

Pediatric outcome after maternal cancer diagnosed during pregnancy (2700 woorden)

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ABSTRACT

Background

The long-term outcome of children antenatally exposed to cancer treatment is still debated. Prospective studies are needed to obtain robust safety data.

Methods

This is a multi-center case-control study including children born from mothers whose pregnancy was complicated by cancer. Neonatal and general health data were collected by a questionnaire. At 18 and 36 months all children were prospectively assessed neurologically (neurological examination and mental scale of the Bayley Scales of Infant Development). Cardiac assessment (ECG and echocardiography) was performed at 36 months. Results were compared to a control group matched for gestational age at birth, test age and country.

Results

In total, 129 study children with a median age of 22 months (range 12-42) were included in Belgium ($N=84$), The Netherlands ($N=26$), Italy ($N=10$), Czech Republic ($N=8$) and Germany ($N=1$). Eighty-nine (69.0%) were exposed to chemotherapy, 4 (3.1%) to radiotherapy, 7 (5.4%) to chemo- and radiotherapy, 1 (0.7%) to herceptin, 1 (0.7%) to interferon β , 13 (10.1%) to surgery only and 14 (10.9%) mothers did not receive treatment during pregnancy. 391 cycles of chemotherapy were administered in 96 patients.

Intrauterine growth restriction was more frequent in study children (27.2%) than in controls (16.0%) ($p = .031$). Biometry and general health problems were comparable in both groups. Cognitive development was not significantly different for study (*Med* 101, range 56-145) and control children (*Med* 101, range 50-145) ($p = .075$). Subanalyses per treatment group also did not show a significant difference. However, GA at birth was negatively correlated to the outcome in both groups. The standardized cognitive score tends to increase 2.2 points (95% CI 1.4-2.9, $p < .001$) for each week increase in GA. Cardiologic evaluation at 3 years of age ($N=47$) demonstrated normal cardiac findings.

Conclusion

Antenatal exposure to cancer treatment results in normal cognitive, cardiac and general development of children in early childhood. Prematurity is related to a worse cognitive outcome and this effect is independent from cancer treatment.

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INTRODUCTION

Fetal development is a very complex process. At different stages of development different aspects can be influenced by external factors (eg. teratogenic drugs, alcohol, smoking, maternal stress, altered nutrition).

In patients diagnosed with cancer during pregnancy, both the maternal illness, diagnostic exams, cancer treatment and high levels of maternal stress, may influence fetal development. Cancer treatment during pregnancy exposes the fetus to potentially toxic substances affecting cell division. Although the placenta acts as a protective barrier for the fetus, chemotherapeutic drugs cross the placenta in variable amounts.^{1,2} The long-term effects have not been well studied. First studies show reassuring results regarding the neurologic, cognitive and cardiac outcome, but larger sample sizes with long-term follow-up in a case-control design are needed to study the fetal impact of maternal cancer.³⁻⁵ It is generally accepted that the lack of safety data results in a high threshold for chemotherapy administration but a low threshold for termination of pregnancy, delay of maternal treatment and/or preterm induction of labor. Also for prenatal exposure to radiotherapy and the use of targeted agents which are relatively new, long-term outcome data are scarce.

Data on fetal impact of antenatal exposure to chemotherapy are largely based on retrospective studies.^{3,4,6} Initial data from a multicenter prospective study of children after antenatal exposure to chemotherapy indicated that, overall, antenatal exposure to cancer treatment can be considered safe.⁷ However, the use of different tests used according to a wide age distribution (16.8 months till 17.6 years of age) and the comparison to standardized scores may limit the reported results. Therefore we enlarged the number of children in a specific age cohort (12-42 months). We examined the general health growth, cognitive development and heart functions of these children and compared the results to a gender and age matched control group.

METHODS

Participants

Study children were recruited from the International Network on Cancer, Infertility and Pregnancy (INCIP) registry. The study is based on a collaboration between national referral centers in Belgium, The Netherlands, Italy and Czech Republic. Controls were children born to healthy mothers, without specific pregnancy-related or neonatal problems. that may have an impact on development. Control children for mental development and general health were

recruited in Belgium (for Belgium and The Netherlands), Italy and the Czech Republic and 1:1 matched for gestational age and test age to the study children of that particular country. Controls for the cardiac examinations were recruited from Belgium and Toronto, and were 1:1 matched for test age and gender.

The study profile is presented in [Figure 1a](#).

Procedures

The study was approved by the Ethical Committee of each institution and is registered as ClinicalTrials.gov, NCT00330447. Written parental informed consent to participate was obtained for each child. Obstetrical, perinatal (including congenital malformations) and oncological data were collected. Between 2005 and 2015, study and control children were invited for follow-up at the age of 18 months and 3 years. A clinical neurological and general paediatric examination was performed in all study children and parents filled out a general health questionnaire.

Mental development was assessed in study and control children using the Bayley Scales of Infant Development (BSID) ([Ref nog toe te voegen](#)). The third edition was used in Italy, while the second edition was used in Belgium, The Netherlands and Czech Republic according to the availability of the most recent edition at the start of inclusion. One experienced clinical psychologist performed the tests for both study and control children in each country.

Cardiac evaluation consisted of a 12-lead electrocardiogram (ECG) and a full echocardiographic evaluation looking for structural abnormalities and included a detailed functional evaluation, performed at 3 years. Specific details on the performance of all measurements are described in the appendix. Fetal radiation dose was calculated according to the dose program “Peridose” developed by van der Giessen.⁸

Statistical analysis

Maternal oncological data and results of the general health questionnaires and the clinical neurological examinations were descriptively analyzed. Child characteristics were compared between study and control group using Mann-Whitney U test for continuous variables and Chi-square or Fisher’s exact test for categorical data depending on sample size and number of categories.

Raw cognitive scores on the Bayley test were converted to standardized cognitive scores (not corrected for prematurity) according to the norms of each country. A univariate and multivariate linear regression model were used to investigate the relationship between GA

and cognitive outcome. Pearson correlations were used to investigate the relationship between parental education levels or the number of chemotherapy cycles and cognitive outcome. Scores between the study and control groups were compared by Wilcoxon signed rank test. ANCOVA was used to control for covariates.

Electrocardiographic measurements were analyzed and compared to normal values in childhood and adolescence published by Dickinson.⁹ All echocardiographic measurements were obtained in three cardiac cycles and averaged. When available, z-scores were calculated. Independent samples t-tests were used to compare echo measurements as well as their z-scores between study and control group. A p -value < 0.05 was considered significant in all analyses.

RESULTS

Patient, disease and treatment characteristics

In total, 129 study children (including four twins) from Belgium/The Netherlands ($N = 110$), Italy ($N = 10$), Czech Republic ($N = 8$) and Germany ($N = 1$) were included, as well as 129 controls from Belgium ($N = 111$), Italy ($N = 10$) and Czech Republic ($N = 8$). Study and control children were both examined at a median age of 22 months (range 12-42) ($p = .152$) and gender was equally distributed (males respectively 46.5% vs. 52.7%, $p = .319$).

Median maternal age and GA at diagnosis were respectively 33 years (range 19–42) and 17.7 weeks (range 1–37.5). Treatment modalities are presented in Table 1. 391 cycles of chemotherapy were administered in 96 pregnant patients. Further details on cancer type and treatment are available in appendix.

Neonatal outcome

Study children were born at a median GA of 36 weeks (range 27-41), of whom 61.2% was born preterm (compared to a normal ratio of 6.8-8.0% in the countries participating in this study).¹⁰ Eleven children were born at 27.0-31.9 weeks, 16 at 32.0-33.9 weeks, 52 at 34.0-36.9 weeks and 50 at term (≥ 37 weeks). Not more or other types of congenital malformations were seen compared to the incidence in general population and the neonatal neurologic and cardiac examinations performed were normal. (appendix) Median birthweight was 2680 g ($N = 125$, range 720-4690; IQR 864). A birth weight below the tenth percentile for gestational age and gender (= intrauterine growth restriction (IUGR)) was noted in 34 of 125 study children and in 20 of 125 control children (27.2% vs 16.0%; $p = .031$). The highest percentages were seen in the children exposed to chemotherapy (30/125; 24%) and more

specifically when exposed to anthracycline-based schemes (22/75; 29.3%) and from mothers diagnosed with hematological malignancies (12/20; 60%). (appendix)

Growth and general health

Biometric data showed similar results between the chemotherapy-exposed and control children for weight, height and head circumference. (Figure 3a)¹¹ In Figure 3b, available follow-up biometric data of study (23/30) and control (15/17) children born with a birthweight below the tenth percentile is shown. Respectively 8 study children and 9 control children (8/23, 34.8% vs. 9/15, 60%; $p = .185$) remained below the tenth percentile at the moment of follow-up. (Figure 3b)

In general, the incidence of medical problems and the need for surgery or paramedical care were not significantly different between study and control children. Only ear tube surgery and circumcision were more frequent in controls ($p = .009$; $p = .034$) (appendix).

Cognitive development

Study and control groups were compared on several background variables (Figure 1b). GA, test age, gender and ethnicity did not differ between the groups (appendix). However, a significant difference was found for education level, noticing that parents of children from the control group were on average higher educated than those of the study group ($p < .001$ for mothers and $p = .014$ for fathers or co-mothers) (appendix). Maternal and paternal education levels were related to the cognitive outcome of study children (respectively, $r = .268$, $p = .003$; $r = .188$, $p = .040$), but not of controls (respectively, $r = -.051$, $p = .607$; $r = -.017$, $p = .862$). Therefore, education levels were added as a covariate in further analyses.

Gender differences in cognitive outcome were found. Girls ($N = 130$, *Med* 104, range 58-145) scored significantly higher than boys ($N = 128$, *Med* 97.5, range 50-145) ($p = .001$), even when controlling for group (study or control) ($p = .001$). GA was related to the cognitive score in both study and control children (Figure 2a). A univariate linear regression model showed that for all study and control children ($N = 258$) the average cognitive score tends to increase by 2.7 points for each week increase in GA at birth (95% CI 2.0-3.5, $p < .001$) (study children: 2.5, 95% CI 1.4-3.6, $p < .001$; controls: 3.0, 95% CI 2.0-4.0, $p < .001$). After controlling for gender, test age, country, education level of parents and ethnicity, an average increase of 2.2 points (95% CI 1.4-2.9, $p < .001$) for each week increase in pregnancy duration was found. However, gender and GA were not included as a covariate in later analyses because they were equally distributed in both groups.

Study and control children were compared within each country and revealed no significant differences for Belgian/Dutch children ($N = 110$ in both study and control group, $p = .189$), Italian children ($N = 10$, $p = .593$) or Czech children ($N = 8$, $p = .263$) (appendix). Scores between the different countries were not statistically compared because of the use of different editions of the BSID and small sample sizes in Italy and Czech Republic.

Normal cognitive development was found for most study and control children (Figure 2b for children exposed to chemotherapy and/or radiotherapy and controls). Cognitive outcome was not significantly different between children exposed to chemotherapy and controls ($p = .427$) (Figure 2c). Even after controlling for parental education levels, both groups did not differ ($p = .525$). The number of cycles of chemotherapy administered during pregnancy was not related to the outcome ($r = .177$, $p = .085$). Subanalyses per type of chemotherapy (anthracyclines, taxanes, platinum derivatives) revealed no significant differences between study and control children (Figure 2c). Compared to matched controls, no significant differences in cognitive outcome were found for children exposed to radiotherapy, surgery only or no treatment during pregnancy (Figure 2c).

Cardiac functions

Cardiac function was assessed in 50 of 54 study children aged 3 years old using ECG and echocardiography. Children <3 years were not included as this would require administration of sedation. Data were compared to 47 age matched controls. Data on 3 children had to be excluded due to lack of cooperation during the study. Data were compared to 47 age matched controls. No significant differences in age, BSA, heart rate, and blood pressure were found between study patients and controls. On echocardiographic examination no structural abnormalities were detected in any of the patients. Table x summarizes the echocardiographic data. Cardiac chamber dimensions and wall thickness were within normal ranges. Ejection fraction (EF) and fractional shortening (FS) were not different between the study group and normal controls. Also no differences in global longitudinal and circumferential strain values were detected between study patients and controls. Finally also different echocardiographic parameters for diastolic function were not different between study patients and controls. We observed small but statistically significant differences in TDI measurements in the IVS but not in the LV lateral wall. These differences were not present in the subgroup of anthracycline-exposed children ($N = 26$). (table or appendix?)

DISCUSSION

In this multicenter prospective case-control study of 129 children, we documented the ~~cognitive and cardiac~~ effects of antenatal exposure to cancer treatment on general health.

pre- and postnatal growth, cognitive development and cardiac functions. 61.2% of study children were born preterm at a median GA of 36 weeks. The results indicate that children who have been antenatally exposed to cancer treatment and in particular to chemotherapy (n=96) develop normally at a median age of 22 months. The outcome of 11 children antenatally exposed to radiotherapy was also reassuring. ~~In particular 96 children antenatally exposed to chemotherapy have a normal outcome, irrespective of the number of chemotherapy cycles that was administered during pregnancy. In contrast, both study and control children who were born preterm have a worse outcome.~~

Cognitive outcome was comparable between the study and control groups and was independent of the number of chemotherapy cycles. This observation is in line with previous studies.^{3,5-7} However, small outcome differences were seen between chemotherapeutic agents. Children exposed to platinum derivatives seem to have slightly lower scores on cognitive assessment than children exposed to taxanes or anthracyclines, however not significantly different from their controls. Although a relatively high transplacental passage rate of 57% of platinum derivatives (ref) may add to this outcome, small groups and the combination with other drugs are confounding factors. Also, the negative prognostic effect of prematurity on cognitive development was confirmed and the effect was comparable for study and control group.

One child was excluded from the study because of the diagnosis of a syndromal entity. This case has been previously described in detail.⁷ Inclusion of this child instead of another study child with the same GA, test age, gender, country and maternal disease did not change the results of cognitive development (appendix).

IUGR was significantly more frequent in children born to mothers with cancer during pregnancy compared to our control children (34/125; 27.2% vs 20/125; 16.0%; $p = .031$). ~~Moreover, a higher incidence of IUGR was found for children of women diagnosed with hematological malignancies, children exposed to chemo- and/or radiotherapy, and more specifically after the exposure to anthracycline-based schemes (22/75; 29.3%).~~ Earlier studies already raised the concern that IUGR is more frequently seen in pregnancies complicated by cancer and/or cancer treatment.^{7,12} ~~In our previous report 21% of the children exposed to chemotherapy had a birthweight below the 10th percentile. Van Galsteren et al. also stated that IUGR was increased in mothers treated and not treated for hematologic malignancies (27.3%), suggesting that cancer by itself may lead to IUGR.~~ IUGR puts an infant at a significant risk of perinatal morbidity and mortality.¹³ Causes for Current knowledge about the physiology and pathology of fetal growth is mainly derived from animal studies, and from patient studies with advanced ultrasound techniques. IUGR include a compromised

placental supply of nutrients and oxygen to the fetus (80-90% of all cases)¹⁴, a disturbance of the metabolic adaptations of pregnancy¹⁵, or chronic inflammation¹⁶⁻¹⁸. One can envisage that several of these phenomena may arise in a pregnancy complicated by cancer but the pathophysiological mechanisms in this setting are so far unexplored. Reassuring is the observation that 65.2% of IUGR children regain their weight during the first 3 years.

[The incidence of health problems](#) was [not increased](#) and

also the cardiac structure and function was normal. This observation is in line with previous studies where cardiac function was evaluated in children during and after pregnancy.^{8,18,29} In the current study conventional parameters for systolic and diastolic function as well as tissue Doppler velocities and myocardial strain measurements were all within normal range and no significant differences were found between patients and controls. These data are very reassuring and suggest that at 3 years of age no changes in cardiac structure or function can be detected in children born from mothers with cancer diagnosed and treated during pregnancy. A subanalysis of children exposed to anthracyclines during pregnancy also revealed no significant differences between the children and the normal control group. There are no signs of cardiac remodeling with normal wall thicknesses and chamber dimensions and all parameters for systolic and diastolic function are within normal range. In the entire group we found very small differences in tissue Doppler velocities in the basal part of the interventricular septum. We believe these are clinically irrelevant as the measurements are within normal range.

The reassuring outcome can be explained by the timing of chemotherapy administration and the role of the placenta. All cycles of chemotherapy in this series were administered after the first trimester of pregnancy. The period until a gestational age of 10 weeks is the most vulnerable since the organogenesis is settled in this period. Administration of chemotherapy after the first trimester does not result in more and/or other congenital malformations.^{5,12,20} ~~In a unique series, Aviles and colleagues reported on 54 children born after first trimester exposure to chemotherapy, and reported no adverse events although the precise timing in the first trimester, duration and dose of chemotherapy exposure remains unknown.~~^{21,22} In addition, the placenta not only nurtures but also protects the fetus from toxic agents. Both the placental brush border and the basolateral membrane contain active drug transporters determining/regulating fetal drug exposure. Apart from the drug-transporter affinity, transplacental passage depends on lipid solubility, molecular weight and binding capacity to plasma proteins. These regulatory mechanisms result in lower fetal plasma levels when

compared to the maternal levels, although variation in transplacental passage is important ranging from 0-57%, for taxanes and carboplatin, respectively.^{1,23,24}

Our study has some limitations. The results of this study cannot be extrapolated to all chemotherapeutic drugs and in particular not to new targeted drugs. In addition, the follow up period is too short to document long-term cardiotoxicity, whereas children are too young to test for cisplatin induced ototoxicity.

In summary, children antenatally exposed to cancer and the associated stress, imaging studies and treatment modalities develop normally. In particular, chemotherapy has no effects on postnatal growth, cognitive and cardiac functions in early childhood. From our experience and the reported data, we believe that the clinical impact of these observations is threefold. Firstly, [the lack of safety data of antenatal exposure to chemotherapy the diagnosis of cancer during pregnancy](#) is no indication to terminate the pregnancy and is secondly, no reason to delay maternal treatment. Thirdly, the administration of chemotherapy during pregnancy can be used to continue pregnancy and to avoid medically induced prematurity and its short and long term consequences. Therefore, these fetal safety data contribute to fetal and maternal chances when cancer treatment during pregnancy is needed.

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