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Fetal neurosonography at 31–35 weeks reveals altered cortical development in pre-eclampsia with and without small-for-gestational-age fetus

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Short title: Cortical development in preeclampsia

Contribution

What are the novel findings of this work?

This is the first study to demonstrate that preeclampsia with a normally grown fetus is associated with an altered pattern of fetal cortical development (shallower Sylvian fissure and greater insula depth) in a similar fashion to what has been described in fetal growth restriction.

What are the clinical implications of this work?

Preeclampsia seems to be associated with differences in the pattern of fetal brain cortical development compared to fetuses from uncomplicated pregnancies regardless of the association with smallness-for-gestational-age and prematurity.

ABSTRACT

Objectives: The aim of this study was to explore the pattern of fetal cortical development in pregnancies complicated by preeclampsia with and without fetal growth restriction compared to uncomplicated pregnancies.

Methods: Prospective observational study including pregnancies complicated by normotensive fetal growth restriction (birthweight <10th centile) (n=77), preeclampsia with a normally grown fetus (n=76), preeclampsia with fetal growth restriction (n=67), and 128 uncomplicated pregnancies matched by gestational age at ultrasound. Detailed neurosonography with transabdominal and transvaginal approach was performed at 31-35 weeks including the measurement of insula, Sylvian fissure and parieto-occipital, cingulate and calcarine sulci. All measurements were adjusted by biparietal diameter. In addition, a grading score of cortical development was assigned to each fissure/sulcus ranging from Grade 0 (no development) to Grade 5 (maximum development). Univariate and multiple regression analysis were conducted.

Results: As previously reported, growth restricted fetuses showed significant differences in cortical development with reduced Sylvian fissure (14.5±2.4 *vs.* 16.6±2.3, p<0.001) and larger insula width (33.2±2 *vs.* 31.8±2, p<0.001). Interestingly, a similar pattern was observed in preeclampsia with and without fetal growth restriction manifested by shallower Sylvian fissure (14.2±2.3 and 14.3±2.3, both p<0.001) and greater insula depth (33.2±2.1 and 32.8±1.7, both p<0.001) compared to controls. No significant differences existed in parieto-occipital, cingulate or calcarine sulci depth across the study groups. Additionally, the Sylvian fissure grading score was significantly lower in normally grown fetuses from preeclamptic pregnancies. All these observed alterations were significantly different even after statistical adjustment for ethnicity, low socioeconomic status, nulliparity, chronic hypertension,

pregestational diabetes, assisted reproductive technologies, smoking and fetal gender with the application of Benjamini-Hochberg procedure for multiple comparisons, compared to controls.

Conclusion: Preeclampsia with or without fetal growth restriction is associated with differential fetal cortical development, similarly to what has been previously described in fetal growth restriction. Future research is warranted to better elucidate the mechanism(s) underlying these changes.

Introduction

Preeclampsia (PE) is a serious pregnancy condition that affects 2-5 % of all pregnancies and is a leading cause of maternal and perinatal mortality and morbidity.[1] A mounting evidence is suggesting that PE is associated with neurodevelopmental disorders in the offspring,[2] including intellectual disability, attention-deficit hyperactivity disorder, autism, epilepsy and cognitive impairement.[2,3,12,13,4–11] This association has been described in preterm and term newborns likewise,[4,6,8] and remained existing after excluding cases with a small-for-gestational-age (SGA) fetus.[6,7]

The association of SGA with abnormal neurodevelopment has been extensively documented. Fetuses with prenatal growth restriction present changes in cortical development, corpus callosum, brain stem, cerebellum and brain metabolism, which are later associated with abnormal neurodevelopment in infants and children.[14–17] These changes have commonly been attributed to chronic restricted supply of nutrients and oxygen in utero.[18–20] Given the common clinical association of PE with SGA, previous studies evaluating neurodevelopment in SGA included a variable proportion of cases where PE was also present. However, it is unknown whether prenatal brain differences could be observed in PE in the absence of SGA and whether they resemble what has been described in SGA.

Evaluation of cortical development is a suitable approach to assess fetal brain development since it can be reliably assessed by neurosonography using a structured examination.[21,22] Changes in fetal cortical patterns are strongly associated with poorer performance in neurodevelopmental test postnatally, supporting that fetal cortical assessment is a surrogate of altered brain development in utero.[16] In this study we aimed to explore the patterns of fetal cortical development, assessed by neurosonography, in pregnancies complicated by the different phenotypes of PE and/or SGA.

Methods

Study population

This was a prospective observational study including singleton pregnancies with a diagnosis of PE and/or SGA who attended the Department of Maternal-Fetal Medicine at BCNatal (Hospital Clinic and Hospital Sant Joan de Déu, Barcelona, Spain) between July 2016 and December 2018 and accepted enrolment in the current study being a part of the project "Phenomapping of fetal growth restriction" which included 1238 patients. Uncomplicated pregnancies with normotensive mothers and appropriate growth for gestational age (AGA) fetuses were randomly selected from our general population to be included as controls and frequency paired with cases by gestational age at fetal neurosonography (±2 weeks).

PE was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on two occasions, at least four hours apart developed after 20 weeks of gestation, and proteinuria (≥ 300 mg/24 hours or protein/creatinine ratio ≥ 0.3), thrombocytopenia (platelet count < 100 x 109/l, renal insufficiency (serum creatinine concentrations > 1.1 mg/dl), impaired liver function (elevated blood concentrations of liver transaminases to twice normal concentration), pulmonary edema or a new-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms.[23] AGA was defined as birthweight ≥10th centile, whereas SGA was considered if birthweight was below the 10th centile.[24] Estimated fetal weight and birthweight centiles were assigned according to local standards.[25] In all pregnancies, gestational age was calculated based on the crown-rump length at first trimester.[26] Pregnancies with chromosomal anomalies, congenital malformations and intrauterine infections were excluded. The study protocol was approved by the local ethics committee (HCB/2016/0253) and patients accepting to participate provided their written informed consent.

Data collection and study protocol

At enrollment, the following variables were recorded: maternal age, ethnicity, socio-economic status, body mass index (BMI), maternal medical history (the presence of autoimmune and/or chronic diseases), obstetric history (parity and mode of conception), smoking and toxics habits. Estimated fetal weight and feto-placental Doppler were obtained at third trimester scan (31-35 weeks). Some of the patients were already diagnosed as PE or SGA at the time of assessment while others had a later diagnosis. Feto-placental Doppler included the assessment of the uterine arteries,[27] the umbilical artery,[28] the fetal middle cerebral artery,[29] with the calculation of the cerebroplacental ratio,[29] and the ductus venosus pulsatility indices.[30] These values were normalized into z-scores accordingly.[27–30] At delivery, perinatal data were also collected including gestational age at birth, birthweight, gender, Apgar score, umbilical artery pH, mode of delivery and any neonatal complications.

Neurosonography

Every patient underwent a detailed neurosonography at 31-35 weeks using a GE Voluson 8 Expert (GE Healthcare, Illinois, USA) by transabdominal and transvaginal approach in pregnancies with cephalic fetal presentation following standard protocols using 2D ultrasound methodology.[21,22] Fetal neurosonography included a comprehensive examination to assess structural brain integrity and rule out any defects in the central nervous system. All images and clips including standard neurosonographic axial, sagittal and coronal planes were stored for later offline analysis and measurements that were performed using Alma Workstation software 4.2.0.25 (2005□2014 Alma IT Systems, S.L. all rights reserved, Barcelona, Spain) by two trained examiners blinded to the study group (AB and CP).

During ultrasound examination, laterality was assessed and marked according to the fetal position in utero. Additionally, special care was taken to avoid as much shadowing as possible

and to obtain a symmetric position of both hemispheres. Biparietal diameter (BPD), head circumference and occipitofrontal diameter were measured in the axial transthalamic plane.[21,22] Cortical evaluation was done using previously described methodology as detailed herein.[31] To provide rigorous perpendicular measurements to the midline, a straight line projecting the interhemispheric fissure was traced horizontally in every plane going from frontal bone to occipital bone in axial views and vertically from the calvarial vault to the skull base (sphenoid bone) in coronal views (skull-oriented midlines especially aligned in the upper part of the image), as shown in Figure 1. Sulci and fissures of both hemispheres were measured in millimeter as previously described by Alonso *et al.*[31]; values were then corrected by BPD to normalize by head size.[32] Moreover, the cortical grading of fissures, sulci and brain areas was classified using the scoring method described by Pistorius *et al.* which is a subjective score ranging from Grade 0 (no development) to Grade 5 (maximum development).[33]

Insula depth was measured in the transthalamic axial plane drawing a perpendicular line from the midline behind the cavum septi pellucidi to the external border of the cortex.[31,33] To measure the Sylvian fissure we continued the line of the insula depth, starting the measurement at the external border of the cortex and terminating at the internal border of the cranium.[31] In the same plane, the cortical grading score of the Sylvian fissure and the frontal and temporal areas were also evaluated. Parieto-occipital sulcus depth and its grading were measured in a superior plane to the transventricular plane in its maximum development with the base starting from the midline as symmetric as possible without including the cortex in the measurement.[31] In this plane, the cortical grading score of the parietal area was also evaluated. The cingulate sulcus depth and its grading were assessed in the transthalamic plane in the coronal view, a perpendicular line was drawn from midline until the apex of the sulcus without including the cortex. The calcarine sulcus depth and its grading were also measured in the coronal view using the transcerebellar plane and tracing a perpendicular line from midline to the apex of the sulcus

not including the cortex.

Reproducibility of these measurements (sulci depth and cortical grading) has been previously assessed by our group[31] showing a good intraobserver and interobserver reproducibility for all the measurements considered in the current study.

Statistical analysis

The study outcome was fetal cortical development. The independent variable of interest was the presence of PE and/or SGA, and the covariates were the ethnicity, low socioeconomic status, nulliparity, the presence of chronic hypertension, diabetes, the use of assisted reproductive technologies, smoking during pregnancy and fetal gender.

Data are presented as mean (standard deviation, SD), median (interquartile range, IQR) or number of subjects (percentage), as appropriate. Statistical analysis included the use of Student *t-test* or Mann Whitney U tests and Pearson χ^2 test for continuous and categorical variables respectively, to compare each group of the cases *vs*. the controls. Following standard methodology, results were adjusted by linear and ordinal logistic regression analyses for confounding factors including ethnicity, low socioeconomic status, nulliparity, the presence of chronic hypertension, diabetes, assisted reproductive technologies, smoking and fetal gender. Benjamini-Hochberg procedure was applied to correct for multiple comparisons. Two-sided p-values <0.05 were considered statistically significant. A sample size of 63 patients in each group of the cases and 126 controls, was calculated by expecting one unit differences in the insula depth/BPD between cases and controls[31,32], for a given 5% α error and 80% power and 1:2 sampling ratio.

The statistical packages IBM SPSS 25.0 (IBM, New York, USA) and STATA 14.2 (StataCorp LLC, Texas, USA) were used to conduct all the statistical analyses.

Results

Baseline and perinatal characteristics

The final cohort comprised a total of 348 pregnancies: normotensive SGA (n=77), PE with a normally grown fetus (n=76), PE with SGA (n=67), and 128 uncomplicated pregnancies matched by gestational age at ultrasound. Baseline characteristics, feto-placental Doppler and perinatal outcomes of the study population are shown in Table 1. The study groups were similar in terms of maternal characteristics, except for significantly higher maternal pregestational BMI and higher prevalence of chronic hypertension and diabetes mellitus among PE groups, and higher prevalence of smoking habits and multiparity in SGA groups. All PE patients were proteinuric. Fetoplacental Doppler parameters were significantly altered in SGA groups, with no differences in PE without SGA compared to controls. In addition, gestational age at delivery was earlier in PE and/or SGA with higher rates of cesarean sections and admissions to neonatal intensive care unit.

Neurosonographic results

Concerning fetal neurosonography, cases complicated by PE and/or SGA showed a different pattern of fetal cortical development alterations manifested by significantly deeper insula and shallower Sylvian fissure ($p<0.001$ in each group of the cases compared to controls), as shown in Figure 2 and Table 2. SGA fetuses from normotensive mothers showed also significantly reduced parieto-occipital sulcus depth ($p=0.003$). No significant differences were observed in cingulate and calcarine sulci depth across the study groups. Relative to cortical grading scores, the Sylvian fissure was significantly less graded in normally grown fetuses from PE pregnancies (Figure 3 and Table 3). The difference in the Sylvian fissure grading score in PE without SGA remained significantly present after statistical adjustment for potential confounders including ethnicity, low socioeconomic status, nulliparity, chronic hypertension,

pregestational diabetes, assisted reproductive technologies, smoking and fetal gender with the application of Benjamini-Hochberg procedure for multiple comparisons. Figure 4 represents an illustration of the Sylvian fissure and the insula depth in controls vs. cases of preeclampsia and/or fetal growth restriction.

Discussion

This study provides evidence that fetuses from mothers with PE, with or without associated SGA, have a different pattern of prenatal cortical development than control fetuses, with significantly reduced Sylvian fissure depth and larger insula. To the best of our knowledge this is the first study to demonstrate cortical development alterations in fetuses from PE mothers in the absence of SGA.

The association between PE and suboptimal neurodevelopment in the offspring has extensively been documented. In follow-up studies, children of preeclamptic mothers show increased risks of impaired early language development, lower neurocognitive functioning, and higher rates of neurobehavioral disorders.[34,35] These observations are supported by population-based studies on data from national registries or recalled by the parents retrospectively.[2,3,12,13,4–11] A concern with the association of PE and neurodevelopment is the potential influence of confounders, mainly prematurity and SGA, which are present in 60-100% and 10-90% of cases, respectively, when reported.[3–9] Previous studies had already addressed the influence of prematurity, reporting that neurodevelopmental changes were observed both in preterm and term PE pregnancies.[10–13] The present study addresses the influence of SGA and provides first evidence that PE is primarily associated with altered brain development in utero, irrespective of the presence of SGA. Our findings are in agreement with previous studies which demonstrated that among growth restricted infants, those born to mothers with PE showed lower intelligence quotient (IQ) scores than those without PE-complicated pregnancies, suggesting that PE itself might contribute independently towards impaired neurodevelopment.[4,6,8]

Our results are consistent with the literature that evaluated brain development antenatally in SGA, reporting altered cortical gyration,[36,37] decreased intracranial volume,[34,35,38] differences

in grey and white matter volume,[34,39] and altered brain networks.[40] These brain changes have been associated with motor, cognitive, language and behavioral dysfunction earlier in life.[41] In the current study, AGA fetuses from PE mothers exhibited changes in cortical development similar to those previously described in growth restricted fetuses, with differences in the Sylvian fissure and the insula between PE and/or SGA fetuses and controls. Functionally, it is known that insula plays a crucial role in the processing of sensory information, as it is critical for emotional wellbeing.[20,39] Changes in grey volumes in the insula have been associated with mood and speech disorders, autism and anxiety.[42]

Since the changes in cortical development are similar in PE and SGA, they suggest a similar pathophysiology related to placental dysfunction, which could be mediated by oxidative stress, impaired angiogenic balance, inflammation and epigenetic dysregulation.[42,43] Placental insufficiency may result in reduced perfusion and oxidative stress causing a suboptimal nutrient and oxygen availability which may affect the developing brain.[44,45] An alternative theory centered on deficient utero-placental angiogenesis and vessel remodeling raises the possibility that an impairment in cerebral angiogenesis in PE fetuses may contribute to reported differences in cognitive functions as well as structural and vascular alterations..[46] Other unexplored pathways which may explain the link between maternal PE and neurocognitive dysregulation could be maternal inflammation as suggested by the correlation between increased levels of C-reactive protein and neurodevelopmental disorders in the offspring.[47,48] Finally, the imprinting genes dysregulation may also play a role explaining the relationship between the prenatal environment and outcomes in the developing child.[49]

This study has several strengths and limitations. We evaluated prospectively recruited patients extensively characterized prenatally, including detailed neurosonography at a matched

gestational age between cases and controls. Ultrasonographic assessments were conducted by trained and experienced neurosonographers. Measurements were done manually by two examiners to reduce interobserver agreement for brain measurements.[2,50] Among limitations, we acknowledge that the differences observed in cortical pattern are subtle and the clinical correlation at an individual level is possibly small. In addition, we admit that it was not possible to obtain all the measurements in all the cases. However, those variables with significant differences, i.e. insula depth, Sylvian fissure and parieto-occipital fissure, were measured in almost all the included pregnancies. In this study, neurosonographic assessment was done between 31 and 35 weeks due to technical considerations. Earlier than 30 weeks, the assessment of cortical development might not be accurate and later than 36 weeks, it is more difficult due to the increased skull calcification and shadowing.[21,22] However, we acknowledge that performing the examination within a limited interval could be associated with some degree of selection bias. Moreover, using 3D multiplanar imaging and applying magnetic resonance imaging (MRI) techniques have the potential to improve the detection of altered cortical development. Of note, we observed a divergence from expected cortical grading scores for the gestational age of the cingulate and calcarine sulci. This observation has been reported as well in previous studies from our group.[31] We believe that this divergence does not have an impact on the study results since it was present in all study groups including control group. Furthermore, postnatal neurodevelopmental outcome was not evaluated, which prevented us from assessing any correlation with postnatal performance. We also acknowledge that the study groups mainly included late-onset cases, representing the most prevalent clinical phenotypes of PE and SGA, which impeded sub-analyses according to the clinical onset.

In conclusion, PE seem to be associated with differences in the pattern of fetal brain cortical development compared to fetuses from uncomplicated pregnancies regardless of the

association with SGA and prematurity. Further studies are warranted to better understand the consequences of delayed neurodevelopment in utero in PE offspring with and without SGA and to identify potential prenatal biomarkers using other imaging techniques such as 3D multiplanar ultrasound, MRI and functional connectivity. Interestingly, a recent study showed a specific blueprint of subcortico-cortical functional connectivity at rest in a group of normally developing fetuses between the 25-32 weeks of gestation. Results show significant functional coupling between subcortical nuclei and cortical networks related to sensorimotor processing, decision making, and learning capabilities. Thus, assessing functional connectivity in PE with or without SGA is of utmost importance and may be relevant for future studies on both prediction and prevention of abnormal neurodevelopment in these fetuses.[51]

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Figure legends

Figure 1. Illustrative neurosonographic images showing the study measurements: A) Axial transthalamic plane, showing falx, anterior horns of lateral ventricles, cavum septi pellucidi (CSP), thalami (Th) and the measurements of the insula depth (#) and the Sylvian fissure (*). In this plane, the cortical grading score of the Sylvian fissure and the frontal and temporal areas were evaluated; B) Axial tranventricular plane, showing the CSP anteriorily and a portion of the posterior horn of the lateral ventricle that is distal to transducer along with the measurement of the parieto-occipital sulcus. In this plane, the cortical grading score of the parieto-occipital sulcus and the parietal area were also evaluated; C) Coronal transthalamic plane showing the thalami bilaterally and the measurement of the cingulate sulcus. In this plane, the grading score of the cingulate sulcus was evaluated; D) Coronal transcerebellar plane showing the cerebellum and the measurement of the calcarine sulcus. In this plane, the grading score of the calcarine sulcus was evaluated

Figure 2. Fetal sulci depth in the study populations.

Bars represent the mean of the depth of each fissure/sulcus adjusted for biparietal diameter and multiplied by 100. Whiskers represent the mean □standard deviation.

AGA, fetuses with appropriate growth for gestational age; SGA, small-for-gestational-age; BPD, biparietal diameter.

*$p<0.05$ by t-test compared to normotensive AGA (unadjusted).

†$p<0.05$ by linear regression adjusted for ethnicity, low socioeconomic status, nulliparity, chronic hypertension, pregestational diabetes, assisted reproductive technologies, smoking and fetal sex with the application of Benjamini-Hochberg procedure for multiple comparisons, compared to normotensive AGA.

Data available for insula (n=348), Sylvian fissure (n=348), parieto-occipital sulcus (n=153), cingulate sulcus (n=108), calcarine sulcus (n=83).

Figure 3. Fetal brain cortical grading in the study populations.

Data are expressed as percentage breakdown in each group.

AGA, fetuses with appropriate growth for gestational age; SGA, small-for-gestational-age.

*$p<0.05$ by Pearson $\chi 2$ test compared to normotensive AGA (unadjusted).

†$p<0.05$ by ordinal logistic regression adjusted for ethnicity, low socioeconomic status, nulliparity, chronic hypertension, pregestational diabetes, assisted reproductive technologies, smoking and fetal sex with the application of Benjamini-Hochberg procedure for multiple comparisons, compared to normotensive AGA.

Data available for Sylvian fissure (n=339), parieto-occipital sulcus (n=230), cingulate sulcus

(n=165), calcarine sulcus (n=142), frontal lobe (n=216), parietal lobe (n=220), temporal lobe (n=228).

Figure 4. Illustrative images of the Sylvian fissure and the insula depth in A) controls and B) cases of preeclampsia and/or fetal growth restriction. The scan was performed at 33±2 weeks' gestation.

A straight line projecting the interhemispheric fissure was traced going from frontal bone to occipital bone in the axial transthalamic view. Insula depth (marked with #) was measured drawing a perpendicular line from the midline behind the cavum septi pellucidi to the external border of the cortex. The Sylvian fissure (marked with *) was measured by continuing the line of the insula depth, starting the measurement at the external border of the cortex and terminating at the internal border of the cranium.

Tables

Table 1. Maternal and perinatal characteristics of the study population.

	Normotensive		**Preeclampsia**	
	AGA	**SGA**	**AGA**	**SGA**
	n=128	n=77	n=76	n=67
Maternal characteristics				
Age (years)	35.9 (31.6 – 38.8)	33.7 (29.8 – 38)	34.5 (30.9 – 38.1)	35.5 (31.7 – 38.4)
Caucasian ethnicity	98 (76.6)	61 (79.2)	39 (51.3)*	52 (77.6)
Low socio-economic status†	31 (24.2)	22 (28.6)	29 (38.2)*	21 (31.3)
Pre-gestational BMI (kg/m^2)	22.2 (20.3 – 24.6)	22.3 (19.5 – 25)	25.9 (23.3 – 29.3)*	22.8 (21 – 26)
Chronic hypertension	4 (3.1)	1 (1.3)	10 (12.8)*	8 (11.3)*
Pre-gestational diabetes	2 (1.6)	0 (0)	12 (15.4)*	2 (2.8)
Nulliparity	71 (55.5)	25 (32.5)*	39 (51.3)	21 (31.3)*
ART	19 (14.8)	9 (11.7)	15 (19.2)	18 (25.4)
Smoking during pregnancy	12 (9.4)	19 (24.7)*	9 (11.8)	14 (20.9)*
Ultrasound assessment				
GA at assessment (weeks)	32.6 (32 - 33.6)	32.6 (32.1 - 34.2)	32.9 (31.8 - 34.1)	32.4 (31.3 - 34.1)
EFW centile	44 (6-61)	5 (1-12)*	58 (14-89)	2 (0-7)*
Uterine arteries mean PI z-score	-0.07 (-1.04 – 0.77)	0.57 (-0.82 – 1.95)*	0.1 (-0.79 – 1.11)	2.48 (1.43 – 3.25)*
Umbilical artery PI z-score	-0.13 (-0.72 – 0.26)	-0.05 (-0.47 – 0.52)	-0.12 (-0.33 – 0.12)	0.33 (-0.12 – 0.9)*
Middle cerebral artery PI z-score	-0.21 (-0.81 – 0.45)	-0.8 (-1.35 – -0.11)*	-0.37 (-1.06 – 0.11)	-1.5 (-2.19 – -0.84)*
Cerebroplacental ratio z-score	-0.22 (-0.78 – 0.53)	-0.69 (-1.52 – -0.21)*	-0.54 (-0.96 – 0.11)	-1.45 (-2.51 – -0.77)*
Ductus venosus PI z-score	-0.25	0.05	-0.82	0.02

	(-0.92 – 0.4)	(-1.01 – 0.89)	(-1.37 – 1.15)	(-0.85 – 0.4)
Perinatal outcomes				
GA at delivery (weeks)	39.9 (38.9 – 40.4)	38.1 (37.1 – 40.1)*	37.4 (36.3 – 38.4)*	35.1 (33.6 – 37.1)*
Early-onset disorder§	-	2 (2.6)	7 (9.2)	19 (28.4)
Cesarean section	32 (25)	30 (39)*	47 (61.8)*	48 (71.6)*
Male gender	63 (49.2)	43 (55.8)	32 (42.1)	41 (61.2)
Birthweight (g)	3175 (2940-3559)	2420 (2135-2692)*	2871 (2628-3226)	1700 (1370-2170)*
Birthweight centile	35 (18 – 72)	2 (0.5 – 5)*	36 (17 – 84)	0.5 (0 – 2)*
APGAR score 5 min <7	0 (0)	0 (0)	0 (0)	1 (1.5)
Umbilical artery pH	7.21 (7.14 – 7.26)	7.22 (7.17 – 7.27)	7.23 (7.17 – 7.28)	7.22 (7.5– 7.26)

Data are presented as median (interquartile range) or n (%) as appropriate.

AGA, fetuses with appropriate growth for gestational age; SGA, small-for-gestational-age; BMI, body mass index; ART: Assisted reproductive technologies; GA: Gestational age; EFW: Estimated fetal weight; PI, pulsatility index.

†Low socioeconomic status was defined as no studies or long-term unemployment or never worked.

§Early-onset disorder was defined as PE and/or SGA requiring delivery before 34 weeks of gestation.

*$p<0.05$ by Student *t-test* or Pearson χ^2 test as appropriate, compared to normotensive AGA (unadjusted).

Table 2. Neurosonography results in the study populations.

	Normotensive		**Preeclampsia**	
	AGA	**SGA**	**AGA**	**SGA**
	n=128	n=77	n=76	n=67
GA at scan (weeks)	32.6 (32 - 33.6)	32.6 (32.1 - 34.2)	32.9 (31.8 - 34.1)	32.4 (31.3 - 34.1)
BPD (mm)	82 (78 - 84)	79 (75 - 83)*†	81 (78 - 86)	78 (74 - 82)*†
Head circumference (mm)	298 (289 - 307)	289 (277 – 301)*†	298 (287 - 315)	285 (274 - 301)*†
Occipitofrontal diameter (mm)	105 (101 - 109)	102 (96 - 106)*	105 (101 - 110)	102 (95- 106) *
Insula depth (mm)	25.67 (1.88)	26.02 (2.2)	26.66 (1.92)*†	25.8 (2.01)
Insula depth/BPD x100	31.76 (2.02)	33.22 (1.95)*†	32.76 (1.74)*†	33.19 (2.12)*†
Sylvian fissure (mm)	13.43 (2.03)	11.39 (2.07)*†	11.63 (2.06)*†	11.06 (2.08)*†
Sylvian fissure/BPD x100	16.6 (2.33)	14.51 (2.36)*†	14.27 (2.28)*†	14.17 (2.32 *†
Parieto-occipital sulcus (mm)	9.12 (3.48)	6.84 (3.47)*	8.6 (1.6)	8.41 (3.25)
Parieto-occipital sulcus/BPD x100	11.17 (4.14)	8.67 (4.2)*	10.79 (2.11)	10.85 (4.11)
Cingulate sulcus (mm)	4.15 (1.25)	3.95 (1.72)	4.72 (1.54)	3.66 (0.95)
Cingulate sulcus/BPD x100	5.11 (1.45)	5.05 (2.15)	5.9 (1.93)	4.81 (1.28)
Calcarine sulcus (mm)	11.08 (3.97)	10.22 (3.5)	11.07 (3.05)	10.57 (2.89)
Calcarine sulcus/BPD x100	13.56 (4.89)	12.9 (4.36)	14.01 (3.83)	13.52 (3.71)

Data are expressed as median (interquartile range), mean (standard deviation).

AGA, fetuses with appropriate growth for gestational age; SGA, small-for-gestational-age; GA, Gestational age; BPD, biparietal diameter.

*$p<0.05$ by *t-test* compared to normotensive AGA (unadjusted).

†$p<0.05$ by linear regression adjusted for ethnicity, low socioeconomic status, nulliparity, chronic hypertension, pregestational diabetes, assisted reproductive technologies, smoking and fetal gender with the application of Benjamini-Hochberg procedure for multiple comparisons, compared to

normotensive AGA.

Data available for BPD (n=348), head circumference (n=341), occipitofrontal diameter (n=205), insula (n=348), Sylvian fissure (n=348), parieto-occipital sulcus (n=153), cingulate sulcus (n=108), calcarine sulcus (n=83).

Table 3. Fetal brain cortical grading in the study populations.

	Normotensive		Preeclampsia	
	AGA	**SGA**	**AGA**	**SGA**
Sylvian fissure				
Grade 3	4 (3.2)	5 (6.8)	3 (4.1)	3 (4.6)
Grade 4	75 (59.5)	31 (41.9)*	68 (93.2)*†	39 (59.1)
Grade 5	47 (37.3)	38 (51.4)	2 (2.7)*†	24 (36.4)
Parieto-occipital sulcus				
Grade 2	5 (5)	11 (17.7)*	0 (0)	2 (5.1)
Grade 3	19 (19)	13 (21)	6 (20.7)	13 (33.3)
Grade 4	74 (74)	32 (51.6)*	23 (79.3)	20 (51.3)*
Grade 5	2 (2)	6 (9.7)*	0 (0)	4 (10.3)*
Cingulate sulcus				
Grade 2	7 (8.9)	10 (24.4)*	0 (0)	2 (8.3)
Grade 3	36 (45.6)	11 (26.8)*	12 (57.1)	10 (41.7)
Grade 4	36 (45.6)	20 (48.8)	9 (42.9)	12 (50)
Calcarine sulcus				
Grade 1	0 (0)	3 (7.7)	0 (0)	0 (0)
Grade 2	4 (5.9)	3 (7.7)	0 (0)	0 (0)
Grade 3	4 (5.9)	5 (12.8)	3 (16.7)	2 (11.8)
Grade 4	53 (77.9)	27 (69.2)	11 (61.1)	14 (82.4)
Grade 5	7 (10.3)	1 (2.6)	4 (22.2)	1 (5.9)
Frontal lobe				
Grade 1	0 (0)	1 (1.7)	0 (0)	0 (0)
Grade 2	0 (0)	4 (6.9)*	0 (0)	0 (0)
Grade 3	36 (37.1)	14 (24.1)	8 (25.8)	4 (13.3)*
Grade 4	55 (56.7)	34 (58.6)	22 (71)	24 (80)*
Grade 5	6 (6.2)	5 (8.6)	1 (3.2)	2 (6.7)
Parietal lobe				

Grade 1	0 (0)	1 (1.8)	0 (0)	0 (0)
Grade 2	3 (3)	3 (5.4)	0 (0)	0 (0)
Grade 3	30 (30.3)	9 (16.1)	10 (32.3)	9 (26.5)
Grade 4	62 (62.6)	38 (67.9)	20 (64.5)	23 (67.7)
Grade 5	4 (4)	5 (8.9)	1 (3.2)	2 (5.9)
Temporal lobe				
Grade 0	0 (0)	1 (1.6)	0 (0)	0 (0)
Grade 1	0 (0)	1 (1.6)	0 (0)	0 (0)
Grade 2	2 (2)	3 (4.9)	0 (0)	0 (0)
Grade 3	35 (35)	15 (24.6)	9 (29)	9 (25)
Grade 4	56 (56)	33 (54.1)	21 (67.7)	24 (66.7)
Grade 5	7 (7)	8 (13.1)	1 (3.2)	3 (8.3)

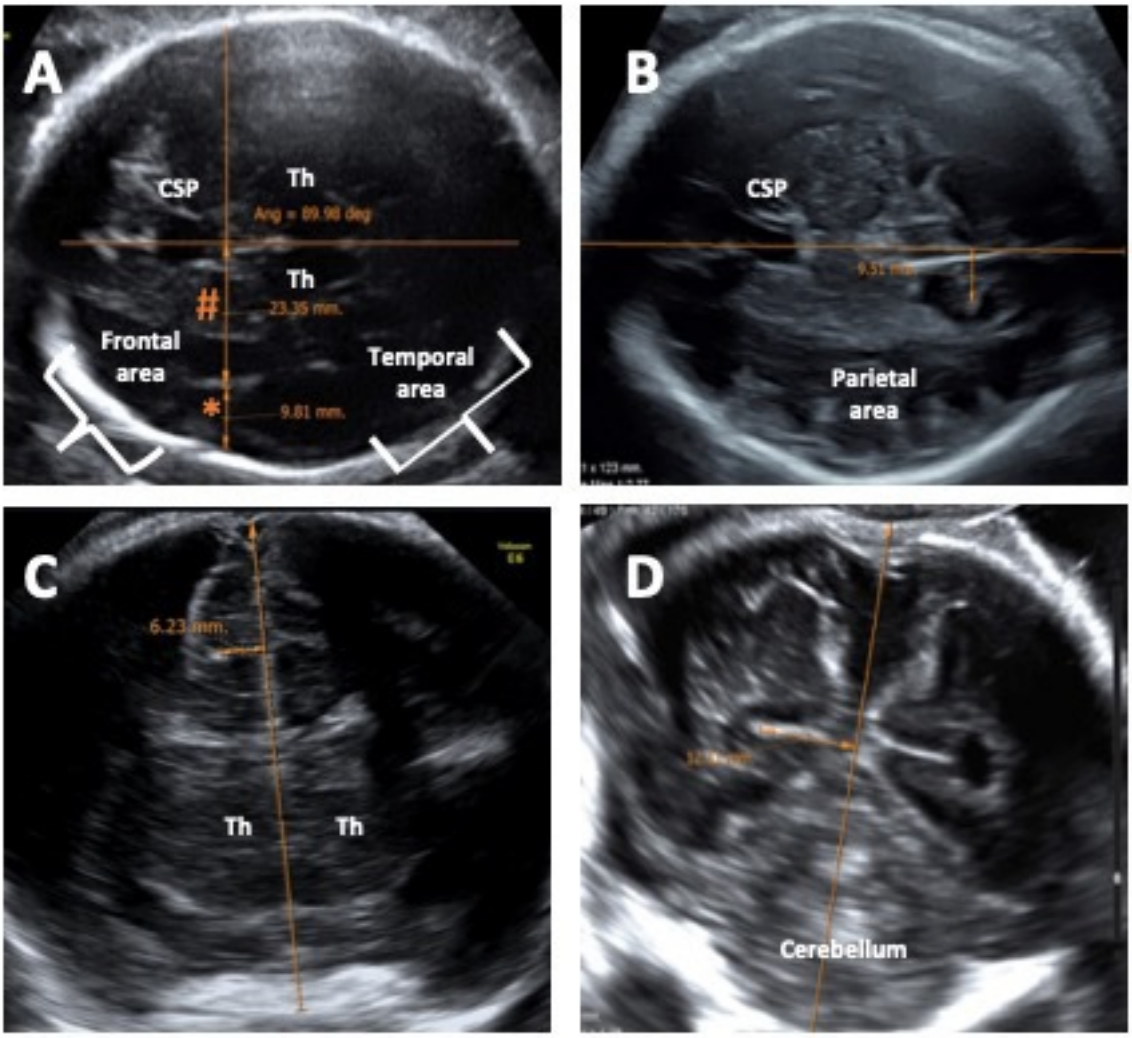
Data are expressed as n (%).

AGA, fetuses with appropriate growth for gestational age; SGA, small-for-gestational-age.

*$p<0.05$ by Pearson χ^2 test compared to normotensive AGA (unadjusted).

†$p<0.05$ by ordinal logistic regression adjusted for ethnicity, low socioeconomic status, nulliparity, chronic hypertension, pregestational diabetes, assisted reproductive technologies, smoking and fetal sex with the application of Benjamini-Hochberg procedure for multiple comparisons, compared to normotensive AGA.

Data available for Sylvian fissure (n=339), parieto-occipital sulcus (n=230), cingulate sulcus (n=165), calcarine sulcus (n=142), frontal lobe (n=216), parietal lobe (n=220), temporal lobe (n=228).



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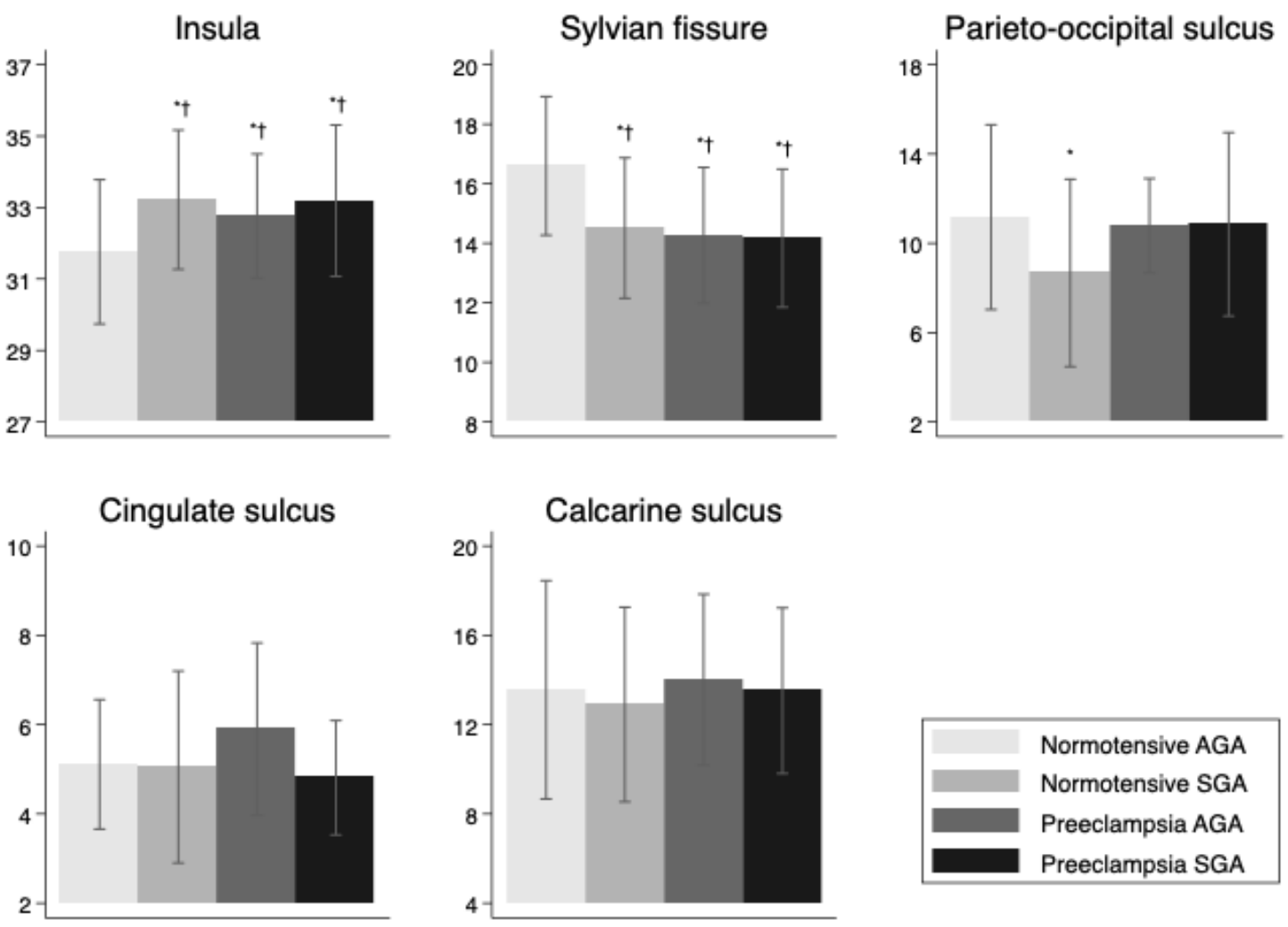

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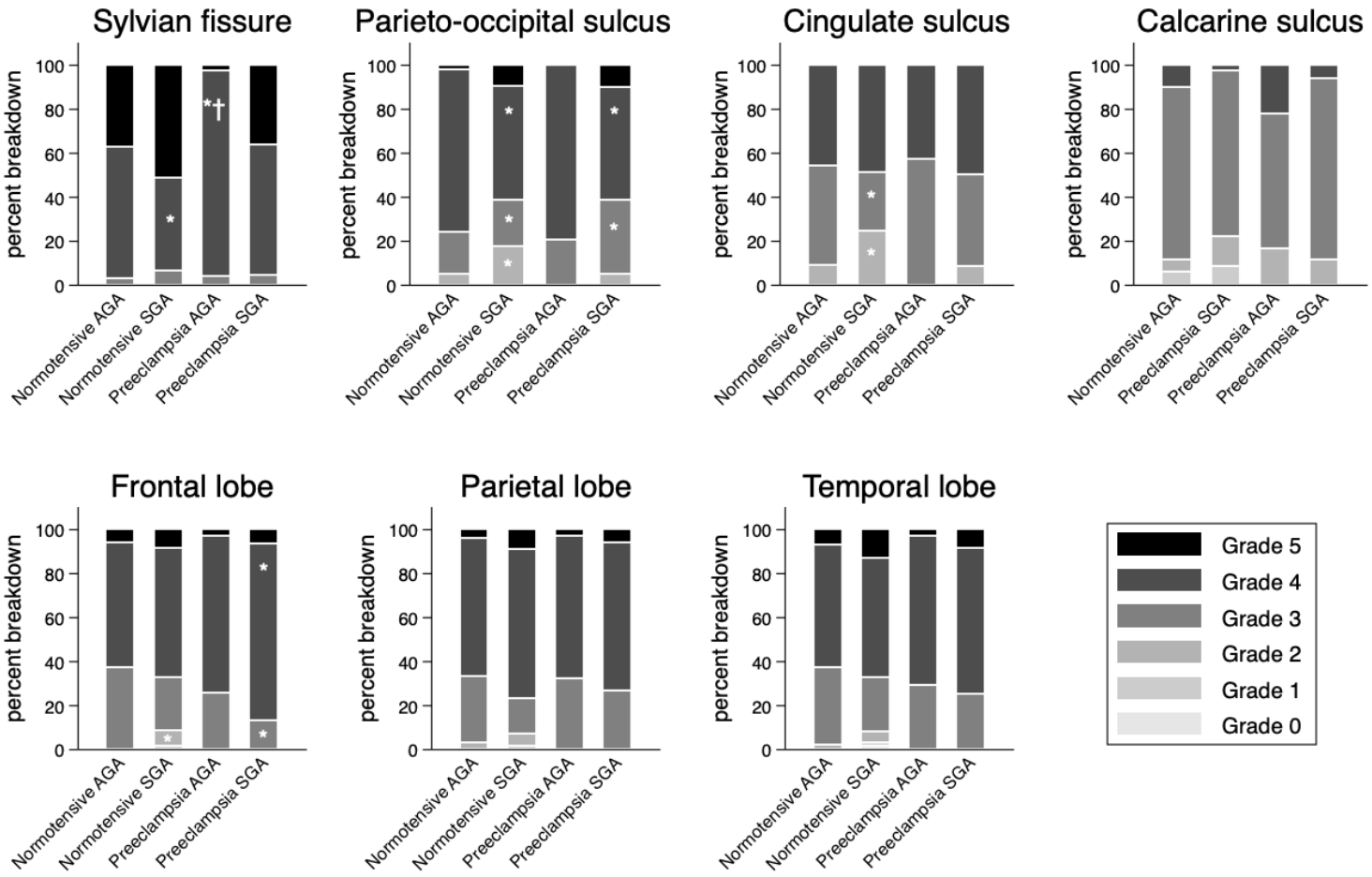

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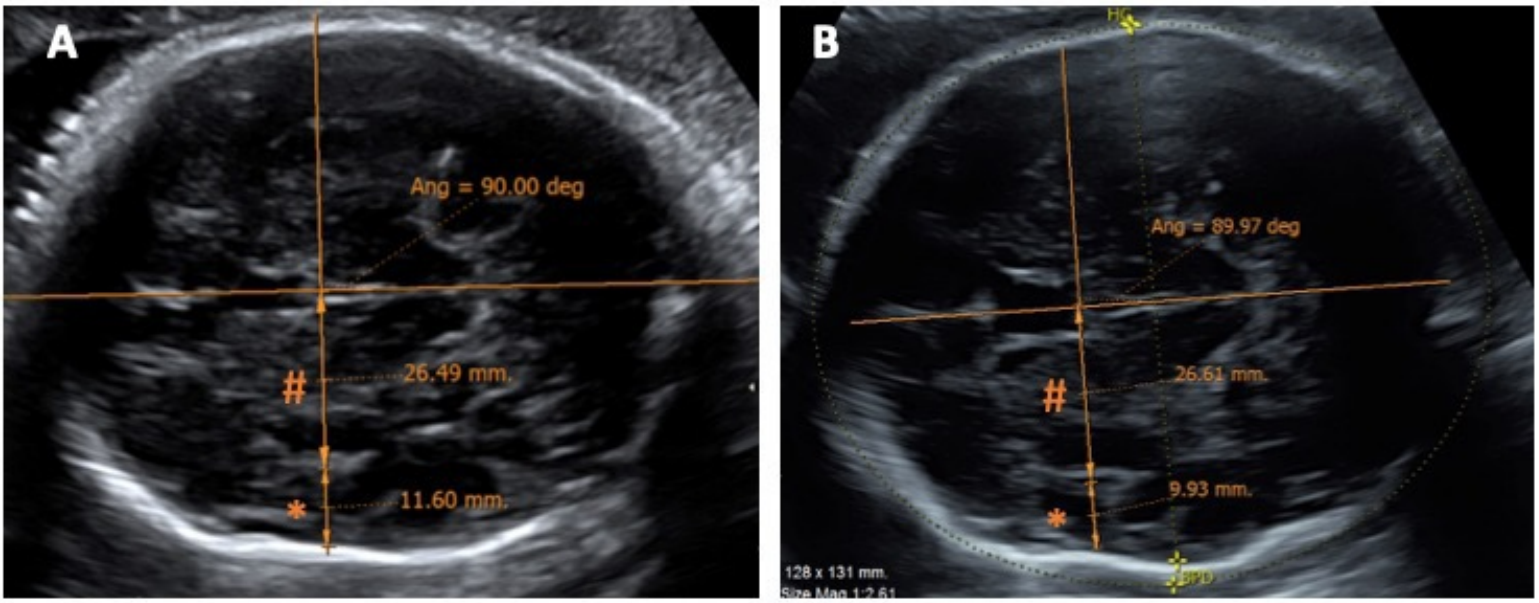

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