ABSTRACT

Objective

Approximately 0.1% of pregnancies are complicated by cancer. Children prenatally exposed to chemotherapy showed normal neurocognitive development at 3 years but concerns regarding fetal brain growth remain high considering its vulnerability to external stimuli. Our aim was to evaluate the impact of in utero chemotherapy exposure on brain growth and its correlation with the neurodevelopmental outcome.

Methods Brain regional volumes at term equivalent age were measured by magnetic resonance imaging (MRI) in exposed children and compared with normal MRI controls. Brain segmentation was performed by Advanced Normalization Tools (ANTs)-based transformations of the Neonatal Brain Atlas (ALBERT). Neurodevelopmental assessment (Bayley-III scales) was performed at 18 months corrected age in both exposed infants and a group of healthy controls. Multiple linear regressions and false discovery rate correction for multiple comparisons were performed.

Results Twenty-one newborns prenatally exposed to chemotherapy (epirubicin administered in 80% of mothers) were enrolled: mean gestational age (GA) 36.4 ± 2.4 weeks and mean birth weight 2753 ± 622 g. Brain MRI was performed at mean GA 41.1 ± 1.4 weeks. No statistically significant differences were identified between the children exposed to chemotherapy and controls in both the total (398 ± 55 cm^3 versus 427 ± 56 cm^3, respectively) and regional brain volumes. Exposed children showed normal Bayley-III scores (cognitive 110.2±14.5, language 99.1±11.3 and motor 102.6±7.3), and no significant correlation was identified between the brain volumes and neurodevelopmental outcome.

Conclusion Prenatal exposure to chemotherapy does not affect fetal brain growth, thus strengthening the overall idea that oncological treatment in pregnant women seems to be feasible and safe for the fetus.

INTRODUCTION

Cancer is diagnosed in approximately 1 per 1000 pregnant women [1] and its incidence is increasing, [2]. The optimization of maternal treatment has led in recent years [1,3] to a decrease in the termination of pregnancy and iatrogenic-induced prematurity [1,4].

The fetal effects of maternal drugs may occur and could depend on many factors, including the amount of drug that crosses the placenta and the capacity of the fetus to metabolize it [5]. Anthracyclines are widely used during pregnancy [6,7] and experimental evidence showed that less than 10% of doxorubicin and epirubicin reaches the fetal tissues [5]. In contrast, cyclophosphamide (CP) shows an easy penetration of most membranes but the immature oxidative metabolism capacity of CP in the fetus limits the conversion of the inactive parent compound into the active metabolite [5].

Despite these considerations, chemotherapy may exert detrimental impacts on the fetus through impairments in vascularization [1] and cellular growth of the placenta [4,8–10]. Moreover, considering the vulnerability of the developing central nervous system (CNS) [11–13], chemotherapy may directly affect cell types, as neurons [14,15] and oligodendrocytes [16,17], and it may have indirect neurotoxic effects related to oxidative stress [18,19] and neuroinflammation [20]. Furthermore, the maternal illness, which may be associated with malnutrition, anemia and high maternal stress, could further negatively impact fetal development [1].

Data regarding short and long term neurodevelopmental outcomes in children prenatally exposed to chemotherapy seem reassuring when it is administered after the 14th week of pregnancy, avoiding organogenesis [21]. The risk of congenital malformations is not increased [11,22] and no consequence of cancer treatment was identified on neurobehavioral performances at 3 years, although

an independent effect of prematurity on cognitive outcome was demonstrated [4]. Contradictory results have been published on the effects of chemotherapy on intrauterine growth but an increase in the rate of small for gestational age (SGA) has recently been reported. [23,24].

Considering the vulnerability of the fetal brain to prenatal exposure to other toxic substances, such as alcohol or drugs, the absence of neuroimaging studies in newborn infants exposed in utero to chemotherapy and the known chemo-brain effect [25–29], further knowledge of the potential detrimental effects of maternal cancer treatment on the developing fetal brain is desirable to tailor maternal therapy and identify infants at risk of impaired neurodevelopment.

The aim of the present study is to assess the effect of prenatal exposure to chemotherapy on fetal brain growth in terms of volumetric development in a case-control setting. As a secondary aim, we explored the correlation between brain growth and infant neurobehavioral outcome at 18 months of age.

MATERIALS AND METHODS

Study participants

We enrolled all infants born from mothers with cancer who were treated with chemotherapy during pregnancy between 2012 and 2017 at the Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico of Milan.

Study design

Prenatally exposed infants were part of the Italian cohort of an international follow-up study by the International Network on Cancer, Infertility, and Pregnancy (INCIP). At term equivalent age (TEA), they underwent brain magnetic resonance imaging (MRI) as part of the routine clinical care, and MRI scans were retrospectively analyzed after informed parental consent was signed. According to the INCIP follow-up research protocol (approved by the local Ethics Committee), infants were assessed

at 18 months of age using the Bayley Scales of infant neurodevelopment, third edition.

Prenatally exposed infants were matched with controls selected among infants born to healthy mothers after an uncomplicated pregnancy and delivered at the same institution, after informed parental consent.

Two different cohorts of control infants were selected:

1. MRI control group - Infants who had normal brain conventional MRI performed at TEA for different clinical indications (prenatal or postnatal US abnormalities, postnatal viral infections, or family history of cerebral malformations). Controls were matched in a 1:1 ratio for GA at birth and percentile of birth weight (BW).

2. Neurodevelopment control group - Infants randomly selected from the hospital database whose parents voluntarily decided to allow their children to participate as controls. The neurodevelopmental assessment was performed at 18 months. Controls were matched in a 1:1 ratio for GA at birth.

The following data were collected (refer to *Supplementary Material-Table ST1* for details*)*. Maternal: age, trimester at diagnosis, type of cancer, and type and dosage of chemotherapy; neonatal: GA, BW and weight centile according to GA, sex, Apgar score, twins, type of delivery, preterm deliveries due to maternal indications; the neonatal perinatal comorbidities: respiratory distress syndrome (RDS) retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), blood transfusion, jaundice, hypoglycemia, patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), early (EOS) and late (LOS)-onset sepsis, and need for surgery; the neonatal data at neurological assessments: GA (weeks) at brain MRI and age (months) at neurodevelopmental test.

MRI scan assessment and volumetric analysis

A 3T scanner (Achieva, Philips Healthcare, Best, The Netherlands) with pediatric-dedicated coil

(Sense Ped, Philips Healthcare, Best, The Netherlands) was used. The brain MRI protocol included: 3D-T1 FFE, T2 TSE coronal, T2 TSE axial, T2 FFE, and DWI (refer to *Supplementary Material- Table ST2* for sequence parameters*).* The infants were scanned while sleeping and monitored by pulse oximetry and electrocardiography (Invivo Process monitoring; Invivo, Orlando, FL). Magnetic Resonance images were assessed by a neuroradiologist blinded to the study group to evaluate the presence of brain injury, malformations and motion artifacts. The image processing pipeline of the volumetric analysis is presented in *Figure 1* and detailed in *supplementary material- Figure SF1*.

Neurodevelopmental assessment

Neurodevelopment was assessed at 18 months using the Bayley Scales of Infant Development (third edition) which produces three composite scores: cognitive, language and motor. The scales have mean index scores of 100 (SD±15): higher scores indicate a more advanced development.

Statistical analysis

Demographic characteristics were reported as the mean (standard deviation - SD) or the number and percentage, as appropriate.

Total brain volume (TBV) were estimated from the volumes of the single region of interest (ROI)s, ventricles excluded, and the relative volume of each ROI was calculated as a fraction of the TBV.

Independent t-test and linear regression were performed to investigate the differences in volume between the prenatally and not exposed groups, corrected for gestational age at MRI. We subsequently performed false discovery rate (FDR) correction for multiple comparisons.

At the 18-month follow-up, differences in neurodevelopment between the groups, corrected for gestational age, were assessed using multiple linear regression. The correlation between the TBV, corrected for the age at scan, and development at 18 months was calculated using partial correlation. Values of $p < 0.05$ were considered significant. Statistical analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of the population

Thirty-one newborns were enrolled in the prenatally exposed group between 2012 and 2017 (*see table 1 for the characteristics and supplementary material – Table ST3 for* details on maternal treatment), of which 21 were included in MRI volumetric analysis at TEA, 21 in the neurodevelopment assessment at 18 months and 15 in both. The flow-chart of the recruitment is presented in *Figure 2.*

Brain growth

The 21 infants included in the MRI analysis were representative of the entire population regarding both maternal and neonatal characteristics: mean GA36.4 ± 2.4 weeks, mean BW 2753 ± 622 g. Seven (33%) infants were preterm among which 5 (23%) late preterm. Four (18%) infants were SGA. The comorbidities were: RDS in 3 (14%) infants, EOS and LOS in 1 (5%) infant, and jaundice in 2 (10%) infants; the extremely preterm (GA 27 weeks) developed both IVH grade I and RDS. Seventeen (81%) of the 21 mothers received epirubicin with a cumulative dosage of 280 mg/m^2 (range 75-450).

The not exposed infants were comparable to the prenatally exposed infants in terms of both maternal and neonatal characteristics: mean BW 2775± 681 g. Five (23%) infants developed RDS, 2 (10%) EOS, 4 (19%) LOS, and 8 (38%) jaundice. IVH grade I and PDA were observed in the extremely preterm infant (GA 27 weeks).

The mean GA at the brain MRI was 41.1 ± 1.4 weeks and 42.8 ± 1.9 weeks in the prenatally exposed group and the not exposed group, respectively ($p = 0.004$).

All infants had a normal neonatal neurological examination at TEA.

Using conventional MRI, congenital brain malformations or acquired brain lesions were not observed in the prenatally exposed infants.

The TBV was calculated for both groups. An effect of gestational age at the MRI scan on the TBV was observed (estimate=22.9, $p<0.001$, $R^2=0.552$), and the brain volume analysis was subsequently corrected for age at scan *(Supplementary material-Figure SF2).*

No significant difference in TBV between prenatally exposed and not exposed groups was observed (398 ± 55 cm^3 and 427 ± 56 cm^3, respectively - IC -39; 16; p=0.393) *(Table 2, Panel A)* and either between the right and left side hemispheres *(Table 2, Panel A)*. Similar results were observed after excluding the SGA infants (p=0.212) from the analysis or separately analyzing the term (p=0.177) or preterm (p=0.809) infants *(Table 2, Panel B).*

The relative volumes of all 48 segmented areas were compared in the 2 groups: no significant differences were demonstrated even before the FDR correction *(Supplementary Material-Table ST4)*. No effect of side (left hemisphere versus right hemisphere) was identified.

A potential effect of the cumulative dosage of epirubicin on brain growth was investigated using a linear regression model: the TBV seemed to have no correlation with the cumulative dosage of epirubicin (estimate=-0,02, p=0.807).

Neurodevelopmental outcome

The 21 infants included in the Neurodevelopmental analysis were representative of the entire population regarding both maternal and neonatal characteristics: mean GA 36.1 ± 2.4 weeks, mean BW 2637 ± 543 g. Ten (47%) infants were preterm, among which 9 (43%) were late preterm. Five (23%) were SGA. The comorbidities were: RDS and jaundice in 3 (14%) infants, EOS, LOS and blood transfusion in 1 (5%) infant and hypoglycemia in 2 (10%) infants. The extremely preterm infant presented IVH-I. Eighteen (85%) of the 21 cases received epirubicin with a cumulative dosage of 262 mg/m^2 (range 75-450).

With regards to the not exposed group, both the maternal and neonatal characteristics were

comparable, presenting a mean BW of 2833 ± 677 g. RDS was observed in 1 (5%) infant, LOS in 1 (5%) infant, and jaundice in 2 (10%) infants.

In the prenatally exposed group, the Bayley assessment was performed at a mean GA of 19.8 ± 3.2 months, while in the not exposed group, it was performed at 18.8 ± 2.5 months (p = 0.098).

All infants had a normal neonatal neurological examination at TEA.

The cognitive (110.2±14.5 vs 111.4±13.8; p=0.787), language (99.1±11.3 vs 101.4 ± 13.5; p=0.563) and motor (102.6±7.3 vs 103.2±11.7; p=0.839) scores were not significantly different between the prenatally exposed and not exposed infants (*Figure 3*), even analyzing preterm and term infants separately (data not shown).

The linear regression model indicated there was no relationship between the cumulative dosage of epirubicin and the neurodevelopmental outcome at 18 months (cognitive: estimate=-0.005, p=0.876; language: estimate=-0.017, p=0.454; and motor: estimate=-0.004, p=0.780).

In the infants (n=15) who underwent both brain MRI at TEA and neurodevelopmental assessment at 18 months (mean of 19.2 ± 2.8 months at the evaluation), we investigated the relationship between the TBV, corrected for GA at brain MRI, and the Bayley scores: no significant correlation was identified for any of the subscales (cognitive: 0.183, p=0.498; motor: 0.309, p=0.206; and language: 0.205, p=0.424).

DISCUSSION

This investigation is the first case–control study that analyzed the effect of prenatal exposure to chemotherapy on fetal brain growth and its correlation with neurodevelopmental outcome. Brain growth was not affected by maternal cancer treatment: infants prenatally exposed to chemotherapy and controls showed comparable total and regional brain volumes.

The magnetic resonance imaging study performed on newborn infants confirmed the absence of even

subtle structural brain abnormalities supporting the safety of chemotherapy administered after the 1st trimester of pregnancy in terms of the risk for congenital abnormalities. This result is a reassuring finding considering the potential harmful effect of chemotherapy administered during the 2nd and 3rd trimesters when fundamental stages of oligodendrogenesis and neurogenesis occur [12,13].

In addition, the absence of acquired brain lesions, as assessed via conventional postnatal MRI, suggests that maternal treatments during pregnancy do not seem to induce detrimental hemodynamic or metabolic perturbations in the fetus.

Brain volumes

Brain volumes were calculated from the MRI scan performed at TEA and are consistent with previous findings [30–32]. Neonatal brain segmentation is a challenging task due to the motion, scan duration and rapid developmental brain changes. We used the ALBERT-ANTs segmentation method which relies on a large atlas composed of manually segmented neonatal brains and the processing pipeline was adjusted to ensure robustness with MR images acquired in clinical setting.

As expected, a positive relationship was observed between the total brain volume and single areas (data not shown) and the gestational age at MRI: a higher gestational age was associated with a larger brain. [31].

Neurodevelopment

Consistently with previous findings, at 18 months of age, both groups showed neurodevelopmental scores within the normal ranges without significant differences between the groups [4].

In patients who underwent both MRI and neurodevelopmental assessment at 18 months, no relationship was observed between the cerebral volumes and cognitive, motor or language outcomes. This result was expected considering that both the brain volumes and neurodevelopmental scores

were within the normal ranges.

Characteristics of the population

Although the rate of prematurity in the exposed children was relatively high (48%) compared to the general population (approximately 10%) [33], this finding is in line with previous data regarding infants prenatally exposed to chemotherapy (49%) [1]. Moreover, most of these infants were born late preterm (39%), and only 1 child was born before 32 weeks GA because of the poor clinical conditions of the mother.

The incidence of SGA was higher than that in the general population (approximately 10%) [34] but comparable to the incidence described for this specific group (21%) [1]. These data are relevant when considering the increased risk for perinatal complications that affect SGA infants [35]. Moreover, the clinical distinction between intra uterine growth restriction (IUGR) versus SGA would be even more significant because the placental insufficiency underlying a fetal growth restriction in this population may be related to the malignancy, the surgery, the anesthesia, the chemotherapy and the general maternal conditions [1].

Consideration regarding chemotherapy

The majority of the pregnant women in our population received chemotherapeutic agents that are not considered neurotoxic. The most commonly used therapeutic scheme for breast cancer includes anthracyclines of which the main side effect is cardiotoxicity. In our population, prenatally exposed infants did not show cardiac abnormalities at the echocardiographic assessment in the first days after birth (results not shown) consistently with studies performed at 3 years of age [4].

Limitations

Our study has some limitations.

The first limitation is represented by the small sample size; however, it reflects the low incidence of cancer in pregnancy. Based on this consideration, we used a robust magnetic resonance volumetric analysis applicable for standard quality images in clinical settings.

The limited spectrum of chemotherapy and the type of cancer analyzed in this study make our promising results not extendable to all infants prenatally exposed to chemotherapy. Nevertheless, considering that breast cancer is the most common type and cyclophosphamide and epirubicin are the most used drugs in women with cancer during pregnancy, our results can be considered quite generalizable.

Conclusion

In conclusion, we demonstrated that the brain of infants prenatally exposed to chemotherapy does not differ from controls in terms of the morphological appearance and volumetric development. These observations shed new light on the management of cancer during pregnancy, although caution is required when interpreting these results. Our results strengthen the overall idea that oncological treatment in pregnant women is feasible and safe for the fetus, thus supporting and encouraging gynecologists and oncologists in handling this delicate and life-threatening condition for both mother and child. Further studies with larger sample sizes, advanced MRI methods and longer follow-up will help further elucidate the microstructural development of the brain in these children and disentangle the potential effects of different chemotherapeutic agents, prematurity and fetal growth.

Competing interests

None declared

Ethics Approval

All infants included were part of the INCIP follow-up research protocol approved by the local Ethics Committee-Comitato Etico Milano Area B on the 15 of July 2014. In accord to the protocol, they

were assessed at 18 months of age using the Bayley Scales of infant neurodevelopment, third edition. At term equivalent age, they underwent brain MRI as part of the routine clinical care, and MRI scans were retrospectively analyzed after informed parental consent was signed.

Patient consent for publication

Not obtained because all the information are sufficiently anonymized.

Author contribution section

Passera Sofia participated to the design of the work and she managed the enrollment of patients (newborns) and the neonatal data collection; she gave substantial contribution to the analysis and interpretation of data. She coordinated the communication between the different participants. She wrote the first draft of the paper, she gave final approval of the version published and she ensured that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Contarino Valeria performed the volumetric analysis of the MRI scans. She wrote the first draft of the paper and she gave final approval of the version published ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Scarfone Giovanna participated in the enrollment of patients (mothers) at moment of cancer diagnosis and was involved in the management of maternal treatment. She gave substantial contributions to the analysis and interpretation of data, especially those regarding the maternal therapy. She revised the work with important intellectual content giving final approval of the version published.

Scola Elisa performed and assessed the MRI scans. She gave technical support to Contarino V regarding the volumetric analysis. She gave substantial contributions to the analysis and interpretation of data, especially those regarding brain morphometry. She revised the work with important

intellectual content giving final approval of the version published.

Fontana Camilla participated in enrollment of patients (newborns) and performed the neurodevelopment assessments. She gave substantial contributions to the analysis and interpretation of data, especially those regarding the follow up of the children. She revised the work with important intellectual content giving final approval of the version published.

Peccatori Fedro contributed to the design of the clinical protocol. He participated in the management of maternal treatment. He gave substantial contributions to the analysis and interpretation of data, especially those regarding the maternal therapy. He revised the work with important intellectual content giving final approval of the version published.

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Cinnante Claudia performed and assessed the MRI scans. She revised the work with important intellectual content giving final approval of the version published.

Counsell Serena participated in finalizing the setting up of the tools to perform the volumetric analysis. She revised the work critically for important intellectual content and he gave final approval of the version published ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Ossola Manuela participated in the management of maternal treatment. She revised the work with important intellectual content giving final approval of the version published.

Pisoni Silvia participated in enrollment of patients (newborns) and in the neonatal data collection. She revised the work with important intellectual content giving final approval of the version published.

Pesenti Nicola performed the statistical analysis and gave a substantial contribution to the

interpretation of data. He wrote and revised the work with important intellectual content and gave final approval of the version published.

Grossi Elena participated in the management of maternal treatment. She revised the work with important intellectual content giving final approval of the version published.

Amant Frédéric revised the work critically for important intellectual content and he gave final approval of the version published ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Mosca Fabio gave a substantial contribution to the conception, design of the work, and interpretation of final data. He participated to the intellectual content revision of the work and he gave his final approval of the published version.

Triulzi Fabio gave a substantial contribution to the conception, design of the work, and interpretation of final data. He participated to the intellectual content revision of the work and he gave his final approval of the published version.

Fumagalli Monica was the project manager of the study. She coordinated and managed the whole project, contributing to the design of the clinical protocol. She gave substantial contribution to the acquisition, analysis and interpretation of data. She contributed to writing the paper and revised the work critically for important intellectual content and she gave final approval of the version published ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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Figure legends section

Figure 1. **Neonatal (A) T1-weighted image and (B) automatic segmentation** based on ALBERT atlas (from left to right: axial, sagittal and coronal views).

Figure 2. **Flow chart of the Study Design and Recruitment**. Thirty-one newborns were enrolled in the prenatally exposed group between 2012 and 2017 including 25 newborns who underwent brain MRI at TEA. Four infants were excluded from the MRI study due to motion artifacts in the MR images, which resulted in 21 MRI scans suitable for volumetric analysis. Twenty-one of the 31

prenatally exposed children were assessed at 18 months of age by the Bayley test: 9 children were younger than 18 months, and one child was lost at follow-up. Fifteen prenatally exposed children underwent both brain MRI at TEA and neurodevelopmental assessment at 18 months * Four of 6 infants excluded from the MRI study because they did not undergo brain MRI were assessed at 18 months using the Bayley scales, while °among the 4 infants excluded from the MRI study because of motion artifacts, 2 infants had Bayley Scales performed at 18 months.

***Figure 3*. Neurodevelopment outcome at 18 months.** Box plot shows the median score (solid horizontal line) and interquartile range (IQR = white box) for cognitive, motor and language scores in prenatally exposed and not exposed infants. Whiskers are extended to the most extreme data point that is no more than 1.5 × IQR away from the box. Data not included between the whiskers are plotted as outliers with a dot. Bayley scores of 10/21 prenatally exposed infants were previously published [4].

Table 1

	Data	Prenatally exposed infants (n=31)
Neonatal characteristics	GA at birth (weeks), mean±SD	36.3 ± 2.3
	Preterm infants (<37 GA), n (%)	15 (48)
	Late preterm infants (34^{+0}-36^{+6} GA), n (%)	12 (39)
	Moderate preterm infants (32^{+0}-33^{+6} GA), n (%)	2 (6)
	Very and extremely preterm infants (<32 GA), n (%)	1 (3)
	Term infants, n (%)	16 (51)
	Birth weight (g), mean±SD	2745 ± 625
	SGA (<10°c*)	5 (16)
	Male, n (%)	16 (51)
	Twins, n (%)	0 (0)
	Apgar 1', median (range)	9 (5-9)
	Apgar 5', median (range)	9 (5-10)
	Cesarean section, n (%)	16 (51)

	Preterm deliveries for maternal indications, n (%)	8 (53)
	GA at MRI scan (weeks), mean±SD	41.1 ± 1.4
	Age at neurodevelopmental test (months), mean±SD	19.8 ± 3.2
Neonatal morbidities	RDS, n (%)	5 (16)
	EOS, n (%)	1 (3)
	LOS, n (%)	1 (3)
	Blood transfusion, n (%)	1 (3)
	Jaundice, n (%)	5 (16)
	Hypoglycemia, n (%)	2 (6)
	IVH 1-2, n (%)	1 (3)
Maternal characteristics	Maternal age (years), mean±SD	35 ± 4.1
	Breast cancer, n (%)	24 (77)
	Diagnosis in the 2nd trimester, n (%)	21 (67)
	Patients exposed to epirubicin, n (%)	26 (83)
	Cumulative dosage of epirubicin (mg/m2), median (range)	252 (75-450)

***Table 1**. **Maternal and neonatal characteristics of prenatally exposed group**. Only observed neonatal morbidities are reported. Maternal and neonatal data of 10/31 prenatally exposed infants were previously published [4]. *according to Fenton (for preterm infants) and the WHO (for term infants) growth chart.*

Table 2

Panel A

	Prenatally exposed infants			Not exposed infants				
Volumes	**Number**	**Mean (cm^3)**	**SD (cm^3)**	**Number**	**Mean (cm^3)**	**SD (cm^3)**	**95% CI**	**p.value**
Total volume	21	398	55	21	427	56	[-39; 16]	0.393
Left volume	21	184	26	21	196	26	[-19; 7]	0.326
Right volume	21	185	26	21	200	26	[-17; 9]	0.524

Panel B

	Prenatally exposed infants			Not exposed infants				
Volumes	**Number**	**Mean (cm^3)**	**SD (cm^3)**	**Number**	**Mean (cm^3)**	**SD (cm^3)**	**95% CI**	**p.value**
Total volume - AGA	17	405	59	17	420	55	[-48; 11]	0.212

Total volume - Preterm	7	420	55	7	414	67	[-52; 41]	0.809
Total volume - Term	14	387	54	14	433	51	[-71; 14]	0.177

Table 2. *Total brain volumes. Comparison between prenatally exposed and not exposed infants in the whole population (Panel A) and AGA, preterm and term analyzed separately (Panel B). Comparisons obtained using multiple linear regression, corrected for GA at brain MRI. The results are expressed as the mean ± SD.*