

OBSTETRICS

Development of children born to mothers with cancer during pregnancy: comparing in utero chemotherapy-exposed children with nonexposed controls

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OBJECTIVE: Cancer is diagnosed in approximately 1 per 1000 pregnant women. Lifesaving cancer therapy given to the mother during pregnancy appears in conflict with the interest of the developing fetus. Often, termination of pregnancy is suggested but has not been proven in any type of cancer to improve maternal prognosis, while very few studies have documented the long-term effects of in utero chemotherapy exposure on child outcome. To counsel patients about the risk of continuing a pregnancy while undergoing cancer treatment, we performed developmental testing to provide more detailed follow-up on children exposed in utero to chemotherapy.

STUDY DESIGN: Mother-infant pairs, enrolled in the Cancer and Pregnancy Registry, were offered developmental testing for children who were ≥ 18 months of age. Based on age, the Bayley Scales of Infant Development—Third Edition, the Wechsler Preschool and Primary Scale of Intelligence—Revised, the Wechsler Intelligence Scale for Children, Third Edition, or the Wechsler Individual Achievement Test was administered. All parents or primary caregivers completed the Child Behavior Checklist, a parent questionnaire to assess behavior and emotional issues. Results of children exposed to chemotherapy before delivery were compared with children whose mothers were also

diagnosed with cancer during pregnancy but did not receive chemotherapy before delivery.

RESULTS: No significant differences were noted in cognitive skills, academic achievement, or behavioral competence between the chemotherapy-exposed group and the unexposed children. Of children, 95% scored within normal limits on cognitive assessments; 71% and 79% of children demonstrated at or above age equivalency in mathematics and reading scores, respectively; and 79% of children scored within normal limits on measures of behavior. Older children had significantly higher rates of internalizing behavior problems.

CONCLUSION: We could not demonstrate a significant difference in cognitive ability, school performance, or behavioral competence for children exposed to chemotherapy in utero compared with nonexposed controls. The majority of these children scored within normal limits on all developmental measures. Premature birth was more prevalent in the chemotherapy-exposed group yet did not predict developmental outcome. Older children in the sample demonstrated higher rates of internalizing behavior problems.

Key words: cancer, chemotherapy, child development, pregnancy

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The diagnosis of cancer during pregnancy creates medical and moral dilemmas for physicians and patients. Pregnant women are hesitant to receive chemotherapy due to concerns about possible effects on the developing fetus, while physicians are hesitant to allow pregnant women to delay cancer

treatment for the remainder of the pregnancy. Often, termination of the pregnancy is recommended. The Cancer and Pregnancy Registry, created in 1997 with approval of the Institutional Review Board at Cooper Medical School at Rowan University, follows up the pregnancies and long-term health of women

diagnosed with cancer during pregnancy. Patients are enrolled at the time of cancer diagnosis, and the treatment during pregnancy is recorded. Several women were advised to terminate their pregnancies without information about receiving cancer treatment while pregnant. Absence of long-term follow-up data on children exposed to chemotherapy in utero influenced some patient and physician decisions regarding continuing a pregnancy complicated by cancer and/or cancer treatment during pregnancy.

A developmental psychologist performed standardized developmental testing for children born to mothers diagnosed with cancer during their pregnancies. The purpose of this study is

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to report developmental outcome for children exposed to chemotherapy in utero compared with a control group of unexposed children whose mothers were diagnosed with cancer while pregnant.

Approximately 1 in 1000 pregnancies is complicated by cancer.¹ The number of births in 2010 was 3,999,386 (National Vital Statistics Report). In the past, providers have recommended termination of pregnancy but are now recognizing that pregnant patients are able to receive chemotherapy. As the majority of women do not receive chemotherapy during organogenesis, the malformation rate is not higher than the general population.²⁻⁶ The majority of organogenesis is completed by 12 weeks, yet the central nervous system continues to develop throughout gestation and after birth. A review summarized 340 fetal exposures to chemotherapy published to date and later expanded to 447 cases in 2008.^{7,8} The literature at that time provided details of the cancer diagnosis, treatment, and general pregnancy outcomes, but long-term follow-up on the children was limited. Avilés and Neri⁹ in 2001 reported long-term follow-up on 84 children born to mothers with hematological malignancies exposed in utero to chemotherapy, ranging in age from 6–29 years. All children were found to be normal physically and neurologically. School performances and standardized intelligence testing were within normal range and were not significantly different from controls (unrelated matched children and unexposed siblings).⁹ Eleven years later, a prospective study on the neurodevelopmental outcomes of 70 children aged 18 months to 18 years exposed to cancer treatment in utero was conducted, assessing health status, cognitive performance, and behavioral competence. This study reported that the majority of these children were doing well, and those children showing delays in development were concentrated in the group delivered preterm.¹⁰ This study lacked a control group of unexposed children and was unable to determine whether developmental delays were related to chemotherapy exposure or prematurity.

Documenting the long-term follow-up on children exposed to chemotherapy in utero could provide women and their physicians the information necessary to make informed decisions during diagnosis of cancer during pregnancy. In the present study, we report on cognitive and behavioral outcomes for children born to mothers with cancer diagnoses during pregnancy with comparisons of those children exposed in utero to chemotherapy with a control group of nonexposed children of mothers diagnosed during pregnancy.

MATERIALS AND METHODS

Study sample

A cohort of women diagnosed with cancer during pregnancy was enrolled and followed up in the international Cancer and Pregnancy Registry. Establishment and conduction of follow-up for the registry was approved by the Institutional Review Board of Cooper Medical School at Rowan University. Since collecting cases in 1997, the registry is compiled of 338 pregnant women diagnosed with various types of cancer. Pregnant women, enrolled at the time of their cancer diagnosis, provide

information, verified by medical records, of their diagnosis and treatment during pregnancy. Treatment course was determined by the oncologist caring for the patient based on stage of cancer and gestational age at diagnosis.

Women participating in ongoing data collection for the Cancer and Pregnancy Registry were offered standardized developmental testing if their child was at least 18 months of age. Letters were sent to 149 eligible participants regardless of cancer type or treatment during pregnancy. Patients were not paid for their participation, but travel expenses and parking were covered by grants from the Cooper Cancer Institute. Parents were allowed to be present during testing. In all, 53 women diagnosed with cancer during their pregnancy provided consent for their children to undergo developmental and behavioral assessments, and in 2 cases primary caregivers in families in which the mothers were deceased provided consent. Study participants were separated into 2 groups depending on type of cancer treatment (eg, chemotherapy vs nonchemotherapy) received before delivery. In the chemotherapy exposure group (n = 35),

TABLE 1
Demographic variables across chemotherapy exposure and controls

Variable	Exposure	n	Mean	SD	n (%)	P value
GA birth, wk	Chemo	35	36.7	±2.5		.04 ^{a,b}
	Controls	22	38.2	±2.7		
Male sex	Chemo	35			24 (68.6)	.16 ^c
	Controls	22			11 (50)	
Children with mother alive	Chemo	35			34 (97.1)	1.0 ^d
	Controls	22			21 (95.5)	
Children with mother undergoing treatment for recurrence	Chemo	34			4 (11.8)	.46 ^d
	Controls	21			4 (19.0)	
Age at evaluation, y	Chemo	35	4.5	±3.1		.59 ^a
	Controls	22	4.9	±2.6		
GA at first chemo treatment, wk (range)		35	22.0	±4.9		(11.7–31.3)

Chemo, chemotherapy; GA, gestational age.

^a Independent *t* test; ^b Denotes significant value; ^c Pearson χ^2 ; ^d Fisher exact test.

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