The Breast 58 (2021) 34–41

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Neurocognitive outcomes following fetal exposure to chemotherapy for gestational breast cancer: A Canadian multi-center cohort study

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ARTICLE INFO

Article history:
Received 9 February 2021
Received in revised form
30 March 2021
Accepted 12 April 2021
Available online 15 April 2021

Keywords:
Breast cancer
Gestational breast cancer
Breast cancer in pregnancy
Chemotherapy
Chemotherapy in pregnancy
In-utero exposure
Neonatal outcomes
Pediatric outcomes
Neurocognitive outcomes

ABSTRACT

Background: Limited knowledge exists on outcomes of children exposed prenatally to chemotherapy for breast cancer (BC). The purpose of this study was to compare long-term neurocognitive, behavioral, developmental, growth, and health outcomes of children exposed in-utero to chemotherapy for BC.

Methods: This is a multi-center matched cross-sectional cohort study involving seven cancer centers across the region of Southern Ontario (Canada), and the Hospital for Sick Children (Toronto, Ontario). Using standardized psychological and behavioral tests, we compared cognitive and behavioral outcomes in children exposed to chemotherapy during pregnancy for BC to age-matched pairs exposed to known non-teratogens.

Results: We recruited 17 parent-child pairs and their matched controls. There were more preterm deliveries in the chemotherapy-exposed group compared to controls ($p < 0.05$). Full Scale IQ of children in the chemotherapy group was significantly confounded by maternal IQ and prematurity. Exposed children born at term were not different in cognitive outcomes. Children from both groups were similar in their developmental milestones, pediatric anthropometric measurements and health problems. There were no cases of autoimmune cytopenia.

Conclusions: This is the first Canadian prospective comparative study designed to assess pediatric cognition following prenatal exposure to chemotherapy for BC. Chemotherapy was not found to be neurotoxic in this cohort and did not affect pediatric health. The decision to plan a preterm birth for initiating or continuing chemotherapy treatment must be taken into consideration in context of pediatric implications. While these results may assist in such decision making, replication with a larger sample is needed for more conclusive findings.

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https://doi.org/10.1016/j.breast.2021.04.005

1. Background

Breast Cancer (BC) is the most commonly diagnosed malignancy in pregnancy, occurring in approximately 0.01-0.04% of pregnancies annually, and its incidence is rising [1]. This is at least in part due to delayed reproduction as breast cancer incidence rises exponentially with age in pre-menopausal women [2–5]. The choice of when and how to treat BC in pregnancy is a challenging decision as it often involves a conflict between maternal survival and potential risk to the fetus.

Standard treatments for premenopausal people with BC include all or some of the following; surgery, chemotherapy, hormonal therapy, biologic therapy (e.g. trastuzumab), and radiation therapy. Hormonal therapy, biologic therapy, and radiation therapy are generally avoided in pregnancy due to the risk of adverse effects on the fetus [4,6–8]. Surgery, under local or general anesthesia, has not been found to be associated with adverse pregnancy outcomes [4,9–11]. Although there are only a few studies reporting on the long-term neurodevelopment of children exposed to general anesthesia during pregnancy, these reports are reassuring [12,13].

Chemotherapy is a recommended treatment modality for young patients with BC as it improves disease-free and overall survival [5]. Delaying chemotherapy by 3-6 months can increase the risk of distant disease recurrence by 5-10% [14,15]. Chemotherapy, however, is not recommended in the first trimester of pregnancy due to the increased risk of major fetal malformations, fetal growth restriction, and/or intrauterine death [16–22]. The standard recommendation is to postpone chemotherapy until after the first trimester [23–25].

Chemotherapy exposure to taxanes (paclitaxel or docetaxel), cyclophosphamide, anthracyclines (doxorubicin or epirubicin) and 5-fluorouracil in the second and third trimesters of pregnancy has not been shown to be associated with adverse pregnancy or neonatal outcomes [26–31]. Given that the CNS develops throughout pregnancy, however, exposure to chemotherapy at any point in pregnancy might confer adverse effects that become apparent after the neonatal period. *Amant* et al. has used the Bayley Scales of Infant Development, a tool to identify *development* during early childhood up to 36 months, and found no impairment in early childhood behavior or development, when controlling for the negative effects of prematurity [27]. Long-term *neurocognitive* development of children exposed to chemotherapy for maternal BC has not previously been extensively described. Although more resource intensive, cognitive testing is more predictive of future child performance compared to assessments of behavior or development.

The knowledge gap concerning the risk and safety of BC chemotherapy for the long-term neurodevelopment of children [30,32] can be a source of apprehension for patients, leading to delay of chemotherapy until after delivery, with consequent risk of adverse BC outcomes. On the other hand, iatrogenic preterm delivery to enable continuation of chemotherapy puts the child at definite risk of impaired neurodevelopment [27].

The purpose of this study was to define neurocognitive and behavioral outcomes of children exposed in-utero to chemotherapy for BC and compare to matched healthy parent-child pairs, and to secondarily describe pediatric health and growth outcomes of these children.

2. Methods

This is a multi-center matched and masked cross-sectional cohort study involving cancer centers across the region of Southern Ontario (Ontario, Canada). The study cohort (Group 1 - Chemotherapy) consisted of pregnant people who were diagnosed with breast cancer and treated any time during pregnancy with either chemotherapy, or chemotherapy and surgery, and their children.

There were two planned comparison groups, each of which was matched for the pregnant person's age at conception (±3 years), the sex of the child, and child's age at testing (±3 months). The first comparison group (Group 2 - Controls) consisted of healthy parent-child pairs exposed prenatally to non-chemotherapy agents, known to be non-teratogens and therefore "pregnancy safe" (such as acetaminophen or penicillin). This group was recruited retrospectively through the prospective *pregnancy risk program* database at the Hospital for Sick Children in which a person who is pregnant or planning a pregnancy calls to inquire whether there is risk to the fetus of exposure to a specific substance during pregnancy. The database for this program consists of two standard forms. The first form (the pregnancy intake form), which is completed at the time of the initial phone call (at time of calling, a person is either pregnant or planning a pregnancy) and is used to collect information concerning prenatal and antenatal medical histories and pregnancy outcomes. The second form (the offspring form) is completed for each child at about 6-9 months after delivery. Both, the pregnancy intake form and the offspring form, which include essential information about the pregnant person's medical and obstetric history, pregnancy and neonatal outcomes, are helpful in accounting for reporting and recall biases when used for research purposes. The second comparison group (Group 3 - Surgery) consisted of parent-child pairs exposed to surgery-only for BC diagnosed during the pregnancy and was aimed to serve as disease controls. Due to a small sample size of this group, Group 3 was not used as a comparison in the analysis as initially intended. The outcomes for Group 3 are presented descriptively (Appendix A).

Following Research Ethic Board approval from all eight hospitals, Groups 1 and 3 were recruited from seven cancer centers across the region of Southern Ontario (Ontario, Canada): Mount Sinai Hospital (Toronto, Ontario), Princess Margaret Hospital (Toronto, Ontario), Women's College Hospital (Toronto, Ontario), St. Michael's Hospital, North York General Hospital (Toronto, Ontario), Juravinski Cancer Center (Hamilton, Ontario), and Kingston Regional Cancer Center – now known as Cancer Center of Southeastern Ontario (Kingston, Ontario). Parent-child pairs meeting the inclusion criteria were identified and communicated to the study coordinator and study physician. The study physician reviewed each case with the referring provider and then contacted the patient to discuss the study and obtain verbal consent. Upon meeting the parent of the child on the assessment day, the study physician repeated the study description and obtained written consent for participation.

The primary outcome measure was childhood cognition, assessed using age-standardized and validated psychological testing of intelligence instruments. These measures consisted of the child Full Scale Intelligence Quotient (FSIQ), Performance Intelligence Quotient (PIQ), Verbal Intelligence Quotient (VIQ), and behavioral profiles. The secondary outcomes included measures of behavioral profiles, and neonatal and long-term pediatric health and growth profiles.

The study physician interviewed the parent that was pregnant with the child (or primary care giver in cases where the pregnant parent [biological mother] was deceased) regarding medical, pregnancy, and breast cancer treatment history, and the child's medical history. Data on socio-economic status and health of the other parent [biological father] was also obtained from the pregnancy parent. Testing of the intelligence of the parent who was pregnant was completed using Wechsler Abbreviated Scale of Intelligence (WASI) test [33], a standardized abbreviated test of intelligence (full scale, verbal, and performance intelligence quotient) for ages 6–89 years. If the pregnant parent was deceased, the child's other biological parent was assessed. This information was collected to control for differences between groups, since children's performance on psychometric tests may be influenced by parent-related factors. The study physician also performed a physical, anthropometric and neurological assessment of the parent and child.

Children were individually assessed during a single 2.5-3-h session at age 2 or older. All testing took place in the Psychology Department at the Hospital for Sick Children. Assessments were administered by a psychometrist under the supervision of a registered psychologist. Both the psychometrist and the psychologist were masked to the child's exposure status. The test order was blocked and was arranged to vary domain requirements, maximize interest, and minimize fatigue factors.

The cognitive performance (FSIQ, PIQ, VIQ) of children between the age of 2 years and 6 months and 7 years and 3 months was tested using the Wechsler Preschool and Primary Scale of Intelligence – 3rd Edition (WPPSI III) [34]. Children who were over 7 years old were tested using Wechsler Intelligence Scale for Children – 4th Edition (WISC-IV), an intelligence test for children 6–16 years of age [35].

Pediatric behavioral outcomes were assessed by parental completion of the Child Behavior Checklist (CBCL) [36]. CBCL is a sex-norm-referenced, widely used indicator of behavioral problems and provides a global behavioral total score and two broad-band scales; the Externalizing Problems scale, which evaluates aggressive and delinquent behaviors, and the Internalizing Problems scale, which evaluates depressed affect and withdrawn behaviors. CBCL raw scores are transformed to T-scores, with T-scores $\geq$64 indicating clinically borderline or significant behavioral disturbances.

Data analysis was conducted using IBM SPSS Statistics Version 27 (IBM Corp, Armonk, NY) and R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Summary and descriptive statistics, as well as frequencies and normality of distribution, were assessed in order to apply parametric or nonparametric statistical tests. For comparative analyses, only Group 1 and 2 were used. Pairwise analysis was performed using *t*-test or chi-square analysis for comparison of continuous variables and categorical outcomes, respectively. All analyses were two-tailed, with $p < 0.05$ considered significant.

Regression analysis was used to examine the relationship between chemotherapy exposure and the primary and secondary outcomes. The IQ of the tested parent and prematurity are potential confounding variables as they are strong predictors of a child's intelligence. The impact of the number of chemotherapy cycles was also considered. Preliminary correlation analyses were done to assist in selecting potential confounders. The role of these confounding variables on the primary outcome was examined as covariates in the statistical analysis.

3. Results

Over a seven-year period, we approached a total of 49 parent-child pairs – 21 exposed to chemotherapy (Group 1), 24 matched controls (Group 2), and 4 exposed to surgery only for breast cancer (Group 3). Of those approached in Group 2, seven declined to participate in the study leaving a total of 17 matched controls. Therefore, we had a total sample size of 38 parent-child pairs – 17 in Group 1 (total of 21, 4 lost to follow-up), 17 in Group 2, and 4 in Group 3. We did not achieve the sample size required to achieve power due to recruitment challenges.

The cohort characteristics, outcomes, and group differences are presented in Table 1. Group 1 and Group 2 were matched appropriately with no significant difference in maternal age at conception or child's age at time of testing. In addition, there was no significant difference in demographics and maternal anthropometrics. The two groups were also comparable with regard to socioeconomic status, family medical history, and substance use. One difference in baseline characteristics between the two groups was a higher rate of parent-child pairs in Group 1 from families where English was the second language (30% vs. 6%); although this did not reach statistical significance ($p = 0.17$).

In the chemotherapy-exposed group, the mean (SD) age of the pregnant individual at diagnosis was 35.3 (4.36) years at a gestational age of 18.78 (8.67) weeks. In 94.1% of diagnoses, BC was a primary diagnosis and not a recurrence. The majority of patients (88%) received 2–-6 cycles of chemotherapy during pregnancy; one parent-child pair received one cycle and one received 12 cycles. Of the 17 patients, ten reported details of their chemotherapy regimen – chemotherapy exposure included 5-fluorouracil, epirubicin, cyclophosphamide, docetaxel, doxorubicin, and trastuzumab. Most patients (76.5%) also received surgical treatment for BC; 17.6% received only chemotherapy; and 5.9% received chemotherapy and radiation. The range of child IQs according to the number of chemotherapy cycles is described in Table 2. Descriptively, there does not appear to be a relationship between the number of cycles

Table 1
Maternal, pregnancy, neonatal, and pediatric characteristics and outcomes.

Variable	Chemotherapy (n = 17)	Controls (n = 17)	Effect Size	p
Pregnant Person				
Age at conception (years)	35.99 [32.45, 38.26]	34.19 [32.64, 37.22]		
Pre-pregnancy weight (kg)	62.11 [55.4, 70.88]	58.96 [54.43, 68.04]		
Head circumference (cm)	54.20 [52.90, 55.25]	55.00 [54.50, 55.30]		
WASI Score				
Full	102.50 [94.25, 109.75]	114 [102.75, 118.25]	**-9.94 (-18.0, -1.87)**	*
Performance	109.00 [97.00, 121.00]	116 [109.00, 124.25]	**-9.62 (-18.40, -0.85)**	*
Verbal	95.00 [83.25, 107.25]	107.00 [93.00, 110.50]	-7.87 (-16.29, 0.54)	
Pregnancy				
Gestational age at birth (weeks)	36 [35, 38]	40 [40, 41]	**-3.83 (-5.52, -2.13)**	***
Gender (female)	10 (58.8)	10 (58.8)	–	–
Weight gain (kilograms)	11.34 [9.04, 13.61]	15.88 [11.34, 22.68]	**-6.17 (-10.26, -2.08)**	**
Number of ultrasounds	9 [4, 10]	3 [2, 4]	**5.12 (2.61, 7.64)**	***
Induction of labour			–	*
No	6 (35.3)	14 (82.4)		
Yes	8 (47.1)	3 (17.6)		
Unspecified	3 (17.6)	0 (0.0)		
Delivery method			–	–
Vaginal	11 (64.7)	11 (64.7)		
Assisted Vaginal	1 (5.9)	1 (5.9)		
Caesarean Section	5 (29.4)	5 (29.4)		
Breastfeeding				***
No	16 (94.1)	2 (11.8)		
Yes	1 (5.9)	14 (82.4)		
Unspecified	0 (0.0)	1 (5.9)		
Neonatal				
Birth weight for GA (percentile)	59.86 [46.97, 67.39]	52.22 [30.70, 71.27]	4.41 (-17.92, 26.73)	
Premature	11 (64.7)	1 (5.9)	29.33 (4.36, 599.39	**
Complications	7 (41.2)	5 (29.4)	1.68 (0.41, 7.31)	
Intensive care admission	5 (29.4)	3 (17.6)	1.94 (0.39, 11.14)	
Congenital anomalies	0 (0.0)	1 (5.9)	–	
Pediatric				
Age at follow-up (years)	4.37 [3.50, 7.00]	3.70 [3.59, 6.98]	0.22 (-1.07, 1.51)	
Health problems	6 (35.3)	11 (64.7)	0.30 (0.07, 1.17)	
Allergy	3 (17.6)	5 (29.4)	0.51 (0.09, 2.55)	
Asthma	2 (11.8)	1 (5.88)	2.13 (0.19 48.75)	
Atopic Dermatitis or eczema	1 (5.9)	1 (5.88)	–	–
Oral thrush (in first year)	0 (0.0)	2 (11.8)	–	–
Significant Infections	1 [1, 3]	2 [1, 5]	-1.82 (-3.82, 0.17)	
Height[a] (percentile for age)	81.27 [66.88, 98.15]	70.22 [45.77, 85.30]	13.99 (-2.87, 30.85)	
Weight[a] (percentile for age)	79.26 [53.83, 96.50]	62.30 [48.47, 77.80]	12.55 (-5.94, 31.04)	
Head Circumference[a] (percentile for age)	40.00 [11.50, 75.00]	50.00 [37.50, 70.00]	-11.24 (-30.68, 8.19)	
Age milestone achieved (months)				
Smile	2 [2, 2]	2 [2, 2]	-0.06 (-0.31, 0.19)	
Lift Head	3 [3, 3]	3 [3, 3]	0 (-0.17, 0.17)	
Sit	6 [6, 7]	6 [6, 7]	-0.12 (-−0.75, 0.51)	
Crawl	9 [9, 9]	9 [8, 9]	0.44 (-0.45, 1.34)	
Stand	9 [9, 10]	9 [9, 10]	0.18 (-0.67, 1.03)	
Speak	11 [10, 12]	10 [9, 11]	0.65 (-1.01, 2.30)	
Walk	13 [11.50, 13]	12 [11, 14]	0.06 (-−1.05, 1.17)	
IQ[b]				
Full	105 [94, 111]	111 [103, 122]	**-9.71 (-18.71, -0.70)**	*
Performance	100 [96.50, 101.50]	109 [103, 115]	**-11.93 (-20.82, -3.04)**	*
Verbal	104 [95, 114]	114 [100, 118]	-9.35 (-18.91, 0.20)	
CBCL ≥64				
Internalizing	1 (5.9)	0	–	–
Externalizing	0	0	–	–
Total	0	0	–	–

Descriptive statistics are median [IQR] or n (%). Effect Sizes are Odds Ratio (95% CI) or mean difference (95% CI)
Bold font indicates results that are statistically significant; * p-value <0.05; ** p-value <0.01; *** p-value <0.001.
Abbreviations: IQR interquartile range; CI confidence interval; GA gestational age; IQ intelligence quotient; WASI Wechsler Abbreviated Scale of Intelligence; CBCL Child Behavior Checklist; WPPSI-III Wechsler Preschool and Primary Scale of Intelligence − 3rd Edition; WISC-IV Wechsler Intelligence Scale for Children − 4th Edition.
Missing data: pregnant person head circumference n = 7, WASI Score n = 2, GA at diagnosis n = 1, ultrasound n = 2, pre-pregnancy weight n = 1, weight gain n = 2, birth weight for GA n = 12, child height/weight/head circumference n = 1; Child Performance IQ n = 9; CBCL n = 1.
[a] at time of testing.
[b] IQ of children were tested using WPPSI III; Children who were over 7 years of were tested using WISC-IV

Table 2
Range of child IQ scores stratified by number of chemotherapy cycles during gestation.

Number of Chemotherapy Cycles	n	FSIQ	PIQ	VIQ
1	1	117	–	114
2	4	75–119	81–100	93–131
3	2	94–103	97	95–104
4	4	83–111	85–117	81–106
5	2	91–109	100–106	87–109
6	3	105–115	100–109	100–116
12	1	124	–	132

Descriptive statistics are reported as ranges.
Abbreviations: FSIQ Full Scale Intelligence Quotient; PIQ Performance Intelligence Quotient; VIQ Verbal Intelligence Quotient.
Missing data: PIQ n = 5.

Table 3
Child IQ Scores in Chemotherapy Exposed vs Controls, adjusted for (A) Parent FSIQ and (B) Prematurity.

Child IQ	Coefficient (95% CI)	Adjusted Coefficient (95% CI)	
		(A)	(B)
FSIQ	**-9.71 (-18.71, -0.70)**	-8.19 (-18.17, 1.79)	-6.74 (-18.23, 4.74)
PIQ	**-11.93 (-20.82, -3.04)**	**-10.65 (-19.90, -1.41)**	-6.48 (-16.74, 3.78)
VIQ	-9.35 (-18.91, 0.20)	-8.08 (-19.06, 2.89)	-10.77 (-23.06, 1.51)

Bold font indicates results that are statistically significant ($p < 0.05$).
Abbreviations: CI confidence interval; IQ Intelligence Quotient; FSIQ Full Scale Intelligence Quotient; PIQ Performance Intelligence Quotient; VIQ Verbal Intelligence Quotient.

and child IQ.

The chemotherapy group had more preterm births (64.7% vs 5.9%, $p < 0.05$) and a higher rate of induction of labour (47.1% vs 17.6%, $p < 0.05$). Of the children born prematurely in the chemotherapy-exposed group, the majority (73%) were induced.

There were two children in the chemotherapy-exposed group whose pregnant parent was not available for testing (e.g. deceased) and therefore, for these children the appropriate primary care giver was tested as per the study protocol. Parent FSIQ and PIQ scores were found to be approximately 10% lower in the chemotherapy group compared to controls ($p < 0.05$); VIQ scores were comparable.

Between the two groups, there was no statistical difference in the age distribution when children were tested, which reflects appropriate age-matching. The median (IQR) age of children at time of testing was 4.37 (3.50, 7.00) years and 3.70 (3.59, 6.98) in the chemotherapy and control group, respectively; 88% of children in both groups were tested before the age of six.

The chemotherapy-exposed children had a significantly lower FSIQ (−9.71 [95% CI -18.71 to −0.70]) and PIQ (−11.93 [95% CI -20.82 to −3.04]). Although VIQ scores were lower (−9.35 [95% CI -18.91, 0.20]), the difference did not reach statistical significance.

Parent IQ and prematurity were identified as confounding factors. When child IQ scores were adjusted for the parent FSIQ (Table 3), the difference in child FSIQ was no longer significant but PIQ remained significantly lower. After adjusting for prematurity (birth before 37 weeks), all three IQ categories were found to be comparable between the two groups.

In our cohort, there was only one child with a CBCL score $\geq$64 and this child was in the chemotherapy group.

Children in both groups achieved postnatal developmental milestones at comparable time points. Similarly, there was no significant difference in pediatric growth parameters, including no difference in head circumference percentile (height, weight, and head circumference) and pediatric health problems, including: atopic triad, oral thrush in the first year of life, and significant number of infections. There were no cases of autoimmune cytopenia in either group.

4. Discussion

Information on the effect of chemotherapy on the developing fetal central nervous system is an essential component of decision making for BC management during pregnancy as a those with a BC may opt to terminate the pregnancy or forego/delay chemotherapy out of concern for the long-term effects of chemotherapy on the fetus.

Although infant developmental and behavioral outcomes have previously been reported not to be significantly influenced by chemotherapy [27], long-term pediatric cognitive and behavioral outcomes after in-utero exposure to chemotherapy is understudied. In this Canadian multicenter study of 17 parent-child pairs exposed to chemotherapy for gestational BC and their matched controls, we used age-appropriate standardized psychological (WPPSI III and WISC IV) and behavioral tests (CBCL) to describe the relationship between chemotherapy exposure and pediatric cognitive and behavior outcomes. In addition, we used a series of childhood physical, and developmental growth parameters to characterize the childhood outcomes that provide additional details describing the long-term pediatric outcomes.

A recent study investigated the impact of child development after maternal cancer diagnosis during pregnancy [37]. Among their cohort, 73.5% were exposed to chemotherapy (alone or in combination with other treatments) and 54% of mothers had a diagnosis of breast cancer. While our study found FSIQ and PIQ to be lower in the chemotherapy-exposed children, *Vandenbroucke* et al. did not find a statistically significant difference for these outcomes. Contrary to our findings, their study did find VIQ to be significantly lower in the chemotherapy-exposed children. In our study, however, IQ scores of children exposed to chemotherapy during pregnancy were comparable to health controls after adjusting for prematurity which provides evidence that chemotherapy exposure itself is not neurotoxic. Of the children born

prematurely in the exposed group, the majority of births were preceded by induction of labour. Preterm induction of labour is common when chemotherapy is started during pregnancy in an effort to continue treatment and minimize fetal chemotherapy exposure. A similar pattern of iatrogenic preterm deliveries has previously been described [38]. Our findings support the existing body of literature that shows an association between prematurity and adverse short and long-term outcomes in neonates [26,27,38–40]. The impact of prematurity on the cognitive outcomes of children exposed to chemotherapy during gestation cannot be overlooked.

It is promising that despite chemotherapy exposure and prematurity, children in this group did not show significant differences in pediatric head circumference and other anthropometric measurements, age at which developmental milestones were achieved, or adverse pediatric health outcomes. In fact, pediatric health problems were found to be lower in the chemotherapy-exposed children (35.3% vs 64.7%), although this did not reach statistical significance.

In the chemotherapy-exposed cohort, there was one child exposed to 12 cycles of chemotherapy across three trimesters and induced at 36 weeks. This child went on to have a FSIQ score of 124. Similarly, five of the 11 premature children achieved FSIQ ranging from 103 to 124 at time of testing – indicating the role of brain plasticity and reinforceable environmental influences – despite prematurity [41]. The other premature children had IQs ranging from 80 to 94, with the parent IQs ranging from 79 to 97, pointing on genetic influence as well.

The results of this study have to be interpreted in context of its limitations. This was a retrospective study and we were not able to adequately recruit a disease control group. In our cohort, parental IQ was significantly lower in the chemotherapy exposure group compared to controls. This may be related to the higher number of households in the chemotherapy group with English as a second language (30% vs. 6%) and consequently, IQs would be underestimated due assessments being performed in English. Finally, our sample size was due to recruitment challenges, including: a small target population, potential distress to parents from discussion of study hypothesis, and maternal morbidity and mortality making it challenging for families to participate.

5. Conclusion

This is the first study designed to assess long-term pediatric cognitive outcomes following prenatal exposure to chemotherapy for BC. In this Canadian study, chemotherapy exposure was not found to be neurotoxic. In addition, chemotherapy was not associated with worse behavioral, developmental, and pediatric health outcomes. These findings are reassuring for those receiving chemotherapy for BC in pregnancy. The findings, however, are limited by the small sample size and challenges in recruitment.

When pregnant patients are diagnosed with BC it is common practice to induce delivery before term. This is done either because of a decision to delay chemotherapy until after delivery, or to minimize fetal exposure if chemotherapy is started during pregnancy. Our findings suggest that consideration could be given to continuation of the pregnancy with careful discussion, shared decision making and informed consent. Although these results may assist in such decision making, in future studies, further research is needed with a larger sample to support these findings.

Funding

This study was funded by the Canadian Breast Cancer Foundation (Award #301909).

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgements

We would like to thank Elena Reydman for her significant contribution in patient recruitment and coordination for this study. We would also like to thank Dr. Rohan D'Souza (University of Toronto) for his contribution to the completion of this manuscript.

Appendix A. Group 3 (Surgery) Maternal, Pregnancy, Neonatal, and Pediatric Characteristics and Outcomes

Variable	Group 3 (n = 4)
Pregnant Person	
Age at conception (years)	34–39
Pre-pregnancy weight (kg)	57–79
Head circumference (cm)	54–55
WASI Score	
Full	105–116
Performance	104–125
Verbal	99–106
Pregnancy	
Gestational age at birth (weeks)	30.5–40
Gender (female)	
Weight gain (kilograms)	9–11
Number of ultrasounds	3–15
Induction of labour	
No	0/4
Yes	3/4
Unspecified	1/4
Delivery method	
Vaginal	3/4
Assisted Vaginal	0/4
Caesarean Section	1/4
Breastfeeding	
No	4/4
Yes	0/4
Unspecified	0/4
Neonatal	
Birth weight for GA (percentile)	52–92
Premature	2/4
Complications	2/4
Intensive care admission	2/4
Congenital anomalies	
Pediatric	
Age at follow-up (months)	43–136
Health problems	3/4
Allergy	1/4
Asthma	1/4
Atopic Dermatitis or eczema	1/4
Oral thrush (in first year)	1/4
Significant Infections	1–3
Height[a] (percentile for age)	50.5–89
Weight[a] (percentile for age)	27–95
Head Circumference[a] (percentile for age)	22–76
Age milestone achieved (months)	
Smile	2–3
Lift Head	3
Sit	4–8
Crawl	7–9
Stand	9–17
Speak	10–17
Walk	12–16
IQ (n = 3)	
Full	88–111
Performance	85–97
Verbal	92–122
CBCL >63	
Internalizing	0/4
Externalizing	0/4
Total	0/4

Descriptive statistics are range or proportion (n/N).

Abbreviations: IQR interquartile range, CI confidence interval; IQ intelligence quotient; WASI Wechsler Abbreviated Scale of Intelligence; CBCL Child Behavior Checklist; WPPSI-III Wechsler Preschool and Primary Scale of Intelligence – 3rd Edition; WISC-IV Wechsler Intelligence Scale for Children – 4th Edition; **Missing data:** pregnant person head circumference n = 2, WASI Score n = 1, weight gain n = 1, number of ultrasounds n = 1, birth weight for GA n = 2, pediatric head circumference n = 3.

‡ IQ of children were tested using WPPSI III; Children who were over 7 years of were tested using WISC-IV.

[a] at time of testing.

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