Obstetrics & Gynecology: Open Access
Spinelli M, et al., Gynecol Obstet Open Acc 8: 217.
www.doi.org/10.29011/2577-2236.100217
www.gavinpublishers.com

Research Article

Delayed Prenatal Development of the Insula Lobe in SGA Fetuses at 2D Ultrasonography: A Perspective-Changing Retrospective Study

Marialuigia Spinelli*#, Natacha Saghir#, Anda Radan, Sofia Amylidi-Mohr, Luigi Raio

Department of Obstetrics and Gynecology, University Hospital Bern, University of Bern, Bern, Switzerland

#Contributed equally to this Work

***Corresponding author**: Marialuigia Spinelli, Department of Obstetrics and Gynecology, University Hospital Bern, University of Bern, Frauenklinikstrasse 10, 3010, Bern, Switzerland

Citation: Spinelli M, Saghir N, Radan A, Amylidi-Mohr S, Raio L (2024) Delayed Prenatal Development of the Insula Lobe in SGA Fetuses at 2D Ultrasonography: A Perspective-Changing Retrospective Study. Gynecol Obstet Open Acc 8: 217. DOI: https://doi.org/10.29011/2577-2236.100217

Received Date: 21 October 2024; **Accepted Date:** 28 October 2024; **Published Date:** 31 October 2024

Abstract

Introduction: delayed fetal cortical development is associated with the risk of future neurological and/or psychomotor issues. However, the process of prenatal brain folding in small for gestational age (SGA) fetuses remains understudied. In this study we evaluated by two-dimensional ultrasound (2D-US) whether there is a difference in the development of the Insula Lobe (IL), the Sylvian Fissure (SF) and/or the SF-ratio between appropriate-for-gestational-age (AGA) and SGA fetuses. **Methods:** a retrospective study was conducted by measuring the IL, SF and SF ratio in 137 SGA-births between 20 and 36 weeks of gestational age (GA), with and without Doppler abnormalities and comparing it to published reference values for AGA cases. **Results:** a significant different development of the IL ($p = 0.025$) was observed for SGA compared with AGA-fetuses. No statistically significant differences were found comparing subgroups without (constitutional SGA) or with Doppler abnormalities (pathological SGA). **Conclusion:** we found a delayed development of the IL in SGA, independently on its constitutional or pathological origin, in comparison with AGA-fetuses at prenatal 2D-US. Further studies, assessing also later cognitive and psychomotor development, are encouraged to address this issue.

Keywords: Small for Gestational Age, Insula Lobe, Cortical Development, Prenatal Ultrasound

Introduction

The Insula Lobe (IL) is the first cerebral fissure that can be seen on fetal imaging at around 18 weeks of gestational age (GA). The development of the IL follows a predictable timetable during cortical maturation, making a follow-up with magnetic resonance imaging (MRI) and/or US possible [1-3]. The absence or the abnormal appearance of the IL - and the Sylvian Fissure (SF) - at a given GA would consequently lead to the suspicion of abnormal or delayed cortical development with the possibility of future neurological and/or psychomotor issues.

Small for gestational age (SGA) can occur following a pathological process or may represent constitutionally small fetuses. However, distinguishing these processes is often difficult, especially in large prenatal studies, where the term SGA is often used as a proxy for a pathological fetal growth [4]. Interestingly, while only SGA due to placental insufficiency is traditionally considered

the most important condition affecting short term morbidity and mortality, recent post-natal research suggests that any SGA, i.e. including the constitutionally small fetuses, are susceptible to abnormal or delayed cortical development, leading to long-term neurodevelopmental impairment [5,6]. However, a thorough understanding of the SGA-mechanisms on brain development is still object of debate, as well as the process of prenatal brain folding in any SGA remains understudied [7-9]. Recently, our group showed how the SF and the IL as well as the SF-ratio can be measured in normal fetuses using transabdominal 2D-US with good reproducibility [10], supporting the use of this simple route to assess such anatomical structures in the routine scan. The aim of the present study was to analyze the SF, the IL and the SF-ratio in SGA-fetuses and compare it to published reference values for AGA-cases.

Material and Methods

Study design

A retrospective study was carried out, focusing on the sonographic evaluation of the fetal IL and the SF. Measurements of the IL and the SF were performed in SGA-fetuses with the routine 2D-US, and the SF ratio was calculated. These measurements were then compared with previous published reference values for AGA cases using an analysis of covariance (ANCOVA).

Study population

A cross-sectional retrospective study of all prenatal US-examinations performed between 2002 and 2018 at our Department was conducted by searching the fetal imaging databases. The present study was undertaken ethically in accordance with the World Medical Association Declaration of Helsinki and the study protocol was approved by the institute's committee on human research (IRB number 2016-00415). All adult participants provided written informed consent to participate in the study. Only patients with SGA- newborns, defined as having a birth weight lower than the 10th centiles for their GA, were included. The GA was determined by a reliable last menstrual period and confirmed by the measurement of crown-rump length (CRL) during the 1st trimester. Only singleton fetuses were included. Exclusion criteria included congenital malformations, chromosomal abnormalities and known perinatal infections.

US- measurements

1. Inclusion criteria for the US-measurements were:
2. availability of detailed prenatal and postnatal data;
3. availability of fetal Doppler measurements;

The availability of images showing a standard trans-thalamic view according the criteria reported by the International Society of Ultrasound in Obstetrics & Gynecology [11] The quality of the US images was assessed by the reviewing sonographer (M.S.). Visual quality assessment was done by scoring the visibility of the midline structures as well as the SF and the IL using a five-point scale. A score of 1 reflected excellent visualization, whereas a score of 5 reflected non-diagnostic images. Only the pictures classified with a score 1 or 2 were used for the study. The ultrasound machines used for 2-dimensional (2D) US were GE Voluson E8 and E10 (GE Healthcare Ultrasound, Milwaukee, WI, USA) equipped with a curved linear array transabdominal transducer (2–5 MHz).

The measurements of the IL, the SF as well the SF-ratio were obtained as previously reported (figure 1) [10]. Briefly, the IL was measured by drawing a perpendicular line from the falx cerebri to the point of maximal prominence of the insular cortex. The depth of the SF was measured by continuing the perpendicular line of the falx cerebri and taking the distance from the insular cortex and the inner surface of the parietal bone. The SF ratio was determined by calculating the ratio between the SF and the sum of the SF and the IL.

All included cases were then further divided in 2 subgroups, based on the indices of the fetal Doppler

- Fetuses with normal Doppler indices (Pulsatility index (PI) of umbilical artery (UA) < 95th percentile)
- Fetuses with abnormal UA Doppler (PI > 95th percentile and/or absent or reversed end diastolic flow).

Every patient was included only once.

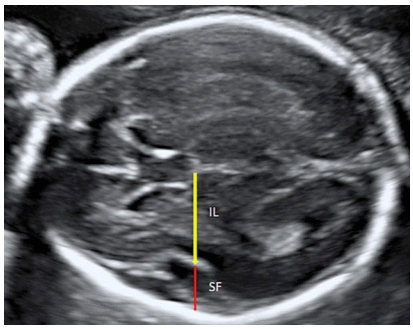

Figure 1: Modified from Authors [10]: demonstrates a standard transthalamic view of the fetal head obtained by transabdominal 2D ultrasound showing the SF and the IL measurements and adjacent anatomical landmarks at 23 weeks of gestation. SF, Sylvian fissure; IL, insular lobe.

Statistical Analysis

Statistical analysis was performed with the SPSS package (SPSS release 26 for Mac OS, IBM, United States of America). The correlation between the GA and the brain parameters (IL, SF and SF ratio) of the different groups was analyzed using the Pearson Correlation Coefficient (PCC). To determine the effect between the groups, the three examined parameters of the SGA and published

reference range of AGA fetuses were compared using an analysis of covariance (ANCOVA). To improve the precision of the results, GA and HC was defined as covariate. The influence of the gender as a covariate was also analyzed. Probability values below 0.05 were considered statistically significant.

Results

Between 2002 and 2018, 161 singleton pregnancies were recruited. After exclusion according to the criteria described earlier, 152 patients were qualified for this study. Further, 15 patients had to be excluded due to low-quality ultrasound images, thus leaving the study cohort with 137 SGA fetuses for analysis. The clinical characteristics of the study's population are reported in table 1. All the analyzed brain parameters (IL, SF, and SF ratio) of the different groups correlated with GA (table 2). Comparing SGA with our published reference range of AGA-fetuses [10], after adjustment for GA and HC, we observed that the IL showed a statistically significant difference (Table 3). This difference however was not significant for the SF and the SF ratio (table 3). Including the gender as a covariate led to no significant difference in the results. Plotting these measurements on the scatterplots showing the correlation of the IL, SF, and SF ratio with GA previously published [10], we observed a decrease of the growth trajectory of the SF and IL depth, as well as a change in the profile of the SF ratio across GA (Figure 2). No statistically significant differences were found comparing fetuses with or without Doppler abnormalities.

Maternal age, years	31.6 ± 5.22
Body mass index	25.9 ± 14.97
Gestational age at delivery, weeks	30.6 ± 2.69
Birth weight centiles [a]	4.6 ± 1.99
Head circumference at birth, cm	26.4 ± 2.73
Males, %	51%
Data are presented as means ± standard deviations where applicable. [a] According to the WHO growth charts for newborns – 2006 (http://www.who.int/childgrowth/standards/en/).	

Table 1: Clinical characteristics of the study population, including perinatal outcome data (n=137)

P and r values	GA and SF	GA and IL	GA and SF Ratio
SGA, all cases	P < 0.0001 / 0.747	P < 0.0001 / 0.861	0.034 / 0.181
SGA with doppler anomalies	P < 0.0001 / 0.701	P < 0.0001 / 0.844	0.252 / 0.113
SGA without doppler anomalies	P < 0.0001 / 0.895	P < 0.0001 / 0.895	0.001 / 0.557

Table 2: Correlation between the GA and the brain parameters (IL, SF and SF ratio) of the different groups using the Pearson Correlation Coefficient (PCC).

	Sylvian Fissure (SF)	Insula Lobe (IL)	Sylvian Fissure (SF) ratio
F value	F (1,407) = 0.050	F (1,407) = 5.071	F (1,407) = 1,094
p-value	p = 0.823	**p = 0.025**	p = 0.296
Partial Eta Squared	η2 = 0.000	η2 = 0.012	η2 = 0.003
Observed Power	β = 0.056	β = 0.613	β = 0.181

Table 3: Analysis of covariance comparing SGA fetuses with our published reference range of AGA fetuses[10], after adjustment for GA and head circumference.

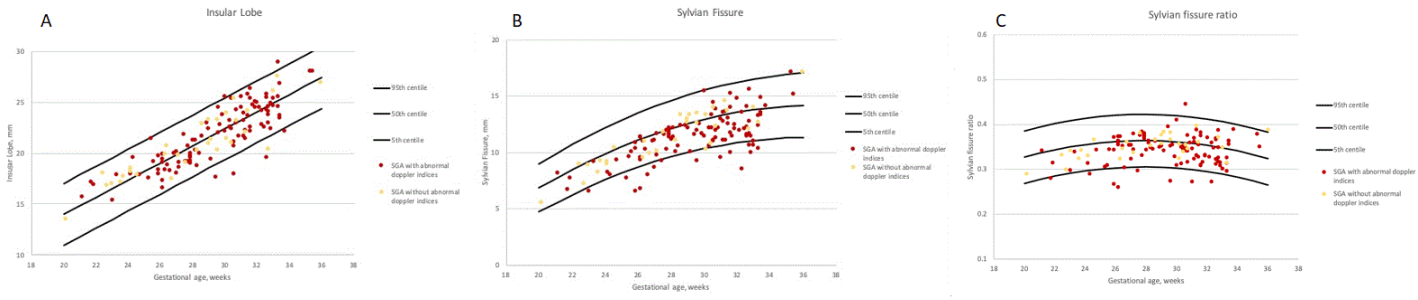

Figure 2: Plot of the measurements of the IL (A), SF (B) and SF ratio (C) on the scatterplots showing the correlation of the IL, SF and SF ratio, respectively, with GA of a previous paper [10].

Discussion

Main results and interpretation

In this study we showed that the IL in SGA fetuses, with or without Doppler abnormalities, had a statistically significant delayed development compared to AGA-fetuses. This is of importance, because the condition of a "small" fetus, and not the presence of any Doppler abnormalities, emerged unexpectedly as key factor in the growing process of the IL Currently, prenatal US assessment of the developing fetal brain still remains a challenge, even for experienced sonographers, as some of the fetal fissures, sulci, and gyri become visible only during late pregnancy. The limitation of this measurement lies in the complex and time-consuming procedure, which requires a skilled sonographer and, preferably, three-dimensional (3D) technology [12-23]. Furthermore, some anomalies in the cortical development may be subtle and may have a variety of appearances that are undetected until birth or even some months after birth [1,2,8]. The SF and the IL are among the most well-studied anatomical structures of the fetal cortex and demonstrate a typical pattern of development throughout gestation. The prenatal study of these structures may be helpful in the early detection of anomalies in cortical development, as this is the first fissure to develop. However, to our knowledge, only a few studies with a small patient cohort have provided objective standardization for the assessment of the IL by US [1-3,8,18,24-27]. It was previously showed that the SF and IL, as well as the SF ratio, can be feasibly measured in AGA-fetuses using transabdominal 2D US with good reproducibility [10]. This is of importance, since the measurement of these parameters may be included in the routine prenatal scan in the next future. Now we tested our parameters in a population of SGA-births. Comparing SGA with published reference range of AGA-fetuses [10], we could observe that the IL showed a statistically significant difference, after adjustment for GA and HC. The SF and the SF-ratio showed also a difference, although not statistically significant. Furthermore, we observed a decrease of the growth trajectory of the SF and IL depth, as well as a change of the profile of the SF-ratio across the GA, comparing SGAs with AGAs. All these data show that SGAs had a different prenatal cortical development, compared with AGA-cases.

These measurements might serve as a non-invasive imaging marker to assess differences in prenatal cortical development between any SGA and AGA fetuses in the future. This may have a huge clinical relevance in our opinion, since several postnatal studies over more than 20 years show that the term SGA is associated with mild to moderate school problems, still present in late puberty and with lower psychological and intellectual performance in young adulthood as compared with AGA-controls [5,6]. Only few authors compared the prenatal cortical development between normal and "small" fetuses. In a study of Padilla et al. [28], the IL of pathological SGA-fetuses were analyzed and compared with preterm and term AGA-fetuses at the age of 12 months. The study demonstrated that the IL-volumes were significantly smaller in SGA infants compared with term infants. The study remained focused on the IL and did not include the analysis and the comparison of the SF. Furthermore, constitutional SGA was not taken into consideration. A newer study from Husen et al. [23] analyzed and compared the SF and the IL between pathological SGA and AGA-fetuses using transabdominal or transvaginal 3D-US. The study showed a significant decrease of the depth of the right SF in SGAs compared to AGAs. However, no significant associations were found between SGA-fetuses and the IL or the left SF. Again, this study did not include constitutional SGA. Furthermore, it did not provide any postnatal data.

Currently, distinguishing constitutional and pathological SGA still represent an issue in the scientific community. The definition SGA encompass indeed both cases and any categorization of these processes prenatally is often difficult, especially in large studies. Considering the current terminological issue, as well as the lack in a thorough distinction between constitutional and pathological SGA, we examined the whole population of "small" newborn, including those both with and without Doppler abnormalities.

A differentiation between normal and pathological SGA was indeed beyond the purposes of this paper, which was intended as a pivotal study of the assessment of the SF, IL and SF-ratio in a population of SGA-births. Comparing subgroups of SGA, with or without Doppler abnormalities, we did not observe any statistical difference. These data confirm the available postnatal findings, suggesting that the SGA itself, independently of the underlying cause – constitution, placental insufficiency, etc. – may be a risk factor for cortical abnormalities. Changing prospective, with a main focus on the condition of the "small" fetus itself - not on any pathological Doppler finding – may help obstetricians and pediatricians in properly preventing, diagnosing and treatment of cortical brain developmental anomalies.

Limitations

The measurements were not divided into left and right hemisphere measurements. Since normal asymmetries between fissures of the right and left cerebral hemispheres have already been described in previous literature [17,23], it is possible that this omission influenced the results and that other conclusions would have been drawn if the measurements had been assigned to either the left or the right hemisphere. As already reported, a substantial number of studies have already described the association between "small" fetuses, including physiological and pathological ones, and increased risks of motor and sensory neurodevelopmental deficits, cognitive and learning impairments, and cerebral palsy [14,29,30]. It would be interesting to analyze the long term neurological and cognitive outcome of our newborn population and to compare the results to former studies. Further studies are encouraged to address this issue.

Conclusion

This paper makes several contributions to the literature. First, this study adds to the relatively small amount of accounting research that examines whether conditions such as SGA do affect not only the growth itself, but also the fetal cortical development. Second, our study focuses on special structures of the fetal brain, the SF and the IL, that are of paramount importance in antenatal diagnostic imaging. The progressive development of the size and the shape of the IL represent a reliable mirror of the whole cortical folding, but, at the same time, these structure is easily measurable throughout the pregnancy without the need of advanced technical and technological equipment or skills. Third, and most importantly, our finding open a new perspective for the understanding the underlying mechanisms of the SGA, as well as for its definition and classification. Whereas previous research focuses exclusively on the consequences of a pathological SGA, this study reveals that every "small" fetus should be carefully evaluated. Our results point out the association between SGA, independently of its constitutional or pathological origin, and the impairment of the process of cortical development and should encourage further research to address this issue.

Considering that these measurements of fetal brain structures by 2D US are feasible and reliable not only in AGA, but also in SGA-fetuses, the screening of the fetal brain should be, in our opinion, included into our practice and be part of a routine prenatal US-screening. Early detection would contribute to the optimization of the obstetrical management as well as the postnatal diagnostic and therapeutic work-up. The results of this study therefore warrant further prenatal and postnatal investigations with larger sample sizes to increase the effect size and the observed power, as well as a long postnatal follow-up to increase the clinical relevance of the data.

Disclosures

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

The authors have no relevant financial or non-financial interests to disclose.

References

1. Monteagudo A, Timor-Tritsch IE (1997) Development of fetal gyri, sulci and fissures: a transvaginal sonographic study. Ultrasound Obstet Gynecol 9: 222-228.
2. Toi A, Lister W, Fong K (2004) How early are fetal cerebral sulci visible at prenatalultrasound and what is the normal pattern of early fetalsulcal development? Ultrasound Obstet Gynecol 24: 706-15.
3. Mittal P, Gonçalves LF, Kusanovic JP, Jimmy Espinoza, Wesley Lee, et al. (2007) Objective evaluation of Sylvian fissure development by multiplanar 3-dimensional ultrasonography. J Ultrasound Med 26: 347-53.
4. Gordijn S, Beune I, Thilaganathan B, A Papageorghiou, A A Baschat et al. (2016) Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol 48: 333-9.
5. Kesavan K, Devaskar S (2019) Intrauterine growth restriction: postnatal monitoring and outcomes. Pediatr Clin North Am 66: 403-23.
6. Chatelain P (2000) Children born with intra-uterine growth retardation (iugr) or small for gestational age (sga): long term growth and metabolic consequences. Endocr Regul 34: 33-6.
7. Rolo LC, Araujo E, Nardozza L, Patrícia Soares de Oliveira, Sérgio Aron Ajzen, et al. (2011) Development of fetal brain sulci and gyri: assessment through two and three-dimensional ultrasound and magnetic resonance imaging. Arch Gynecol Obstet 283: 149–58.
8. Ghai S, Fong K, Toi A, David Chitayat, Sophia Pantazi, et al. (2006) Prenatal us and mr imaging findings of lissencephaly: review of fetal cerebral sulcal development. RadioGraphics 26: 389-406.
9. Lerman-Sagie T, Malinger G (2008) Focus on the fetal Sylvian fissure. Ultrasound Obstet Gynecol 32: 3-4.

10. Spinelli M, Sica C, Ghezzi F, Antonella Cromi, Daniel Surbek, et al. (2018) Nomograms of the fetal Sylvian fissure and Insular lobe throughout gestation: a multicentric, ultrasonographic cross-sectional study. Fetal Diagn Ther 45: 325-31.

11. Salomon L, Alfirevic Z, Da Silva Costa F, R L Deter 5, F Figueras, et al. (2019) ISUOG practice guidelines: ultrasound assessment of fetal biometry and growth. Ultrasound Obstet Gynecol 53: 715-23.

12. Egaña-Ugrinovic G, Sanz-Cortes M, Figueras F, Couve-Perez, E Gratacós, et al. (2014) Fetal mri insular cortical morphometry and its association with neurobehavior in late-onset small-for-gestational-age fetuses. Ultrasound Obstet Gynecol 44: 322□9.

13. Egaña-Ugrinovic G, Sanz-Cortes M, Figueras F, Nuria Bargalló, Eduard Gratacós, et al. (2013) Differences in cortical development assessed by fetal mri in late-onset intrauterine growth restriction. Am J Obstet Gynecol 209: 126-8.

14. Eixarch E, Meler E, Illa M, (2008) Neurodevelopmental outcome in 2□year□old infants who were small□for□gestational age term fetuses with cerebral blood flow redistribution. Ultrasound Obstet Gynecol 32: 894-9.

15. Budday S, Steinmann P, Kuhl E (2015) Physical biology of human brain development. Front Cell Neurosci 9: 257.

16. Quarello E, Stirnemann J, Ville Y, Guibaud L (2008). Assessment of fetal Sylvian fissure operculization between 22 and 32 weeks: a subjective approach. Ultrasound Obstet Gynecol 32: 44-9.

17. Glenn O (2009) Normal development of the fetal brain by mri. Semin Perinatol 33: 208-19.

18. Garel C, Chantrel E, Brisse H, M Elmaleh, D Luton, et al. (2001) Fetal Cerebral Cortex: Normal gestational landmarks identified using prenatal mr imaging. Am J Neuroradiol 22:184–9.

19. Garel C, Chantrel E, Elmaleh M, Hervé Brisse, Guy Sebag, et al. (2003) Fetal mri: normal gestational landmarks for cerebral biometry, gyration and myelination. Childs Nerv Syst 19: 422□5.

20. Sandeep G, Katherine W, Ants T, David Chitayat, Sophia Pantazi, et al. (2006) Prenatal us and mr imaging findings of lissencephaly: review of fetal cerebral sulcal development. RadioGraphics 26: 389-405.

21. Habas P, Scott J, Roosta A, Vidya Rajagopalan, Kio Kim, et al. (2012) Early folding patterns and asymmetries of the normal human brain detected from in utero mri. Cerebral Cortex 22: 13-25.

22. Nordahl C, Dierker D, Mostafavi I, Cynthia M Schumann, Susan M Rivera, et al. (2007) Cortical folding abnormalities in autism revealed by surface-based morphometry. J Neurosci 27: 11725–35.

23. Husen S, Koning I, Go A, van Graafeiland A (2019) Three-dimensional ultrasound imaging of fetal brain fissures in the growth restricted fetus. PLoS One 14: 1-14.

24. Alves C, Araujo Júnior E, Nardozza L, Susan Menasce Goldman, Luiz Henrique Martinez, et al. (2013) Reference ranges for fetal brain fissure development on 3-dimensional sonography in the multiplanar mode. J Ultrasound Med 32: 269-77.

25. Correa F, Lara C, Bellver J, J Remohí, A Pellicer, V Serra, et al. (2006) Examination of the fetal brain by transabdominal three-dimensional ultrasound: potential for routine neurosonographic studies. Ultrasound Obstet Gynecol 27: 503□8.

26. Pooh R, Machida M, Nakamura T, K Uenishi, H Chiyo, et al. (2019) Increased Sylvian fissure angle as earl sonographic sign of malformation of cortical development. Ultrasound Obstet Gynecol 54: 199-206.

27. Poon L, Sahota D, Chaemsaithong P, T Nakamura, M Machida, et al. (2019) Transvaginal three-dimensional ultrasound assessment of Sylvian fissures at 18-30 weeks' gestation. Ultrasound Obstet Gynecol 54: 190-8.

28. Padilla N, Falcónd C, Sanz-Cortés M, Francesc Figueras, Núria Bargallo, et al. (2011) Differential effects of intrauterine growth restriction on brain structure and development in preterm infants: a magnetic resonance imaging study. Brain Res 1382: 98-108.

29. Jarvis S, Glinianaia SV, Torrioli MG, Mary-Jane Platt, Maria Miceli, et al. (2003) Cerebral palsy and intrauterine growth in single births: european collaborative study. Lancet 362: 1106-11.

30. Miller S, Huppi P, Mallard C (2016) The consequences of fetal growth restriction on brain structure and neurodevelopmental outcome. J Physiol. 594: 807-23.