Pediatric Outcome after Maternal Cancer Diagnosed During Pregnancy

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ABSTRACT

Background

The long-term outcome of children antenatally exposed to cancer treatment is still debated.

Methods

This is a multi-center case-control study comparing children born from mothers whose pregnancies were complicated by a cancer diagnosis to matched children of women without a cancer diagnosis. Neonatal and general health data were collected by a health questionnaire and from the medical files. At 18 and 36 months all children were prospectively assessed neurologically (neurological examination and Bayley Scales of Infant Development). Cardiac assessment was performed at 36 months.

Results

In total, 129 children (median age of 22 months [range 12-42]) were included. 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. Birth weight was below the tenth percentile in 22.0 and 15.1% of study and control children, respectively (P=0.163). Cognitive development was not significantly different between study (Bayley score, median 101, range 56-145) and control children (median 101, range 50-145) (P=0.075). Subanalyses per treatment group did not show significant differences. Gestational age at birth was negatively correlated to the cognitive outcome in both groups. Cardiologic evaluation at 3 years of age (N=47) demonstrated normal cardiac findings.

Conclusion

Antenatal exposure to cancer diagnosis and treatment does not impair cognitive, cardiac and general development of children in early childhood. Prematurity is related to a worse cognitive outcome but this effect is independent from cancer treatment.

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INTRODUCTION

Fetal development is a 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, maternal illness, diagnostic tests, cancer treatment and increased levels of maternal stress, can negatively influence fetal development. Cancer treatment during pregnancy exposes the fetus to potentially toxic substances influencing cell division. Chemotherapeutic drugs can cross the placenta in variable amounts.[1,2] The information on fetal effects of maternal cancer treatment is mainly based on retrospective cohort studies.[3-6] From our 10-year experience, it appears that the limited availability of safety data can influence therapeutic decision-making resulting in a high threshold for initiating chemotherapy and a low threshold for termination of pregnancy. It can also delay maternal treatment and result in preterm induction of labor. Limited data are also available on prenatal exposure to radiotherapy.[7]

Our group published combined prospective and retrospective data from a multicenter study including children antenatally exposed to chemotherapy. Our initial data seemed to suggest that fetal exposure to maternal cancer treatments did not seem to be associated with cognitive or cardiac abnormalities.[8] The combined retrospective and prospective design limited the interpretation of the results as results from different tests at different ages (16.8 months till 17.6 years of age) were pooled. Therefore we enlarged the prospective cohort (12-42 months) and evaluated the general health status, growth, cognitive development and cardiac structure and function comparing the results to a matched control group.

METHODS

Participants

The study is based on a collaboration between national referral centers in Belgium, The Netherlands, Italy and Czech Republic, all members of the International Network on Cancer, Infertility and Pregnancy (INCIP). Study children were born from mothers diagnosed with cancer during pregnancy with or without treatment during pregnancy. Controls were children born to healthy mothers, after

uncomplicated pregnancies and deliveries. The study design and recruitment are summarized in Fig. 1. For the cognitive developmental and general health examinations, controls 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 in Belgium and Toronto, and were 1:1 matched for test age and gender. Details on the recruitment are provided in appendix. 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.

Study tests

Obstetrical, perinatal (including congenital malformations) and oncological data were collected. Birth weight percentiles were calculated considering the gestational age at birth, birth weight, sex, ethnicity, parity, and maternal length and weight when available (www.gestation.net, v6.7.5.7(NL),2014) (appendix). Fetal radiation dose was calculated according to the dose program "Peridose" developed by van der Giessen.[9] 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 pediatric examination was performed in all study children and parents completed a health questionnaire (appendix).

Cognitive development was assessed in study and control children using the Bayley Scales of Infant Development.[10,11] The third edition (cognitive scale) was used in Italy, while the second edition (mental scale) was used in Belgium, The Netherlands and the Czech Republic, according to the availability of the most recent edition at the start of inclusion. Bayley III cognitive scores were found to be significantly higher than Bayley II mental developmental index scores in children born both at term and preterm.[12] We handled this finding in our study by a 1:1 matched comparison of study and control children assessed in the same country with the same Bayley edition and by calculating correlations and regression models only on Bayley II scores.

Cardiac evaluation was performed at 3 years of age to avoid having to use sedation for the tests. It consisted of a 12-lead electrocardiogram (ECG) and a detailed echocardiographic examination.

Standard views and measurements were performed according to guidelines published by the American Society of Echocardiography.[13,14] Details on the echocardiographic protocol are included in the appendix.

Statistical analysis

Descriptive statistics were used to describe maternal oncological data, results of the health questionnaires and clinical neurological evaluations. Background variables (child and maternal age, gestational age, sex, birth weight, ethnicity, maternal length and weight, parity and parental education levels) 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 distribution characteristics, sample size and number of categories.

Raw cognitive scores were converted to standardized cognitive scores (not corrected for prematurity) according to normative data for each country in the Bayley manual. Univariate and multivariate linear regression models were used to look at the relationship between gestational age and cognitive outcome. Pearson correlations were used to investigate the relationship between parental education levels or the number of chemotherapy cycles and cognitive outcome. The relationship between the estimated fetal dose of radiation and cognitive outcome was investigated by means of a Spearman rho correlation. Cognitive scores were compared between the study and control groups by Wilcoxon signed rank test. ANCOVA was used to control for covariates.

Electrocardiographic measurements were interpreted by an experienced cardiologist. All echocardiographic measurements were obtained in three cardiac cycles and averaged. When appropriate, measurements were corrected for body surface area and 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 2-sided P value < 0.05 was considered significant for all analyses. Up to 6 significant results can be expected on the basis of chance alone given the plan to perform 110 (sub)group analyses.

RESULTS

Patient characteristics

In total, 129 study children (including four pairs of twins) from Belgium (N=103), The Netherlands (N=8), Italy (N=10) and the Czech Republic (N=8) were included. The study children were matched to 129 controls from Belgium (N=111), Italy (N=10) and the Czech Republic (N=8). Study and control children were both examined at a median age of 22 months (range 12-42) (P=0.152) and sex was equally distributed (males respectively 46.5% vs. 52.7%, P=0.319) (Table 1).

Median maternal age and gestational age at diagnosis were respectively 33 years (range 19–42) and 17.7 weeks (range 1–37.5). During pregnancy, 100 children were exposed to chemotherapy and/or radiotherapy. In total, 391 cycles of chemotherapy were administered in 93 pregnancies, exposing 96 children. Eleven children, including one pair of twins, were exposed to radiotherapy. Further details on cancer type and treatment are shown in Table 2.

Perinatal outcome

Study children were born at a median gestational age of 36 weeks (range 27-41). In total 61.2% were born preterm (compared to a general percentage of preterm births ranging between 6.8-8.0% in the participating countries).[15] Eleven children were born between 27.0-31.9 weeks (very preterm), 16 at 32.0-33.9 weeks (moderate preterm), 52 at 34.0-36.9 weeks (late preterm) and 50 ≥ 37 weeks (full-term). The number and type of congenital malformations were comparable to the general population and the neonatal neurologic examinations performed were normal (appendix). Median birth weight was 2705 g (N=127, range 720-4690 g; IQR 865 g). A birth weight below the tenth percentile (= small for gestational age was noted in 28 of 127 study children and in 19 of 125 control children (22.0 vs. 15.1%; P=0.163). More specifically, small for gestational age babies were observed in 24 of 95

(25.3%) and in 4 of 11 children (36.4%) exposed to chemotherapy and radiotherapy, respectively (Table 2).

Growth and general health

The incidence of medical problems and the need for surgery or medical care were comparable between study and control children (appendix). However, one study child was excluded from further analyses because of the diagnosis of a syndromal entity. This case has been previously described in detail.[8]

Registered biometric data showed similar results between the study and control children for weight, height and head circumference (data not shown).[16] In the subgroup of small for gestational age children exposed to chemotherapy, we observed a catch-up weight at test age in 63.6% (14/22 children, 2 unknown).

Cognitive development

Study and control groups were compared for several background variables (Table 1). Gestational age, test age, sex and ethnicity did not differ between the groups. A significant difference was found for education level, as parents of children from the control group were on average more highly educated than those of the study group ($P<0.001$ for mothers and $P=0.015$ for fathers or co-mothers) (Table 1). Maternal and paternal education levels were related to the cognitive outcome (Bayley II) of study children (respectively, $r=0.303$, $P=0.001$; $r=0.211$, $P=0.025$), but not of controls (respectively, $r=0.020$, $P=0.843$; $r=0.009$, $P=0.932$). In further analyses, parental education levels were included as a covariate.

Sex differences in cognitive outcome were found. Girls (N=130, median 104, range 58-145) scored significantly higher than boys (N=128, median 97.5, range 50-145) ($P=0.001$), even when controlling for group (study or control) ($P=0.001$). Gestational age was related to the cognitive score in both study and control children (Fig. 2A). A univariate linear regression model showed that for all study and control children assessed by means of Bayley II (N=238), the average cognitive score tends to increase by 2.9 points for each week increase in gestational age at birth (95% CI, 2.2 to 3.7, $P<0.001$) (study

children: 2.8, 95% CI, 1.6 to 3.9, P<0.001; controls: 3.1, 95% CI, 2.0 to 4.1, P<0.001). In a regression model with gestational age, group (study or control) and the interaction between gestational age and group as predictors of cognitive outcome, the interaction term was non-significant (P=0.681) (GA: P=0.052, group: P=0.616). After controlling for sex, test age, country, parental education level and ethnicity, an average increase of 2.2 points (95% CI, 1.5 to 3.0, P<0.001) for each week increase in pregnancy duration was found. However, sex and gestational age were not included as a covariate in latter analyses because they were equally distributed in both groups.

Study and control children were compared within each country and revealed no significant differences (appendix).

Normal cognitive development was found for most study and control children (Fig. 2B) and the results were not significantly different (P=0.075) (Fig. 2C). Cognitive outcome was not significantly different between children exposed to chemotherapy and controls (P=0.427) (Fig. 2C). Even after controlling for parental education levels, the groups did not differ (P=0.525). Cognitive outcome (Bayley II) was not related to the number of chemotherapy cycles administered during pregnancy (r=0.126, P=0.245) (Fig. 2D). Subanalyses per type of chemotherapy (anthracyclines, taxanes, platinum derivatives) revealed no significant differences between study and control children (Fig. 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 (Fig. 2C). Cognitive outcome was not related to the estimated fetal dose of radiation (r=0.110, P=0.747) (Fig. 2E).

Inclusion of the child with a syndromal entity, instead of another study child with the same gestational age, test age, sex, country and maternal disease did not change the results of cognitive development (data not shown).

Cardiac evaluation at 3 years

Cardiac function was assessed in 50 of 54 study children aged 3 years old using ECG and echocardiography. Data from 3 children were excluded due to lack of cooperation during the examinations. Data were compared to 47 age- and sex-matched controls. No significant differences in

age, body surface area, heart rate, and blood pressure were found between study children and controls. On echocardiographic examination no structural abnormalities were detected in any of the patients. Table 3 summarizes the echocardiographic data. Cardiac chamber dimensions and wall thickness were within normal ranges. Ejection fraction and fractional shortening were not different between the study and control group. Also no differences in global longitudinal and circumferential strain values were detected between study children and controls. Different echocardiographic parameters for diastolic function were not different between the study and control group. We observed small but statistically significant differences in tissue Doppler imaging measurements in the interventricular septum but not in the left ventricular lateral wall. These tissue Doppler velocities differences were not present in the subgroup of anthracycline-exposed children (N=26) (appendix).

DISCUSSION

In this multicenter prospective case-control study of 129 children, we documented the effects of antenatal exposure to cancer and cancer treatment on general health, pre- and postnatal growth, cognitive development and cardiac structure and function. The incidence of preterm delivery in the study group was high (61.2%). Development of the study children was normal at a median age of 22 months. In particular, the subgroup of children who have been antenatally exposed to chemotherapy (N=96) and radiotherapy (N=11) develop normally.

Health problems and cognitive outcomes were comparable between the study and control groups, which is consistent with previous studies.[3,5,8,17] Cognitive outcomes seemed independent of the number of chemotherapy cycles. Also, the negative prognostic effect of prematurity on cognitive development was confirmed and the effect was comparable for study and control group.

Small for gestational age children were more frequently born to mothers with cancer during pregnancy compared to our control children (22.0 vs. 15.1%); however, the difference is not statistically significant. Earlier studies already highlighted that small for gestational age children are more frequently observed in pregnancies complicated by maternal cancer.[18] Small for gestational age children are at increased risk of perinatal morbidity and mortality.[19] Causes of small for gestational

age births include a compromised placental supply of nutrients and oxygen to the fetus (80-90% of all cases), altered metabolic adaptations of pregnancy, or chronic inflammation.[20-23] One can hypothesize that several of these factors are present in a pregnancy complicated by cancer (further information in appendix).

In children evaluated at 3 years of age using ECG and echocardiography, cardiac structure and function were normal. This observation is consistent with previous studies where cardiac function was evaluated in fetuses, newborns and children.[4,8,24] 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 study children and controls. A subanalysis of children exposed to anthracyclines (N=26) during pregnancy also revealed no significant differences between the study and control group. There were no signs of early cardiac remodeling with normal wall thicknesses and chamber dimensions and all parameters for systolic and diastolic function were within normal range. In the entire study group, we found 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 may 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 occurring in this period. Administration of chemotherapy after the first trimester does not result in more and/or other congenital malformations.[17,18,25] Both the placental brush border and the basolateral membrane contain active drug transporters that influence fetal drug exposure. Apart from the drug-transporter affinity, transplacental passage depends on lipid solubility, molecular weight, binding capacity to plasma proteins and placental metabolism of the agents. These regulatory mechanisms result in lower fetal plasma levels when compared to the maternal levels, although variation in transplacental passage ranges from 0 to 57%, for taxanes and carboplatin, respectively.[1,2,26,27]

Our study has 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 and neurocognitive problems that may become more apparent later in life.

In summary, children antenatally exposed to cancer and the associated stress, imaging studies and treatment modalities seem to develop normally. In particular, chemotherapy has no clear adverse effects on postnatal growth, cognitive and cardiac function in early childhood. Our data suggest that the diagnosis of cancer during pregnancy is not necessarily an indication to terminate the pregnancy. While caution is always indicated, treatment of the maternal cancer in the second trimester or later may not be harmful to the fetus. Pregnant women may be informed that their unborn child is more likely to be premature than in the general population, but among premature babies, the child is unlikely to have unique problems more serious than premature babies born of women without cancer during their pregnancy. However, the administration of chemotherapy during pregnancy can be used to avoid medically induced prematurity and its short and long term consequences.

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Figure legend:

Figure 1. Study design and recruitment of study and control children

Figure 2. Cognitive outcome

A. Cognitive outcome (reported as Bayley II score) in relation to gestational age at birth for study (N=119) and control (N=119) group

B. Cognitive outcome of the study (N=129) and control (N=129) group: the distribution of the results of the last performed Bayley Scales of Infant Development (second or third edition) for each child

C. Cognitive outcome (reported as Bayley II or III score) per treatment group comparing study and control (C) groups (median, range)

D. Cognitive outcome (reported as Bayley II score) in relation to the number of chemotherapy cycles administered during pregnancy (N=87)

E. Cognitive outcome (reported as Bayley II score) in relation to the estimated fetal dose of radiation exposure during pregnancy (N=11)

Table 1. Baseline characteristics of study and control group

	Study group (N=129)		**Control group (N=129)**		
	Median (range) / N (%)		**Median (range) / N (%)**		**P value**
Age (months)	22 (12-42)		22 (12-42)		0.152
GA (weeks)	36 (27-41)		36 (27-41)		0.995
Birth weight (g)	2705 (720-4690)		2755 (1100-4905)		0.502
Maternal age (years)	33.4 (19.6-43.5)		31.0 (20.6-40.2)		0.001***
Sex					0.319
Male	60 (46.5%)		68 (52.7%)		
Female	69 (53.5%)		61 (47.3%)		
Ethnicity					0.123
Caucasian	108 (85.7%)		106 (91.4%)		
African	11 (8.7%)		3 (2.6%)		
Other	7 (5.4%)		7 (6.0%)		
Unknown	3		13		
Highest level of education of mother and father (or co-mother)	Mother	Father	Mother	Father	Mother: <0.001*** Father: 0.015*
No education	0	1 (0.8%)	0	0	
Primary school	3 (2.4%)	3 (2.5%)	0	0	
Secondary school	50 (40.7%)	52 (42.6%)	18 (17.0%)	29 (27.6%)	
Bachelor	29 (23.6%)	30 (24.6%)	29 (27.4%)	25 (23.8%)	
Master	41 (33.3%)	36 (29.5%)	59 (55.7%)	51 (48.6%)	
Unknown	6	7	23	24	

* $p \leq .05$

***$p \leq .001$

Control groups for the cognitive and cardiac examinations include largely the same children. However, some controls are different because of the different matching criteria for cognitive and cardiac results. Above we presented the baseline characteristics for the control group included for the Bayley test, general health examinations and customized growth curves.

The highest level of education is presented according to the European education system. A bachelor-level degree is earned at both traditional universities and non-university institutions of higher education and requires between three and four years of full-time study, or 180 to 240 ECTS (European Credit Transfer and accumulation System) credits. A master-level degree is earned at university and requires between one and two years of full-time study, or 60 to 120 ECTS credits. A master-level degree can only be obtained after a bachelor-level degree.

Table 2. Tumor types and treatment modalities

A. Maternal tumor types treated during pregnancy (125 mothers, 129 children) and the incidence of small for gestational age (SGA) children

Maternal malignancy	N mothers	% mothers	N SGA*	% SGA
Breast cancer	69 (2 twin pregnancies)	55.2	9	12.7
Hematological Malignancy	20	16.0	8	40.0
- Acute Lymphoid Leukemia	1	0.8	1	100.0
- Acute Myeloid Leukemia	4	3.2	1	25.0
- Chronic Myeloid Leukemia	1	0.8	1	100.0
- Hodgkin's Disease	8	6.4	3	37.5
- Non-Hodgkin's Disease	6	4.8	2	33.3
Cervical cancer	10 (1 twin pregnancy)	8.0	2	18.2
Ovarian cancer	9	7.2	2	22.2
Brain tumor	3	2.4	1	33.3
Colon cancer	3	2.4	1	33.3
Gastric cancer	2	1.6	1	50.0
Renal cell cancer	1	0.8	0	0.0
Tongue cancer	2 (1 twin pregnancy)	1.6	3	100.0

Lung cancer	1	0.8	0	0.0
Thyroid cancer	2	1.6	1	50.0
Melanoma	1	0.8	0	0.0
Ewing sarcoma	1	0.8	0	0.0
Soft tissue sarcoma	1	0.8	0	0.0

*Birth weight was available for 127 of 129 children.

B. Type of cancer treatment during pregnancy and the incidence of small for gestational age (SGA)

Cancer treatment during pregnancy	**N children**	**%**	**N SGA***	**% SGA***
Surgery	13**	10.1	2	15.4
Chemotherapy	41	31.8	11	27.5
Radiotherapy	1	0.8	0	0.0
Surgery + Chemotherapy	48**	37.2	10	20.8
Surgery + Radiotherapy	3	2.3	1	33.3
Chemotherapy + Radiotherapy	3**	2.3	2	66.7
Surgery + Chemotherapy + Radiotherapy	4	3.1	1	25.0
Trastuzumab	1	0.8	0	0.0
Interferon-β	1	0.8	1	100.0
No treatment	14	10.9	0	0.0
Total	129	100.0	28	22.0

*Birth weight was available for 127 of 129 children, 1 unknown in the no treatment and 1 in the chemotherapy group.

**One twin was exposed to chemotherapy and radiotherapy, one twin to surgery only and two twins to surgery and chemotherapy.

C. Chemotherapy regimens applied during pregnancy in 93 women (including 3 twin-pregnancies)

Chemotherapy scheme	N cycles	N patients	% patients	N SGA***	% SGA***	GA (median (rang
(F)AC/(F)E(C)†**	195	58	53.7	8	13.8	32.0 (18.5-34.8
ABVD†	41	7	6.5	2	28.6	27.8 (22.7-33.0
(R) - CHOP†	34	7	6.5	3	42.9	27.7 (22.6-34.1
Cisplatin (± Epirubicin)†	27	6	5.6	2	33.3	22.7 (17.3-28.3
Carboplatin (± 5-Fluorouracil)**	3	1	0.9	2**	100.0	17.7 (14.7-20.7
Paclitaxel-Cis/Carboplatin**	36	9	8.3	4	44.4	24.9 (20.0-33.5
Paclitaxel/Docetaxel	38	14	13.0	3	21.4	31.0 (24.9-34.9
Hovon 37†	2	1	0.9	1	100.0	23.7 (21.0-26.3
Temozolomide	5	1	0.9	0	0.0	26.0 (18.0-33.9
Idarubicin-AraC†	4	1	0.9	1	100.0	22.0 (15.0-29.0
Daunorubicin-AraC†	2	1	0.9	0	0.0	22.4 (19.9-24.9
5-Fluorouracil	3	1	0.9	1	100.0	31.2 (29.1-33.3
VIM (without MTX)	1	1	0.9	0	0.0	29.1
TOTAL	391	108*	100	24††	25.3	26.6 (20.5-32.5

Abbreviations: SGA, small for gestational age; GA, gestational age; (F)AC, 5-fluorouracil, doxorubicin, cyclophosphamide; (F)
5-fluorouracil, epirubicin, cyclophosphamide; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; (R)-CHOP, rituximab,
cyclophosphamide, doxorubicin, vincristine, prednisolone; Hovon 37, cycle 1 prednisolone, vincristine, daunorubicin, L-apargin
MTX, and cycle 2 cytarabine, mitoxantrone, intrathecal MTX; AraC, cytarabine; MTX, methotrexate; VIM, ifosfamide, etoposi
MTX; *15 patients received 2 different schemes; † including anthracyclines; ** including 1 twin-pregnancy

††Two SGA children were exposed to both FEC and docetaxel and 1 SGA child to both AC and docetaxel. Therefore they are mentioned double in the table. In total, 24 chemotherapy-exposed children were born SGA.

***Birth weight was available for 95 of 96 chemotherapy-exposed children, 1 unknown in the paclitaxel-carboplatin group.

Table 3. **Echocardiographic measurements, pulsed tissue Doppler imaging (TDI) and speckle-tracking measurements in 3-year old children compared to normal controls**

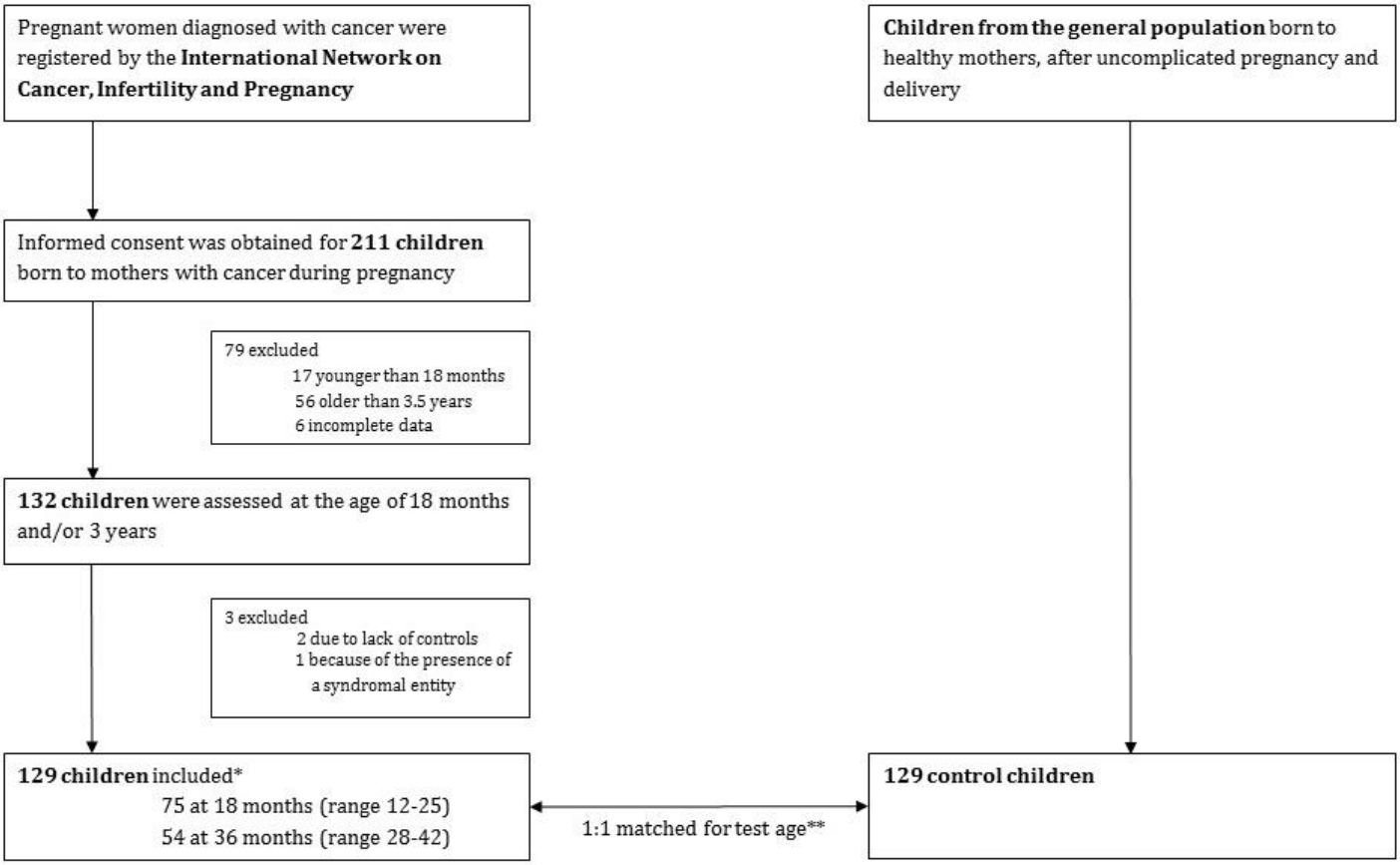
	N	Patients (N=47)	Controls (N=47)	P value
Age	94	3.11 (2.15-3.62)	3.15 (2.00-3.50)	0.586
Body Surface Area (m^2)	94	0.63 (0.54-0.74)	0.62 (0.50-0.76)	0.351
Systolic blood pressure (mmHg)	91	99 (81-124)	97 (75-117)	0.230
Diastolic blood pressure (mmHg)	91	59 (47-76)	56 (40-70)	0.060
Heart Rate (beats per minute)	94	99 (74-145)	98 (76-128)	0.706
LV shortening fraction (%)	93	35 (30-39)	36 (32-46)	0.146
LV ejection fraction (%)	93	65 (59-71)	66 (61-79)	0.265
LVEDD (cm)	94	3.15 (2.79-3.64)	3.20 (2.74-3.70)	0.298
RVEDD (cm)	94	1.45 (1.05-1.76)	1.39 (0.92-1.70)	0.896
LVPW thickness (cm)	94	0.46 (0.36-0.60)	0.44 (0.33-0.57)	0.081
IVS thickness (cm)	94	0.46 (0.39-0.60)	0.47 (0.38-0.66)	0.546
TDI basal segment LV lateral wall	85			
Peak systolic velocity (cm/s)		6.6 (4.6-9.6)	7.2 (5-11.8)	0.087
Peak early diastolic velocity (cm/s)		14.3 (10.3-17.9)	15.1 (11.5-23.2)	0.132
Mean global LV longitudinal strain (%)	69*	20.9 (15.6-27.5)	21 (16.6-28.8)	0.835
Mean global LV circumferential strain (%)	42*	21.8 (16.8-24.9)	20.8 (15.8-24.4)	0.199

Data are expressed as mean (range).

Abbreviations: LV, Left Ventricle; LVEDD, Left ventricular end-diastolic diameter; RVEDD, Right ventricular end-diastolic diameter; LVPW, Left ventricle posterior wall; IVS, Interventricular septum.

*Data were not included when tracking could not be performed due to bad image quality.

Figure 1. Study design and recruitment of study and control children

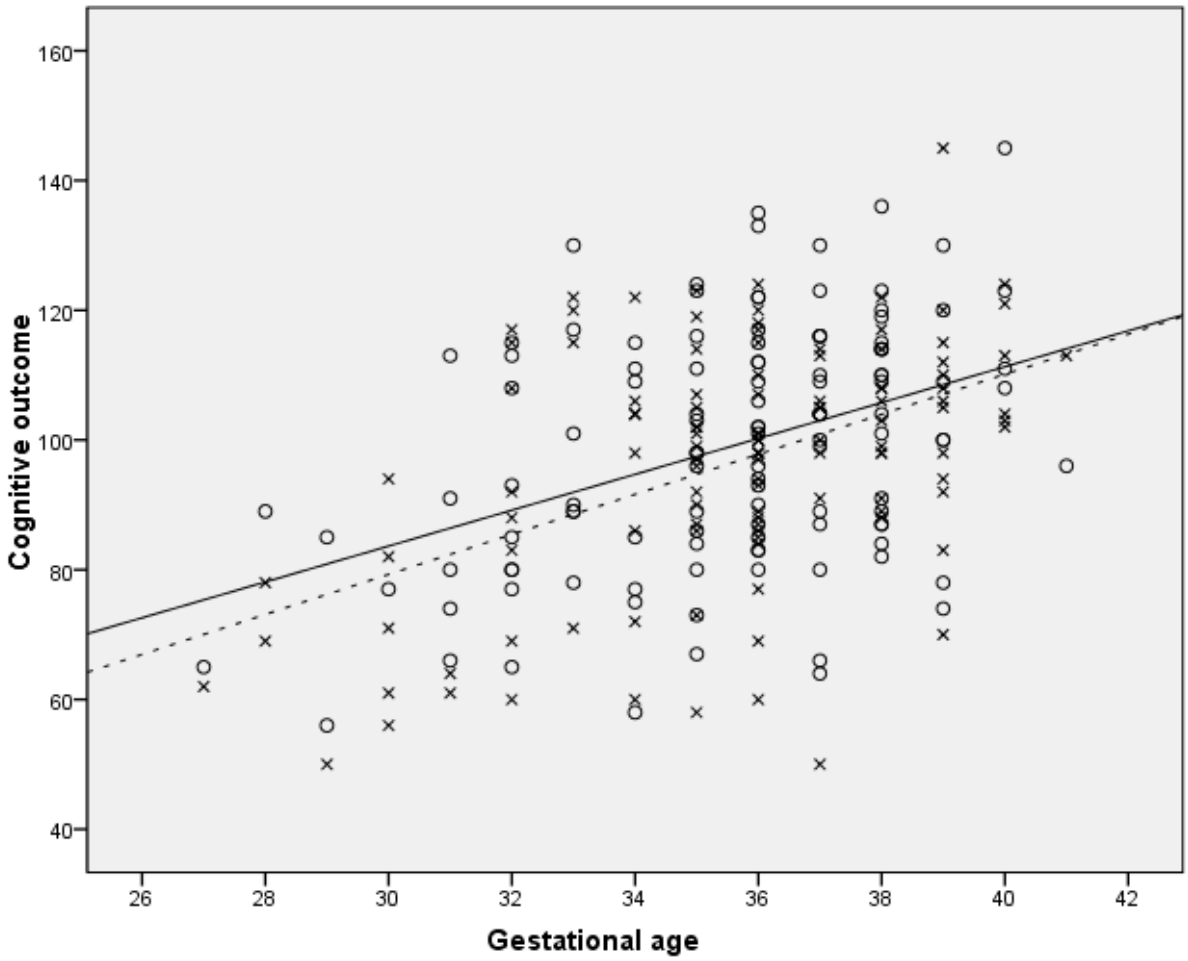


*New Bayley results of 98 children were included, together with results of 31 children that were previously published.[8] All results of cardiac examinations were never published before.

**Besides, controls for the cognitive assessment were matched for gestational age, country and Bayley edition. Controls for the cardiac assessment were matched for gender.

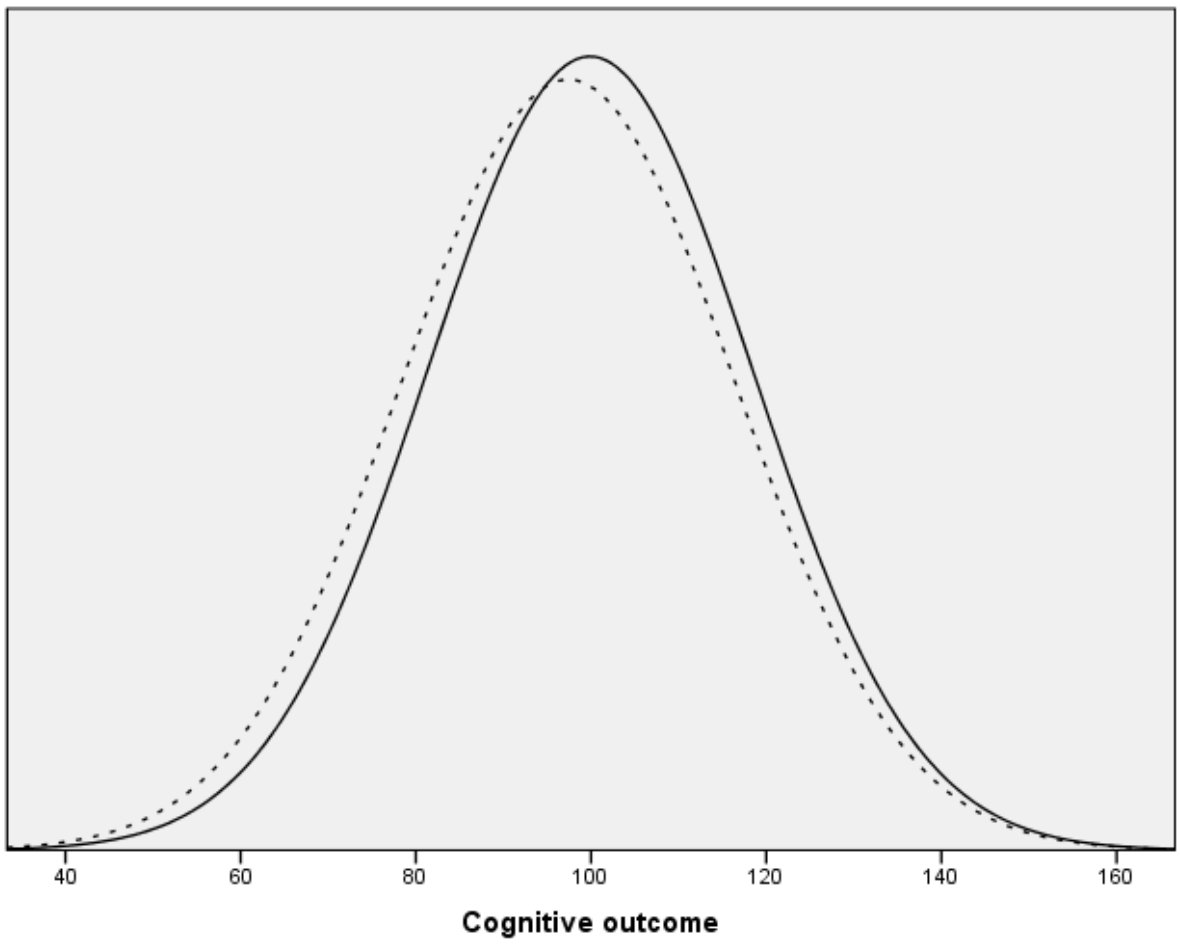
Figure 2. Cognitive outcome

A. Cognitive outcome (reported as Bayley II score) in relation to gestational age at birth for study (N=119) and control (N=119) group



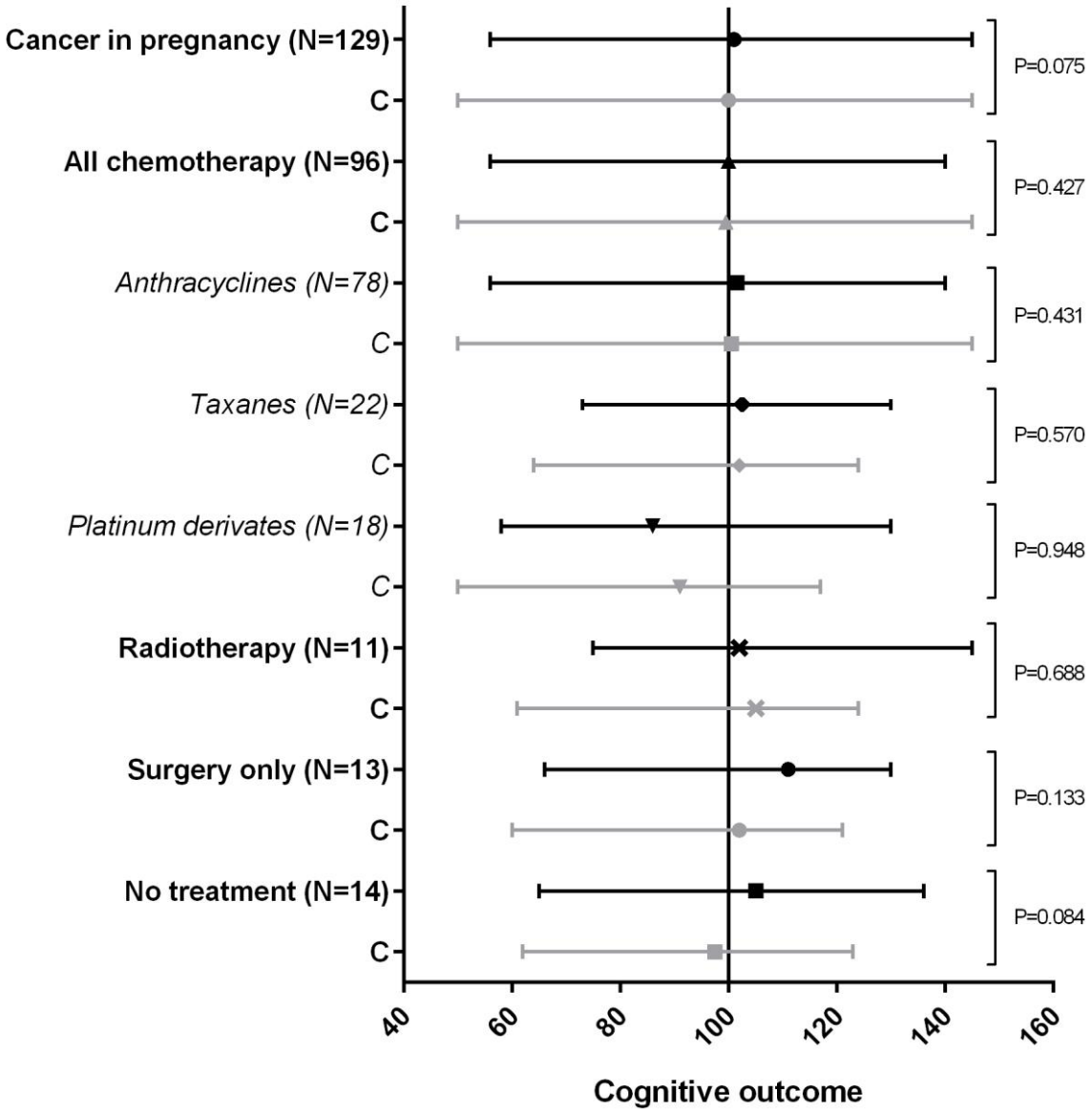
The study group is presented as circles (○) and a full line (——). The control group is presented as crosses (x) and a dotted line (-----).

B. Cognitive outcome of the study (N=129) and control (N=129) group: the distribution of the results of the last performed Bayley Scales of Infant Development (second or third edition) for each child



The study group is presented as a full line (——), the control group as a dotted line (-----).

C. Cognitive outcome (reported as Bayley II or III score) per treatment group comparing study and control (C) groups (median, range)

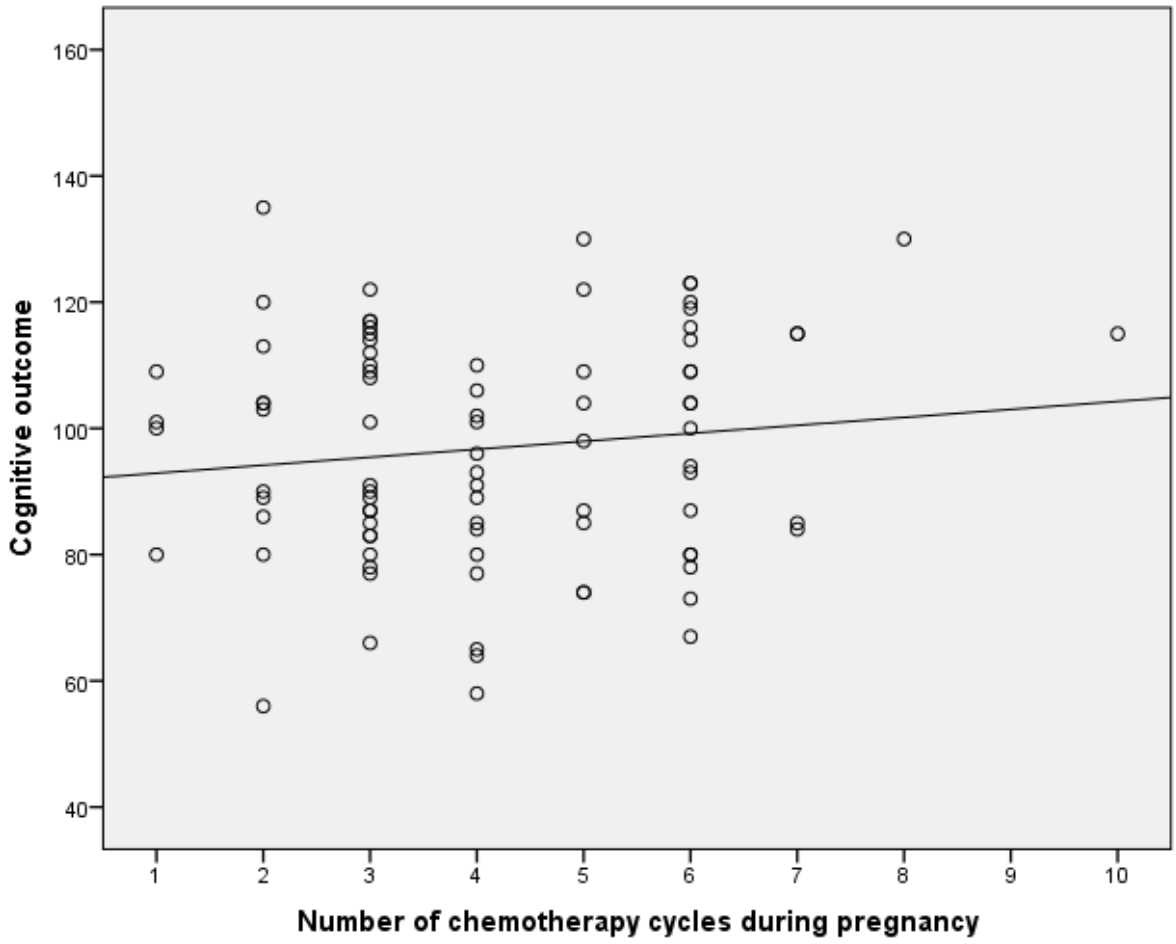


Abbreviations: C, Control group

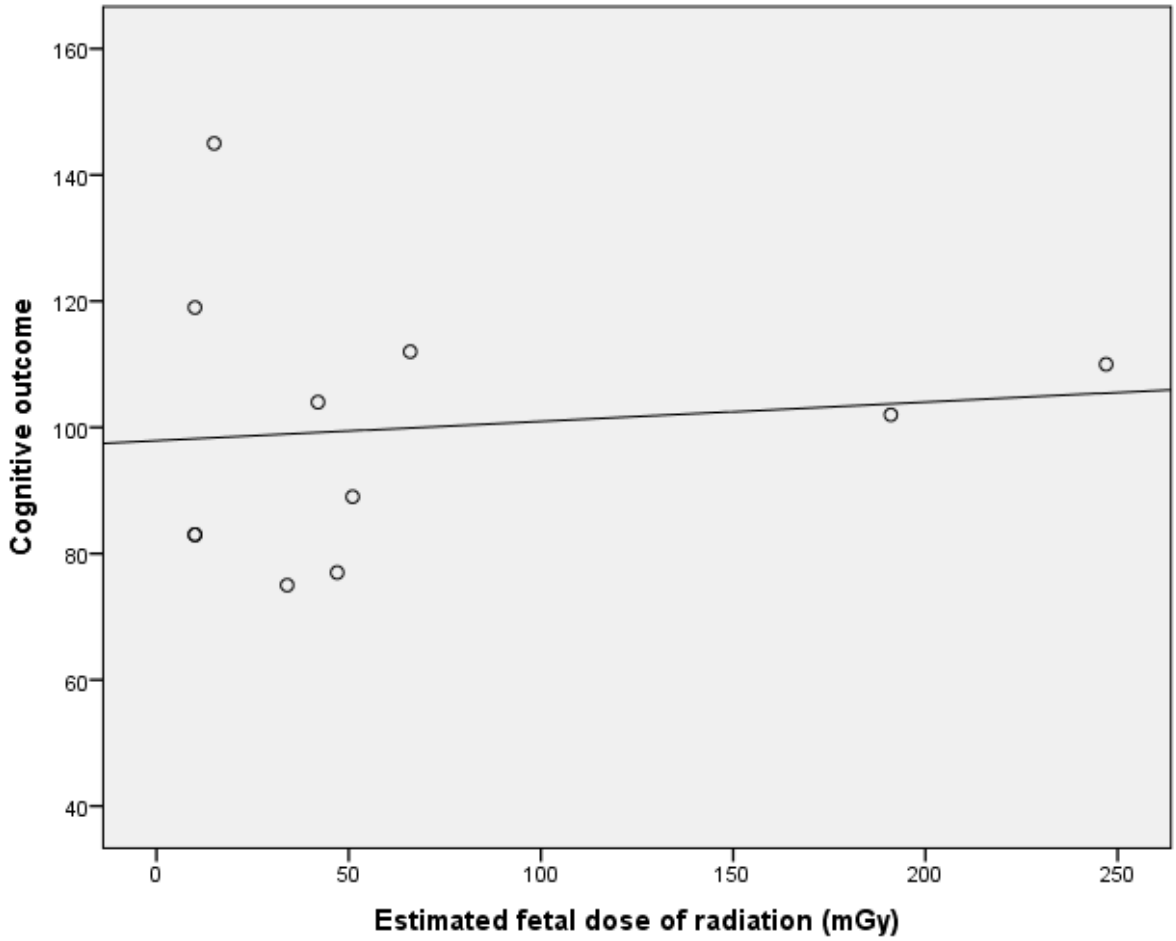
Each study group is 1:1 matched for gestational age and test age to the control group presented directly beneath the study group.

Some children have been prenatally exposed to a combination of treatment options (e.g. taxanes + platinum derivates) and therefore are part of more than one group.

D. Cognitive outcome (reported as Bayley II score) in relation to the number of chemotherapy cycles administered during pregnancy (N=87)



E. Cognitive outcome (reported as Bayley II score) in relation to the estimated fetal dose of radiation exposure during pregnancy (N=11)



Abbreviations: mGy, milliGray