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Original Research

Longitudinal evolution of Central Nervous System anomalies in fetuses with open spina bifida fetoscopic repair and correlation with neurological outcome

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AJOG AT A GLANCE

A. Why was this study conducted?

- Central nervous system anomalies such as abnormal corpus callosum have been reported in around half of cases with open spina bifida before surgery.
- No data concerning the effect of open spina bifida prenatal repair in the central nervous system anomalies have been reported.
- An evaluation of the relationship between prenatal central nervous system anomalies and postnatal neurological outcomes would be beneficial for prenatal counseling.

B. What are the key findings?

- Prenatal repair of open spina bifida does not have any effect on the proportion of anomalies in the corpus callosum.
- Combination of abnormal corpus callosum and severe ventriculomegaly ($\geq$ 15mm) is associated with worst postnatal neurodevelopment outcomes.

C. What does this study add to what is already known?

- The combination of abnormal corpus callosum and severe ventriculomegaly ($\geq$ 15mm) is associated to a two-folds increased risk of suboptimal neurodevelopment.
- This information could be of interest in presurgical counseling.

ABSTRACT

Background: Open spina bifida (OSB) is associated with Central Nervous System anomalies, as abnormal Corpus callosum (CC) and heterotopias. However, the impact of prenatal surgery over these structures remains unclear.

Objectives: To describe longitudinal changes of Central Nervous System anomalies before and after prenatal OSB repair, and to evaluate their relationship with postnatal neurological outcomes.

Study Design: Retrospective cohort study of fetuses with OSB who underwent Percutaneous fetoscopic repair from January 2009 to August 2020. All women had pre- and postsurgical fetal Magnetic Resonance (MR), with an average of one week prior and four weeks after surgery, respectively. We evaluated defect characteristics in the presurgical MR; fetal head biometry, clivus supra-occiput angle, and the presence of structural CNS anomalies, as abnormalities in CC, heterotopias, ventriculomegaly (VMG), and hindbrain herniation (HBH) in both pre- and postsurgical MR. Neurological assessment was performed using the Pediatric Evaluation of Disability Inventory (PEDI) scale in children with 12-months or older, covering three different sections: self-care, mobility, and social/cognitive function.

Results: Forty-six fetuses were evaluated. Pre-and post-surgery MR were performed at a median GA of 25.3 and 30.6 weeks, with a median interval of 0.8 weeks prior surgery, and 4.0 weeks after surgery. There was a 70% reduction in HBH (100% vs. 32.6%, p<0.001), and a normalization of the clivus supra-occiput angle after surgery (55.3 (48.8,61.0) vs. 79.9 (75.2,85.4), p<0.001). No significant increase in abnormal CC (50.0% vs. 58.7%, p=0.157) or heterotopia (10.8% vs. 13.0%, p=0.706) was observed. Ventricular dilation was higher after surgery (15.6 (12.7,18.1) vs. 18.8 (13.7,22.9) mm, p<0.001), with a higher proportion of severe ventricular dilation after surgery (≥15mm) (52.2% vs. 67.4%, p=0.020). Thirty-four children underwent neurological assessment, with 50% presenting a global optimal PEDI result and 100% presenting a normal social/cognitive function. Children with optimal global PEDI presented a lower rate of

presurgical anomalies in CC and severe VMG. When analyzed as independent variables to global PEDI scale, the presence of abnormal CC and severe VMG showed an Odds-Ratio of 27.7 (p=0.025, CI 1.53-500.71) for a suboptimal result.

Conclusions: Prenatal OSB repair did not change the proportion of abnormal CC nor heterotopias after surgery. The combination of presurgical abnormal CC and severe ventricular dilation (≥ 15 mm) is associated with an increased risk of suboptimal neurodevelopment.

KEY WORDS

Spina bifida; Central Nervous System; Fetal surgery; Neurological assessment; Brain; Magnetic Resonance Imaging

INTRODUCTION

Open spina bifida (OSB) is the most common neural tube defect, affecting up to 0.5% of pregnant women worldwide (1,2). In 2011, after the Management of Myelomeningocele Study (MOMS) results, prenatal surgery was defined as the gold standard for OSB repair (3). MOMS follow-up studies showed a significant reduction of postnatal cerebrospinal fluid (CSF) diversion, and better mental and motor function development up to 5 years of age (3–5), confirmed by other series (6–9). Since then, studies have mainly focused in the need for shunting and motor function evolution (10–13), whilst fetal CNS structures and its association with neurodevelopment remained poorly investigated (14–16).

In prenatal life, OSB is associated to hindbrain herniation, resulting in brain changes named Chiari II malformation. Ventriculomegaly (17) is part of Chiari II and can require CSF diversion after birth (18,19). In addition, other CNS anomalies have been reported as part of the OSB spectrum, mainly in long-term studies with 75% of cases with

abnormal corpus callosum (CC) and abnormalities in cortical development (20–23), both related to poorer cognitive and motor outcomes (24,25). Periventricular heterotopias are also part of the OSB spectrum and postnatal studies have associated them to certain neurological impairment and seizures (26,27). There is scarce data about fetal period, but some reports demonstrated that these changes are already present before birth (15,26–31), although their development remains unclear. In addition, little is known about the influence of prenatal repair and whether these anomalies can be related to this postnatal outcome.

The objective of our study was to describe longitudinal changes of CNS anomalies before and after prenatal OSB repair, and to evaluate their relationship with postnatal neurological outcomes.

MATERIAL AND METHODS

The study was approved by the Ethics Committee of Hospital Israelita Albert Einstein in Sao Paulo, Brazil, under the number SGPP-3715-19. The manuscript writing followed the STROBE guidelines for observational studies.

Study population

This was a retrospective cohort study of 49 fetuses with OSB who underwent fetoscopic repair from January 2009 to August 2020. All women had pre- and postsurgical fetal Magnet Resonance (MR) assessment, with an average of one week prior and four weeks after surgery, respectively. Inclusion criteria were similar to MOMS trial (3), except that there was no upper limit for gestational age (GA). Fetuses with low quality images that could jeopardize their brain structures evaluation were excluded (n= 3).

Operating team

Since 2013, surgeries were always performed by the same experienced team of fetal medicine specialists (32) and an experienced laparoscopic gynecological surgeon.

Image acquisition

Fetal MR was performed without fetal sedation and according to the American College of Radiology guidelines for MR during pregnancy and lactation (33). Images were obtained in the three orthogonal planes for the brain, while spinal images were acquired in axial and sagittal planes, using two 1.5 Tesla scanners (Optima, GE Healthcare, Waukesha, WI, USA, and Espree, Siemens Healthineers AG, Erlangen,

Germany), with 8-channel body coils. Acquisitions were as follows: GE scanner was a single-shot fast spin echo (SSSE) T2-weighted sequences (TR 2825 milliseconds (ms), TE 200 ms, FOV 350 millimeters (mm) and matrix 288x256), and Siemens scanner was a Half Fourier Acquisition Single Shot Turbo Spin Echo (HASTE) T2 weighted sequence (TR 1000 ms, TE 85 ms, FOV 370 mm and matrix 256 x 205). The slice thickness varied according to gestational age: 3.0 mm (<28 weeks) and 4.0 mm (>28 weeks), with no gaps. Images were assessed by a trained obstetrician and reviewed by an expert Neuroradiologist.

Image analysis

In the presurgical MR, we determined the upper level of the lesion (ULL) defined as the highest vertebral level affected in a midsagittal image of the spine, as previously described (34). We divided the ULL in three groups: thoracic-L2 (group 1), L3-L4 (group 2), and L5-sacral (group 3). We also characterized the defect in myelomeningocele (MMC) or myeloschisis (MS), according to the presence/absence of a cyst. Finally, the defect area was obtained by multiplying its largest sagittal and axial diameters by ∏ and divided by 4.

At both pre- and postsurgical MR, we assessed the presence of structural CNS anomalies at different levels including *cavum septum pellucidum* (CSP) and *corpus callosum* (CC) anomalies, nodular heterotopias, ventriculomegaly, aqueduct stenosis, hindbrain herniation (HBH), and interhemispheric cyst. In addition, we performed anatomical measurements of biparietal diameter (BPD), occipitofrontal diameter (OFD), transverse cerebellar diameter (TCD), HBH, clivus-supra-occiput angle (CSA), and lateral ventricles, as previously described (31). Diameters were transformed into z-

scores according to a standard reference for fetal MR biometry (35) and HBH was represented as negative values when below the foramen magnum, and positive when above.

Neurological assessment

We performed the Pediatric Evaluation of Disability Inventory (PEDI) scale, translated and validated in Portuguese (36). The PEDI scale consists of a questionnaire of 197 questions that cover self-care (73 questions), mobility (59 questions) and social function/cognitive domains (65 questions) for children from 6 months to 7.5 years. It has been used worldwide as an important tool to identify functional independence delays or impairments (36–42). All questions are answered by the child's caregiver and describe the child as unable (score 0) or capable (score 1) of performing each task. For each section (self-care, mobility, and social function), the total score is normalized for the expected score according to their age, generating a final normative score. This score is considered optimal for the child's age when $\geq$ 30, and suboptimal when < 30. Finally, a PEDI scale is considered as optimal for the child's age when at least 2 out of 3 final scores have been classified as optimal.

The PEDI was applied by a certified occupational therapist in two moments of the study. Initially, the interviews were done during the Spina Bifida Marathon in September 2019, at the Hospital Israelita Albert Einstein, Sao Paulo, Brazil. Due to COVID-19 pandemic, the second half of interviews were done online, by means of Zoom meeting platform (©2020 Zoom Video Communications, Inc), in those children who were at least 12-months of age.

Statistical Analysis

Data were stored and analyzed using STATA (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP). Categorical variables are presented as number of cases and percentage and were compared by means of McNemar test when comparing pre- and postsurgical findings for each individual. Pearson's X^2 or Fisher's exact test were used in sub-analysis groups, when appropriate. Continuous variables are presented in median and interquartile range and were compared by Wilcoxon signed-rank test to compare quantitative data. Multiple logistic regression was done to obtain independent variables associated to neurodevelopmental scale results. To rule out high correlations between groups, tetrachronic correlation for binary variables was adopted. A p-value < 0.05 was set as statistically significant.

RESULTS

Table 1 describes population characteristics. Sixty-three percent of our cases (29/46) were operated at a GA over 26 weeks. Pre and postsurgical MR were performed at a median (IQR) GA of 25.3 (23.9,26.9) and 30.6 (29.7,31.6) weeks, respectively and with a median interval of 0.8 (0.4,1.8) weeks prior surgery and 4.0 (3.6,4.6) weeks after surgery.

Table 2 summarizes the CNS findings in both pre- and postsurgical MR. All cases presented presurgical HBH, with a significant reduction of herniation post-surgery (100% vs. 32.6%, p<0.001). No significant changes were observed among CNS anomalies, such as abnormal CC (50.0% vs. 58.7%, p=0.157), heterotopias (10.9% vs. 13.0%, p=0.706), abnormal ventricular wall contour (30.2% vs. 32.6%, p=0.796) or abnormal CSP (32.6% vs. 41.3%, p=0.157), neither when considering abnormal CC and/or heterotopias together, as the major CNS anomalies (26 (56.5%) vs. 31 (67.4%), p=0.140). After surgery, fetuses presented a wider CSA (55.3 (48.8,61.0) vs. 79.9 (75.2,85.4), p<0.001), and larger lateral ventricles (15.6 (12.7,18.1) mm vs. 18.8 (13.7,22.9), p<0.001), with a higher proportion of severe ventricular dilation ($\geq$ 15 mm) (52.2% vs. 67.4%, p=0.020). Finally, when comparing CNS anomalies between those operated under and after 26 weeks, no significant difference was found concerning abnormal CC (p=0.737) or heterotopias (p=0.369).

Neurological assessment was performed in all children with at least 12 months (n = 34), as shown in **Table 3**. Fifty percent of the children presented a global optimal neurological assessment, and 100% of the children had normal social/cognitive

function. Children with an optimal global PEDI result presented lower rate of postnatal CSF diversion during the first year of their lives (23.5% vs. 70.6%, p=0.022). Prenatal CNS findings and postnatal characteristics according to PEDI results are shown in **Supplementary Table 1**. Children with an optimal global PEDI result had smaller presurgical lateral ventricles (13.4 (12.7,18.1) mm vs. 16.2 (13.1,18.9) mm, p=0.027), and lower proportion of severe ventriculomegaly (35.3% vs. 58.8%, p=0.025) and CC anomalies (35.3% vs. 64.7%, p=0.033).

We explored the relation between global PEDI result and the presence of severe VMG and/or abnormal CC. Multiple logistic regression showed that the presence of both presurgical abnormal CC and severe VMG increases the risk for a suboptimal global PEDI scale result (OR 27.70, p=0.025, IC 1.53-500.71), whereas if only one of them is present this association disappears (OR 9.36, p=0.094, IC 0.69-127.72) (**Supplementary Table 2**). Finally, we have explored whether abnormal CC and severe VMG were correlated, as occurs in cases with primary CC anomaly, but tetrachronic correlation showed a correlation index of 0.345, not supporting this correlation.

COMMENT

PRINCIPAL FINDINGS

This study demonstrated that proportion of CNS anomalies associated to OSB including abnormal CC and heterotopias did not change after prenatal repair. In addition, we found that the isolated diagnosis of abnormal CC was not associated with increased risk of suboptimal neurodevelopment, but the combination of presurgical abnormal CC and severe ventricular dilation increased its risk significantly.

REVIEW IN THE CONTEXT OF WHAT IS KNOWN

Our results are in line with previous data showing that half of OSB fetuses had abnormal CC which were already identified during presurgical MR (28,31,43,44) with no significant increase in postsurgical MR. As for heterotopias, cases varied from 10.9% presurgical to 13.0% postsurgical, also in line with previous data (44). This non-significant increase could be expected by the improvement of imaging quality due to more advanced GA and in regard to heterotopias, also due to the natural history of this condition being more apparent in latter stages.

All our fetuses presented presurgical HBH, and almost 70% of them showed a complete reversion after surgery. This is in line with previous data regarding fetal surgery for spina bifida in animal models, single center experiences, and the MOMS trial (3,8,32,45–48). We also identified a more acute clivus supra-occiput angle in the presurgical MR (55.3 ± 12.1^{o}), as described by D'Addario et al (49) in fetuses with CIIM and Woitek et al (50) in fetus with OSB. Interestingly, in our cohort, the CSA normalized after surgery, reaching an angle of 79.9 ± 10.2^{o}, even performing repair in

later GA. Both HBH reversal and CSA normalization reinforced the benefits of a later OSB fetoscopic repair even in this group of fetuses.

Finally, ventricular size increased after surgery in our population, similar to previous data (19,48,51). Recently data has shown that prenatal OSB repair does not slow the progression of ventriculomegaly (52). Fetuses who undergo prenatal repair may have a sudden increase in ventricular size immediately after surgery, whereas those postnatally repaired have an increase of their ventricular size around 30 weeks of gestation (52). Presurgical severe VMG showed to be an important marker for the need of postnatal CSF diversion, as also showed by Tulipan et al (53). This severe VMG was more prevalent in myelomeningocele fetuses (91.3% vs. 63.6%, p=0.035) who presented increased HBH (-12.0 (-13.7,-9.9) vs. -8.6 (-11,-5.9), p=0.004). Our presurgical findings agreed with Zarutskie et al(19), that highlighted these parameters as important presurgical markers for postnatal hydrocephalus treatment (19). In our population, 68.8% (11/16) of the severe VMG ($\geq$ 15 mm) and only 27.8% (5/18) of the non-severe VMG fetuses underwent a CSF diversion within the first year of their lives (p=0.017). Interestingly, the pre- and post-surgical lateral ventricle range was wider in fetuses that already had severe VMG prior to surgery (4.0 (2.6,5.3) vs. 2.1 (0.3,3.4), p=0.030), in agreement with Zarutskie et al (19).

Regarding neurodevelopment, although we have a slightly higher rate of suboptimal results in comparison to other series (9,54), this does not represent the entire cohort of patients, but only those with pre- and post-surgical MR. In addition, all children included in the study had an optimal cognitive function according the neurodevelopment scale. Children with a suboptimal neurodevelopment presented higher proportion of abnormal CC, reinforcing the already described relation of an

abnormal CC and some neurological impairment (25,55). In addition, the combination of both presurgical severe VMG and abnormal CC resulted in a higher risk of abnormal neurodevelopment, which was also reported by Li et al (56), that showed a significant increase of moderate to severe suboptimal neurodevelopment in children with CC abnormalities and VMG in comparison to those with isolated CC abnormalities (67% vs 7%, p=0.003).

CLINICAL APPLICATIONS

Our findings stress the importance of a detailed presurgical scan, which will allow us to diagnose CNS anomalies and give a more personalized prenatal counseling in each case.

The diagnosis of severe VMG or abnormal CC at presurgical MR does not contraindicates fetal surgery, but its combination is more associated with suboptimal neurodevelopmental outcome and should be considered in the decision-making process with the parents. In addition, we have shown that a prenatal repair of OSB beyond 26 weeks is not related to a significant increase in CNS anomalies as compared with other series (29,31,43), including abnormal CC and heterotopias. As improvements in ambulation and reduction of CSF diversion and bladder catheterization have already been shown in this profile of patients (57), our findings reinforce that the neuroprotection of the procedure is not affected in fetuses operated beyond the standard age of the MOMS trial (19-25.9 weeks). The concept of "the earlier the better" may not apply for risk of CSF deviation, and operating after 26 weeks avoids the risk of extreme premature birth.

STRENGHTS AND LIMITATIONS

Our study has some limitations that must be taken into consideration. First, the time range between our first and last OSB was of 10 years. This is due to the difficulty of managing patients and the impossibility of performing MR scan as protocol in some cases, due to financial and/or geographical matters in Brazil, preventing inclusion of all cases managed in the center. As a retrospective analysis, in which all cases were operated using the same technique (SAFER technique), our results may not be extrapolated to other techniques. Moreover, when analyzing our postnatal outcomes in children with at least 12-months, only 34 out of our 46 children had reached that age, reducing the final population for statistical analysis, with a follow-up rate of 73.9%. The main strength of our study is that it is the first that has analyzed the longitudinal evolution of pre- and postsurgical CNS anomalies and its correlation with postnatal neurological outcomes.

CONCLUSIONS

We have shown that prenatal OSB repair did not change the proportion of abnormal CC nor heterotopias associated to this condition. We have also demonstrated that the combination of presurgical abnormal CC and severe ventricular dilation is associated with higher risk of suboptimal neurodevelopment. Further studies evaluating long-term results of SAFER exploring the specific effect of early versus late repair, aiming to reduce the risk of extreme prematurity, are warranted.

REFERENCES

1. Atta CAM, Fiest KM, Frolkis AD, et al. Global birth prevalence of spina bifida by folic acid fortification status: A systematic review and meta-analysis. Am J Public Health. 2016;106(1):e24–34.

2. Khoshnood B, Loane M, De Walle H, Arriola L, Addor MC, Barisic I, et al. Long term trends in prevalence of neural tube defects in Europe: Population based study. BMJ. 2015;351:1–6.

3. Adzick N, Thom E, Spong C, et al. A Randomized Trial of Prenatal versus Postnatal Repair of Myelomeningocele. N Engl J Med. 2011;364(11):1959–68.

4. Farmer DL, Thom EA, Brock JW, et al. The Management of Myelomeningocele Study: full cohort 30-month pediatric outcomes. Am J Obstet Gynecol. 2018;218(2):256.e1-256.e13.

5. Houtrow AJ, Macpherson C, Jackson-coty J, et al. Prenatal Repair and Physical Functioning Among Children With Myelomeningocele A Secondary Analysis of a Randomized Clinical Trial. JAMA Pediatr. 2021;Apr;1;175(4):e205674.

6. Moldenhauer JS, Soni S, Rintoul NE, et al. Fetal Myelomeningocele Repair: The Post-MOMS Experience at the Children's Hospital of Philadelphia. Fetal Diagn Ther. 2015 Apr;37(3):235–40.

7. Flanders TM, Madsen PJ, Pisapia JM, et al. Improved Postoperative Metrics with Modified Myofascial Closure in Fetal Myelomeningocele Repair. Oper Neurosurg. 2019 Jun;18(2):158–65.

8. Belfort MA, Whitehead WE, Shamshirsaz AA, et al. Comparison of two fetoscopic open neural tube defect repair techniques: single- vs three-layer closure. Ultrasound Obstet Gynecol. 2020;56(4):532–40.

9. Diehl D, Belke F, Axt-Fliedner R, et al. Intrauterine total percutaneous fetoscopic repair of myelomeningocele: 30 months follow up data. Ultrasound Obstet Gynecol. 2020;(May 2020):113–8.

10. Pedreira DA, Reece EA, Chmait RH, Kontopoulos E V, Quintero RA. Fetoscopic

repair of spina bifida: safer and better? Ultrasound Obs Gynecol. 2016;48(2):141–7.

11. Corroenne R, Zarutskie A, Guimaraes C, Yepez M, Torres P, Shetty AN, et al. VP21.08: Can ventriculomegaly and hindbrain herniation seen before and after prenatal neural tube defect repair predict a poor motor function at birth? Ultrasound Obstet Gynecol. 2020;56(S1):146–146.
12. Corroenne R, Yepez M, Pyarali M, et al. Longitudinal evaluation of motor function in patients who underwent a prenatal or postnatal neural tube defect repair. Ultrasound Obstet Gynecol. 2021;Aug;58(2):221-229.
13. Corroenne R, Yepez M, Pyarali M, et al. Prenatal predictors of motor function in children with open spina bifida: a retrospective cohort study. BJOG An Int J Obstet Gynaecol. 2021;128(2):384–91.
14. Inversetti A, Van der Veeken L, Thompson D, et al. Neurodevelopmental outcome of children with spina bifida aperta repaired prenatally vs postnatally: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2019;53(3):293–301.
15. Sanz Cortes M, Torres P, Yepez M, et al. Comparison of brain microstructure after prenatal spina bifida repair by either laparotomy-assisted fetoscopic or open approach. Ultrasound Obstet Gynecol. 2020;55(1):87–95.
16. Houtrow AJ, Thom EA, Fletcher JM, et al. Prenatal repair of myelomeningocele and school-age functional outcomes. Pediatrics. 2020; Feb;145(2):e20191544.
17. Joyeux L, Danzer E, Flake AW, Deprest J. Fetal surgery for spina bifida aperta. Arch Dis Child Fetal Neonatal Ed. 2018;103(6):F589–95.
18. Khalil A, Caric V, Papageorghiou A, Bhide A, Akolekar R, Thilaganathan B.

Prenatal prediction of need for ventriculoperitoneal shunt in open spina bifida. Ultrasound Obstet Gynecol. 2014;43(2):159–64.

19. Zarutskie A, Guimaraes C, Yepez M, et al. Prenatal brain imaging for predicting need for postnatal hydrocephalus treatment in fetuses that had neural tube defect repair in utero. Ultrasound Obstet Gynecol. 2019;53(3):324–34.
20. Juranek J, Fletcher JM, Hasan KM, et al. Neocortical Reorganization in Spina Bifida. Neuroimage. 2008;40(4):1516–22.
21. Treble A, Juranek J, Stuebing KK, Dennis M, Fletcher JM. Functional significance of atypical cortical organization in spina bifida myelomeningocele: Relations of cortical thickness and gyrification with IQ and fine motor dexterity. Cereb Cortex. 2013;23(10):2357–69.
22. Kulesz PA, Treble-Barna A, Williams VJ, et al. Attention in spina bifida myelomeningocele: Relations with brain volume and integrity. NeuroImage Clin. 2015;8:72–8.
23. McLone DG, Dias MS. The Chiari II malformation: Cause and impact. Child's Nerv Syst. 2003;19(7–8):540–50.
24. Ware AL, Kulesz PA, Juranek J, Cirino PT, Fletcher JM. Cognitive control and associated neural correlates in adults with spina bifida myelomeningocele. Neuropsychology. 2017;31(4):411–23.
25. Juranek J, Salman MS. Anomalous development of brain structure and function in spina bifida myelomeningocele. Dev Disabil Res Rev. 2010;16(1):23–30.
26. Nagaraj UD, Peiro JL, Bierbrauer KS, Kline-Fath BM. Evaluation of Subependymal gray matter heterotopias on fetal MRI. Am J Neuroradiol. 2016;37(4):720–5.
27. Rethmann C, Scheer I, Meuli M, Mazzone L, Moehrlen U, Kellenberger CJ.

Evolution of posterior fossa and brain morphology after in utero repair of open neural tube defects assessed by MRI. Eur Radiol. 2017;27(11):4571–80.

28. Kunpalin Y, Thompson D, David AL, Deprest J. Cranial findings detected by second trimester ultrasound in fetuses with myelomeningocele: a systematic review. BJOG An Int J Obstet Gynaecol. 2021; Jan;128(2):366-374.

29. Kunpalin Y, Deprest J, Papastefanou I, et al. Incidence and patterns of abnormal corpus callosum in fetuses with isolated spina bifida aperta. Prenat Diagn. 2021;Jul;41(8):957-964.

30. Mufti N, Sacco A, Aertsen M, et al. VP28.09: What brain abnormalities can magnetic resonance imaging detect in fetal and early neonatal spina bifida: a systematic review. Ultrasound Obstet Gynecol. 2020;56(S1):180.

31. Trigo L, Eixarch E, Bottura I, Dalaqua M, Barbosa AA, De Catte L, et al. Prevalence of supratentorial anomalies assessed by fetal magnetic resonance in fetuses with open spina bifida. Ultrasound Obstet Gynecol. 2021;0–3.

32. Pedreira DAL, Zanon N, Nishikuni K, Moreira De Sá RA, Acacio GL, Chmait RH, et al. Endoscopic surgery for the antenatal treatment of myelomeningocele: The CECAM trial. Am J Obstet Gynecol. 2016;214(1):111.e1-111.e11.

33. Tremblay E, Thérasse E, Thomassin-Naggara I, Trop I. Guidelines for use of medical imaging during pregnancy and lactation. (Quality initiatives). Radiographics. 2012;32(3):897–911.

34. Chao TT, Dashe JS, Adams RC. Fetal spine findings on MRI and associated outcomes in children with open neural tube defects. Am J Roentgenol. 2011;197(5):956–61.

35. Kyriakopoulou V, Vatansever D, Davidson A, et al. Normative biometry of the

fetal brain using magnetic resonance imaging. Brain Struct Funct. 2017;222(5):2295–307.

36. Mancini M. Inventário de Avaliação Pediátrica de Incapacidade (PEDI). UFMG. Belo Horizonte; 2005.

37. Al-Khudair RI, Al-Eisa E. Applicability of the pediatric evaluation of disability inventory among Saudi children. Disabil Rehabil. 2014;36(8):658–64.

38. Mancini MC, Coster WJ, Amaral MF, Avelar BS, Freitas R, Sampaio RF. New version of the pediatric evaluation of disability inventory (PEDI-CAT): Translation, cultural adaptation to Brazil and analyses of psychometric properties. Brazilian J Phys Ther. 2016;20(6):561–70.

39. Onogi K, Kondo I, Asagai Y. Differences in evaluation of functional skills of the Pediatric Evaluation of Disability Inventory (PEDI) between normally developing children and children with cerebral palsy. Japanese J Compr Rehabil Sci. 2017;8:37–43.

40. Amer A, Kakooza-Mwesige A, Jarl G, et al. The Ugandan version of the Pediatric Evaluation of Disability Inventory (PEDI-UG). Part II: Psychometric properties. Child Care Health Dev. 2018;44(4):562–71.

41. Tofani M, Galeoto G, Cazzetta D, Berardi A, Sansoni J, Valente D. Validation of the pediatric evaluation of disability inventory in an Italian population with autism spectrum disorder: A cross-sectional study. Clin Ter. 2019;170(6):E460–4.

42. Schulze C, Meichtry A, Page J, Kottorp A. Psychometric properties of the German Version of the Pediatric Evaluation of Disability Inventory (PEDI-G): A factor analysis. Scand J Occup Ther. 2019;0(0):1–10.

43. Sanz Cortes M, Guimaraes C, Yepez M, et al. OC14.04: Brain abnormalities in

fetuses and infants that underwent a prenatal neural tube defect (NTD) repair using a fetoscopic and open approach. Ultrasound Obstet Gynecol. 2018;52(S1):33–4.

44. Maurice P, Garel J, Garel C, et al. New insights in cerebral findings associated with fetal myelomeningocele: a retrospective cohort study in a single tertiary centre. BJOG An Int J Obstet Gynaecol. 2020;1–8.

45. Bouchard S, Davey MG, Rintoul NE, et al. Correction of hindbrain herniation and anatomy of the vermis after in utero repair of myelomeningocele in sheep. J Pediatr Surg. 2003;38(3):451–8.

46. Lapa Pedreira DA, Quintero RA, Acácio GL, Espin Garcia Caldini ET, Nascimento Saldiva PH. Neoskin development in the fetus with the use of a three-layer graft: An animal model for in utero closure of large skin defects. J Matern Neonatal Med. 2011;24(10):1243–8.

47. Pedreira DAL, Zanon N, De Sá RAM, et al. Fetoscopic single-layer repair of open spina bifida using a cellulose patch: Preliminary clinical experience. J Matern Neonatal Med. 2014;27(16):1613–9.

48. Flanders TM, Heuer GG, Madsen PJ, et al. Detailed Analysis of Hydrocephalus and Hindbrain Herniation after Prenatal and Postnatal Myelomeningocele Closure: Report from a Single Institution. Neurosurgery. 2020;86(5):637–45.

49. D'Addario V, Pinto V, Del Bianco A, et al. The clivus-supraocciput angle: A useful measurement to evaluate the shape and size of the fetal posterior fossa and to diagnose Chiari II malformation. Ultrasound Obstet Gynecol. 2001;18(2):146–9.

50. Woitek R, Dvorak A, Weber M, et al. MR-based morphometry of the posterior fossa in fetuses with neural tube defects of the Spine. PLoS One. 2014;9(11).

51. Lu VM, Snyder KA, Ibirogba ER, Ruano R, Daniels DJ, Ahn ES. Progressive hydrocephalus despite early complete reversal of hindbrain herniation after prenatal open myelomeningocele repair. Neurosurg Focus. 2019;47(4):1–6.

52. Donepudi R, Brock C, Schulte S, et al. Trend in ventricle size during pregnancy and its use for prediction of ventriculoperitoneal shunt in fetal open neural tube defect. Ultrasound Obstet Gynecol. 2020;56(5):678–83.

53. Tulipan N, Wellons II JC, Thom EA, et al. Prenatal surgery for myelomeningocele and the need for cerebrospinal fluid shunt placement. J Neurosurg Pediatr. 2015;December;(6):613–620.

54. Johnson MP, Gerdes M, Rintoul N, et al. Maternal-fetal surgery for myelomeningocele: Neurodevelopmental outcomes at 2 years of age. Am J Obstet Gynecol. 2006;194(4):1145–50.

55. Margari L, Palumbi R, Campa MG, et al. Clinical manifestations in children and adolescents with corpus callosum abnormalities. J Neurol. 2016;263(10):1939–45.

56. Li Y, Estroff J, Khwaja O, et al. Callosal dysgenesis in fetuses with ventriculomegaly: levels of agreement between imaging modalities and postnatal outcome. Ultrasound Obstet Gynecol. 2012;40(5):522–9.

57. Lapa DA, Chmait RH, Gielchinsky Y, et al. Percutaneous fetoscopic spina bifida repair: effect on ambulation and need for postnatal cerebrospinal fluid diversion and bladder catheterization. Ultrasound Obstet Gynecol. 2021;Oct;58(4):582-589.

CONDENSATION

The proportion of central nervous system anomalies such as abnormal corpus callosum and heterotopias does not change after fetoscopic repair of open spina bifida.

Declaration of Competing Interest

The authors report no conflict of interest.

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Table 1. Maternal and fetal characteristics

Maternal characteristics	
Age (years)	32.6 (27.4,34.8)
Caucasian, n (%)	31 (67.4)
Preconceptionally folic acid usage, n (%)	22 (47.8)
Number of previous pregnancies	0 (0-1)
Diabetes, n (%)	1 (2.2)
Hypothyroidism, n (%)	5 (10.9)
Fetal characteristics	
Gestational age at presurgical MRI (weeks)	25.3 (23.9,26.9)
Gestational age at surgery (weeks)	26.5 (25.6,27.5)
Gestational age at postsurgical MRI (weeks)	30.6 (29.7,31.6)
Gestational age at birth (weeks)	33.9 (32.9,35.1)
Male sex, n (%)	22 (47.8)
Bilateral prenatal clubfoot, n (%)	5 (10.9)
Type of defect, n (%)	
Myelomeningocele	36 (78.3)
Myeloschisis	10 (21.7)
Level of defect, n (%)	
T12-L2	8 (17.4)
L3-L4	21 (45.6)
L5-S1	17 (37.0)
Kyphosis, n (%)	1 (2.2)
Tethered Cord, n (%)	44 (95.7)

Data are presented in median (IQR) or number of cases (%).

Table 2. Central Nervous System findings in pre- and postsurgical fetal MR

CNS findings			
Hindbrain herniation, n (%)	46 (100.0)	15 (32.6)	**< 0.001**
Hindbrain herniation (mm)	-10.4 (-13.1,-8.2)	1.5 (-4.7,4.1)	**< 0.001**
Abnormal corpus callosum, n (%)	23 (50.0)	27 (58.7)	0.157
Abnormal ventricular contour, n (%)	13 (30.2)	14 (32.6)	0.796
Heterotopias, n (%)	5 (10.9)	6 (13.0)	0.706
Major CNS (CC/HT), n (%)	26 (56.5)	31 (67.4)	**0.140**
Abnormal cavum, n (%)	15 (32.6)	19 (41.3)	0.157
Tectal beaking, n (%)	40 (86.9)	41 (89.1)	0.739
Interhemispheric cyst	0 (0.0)	3 (6.5)	0.083
CSA (degrees)	55.3 (48.8,61.0)	79.9 (75.2,85.4)	**< 0.001**
Larger lateral ventricle (mm)	15.6 (12.7,18.1)	18.8 (13.7,22.9)	**< 0.001**
Ventricular dilation ≥ 10mm, n (%)	42 (91.3)	45 (97.8)	0.083
Ventricular dilation ≥ 15mm, n (%)	24 (52.2)	31 (67.4)	**0.020**
TCD z-score	-3.0 (-4.0,-1.3)	-2.8 (-4.6,-2.1)	0.177
BPD z-score	0.0 (-1.5,0.9)	0.6 (-1.0,1.5)	**0.020**
OFD z-score	1.8 (0.2,2.6)	3.9 (1.3,5.2)	**< 0.001**

Data are presented in median (IQR) or number of cases (%).

Table 3. Neurological assessment and characteristics in children ≥ 12 months of age.

	n = 34
Optimal PEDI scale	17 (50.0)
Optimal selfcare domain	16 (47.1)
Optimal mobility domain	5 (14.7)
Optimal social/cognitive function domain	34 (100.0)
Need of shunt	
<12 months	16 (47.1)
12-30 months	3 (8.8)
Replacement	6 (17.7)
Seizure >28 days	7 (20.6)

Data are presented in number of cases (%).