**Observational study on the long term cognitive and cardiac outcome after prenatal exposure to chemotherapy in children 18 months or older**

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**Summary**

**Background** While oncologic treatment of maternal cancer during pregnancy has become more acceptable in the last decade, the effect of prenatal exposure to chemotherapy on cardiac and neurodevelopmental outcomes of the offspring is still uncertain. We aimed to document general health, cardiac function and neurodevelopmental outcome in children who were prenatally exposed to chemotherapy.

**Methods** This is an interim analysis of a prospective multicentre study examining children who were prenatally exposed to maternal cancer staging and treatment, including chemotherapy. Children were examined at birth, at the age of 18 months, 5-6, 8-9, 11-12, 15-16, or 18 years. The tests comprised a clinical neurologic examination, testing of the general level of cognitive functioning (Bayley/IQ-test), an electro- and echocardiography and questionnaire on general health and development. From the age of five years, also an audiometry, Auditory Verbal Learning Test and subtasks of the Children’s Memory Scale and Test of Everyday Attention for Children were performed and the Child Behavior Checklist was completed. This study is registered, clinicaltrials.gov number NCT00330447.

**Findings** In total, 236 cycles of chemotherapy were administered in 68 pregnancies. Seventy children, born at a median gestational age of 35·7 weeks (range, 28·3 – 41·0; 47/70 <37weeks), were included with a median follow-up period of 22·3 months (range, 16·8 –211·6). Although neurocognitive outcomes were within normal ranges, the high incidence of preterm birth had a negative influence on cognitive development. Children’s behaviour, general health, hearing and growth were reported as in a general population. A severe neurodevelopmental delay was seen in both members of a twin (3%). Cardiac dimensions and functions were within normal ranges.

**Interpretation** Fetal exposure to chemotherapy was not associated with increased morbidity at the level of the central nervous system, cardiac, and auditory functions, as well as general health and growth. More subtle changes in cardiac and neurocognitive measurements emphasize the need for longer follow up. Prematurity was frequently encountered, and was associated with impairment in cognitive development. Therefore, iatrogenic preterm delivery should be avoided as much as possible.

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**Introduction**

The unintended use of urethane to treat chronic myeloid leukemia in a pregnant woman in 1948 is one of the first reports of chemotherapy use during pregnancy.1 Since then, more experience has been gained and chemotherapy is now regularly given after the first trimester when cancer treatment is needed during pregnancy.2,3 It is estimated that cancer complicates 1/1000-2000 pregnancies and the incidence yearly increases with 2·5%.4-6 However, the effect of the malignancy and its treatment on fetal health remains a serious concern.

Chemotherapy during the first trimester increases the risk for congenital malformations, whereas fetal effects of chemotherapy beyond the first trimester could potentially affect brain and cardiac development. A first concern is the potential effect on cerebral frontal functions (attention, memory and executive functions) as these have been shown to be most affected by cytotoxic treatment in adults and children.7 These cognitive functions are also the most vulnerable in infants-at-risk, such as preterm born children, children with periventricular leucomalacia, children in utero exposed to toxic products like cocaine, tobacco, alcohol intake or to maternal emotional disturbance and distress during pregnancy.8-10 A second concern is the potential cardiotoxic effect of anthracyclines which are frequently used in the treatment of breast cancer and hematologic malignancies, the most common cancer types during pregnancy.11

So far, solely retrospective and limited data exist on the long term outcome of children exposed to chemotherapy in utero.12-14

This prospective study looks at the general health, cardiac function and neurodevelopmental outcome including intelligence, memory, attention and executive functions, in children who were prenatally exposed to chemotherapy.

**Methods**

*Study design*

This is a multicentre prospective cohort study that was initiated in 2005 in three European countries and based on a collaboration between national referral centres in Belgium (University Hospitals Leuven), The Netherlands (Radboud University Nijmegen Medical Centre) and the Czech Republic (Faculty Hospital Motol, Charles University, Prague). The study contains a retrospective part since children prenatally exposed to chemotherapy before 2005, were also included. This study documents long-term, defined as a minimum follow-up period of 18 months, toxicities secondary to in-utero exposure to chemotherapy. The research protocol was approved by the institutional review board of all participating centres. A standardized study protocol was used in the three participating centres. Children who were prenatally exposed to cytotoxic drugs for cancer treatment were included but children who were exposed to low dose chemotherapy for skin or inflammatory disorders were excluded. We explained in the webappendix† how the children were identified. Parental permission to participate in this prospectively designed study was obtained for each child. Maternal disease, staging examinations and all treatments administered in pregnancy were recorded. The study enrollment is presented in figure 1.15-20 A standardized assessment of the general health and development, cardiological, cognitive, behavioral and neurological development of the children was organized, including evaluations at birth, at the age of 18 months (age range that was allowed in this cohort is 17-29 months) and at the age of 5-6, 8-9, 11-12, 15-16, or 18 years. Children from historical datasets from the 3 centres were also included and when they entered the study at an age between the predefined ages, the developmental milestones were assessed by a pediatric neurologist. At the time these children reached the predefined ages, they were examined according to the protocol. The first child was examined on the 18th of May 2005 and the cut-off date for inclusions in this interim analysis was set at the first of March, 2011.

All children born after prenatal chemotherapy exposure (retro -and prospectively included) were born in hospital and examined by a neonatologist. For the prospective group we asked the neonatologists to complete a datasheet (general physical examination and neurological assessment: tonus, reflexes, active and passive movements, eye movements). Since these are standard examinations performed in neonates, for all retrospectively included patients this information was written in the medical files of the neonates.From the age of 18 months onwards, evaluation was performed in the national study centre. At each visit biometric data and a questionnaire on general health status, school performance, recreation and social situation was systematically collected from the parents.† For the cognitive assessment, an age-adapted test battery was developed for the evaluation of intelligence, verbal and nonverbal memory, attention, working memory and executive functions (figure 1).† The Child Behaviour Checklist (CBCL)20, a questionnaire that screens for behavioural and emotional problems, was completed by the parents while their child was tested. From the age of five years onwards an audiometry was performed once. Tests and questionnaires were completed in the children’s native languages.

Cardiac evaluation consisted of a 12-lead electrocardiography (ECG) and a full echocardiographic evaluation looking for structural and functional parameters.† In children in whom certain examinations were performed twice, the most recent data were used for further analysis.

*Data analysis*

Statistical analysis was performed using the Statistical Analysis System version 9·2 (SAS Institute, Cary, USA) and Statistical Package for Social Sciences for Windows version 16 (SPSS Inc, Chicago, USA). The results were compared to available norms (national data for height, weight, head circumference, national and international reference data available for neurodevelopmental tests). The cardiac results were compared to a control group. Some children were examined twice and before we decided to take the results of the last performed test we made sure there were no important differences between the two sets of results. In no case we did find differences and only after this reassurance we used the most recent one.For all cognitive tests raw scores were converted to standardized scores using published normative data for the specific age-group as provided by the respective tests. For the Bayley and Wechsler intelligence tests the normal range of index scores is considered 100+15 (mean+1 SD). For the data analysis and representation of the TEA-Ch, CMS and AVLT all scores were converted to z-scores, with a normal range defined as a z-score of 0+1 (mean+1 SD). The relation between IQ scores and gestational age at birth was examined by linear (ordinary least squares) regression. The effect size was estimated using omega-squared measure of explained variance (ω2). Age and gender were added as covariates, together with a random effect for country.

Electrocardiographic measurements were analyzed and compared with normal values in childhood and adolescence published by Dickinson.21 All echocardiographic measurements were obtained in three cardiac cycles and averaged. All cardiac measurements were compared to the measurements in a 1:1 matched control group (from Toronto and Leuven) with age (+12 months) and gender as matching factors. Cardiac dimensions were compared to reference values from a historical dataset and represented as standard deviation z-scores. To circumvent violations of the linear regression assumptions, mainly the assumption of normality of the residuals due to skewed distributions for some cardiac parameters, the independent effect of chemotherapy was estimated using median regression. The matching was accounting for by stratifying the regression models by age (six strata) and adding gender as a covariate.22 When using both age and gender as covariates, as a sensitivity analysis, similar results were obtained. Correction for multiple testing was performed using Holm’s method for all cardiac measurements.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

**Results**

A total of 70 children (32 female, 38 male), exposed to chemotherapy in utero (236 cycles) during 68 pregnancies (two twin pregnancies), were included. Nineteen different regimens of chemotherapy were administered† Anthracyclines were most commonly used (53 patients). Median cumulative dosage (mg/m²) (range) for doxorubicin (n=33), epirubicin (n=14), idarubicin (n=3) and daunorubicin (n=4;) was 180 (50-400), 450 (200 – 600), 72 (36 – 108), 240 (120 – 360), respectively.

The median follow-up period at last examination of the children was 22·3 months (range, 16·8–211·6 months). Two children had an echocardiography at the age of 12 months. Distribution of children among countries was as follows: 42 in Belgium, 20 in The Netherlands and 8 in the Czech Republic.

**Pregnancy and neonatal examination**

Median maternal age and gestational age at diagnosis were 32·9 years (range, 23·4-41·7) and 18·1 weeks (range, 1·7–33·1)(n=68), respectively. Maternal disease, staging examinations, cancer treatment and drugs administered in pregnancy are shown in the webappendix. The median gestational age at birth was 35·7 weeks (range, 28·3–41·0)(n=70). Seven children were born at 28·0-31·9 weeks, 9 at 32·0-33·9 weeks, 31 at 34·0-36·9 weeks and 23 at term (>37 weeks). The median birth weight was 2612 grams (range, 720–3970). Birth weight was below the tenth percentile for gestational age and gender in 14/70 children (20·6%, one-tailed binomial test p=0·009, 95% CI is 12.3-30.8).23 The incidence and type of congenital malformations were similar to the general population.† Furthermore, neonatal physical examination and echocardiographic assessments (n=21) were within normal limits (data not shown). Neonatal neurological examination was normal in 64/70(91·4%) children. One child, born at 28 weeks, presented with a contracture of the right elbow, which resolved later. In five children a transient neonatal hypotonia was noted; one of these children also presented with benign sleep myoclonus.

**Biometry**

Biometry per gender is presented in figure 2. Comparison is made to values obtained in a general population.24 For weight, height and head circumference, the tested children have a normal growth.

**General health status and development**

The questionnaire on general health status and developmentwas completed by 57 parents (81·4%). Medical problems (n=58) reported by the parents are frequently seen in the general population.† No malignancies were seen. General development was reported as seriously impaired in both children of a twin pregnancy. Apart from these children, all school-aged children attended regular school (n=25). Social and leisure activities were comparable to the general population (data not shown). Children with missing questionnaires mainly live in The Netherlands and the French speaking part of Belgium. Apart from their different cultural background, we had less personal contact with these parents since we were not the treating physician. However, we did not identify differences in maternal history and children’ outcomes when compared to parents who completed the questionnaires, emphasising the internal validity.

**Cognitive, behavioural and neurological development**

In the majority of children, we observed a normal cognitive development. Figure 3A shows the distribution of the results for the last cognitive evaluation (Bayley test (n=40), Wechsler/SON intelligence-test (n=26), clinical neurological examination in between standardized ages (n=4)).

The children who performed below normal ranges were mainly seen in the preterm group. A univariable linear regression model indicated that the average IQ-score increases with 11.1 points (95% CI:5·4-16·8) for each month increase in pregnancy duration (p=0·0003; explained variation was 16%)(figure 3B). When controlling for age, gender, and country, the effect remained: the IQ-score increased on average with 11.6 (6·0-17·1, p<0.0001).

Two children had a significant neurodevelopmental delay which made it impossible to perform the complete proposed in-depth cognitive test battery.† These two children were excluded from further cognitive and behavioral assessment.

***Clinical neurological examination***

Clinical neurological examination (n=68) did not show any focal or other neurological abnormalities.

***General level of cognitive functioning***

***Bayley test (18 months)***

The mean (+SD) Bayley mental developmental index score was 96·8+14·9 (n=40, at a median age of 18·2 months (range, 16·8-28·6)). Index scores for children who were born term (n=13) and preterm (n=27) were 103·1+13·6 and 94·6+14·6, respectively.

***Intelligence test (Wechsler test n=23, SON-R n=2)***

Total IQ-scores (mean+SD) of the children were within normal ranges (n=25; 103+14·5). Comparing verbal IQ (VIQ) and performance IQ (PIQ) scores obtained in the Wechsler tests (n=23), paired t-test revealed a significant difference (VIQ 104·8+14·5 vs PIQ 97·9+14·1, paired t-test p=0·033). In 9/23 children (39·1%) a significant difference between VIQ and PIQ was seen (figure 3C).

***Memory***

Average group results on the different subtasks for verbal and nonverbal memory were within normal ranges (figure 4) (n=25).

***Attention***

Attentional function was within the normal range (n=12). Detailed results grouped per attentional function (focused attention, sustained attention, attentional flexibility, divided attention and response inhibition) are shown in figure 4.

***Behavioural functioning and emotional problems***

The CBCL was available for 21 children (1 missing, 3 not available in native language) at a median age of 8·7 years (range, 5·0-15·9) and the average score was within the normal ranges (figure 4). For both internalizing, externalizing and total problems, in 6 of the 21 children (28·6%) an increased score (z-score >1·0) was seen. No significant relation was seen with prematurity. All these children attended regular school.

***Audiometric examination***

Auditory function was tested in 21 children at the median age of 6·5 years (range,5·0–17·4). In 18 children (85·7%), no abnormalities were noticed (four received cisplatin). In three children with hearing loss, middle ear infection (n=1) and neurodevelopmental problems (n=2) were confounding factors*.*†

**Cardiac evaluation**

70 children between one and 18 years old underwent a non-sedated ECG and echocardiographic examination. Five children (7·1%) were excluded because it was impossible to complete the examination due to lack of cooperation. When compared to controls, no statistically significant differences were observed for the weight, the height, the body surface area and the systolic blood pressure (all p-values ≥ 0·45). 49/64 (78%) pregnancies had been exposed to anthracyclines. A higher heart rate was observed in the study patients.† Analysis of ECG measurements revealed no arrhythmia or conduction abnormalities.† During the echocardiographic examination, no structural cardiac defects could be detected. Table 1 summarizes the echocardiographic measurements of cardiac dimensions and systolic function in children exposed to anthracyclines. All cardiac dimensions were within the normal range for children exposed to anthracyclines and for control children. Compared to the control group, we noticed clinically small but statistically significant decrease for the patient group concerning ejection fraction, fractional shortening, and interventricular septum (IVS) thickness. All patients however were within the normal range and no patient had an abnormal value. Diastolic parameters were also within normal range with some clinically small but statistically significant differences between both groups. Mitral valve (MV) E-velocity was lower, MV a-duration was shorter and isovolumetric relaxation time (IVRT) was shorter in the patient group compared to the normal controls.† These parameters are heart rate-dependent.

**Discussion**

Despite prenatal exposure to chemotherapy (n=70), radiotherapy (n=7), staging examinations and co-medications, the outcome of children is not different from the general population. In particular, we observed an age adequate cognitive development and normal cardiac outcome among a cohort of children at least 18 months of age and prenatally exposed to chemotherapy whom we had tested at predefined ages. The negative prognostic influence of prematurity on cognitive development (Bayley/IQ-score)8,9 is confirmed in this cohort. However, we cannot exclude an additional effect of chemotherapy and other drugs or radiation exposure in these preterm born children. The decision to induce the delivery for non-obstetrical reasons, being mostly to start cancer treatment or in a few cases because of deterioration of the maternal condition, was taken in 38/68 pregnancies (58%). Twenty-eight of these 38 patients (74%) delivered -iatrogenically- preterm. We believe that the start of cancer treatment (including chemotherapy) during pregnancy may prevent iatrogenic prematurity and add to the preservation of the long-term neurocognitive outcome.

These data should be interpreted with caution since two children (3%), both members of a twin pregnancy, presented with an important neurodevelopmental delay. In the boy a cortical malformation with multiple dysmorphic characteristics was seen. Although a syndromal entity is likely in this child, we were unable to diagnose a clinical syndrome. The fetal cortex changes during development from a smooth cerebral surface at 14 gestational weeks to a complex association of sulci and gyri. Polymicrogyria is the end point of different pathological processes.25 We cannot rule out that the prenatal exposure to chemotherapy after 15 weeks of gestational age has an influence in the developmental delay, although the syndromal picture makes the causal relation less likely. Moreover, in the children older than six years who performed a Wechsler intelligence test (n=23), a disharmonic intelligence profile was seen in 39% (15% in the normal population). Although this finding is not directly indicative for neuropsychological impairment, verbal/performance IQ discrepancies have been associated with several neurological disorders and learning problems. Furthermore, children with disharmonic intelligence profiles more often have behavioral problems than children with harmonic intelligence profiles.26 In our series the average results of the CBCL were within normal ranges, though in 6 of the 21 children (28·6%) the total problem score was increased, which is higher than expected (15% in the general population).9 Although the general neurodevelopmental assessment is within normal ranges, these results show that more subtle changes in neurodevelopment are possible. Therefore we need to remain prudent till a larger group of children has been examined with a longer follow-up period.

Children also underwent a detailed cardiac evaluation. In our study, fetal exposure to chemotherapy in utero was not associated with congenital cardiac abnormalities. For the children exposed to anthracyclines, parameters for systolic and diastolic function were all within normal ranges. We found a significant difference in ejection fraction and fractional shortening between the patients and age and gender matched controls. However as values obtained in all patients in the anthracycline group were normal, as in the report of Aviles in 2006,14 we do not believe this difference is clinically relevant. Some of the diastolic parameters (IVRT and mitral A-duration) were different between patients and controls, but also these data were within normal range and the differences can probably be explained by the higher heart rate in the patient group. It is reassuring that cardiac dimensions, wall thickness and LV mass index were all within normal range. We discussed the need for matching for prematurity with our cardiologists though prematurity is not a predictor of heart dysfunction. In addition, heart dysfunction was not observed for premature children in our study.

We believe that probably three important factors contributed to this overall re-assuring outcome. Firstly, chemotherapy was only administered after the first trimester, which is the most vulnerable time frame for toxic effects.27 Chemotherapy administered during the second and third trimester does not increase congenital malformations.11,28 Secondly, in contrast to previous belief that the fetal blood-brain barrier is immature and leaky, recent data suggest that the fetal brain is well protected.29-31 Compared to the situation in adults, fetal cerebrospinal fluid contains high concentrations of proteins, which is related to specialized transcellular transfer and needed for fetal brain development.30 Erroneously, these high protein levels used to be interpreted as a consequence of a leaky blood-brain barrier. During embryogenesis, almost all neurons are formed by 6-18 weeks of gestation, but the brain continues to develop later in pregnancy and also postnatally, through neuronal migration, differentiation and synaptic maturation and myelinisation. The underlying morphological features of the blood-brain barrier are the presence of tight junctions, low rates of transcytosis, and the expression of specialized influx and efflux transporters, which are present early in embryological development.30 Moreover pericytes inhibit the expression of molecules that increase vascular permeability and central nervous system immune cell infiltration.29Tight junctions are present between cerebral endothelial cells and between choroid plexus epithelial cells and restrict the entry of proteins into brain and cerebrospinal fluid. In the immature brain there are additional morphological barriers at the interface between cerebrospinal fluid and brain tissue: strap junctions at the inner neuroependymal surface and these and other intercellular membrane specializations at the outer (pia-arachnoid) surface. These barriers disappear later in development and are absent in the adult.30 Apart from this morphological protection, the presence of functional efflux transporters including P-glycoprotein (P-gp) reduces brain penetration of drugs.32 Virgintino et al reported on the expression of P-gp early in human fetuses during cerebral cortex formation. At the earliest examined stage, 12 weeks of gestation, P-gp was detectable as diffuse cytoplasmic labeling of the endothelial cells lining the primary cortex microvessels. At 18 weeks of gestation, a punctate P-gp staining pattern was detected on cortex and subcortical vessels and on their side branches. At 22 weeks of gestation, P-gp staining was linear and concentrated on endothelial cell membranes.31Thirdly, the placenta filters cytotoxic drugs and shields a proportion from the fetus. Human data are anecdotal, but transfer rates in a pregnant baboon model vary and range from 0-57% of the maternal serum levels.33,34

The limitations of this study include a moderate sample size, a relative short follow-up period and a lack of a direct comparison with identically assessed children, born at the same gestational age but without prenatal exposure to chemotherapy. To tackle the latter, we have now started to build a control group: children matched for the gestational age at birth, which will be followed up according to the same protocol as the chemo-exposed children. With respect to the short follow up period, this study does not allow to document secondary malignancies. In children, the use of low-dose etoposide is associated with secondary leukaemia, but genetic susceptibility to neoplasia may be a confounding factor.35 To date, only one case of second neoplasm after transplacental exposure to chemotherapy has been described. One member of a twin exposed to DNA-damaging cyclophosphamide and prednisone for acute lymphocytic leukemia was born with congenital malformations and was diagnosed with papillary thyroid cancer at 11 years of age and neuroblastoma at 14 years of age.36 Given the unknown effect on secondary malignancies, where possible, preference to microtubule-targeting agents and especially taxanes should be given.2,37 Long term follow-up is thus mandatory but sensitive for biases. In order to have the 18 year planned follow up, they need to survive to 18 years (survivor bias). In addition, all children should be followed and reasons for exclusion, loss of follow-up or refusal for participation need to be documented properly (figure 1).

In summary, we show that children who were prenatally exposed to chemotherapy, perform as good as other children. Especially when we consider confounding factors as prematurity and maternal stress,8-10 based on current data the long term effect of prenatal exposure to chemotherapy seems to outweigh the maternal need for treatment during pregnancy. Although a role of chemotherapy in the poor outcome of a twin and a higher incidence of disharmonic intelligence profiles cannot be excluded, the results allow recommendation of chemotherapy during pregnancy, if needed. The decision to administer chemotherapy should follow the same guidelines as in non-pregnant patients.3 In practice, it is possible to administer chemotherapy from 14 weeks gestational age onwards and prenatal care deserves specific attention.3 To allow the bone marrow to recover and to minimize the risk of maternal and foetal sepsis and haemorrhage, delivery should be planned at least 3 weeks after the last cycle of chemotherapy, and chemotherapy should not be administered after 35 weeks since spontaneous labor becomes more likely.3 Furthermore, neonates, especially preterm babies, have limited capacity to metabolize and eliminate drugs due to liver and renal immaturity. The delay of delivery after chemotherapy will allow foetal drug excretion via the placenta.3 Given the negative prognostic influence of prematurity on cognitive development, preterm birth should be avoided, if possible. Only time will inform us on the full consequences, including fertility and secondary malignancies (especially if DNA damaging drugs are used), of fetal exposure to chemotherapy. Therefore, we continue this international collaborative initiative ([www.cancerinpregnancy.org](http://www.cancerinpregnancy.org) (accessed November 13, 2011)) and strive for more children with longer follow-up to ascertain health.

***Panel*: Research in context**

**Systematic review**

To our knowledge, this is the first comprehensive report on the long term outcome of children after prenatal exposure to chemotherapy. We searched PubMed for reports published from 1990-2011, using the search terms “pregnancy”, “cancer”, “children”, “chemotherapy”, “outcome” without language restrictions. We also searched review papers. No data on the examination of children long after prenatal exposure were published at the time of the search.

**Interpretation**

This study suggests that after the administration of chemotherapy during pregnancy the outcome of children is not different from the general population. Among a cohort of children that were prenatally exposed to chemotherapy, general health and growth, central nervous system, cardiac, and auditory functions did not differ from the normal population. These results do not support a strategy of delay of chemotherapy administration or iatrogenic preterm delivery with postpartum chemotherapy administration in order not to harm the fetus. Subtle changes were however noted and underscore the need for longer follow up in more children.

**Contributors**

FA designed the concept. FA and KVC performed the literature search. FA, MJH and PBO were the national study coordinators. FA, KVC, MM, LH, SNH, MJH and PBO identified children and organised examinations in the national study centres. They collected all clinical data and study results. MM, LK and VT performed cardiac assessments. FA, MM, LM, WH and LK performed cardiac data analysis and interpretation. FA, KVC, MJH, LL, MAW and HW performed the cognitive tests, cognitive data analysis and interpretation. KVC and BVC performed the statistical analyses. FA and KVC wrote the first draft of the manuscript. All authors approved the final manuscript.

**Conflict of interest**

We declare that we have no conflicts of interest.

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