%)	45 (35%)	70 (54%)	32 (25%)	76 (59%)	Positive = 3
									Negative = 34
									Not tested = 63

ER indicates estrogen receptor + or − (positive or negative); PR, progesterone receptor + or − (positive or negative); Her-2neu, human epidermal growth factor receptor 2; BRCA, *breast cancer gene 1 or 2.*

vant chemotherapy, 27 patients received chemotherapy alone, and 3 patients received no treatment during pregnancy. Including 3 sets of twins, 116 infants were delivered, 75 by a vaginal delivery, 37 by cesarean section, and 4 with an unknown mode of delivery.

Chemotherapy was given during pregnancy in 104 cases. The first chemotherapy treatment was given at a mean gestational age of 20.4 ± 5.4 weeks. The majority of patients, 69%, received adriamycin and cytoxan during pregnancy. Other regimens included 5-fluorurical, adriamycin, and cytoxan; 5-fluoruricil, epirubicin, and cytoxan; and adriamycin or navelbine alone. In 11 cases, paclitaxel, docetaxel, or taxotere were also given. Table 3 describes the number of cases exposed to a particular regimen, the trimester during which treatment was given, any pregnancy complications, and age of the

TABLE 3. Chemotherapy Regimens and Pregnancy Outcome

N	Trimester Tx Given	Pregnancy Complications	Fetal/Neonatal Phenotype, Age Follow-Up (yr)	Agents
58	2,3		Nl, age range 0.5–13.2 (more than 50% older than 1 yr)	A and C
5	2	IUGR in 5	Nl, range birth to age 9 yr	A and C
1	2	Temporary feeding tube		A and C
1	2	Apnea of prematurity, respiratory distress, and GE reflux	Nl, age 3.6	A and C
1	2,3	Echo with small main pulmonary artery fistula, asymptomatic	Nl, age 3.1	A and C
1	2,3	Placental abruption, GE reflux as preemie	Nl, age 2.1	A and C
1	2,3	Meconium, IUGR, neonatal thrombocytopenia, and rash	Neonatal death 1 yr secondary to severe autoimmune disorder	A and C
2	2,3	Transient tachypnea of newborn	Nl, age 1.5–2	A and C
1	2,3	Transient tachypnea of newborn then hyperventilation to hypocapnia, periventricular leukomalacia diagnosed 2 mo, developmental delay	No seizures over 1 yr, now 6.5	A and C
1	2	Placenta previa, delivery 33 wk, RDS, sepsis, and anemia	Nl, age 1	A and C
12	2,3		Nl, age range birth to age 4.3	A, C, and F
1	2,3	Transient tachypnea of newborn	Nl, age 11.3	A, C, and F
1	2,3	Jaundiced at birth	Nl, age 0.3	A, C, and F
1	2,3			A, C, and F
1	2,3	IUGR		A
1	2,3	IUGR, hyperbilirubinemia	Nl, age 0.42	A, C, and F then P
2	2,3		Nl, age range 1.3 to 3.8	F, E, and C
4	2,3	1 Hyperbilirubinemia	Nl, range age 1.4 to 7.3	A and C then P
2	2,3		Nl, at birth	A, C, and P then D
1	2,3	Neutropenia, pyloric stenosis	Nl, 0.2	A, C, and P then D
1	2,3		Nl, age 1	A and C then D
1	2,3	Holoprosencephaly suspected at birth	Nl, age 2.6, prominence of lateral ventricles otherwise unremarkable	A and C then D
1	2,3		Nl, age 1.3	E and C
1	2,3	Left eye hemangioma, talipies	Nl, age 3 except for "eye squinting"	E and C
1	2,3		Nl, at birth	E and D
1	2,3		Nl, age 4 mo	N

IUGR indicates intrauterine growth restriction; RDS, respiratory distress syndrome; A, adriamycin; C, cytoxan; F, 5-flurouracil; P, paclitaxel; D, docetaxel; E, epirubicin; N, navelbine.

TABLE 4. Maternal Side Effects or Complications During Chemotherapy in Pregnancy

Side Effect/Complications	N	Agents
Mouth ulcers	3	AC, EC
Cellulitis of arm	2	AC, D
Vaginal candidiasis	1	AC
Neutropenia	5	FAC, AC, EC
Neuropathy	1	P
Anaphylaxis	2	P
Bone pain	1	FAC
Pneumonitis	1	AC
Constipation	2	AC
Tachycardia	2	AC, D
Edema	1	D

A indicates adriamycin; C, cytoxan; E, epirubucin; P, paclitaxol; D, docetaxol.

exposed child at latest follow-up. Mean number of cycles given during pregnancy was 4.3 ± SD 1.7. The mean number of days between the last antenatal treatment and delivery was 39.6 ± 26.7 days. Maternal side effects or complications during chemotherapy in pregnancy are listed in Table 4. Of the patients who were HER-2/neu positive, none received herceptin during pregnancy. **T4**

Pregnancy and Neonatal Outcomes

One hundred thirty women were diagnosed with breast cancer during pregnancy. Ten patients elected termination of pregnancy, and 6 had a spontaneous miscarriage. One hundred thirteen women continued their pregnancies and including 3 sets of twins delivered 116 infants. The mean gestational age at delivery was 36 ± 2.7 weeks, and the birth weight was 2690 ± 731 g. For neonates exposed to chemotherapy, the mean gestational age and birth weight at delivery were 35.8 ± 1.9 weeks and 2836 ± 1075 g, respectively. Note that the mean gestational age of this cohort is less than 37 weeks, which is considered a "late preterm" delivery. This gestational age is somewhat iatrogenic as several patients who required paclitaxel/docetaxel or radiation therapy postpartum were electively delivered between 34 and 36 weeks to have such treatment sooner after completing anthracycline therapy during pregnancy. Also, influential was the fact that chemotherapy was not given after 34 weeks, so that the patients would not go into spontaneous labor during the nadir period. If the patient required additional treatment after delivery, decision was made to not await spontaneous labor after 34 weeks because this could potentially cause an additional 6 weeks delay in treatment before the patient's due date of 40 weeks.

TABLE 5. Delivery Outcomes by Treatment in Pregnancy

Treatment in Pregnancy	N	Gestational Age (wk)	Birth Weight (g)
None	2	35.00 ± 4.24	2.630 ± 891
Surgery only	10	37.5 ± 3.5	2880 ± 689
Chemo only	23	35.8 ± 1.92	2836 ± 1075
Chemo and surgery	81	35.9 ± 2.82	2615 ± 603

Other etiologies for preterm delivery included placental abruption at 28 and 35 weeks, 3 weeks, and 3 days after the last chemotherapy treatment. Two patients were induced for preeclampsia, another delivered preterm for oligohydramnios, and 1 case of spontaneous preterm labor occurred, at 29 weeks, 18 days after chemotherapy. Two patients were delivered preterm for nonreassuring fetal testing 5 and 20 days after chemotherapy. Neither infant was growth restricted. No significant differences were found for the gestational age at delivery or birth weight according to the treatment given during pregnancy (Table 5). T5

Eight women delivered infants with birth weight less than the 10% for gestational age, all in either the group treated with chemotherapy alone or chemotherapy and surgery. Details about the chemotherapy regimen and pregnancy complications are listed in the Table 3. Most interesting, pregnant women experienced more nausea and side effects, such as parasthesias, while receiving chemotherapy during pregnancy than they experienced postpartum with the same agents. Although the nausea may be related to the hormonal influence of pregnancy, one must be concerned that the physiologic changes of pregnancy affecting drug metabolism and excretion, and the increased blood volume may affect active drug levels. This perceived decreased side effects while chemotherapy during pregnancy has not yet been reported. Unfortunately, we do not have pharmacokinetic studies on these patients. Pregnancy complications occurred in 19 cases including meconium, jaundice, grunting, neutropenia, hyperbilirubinemia, abnormal hearing, respiratory distress, and apnea. Birth defects were reported in 4 cases exposed to chemotherapy and included pyloric stenosis, asymptomatic pulmonary artery fistula, holoprosencephalopathy, and talipes and a hemangioma in the same child. This malformation rate of 3.8% among those exposed to chemotherapy is not higher than that reported in the general population.[7] One child not exposed to chemotherapy was diagnosed with neurofibromatosis. One neonate electively delivered at 35 weeks by repeat cesarean section suffered from tachypnea for 24 hours before intubation after which 2 spontaneous pneumothoraces occurred. Intubation complications included extreme hypocapnia. One child born with a birth weight less than 10% developed thrombocytopenia and a rash soon after birth. Maternal platelet antibodies were excluded. She developed retinal detachment and was diagnosed with a systemic autoimmune disorder resulting in her demise at 13 months of age. Her mother had received 2 courses of adriamycin/cytoxan during pregnancy, the last 26 days before delivery.

Complete blood counts with differential were requested for all neonates exposed to chemotherapy in utero but only 15 physicians complied. One case of neutropenia occurred. All neonates had hair at birth. Placental pathology was requested in all cases regardless of cancer treatment, but the results were received in only 16 cases. Calcifications, focal infarcts, villous edema, hypovascularity, acute chorioamnionitis, and intervillous fibrin were noted. Breast feeding was prohibited if chemotherapy was not completed before delivery. For women who completed chemotherapy before delivery, and 38 attempted breast feeding; however, breast feeding was only successful in 55% of patients. Seventeen women (45%) of patients, reported little milk production. The decreased breast milk production after antenatal chemotherapy has not been reported previously. This is a consistent observation and complaint of the majority of patients treated with chemotherapy for breast cancer during pregnancy.

Ninety-three pediatricians provided long-term follow-up for the children in the Registry, with the mean age of follow-up being 41.8 ± 32 months; mean weight and height percentiles are 48% and 58%, respectively. Medical issues include gastroesophageal reflux, pneumonia, corneal abrasion, IgA deficiency, otitis media, and speech delays in 2 cases exposed to chemotherapy in utero. Long-term medical issues affecting children not exposed to chemotherapy include speech delay in 1 case and neurofibromatosis as described earlier.

Maternal Survival

One hundred thirteen women were followed up for of 3.14 ± 2.5 years. Of those followed up, 103 had been diagnosed with primary breast cancer during pregnancy, 8 with a recurrence, and 2 with a new primary. Oncologists reported that a recurrence occurred in 30 patients at an average of 16.2 ± 10.8 months from delivery to recurrence. Among those patients with recurrent disease, 20 were diagnosed with a stage IV recurrence. Twenty-one patients are deceased with an average of 24.71 ± 15.32 months from delivery to death. One patient reported a new primary. Survival by stage for a primary diagnosis in pregnancy is as follows: stage I, 100%; stage II, 86%; stage III, 86%; and stage IV, 0% (Table 6). There was no significant difference in survival for primary disease if the patient elected termination of the pregnancy, had a spontaneous miscarriage or continued the pregnancy, and delivered a live born infant (Tables 7 and 8). Survival in those who elected termination was 83% (5 of 6), and in those with a live born, the survival was 85% (81 of 95), $P = 1.000$, Fisher exact test was used. T6 T7–8,A

DISCUSSION

Breast cancer is one of the most common cancers complicating pregnancy. Seven percent to 15% of premenopausal cases occur during pregnancy. The Cancer and Pregnancy Registry has data on the largest cohort of pregnant patients diagnosed with breast cancer, the majority followed up prospectively, of whom 104 were treated with chemotherapy. Consistent with the literature, the majority of pregnant women in this series were diagnosed with stage II or III disease. Similar to nonpregnant women, pregnant women with breast cancer often present with a palpable mass. A delay in diagnosis occurs in pregnant women because the changes that occur in the breast during pregnancy, masses or lumps, may be ascribed to the "normal" changes of pregnancy. To avoid a delay in diagnosis, any solitary mass found during pregnancy or postpartum period should be evaluated promptly. As in premenopausal nonpregnant women, most tumors in pregnant women are estrogen receptor negative.[8]

TABLE 6. Neonatal Outcome

Ongoing Pregnancies	Follow-Up Provided	Mean Follow-Up: Age (mo)	Mean Height Percentile	Mean Weight Percentile
112	93	41.8 ± 32	59%	48%

TABLE 7. Neonatal Complications

	N
Exposed to chemotherapy	
Reactive airway disease	2
Recurrent otitis media	2
Recurrent otitis media and upper respiratory infections	1
Selective IgA deficiency	1
Speech delay	2
Recurrent otitis media and myringotomy tubes and minor hearing loss	1
Hypocapnia at birth, hypotonia, and periventricular leukomalacia	1
Autoimmune disorder resulting in death at 13 mo	1
GERD and anemia of prematurity	1
Unexposed to chemotherapy	
Spontaneous mutation for neurofibrmoatosis	1
Expressive speech deficit	1

GERD indicates gastroesophageal reflux disease.

Several authors have reported no survival difference between women diagnosed with breast cancer during pregnancy and stage-matched nonpregnant women. Nugent and O'Connell compared 19 pregnant women with 155 nonpregnant women matched for age and stage of breast cancer at diagnosis.[1] Pregnant women were more likely to be diagnosed at stage II compared with nonpregnant women (74% vs 37%) and less likely to be diagnosed with early stage disease (21% vs 54%). Five-year survival compared at each stage showed no significant difference between pregnant and nonpregnant women.[1]

In our cohort, survival by stage was I, 100%; II and III, 86%; and IV, 0. According to the American Cancer Society Surveillance Research in 2007, 5-year survival rates for localized disease is 98%, regional spread 83%, and distant spread 26%.[9] Survival rates at 3 years for pregnant women diagnosed with stages I to III seem comparable with nonpregnant women at 5 years. Women diagnosed with stage IV in pregnancy seem to do worse than nonpregnant women but only 4 women in the registry were diagnosed with primary breast cancer at this stage.

Routine termination of pregnancy after a diagnosis of breast cancer does not seem to improve survival. There was a worsening trend for survival in patients choosing termination, but no statistically significant difference in 5-year survival when these groups were compared by several authors. Nugent and O'Connell reported 19 women diagnosed with breast cancer during pregnancy and found no difference in survival after termination of the pregnancy.[1] Deemarsky and Neishtadt reported a worse prognosis for 14 women who terminated the pregnancy, compared with 8 who continued the pregnancy.[2] King et al reported a 43% 5-year survival for 27 women who terminated the pregnancy, compared with a 59% 5-year survival for 39 patients who carried the pregnancy to term; a statistical analysis was not provided.[3] Clark and Reid reported that 21 women who elected termination had a worse survival compared with 116 women who continued the pregnancy.[4] Finally, Zemlickis and Lishner reported no difference in survival between 32 women who continued their pregnancy versus 9 who elected termination or had a spontaneous loss.[5] Not all studies matched patients for stage of disease or provided explanations affecting patient choices. Therefore, it is difficult to determine whether women with advanced stage disease, or a worse prognosis at diagnosis, were encouraged to terminate their pregnancy, whereas women with earlier stage disease, or a better prognosis at diagnosis were not. Still, routine termination of pregnancy has not been demonstrated to offer a survival advantage for pregnant women diagnosed with primary breast cancer.

In the cohort reported here, there was no significant difference in survival if the patient elected termination of the pregnancy, had a spontaneous miscarriage, or continued the pregnancy and delivered a live born infant. Follow-up was more difficult to obtain for the patients who chose pregnancy termination. It remains of the goal of this registry to request oncology follow-up on patients who have chosen termination of pregnancy.

Estrogen receptor and HER-2/neu status were comparable with other cohorts of nonpregnant women with breast cancer. In a recent review by Barnes and Newman,[10] estrogen receptors were positive in 27% to50% of pregnant women compared with 44% to 64% in nonpregnant patients. In this cohort, 42% of tumors were estrogen positive. Elledge and Ciocca[11] reported that 58% of cancers diagnosed during pregnancy were positive for HER-2/neu compared with only 16% of the tumors of nonpregnant women. Other authors found the rate similar in nonpregnant age-matched women. The expression of HER-2/neu in the tumors of nonpregnant women less than 35 years of age is 25% to 50%.[12] The incidence in pregnant women ranges between 28% and 58%. Middleton and Amin[13] too

TABLE 8. Maternal Follow-Up by Pregnancy Outcome and Stage

Stage	LB	LB Rec	LB Death	%S	VIP/SAB	VIP/SAB Rec	VIP/SAB Death	%S
Primary disease (N = 103)								
Unknown	5	2	2	60	1	0	0	100
Stage I	17	1	0	100	3	0	0	100
Stage II	49	17	7	86	2	0	0	100
Stage III	21	4	3	86	0	0	0	NA
Stage IV	3	3	3	0	1	1	1	0
Recurrent disease and new primary (N = 10)								
Recurrent unknown	1	0	1	0	0	0	0	NA
Rec stage I	1	0	0	100	0	0	0	NA
Rec stage III	1	1	1	0	0	0	0	NA
Rec stage IV	4	1	2	50	1	0	1	0
NP stage Unk	1	0	0	100	0	0	0	NA
NP stage IV	1	0	1	50	0	0	0	NA

LB indicates livebirth; VIP/SAB, termination or spontaneous miscarriage; %S, survival among patients providing follow-up; Rec, recurrence; Rec Unk, stage of recurrence unknown; NP, new primary.

found the incidence of HER-2/neu to be similar to age-matched nonpregnant women. In this cohort, 25% of tumors were positive for HER-2/neu.

Thirty patients in this cohort underwent sentinel node biopsy in pregnancy. Using Technitium-99m sulfur colloid injected, only a minimal dose (500–600uCi) of double filtered Tc-99msulfur colloid is injected at the site of the breast tumor. As the entire radioisotope stays trapped at the sight of injection or within the lymphatics until decay occurs—the half-life is 6 hours—this does not expose the fetus to dangerous amounts of radiation.[14] A recent study explored the safety of lymphatic mapping in pregnant women with breast cancer and found no adverse effects on the fetus.[15] There is limited information on the use of blue dyes, such as lymphazurin, for sentinel node mapping in pregnancy and anaphylactic reactions are an adverse risk. Whether only using radioactive material alone lowers the sensitivity of sentinel node biopsy during pregnancy is unknown.

Between 1966 and 2004, there are 72 cases reported on pregnant women exposed to chemotherapy for breast cancer in the literature.[16] Patients were exposed to cyclophosphamide and 5-fluorouracil with methotrexate or doxorubicin. In 2006, Hahn et al prospectively followed up 57 women treated with 5-florouracil, doxorubicin, and cyclophosphamide during pregnancy. Mean gestational age at delivery was 37 weeks; mean birth weight was 2890 g. Congenital anomalies were reported in 3 cases (5.2%).[17] In this current series, 104 neonates were exposed in utero to chemotherapy without an increase in growth restriction at birth or congenital anomalies compared with population standards. If chemotherapy is indicated, it is best to avoid treatment in the first trimester as the majority of fetal organogenesis occurs between 3 and 10 weeks gestation. The option of delaying chemotherapy will depend on patient's stage and aggressiveness of disease. Women diagnosed early in the first trimester will need to take into account the impact of delaying chemotherapy until the second trimester in making a decision about continuing the pregnancy. Surgery for breast cancer can be performed at any gestational age. Patients can chose to undergo mastectomy in the first trimester and have chemotherapy in the second as opposed to delaying both surgical and systemic treatment until after 12 weeks. Patients who underwent surgery in the first trimester did not have a higher rate of spontaneous loss compared with the general population. For those patients diagnosed with breast cancer during pregnancy who undergo lumpectomy, subsequent radiation is delayed until postpartum.

Limitations of this study include the inherent risks in collecting information through a voluntary registry. Women or physicians may have moved between yearly inquiries limiting long-term follow-up. The completeness of records received varies, and not all information is available on each patient as is the nature of a voluntary registry. Although a follow-up of 3 years is a relatively short period, it is on-going and in the interest of women currently diagnosed during pregnancy that we publish our findings to date, so that women are able to make an informed choice about their cancer treatment and pregnancy.

CONCLUSION

Pregnant women diagnosed with breast cancer can receive treatment comparable with nonpregnant women leading to a similar survival when matched for stage at diagnosis. More information is necessary for patients diagnosed with stage IV breast cancer during pregnancy. Collecting cases from multiple institutions increases our awareness of the possibility that pregnant women despite their young age can be diagnosed with breast cancer, and mother and fetus can tolerate life-saving treatment during gestation.

We report the single largest cohort of women diagnosed with breast cancer during pregnancy. Few women elected termination of the pregnancy. It is a difficult decision for any patient to accept chemotherapy during pregnancy. Given, however, that the majority of pregnant women are diagnosed with at least stage II disease, accumulating information on the relative safety of chemotherapy during pregnancy will help patients, their families and their physicians make informed decisions about the treatment options for pregnant women diagnosed with breast cancer. Future studies should address the metabolism of chemotherapy in pregnant women given the physiologic changes during pregnancy, which can affect protein binding, clearance, and free drug levels.

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