Reference charts of fetal brain structures for magnetic resonance imaging: a systematic review

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Contribution

What are the novel findings of this work?

There is a substantial heterogeneity and a low to moderate methodological quality among the included studies reporting fetal brain charts at MRI, as previously reported for ultrasound studies.

What are the clinical implications of this work?

Further large prospective studies aiming at constructing longitudinal growth charts for different fetal brain structures at MRI are needed to improve prenatal diagnosis and counseling of fetal CNS anomalies.

ABSTRACT

Objectives: To evaluate the methodology of studies reporting reference charts of fetal brain structures at magnetic resonance imaging (MRI).

Methods: MEDLINE, EMBASE, CINAHL and the Web of Science databases were searched electronically up to December 31, 2020. The primary outcome was to evaluate the methodology of the studies investigating the biometry and growth of the fetal brain. A list of 26 quality criteria divided into two domains according to either "study design", "reporting and statistical methods" and "specific relevant MRI aspects" was developed to evaluate the methodological appropriateness of the included studies. The overall quality score was defined as the sum of risk of bias marks, with the range of possible scores being 0–26, and then expressed as a percentage (the lowest the percentage, the highest the risk of bias). This quality assessment was applied to each individual study reporting reference ranges of fetal brain structures at MRI.

Results: Fifteen studies were included. The overall mean quality score of the studies evaluated in this review was 48.7%. When focusing on each domain, the mean quality score was 42% for "study design", 59.4% for "statistical and reporting methods" and 33.3% for "specific relevant MRI aspects". For the "study design" domain, the sample size calculation and the consecutive enrollment of women were the items found at the highest risk of bias. For the "statistical and reporting methods" domain, the presence of regression equations for mean and SD for each measurement, the number of measurements taken for each variable and the presence of postnatal assessment information were the items found at the highest risk of bias. For the "specific relevant MRI aspects" domain, a whole fetal brain assessment was performed in none of the included studies and therefore was considered as the item at the highest risk of bias.

Conclusions: Most of the previously published charts evaluating fetal brain charts at MRI show a high heterogeneity and a low to moderate quality in terms of methodology, as already reported for ultrasound.

INTRODUCTION

Advances in prenatal diagnostic techniques have allowed a more comprehensive assessment of fetal brain anatomy. Ultrasound is commonly used as the primary tool to assess the fetal central nervous system (CNS), while fetal magnetic resonance (MRI) is performed to confirm the diagnosis and to look for associated anomalies which might impact the short- and long-term prognosis of these children.[1-5]

Despite this, the actual role of fetal MRI has been subject of debate for a long time, with several studies reporting a higher diagnostic accuracy of fetal MRI compared to ultrasound in detecting CNS anomalies while others reporting a negligible contribution of such technique in assessing brain anatomy. We have recently reported that MRI is a fundamental diagnostic tool to assess fetal anatomy following a detailed ultrasound assessment (the so called "neurosonography") of the brain in case of suspected fetal anomalies and that integration of the two techniques is warranted to improve the predictive accuracy of CNS malformations prenatally.[6-7]

Apart from the assessment of the morphology, biometric evaluation of brain structures is a fundamental part of both the screening and detailed assessment of fetal CNS. Several CNS anomalies are suspected based on a reduced size of a given brain structure, such as microcephaly, cerebellar vermis or corpus callosum hypoplasia. We have recently reported that most previously published studies reporting ultrasound fetal brain charts suffers from poor methodology and are at high risk of bias.[8]

Of note, the methodological robustness of fetal brain MRI charts has yet to be elucidated. Regardless of the imaging technique, previous studies showed that suboptimal methodology when focusing on fetal size charts is likely to hamper the possibility of discriminating the healthy from pathological conditions, thus highlighting the intuitive importance of standardization and quality control also for the assessment of fetal brain structures.[9]

The aim of this systematic review was to evaluate the methodological consistency of studies reporting reference charts for the different fetal brain structures at MRI.

METHODS

Protocol, information sources and literature search

This systematic review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis.[10-12] MEDLINE, EMBASE, CINAHL and the Web of Science databases were searched electronically up to December 31, 2020 using the following search terms (as words in the title/abstract), combined in various strings: (1) fetal brain charts OR fetal brain reference range OR fetal brain measurement* OR fetal brain biometry OR fetal brain growth OR fetal brain nomogram* OR fetal brain curve*; (2) corpus callosum reference range OR corpus callosum reference charts OR corpus callosum measurement* OR corpus callosum biometry OR corpus callosum growth OR corpus callosum nomogram* OR corpus callosum curve*; (3) cerebellum reference range OR cerebellum reference charts OR cerebellum measurement* OR cerebellum biometry OR cerebellum growth OR cerebellum nomogram* OR cerebellum curve*; (4) cavum septi pellucidi reference range OR cavum septi pellucidi reference charts OR cavum septi pellucidi measurement* OR cavum septi pellucidi biometry OR cavum septi pellucidi growth; (5) cisterna magna reference range OR cisterna magna reference charts OR cisterna magna measurement* OR cisterna magna biometry OR cisterna magna growth; (6) thalamus reference range OR thalamus reference charts OR thalamus measurement* OR thalamus biometry OR thalamus growth OR thalamus nomogram*; (7) brain ventricle reference range OR brain ventricle reference charts OR brain ventricle biometry OR brain ventricle growth; sylvian fissure measurement*; parieto-occipital fissure measurement*.

The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA guidelines were followed.[13-15]

Outcomes measures, study selection and data collection

The primary aim of this systematic review was to evaluate the methodology of the studies reporting the growth of different fetal brain structures at MRI throughout gestation.

In particular, the biometry data variables assessed were:

- biparietal diameter (BPD)
- fronto-occipital diameter (FOD)
- transverse cerebellar diameter (TCD)
- vermis height
- anteroposterior diameter of the vermis
- cerebellar volume
- cisterna magna width

- width of the posterior horn of the lateral ventricle
- third ventricle width
- cavum septi pellucidi length
- cavum septi pellucidi width
- corpus callosum length (CC)
- anteroposterior diameter of the pons
- total brain volume

Observational longitudinal or cross-sectional studies reporting growth charts for different fetal brain structures were included. Case–control studies, as well as those where the primary aim was not to construct specific fetal brain structure growth charts or evaluating biometry of fetuses with already known anomalies, were excluded from the analysis.

Two authors reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus. Full text copies of those papers were obtained, and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author.

Methodological quality assessment

The methodological quality of the included studies was assessed by the same reviewers and a medical statistician. A list of methodological quality criteria (Table 1) was developed by consensus among the authors. These quality criteria are based on the available published research[16-18] and are divided into three domains: (1) study design, (2) reporting and statistical methods (3) specific relevant MRI aspects. In total, 26 quality criteria were evaluated.

This quality assessment was applied to each individual study reporting reference ranges for fetal brain structures assessed using MRI.

Data extraction and synthesis

Following the review of the included studies, all study details were entered into a dedicated Microsoft Excel 2019 spreadsheet. Every study was assessed against each of the criteria within the checklist and was scored as either 0 or 1 if there was a high or low risk of bias, respectively. The overall quality score was defined as the sum of risk of bias marks - with the range of possible scores being 0–26 – and then expressed as a percentage (the lowest the percentage, the highest the risk of bias). Statistical analyses were performed using Microsoft Excel 2019 and IBM SPSS Statistics version 20 (IBM, Armonk, NY, USA).

RESULTS

Study selection and characteristics

One-hundred and forty articles were identified, thirty were assessed with respect to their eligibility for inclusion and 15 studies were included in the systematic review (Table 2, Figure 1, Supplementary Table 1).[19-33]

These 15 studies included two cross-sectional studies,[25,29] while the type of data collection was unclear in the other 13 studies.[19-24,26-28,30-33] Eleven studies were retrospective,[19-25,28,30-31,33] two were prospective,[27,29] while the nature of two studies was unclear in two other studies.[26,32]

These studies took place in six countries, with the oldest study published in 2003[19] and the most recent ones in 2021.[33] The median sample size was 169 fetuses, with the smaller sample size including 20 fetuses[29] and the larger one 589 fetuses.[22]

Only three studies reported any data on the correlation between antenatal and postnatal imaging.[19,21-22]

Synthesis of the results

The overall mean quality score of the studies evaluated in this review was 48.7%. When focusing on each domain, the mean quality score was 42% for "study design", 59.4% for "statistical and reporting methods" and 33.3% for "specific relevant MRI aspects" (Supplementary Tables 2-4).

For the "study design" domain, the sample size calculation (item 1.05) and the consecutive enrollment of women (item 1.07) were the items found at the highest risk of bias, as these two items were reported in none of the included studies. The study design (item 1.01) and the prospective data collection (item 1.04) were also at high risk of bias, both with a quality score of 13.3% (Figure 2). The overall quality score for the "indication for MRI" item (item 1.03) was 73.3%.

For the "statistical and reporting methods" domain, the presence of regression equations for mean (and SD if relevant) for each measurement (item 2.11), the number of measurements taken for each variable (at least three measures per fetus per scan) (item 2.08) and the presence of postnatal assessment information (item 2.01) were the items found at the highest risk of bias, with a quality score of 0%, 6.7% and 26.6% (Figure 3).

Finally, for the "specific relevant MRI aspects" domain, a whole fetal brain assessment was performed in none of the included studies (item 3.01) and therefore was considered as the item at the highest risk of bias. The reported concordance between ultrasound and MRI (if reported) (item 3.02) and the concordance of imaging planes taken at US and MRI (if reported) (item 3.02) were also at high risk of bias, with a quality score of 13.3% and 20%, respectively (Figure 4). Conversely, all the

included studies provided unambiguous details of measurement technique (item 3.04), thus being at the lowest risk of bias.

DISCUSSION

Main findings

The findings from this systematic review showed that there is substantial heterogeneity and a low moderate methodological quality among the included studies reporting fetal brain charts at MRI, as previously reported for ultrasound studies. Most of these studies were retrospective and did not report any valuable information of the concordance between ultrasound and MRI, in terms of both quantitative and qualitative assessment.

Strengths and limitations

To our knowledge, this is the first systematic review assessing methodological criteria of studies reporting fetal brain charts at MRI. The robust methodology and the quality score checklist which was modified and integrated from that used in previous studies[16-18] represent the major strengths of this study.

The main limitations of this systematic review are those inherent in the included studies, and in particular the heterogeneity of the methodology and the differences among the indications for MRI, as well as the differences in MRI techniques and level of expertise of the operators in each study.

Clinical and research implications

Fetal MRI is nowadays a mainstay of prenatal imaging and diagnosis of fetal anomalies adjunct to ultrasonography, and mainly for the assessment of fetal brain development.[5]

In the last decade, the superiority of MRI over ultrasound in the detection of fetal CNS anomalies has been largely debated, after the findings of few studies reporting a significantly higher diagnostic accuracy of MRI compared to ultrasound in case of fetal brain abnormalities.[34-35]

However, these results have been subsequently questioned when fetal MRI was compared with expert neurosonography, thus demonstrating that the difference in the detection rate between MRI and ultrasound is clearly lower when focusing on two imaging modalities both requiring high levels of expertise.[1-4] Despite this, integration between the two imaging techniques is recommended for more accurate phenotyping and counselling in case of suspected CNS anomalies.

Aside from qualitative assessment, quantitative evaluation is also pivotal when focusing on fetal brain, as several in-utero developmental abnormalities are associated with a poor, postnatal neurological outcome, thus also highlighting the importance of the biometric assessment of a suspected brain structure at both ultrasound and MRI examination.

The finding from this study shows that most of the previously published charts evaluating fetal brain structures' growth at MRI share a low to moderate quality in terms of methodology, thus leading to potential risk of bias, possibly affecting prenatal diagnosis and counselling.

One possible explanation for that could be the generally rather limited access to fetal MRI and its higher overall costs. Due to limited data regarding imaging safety in fetal MRI, institutional review boards have traditionally been restrictive in allowing large prospective trials including representative cohorts of low-risk pregnancies, thus potentially explaining the low rate of consecutive inclusions of normal subjects. However, the findings from this systematic review emphasizes the importance of future prospective MRI studies, mostly aiming at assessing biometrical measurements in normal pregnancies.

Of note, the suboptimal quality was particularly noted when focusing on concordance between ultrasound and MRI quantitative and qualitative findings. In the authors' opinion, this is highly remarkable, as a potential methodological bias in a study reporting a biometric chart for a fetal brain structure may be associated with potential misdiagnoses of CNS anomalies, thus leading to inaccurate prenatal counselling. We believe that the main aim of prenatal diagnosis should be to provide an objective counselling on which parents will base their decision about the management of the pregnancy.[36-37] Therefore, the integration of ultrasound and MRI, rather than the comparison between the two techniques, should be considered as the key for an accurate anatomical evaluation of the fetus when faced with suspected CNS anomalies.

In this scenario, further studies providing a longitudinal growth assessment of fetal brain structures at MRI, sharing a rigorous methodology are needed in order to provide robust growth charts for the different fetal CNS structures in order to improve prenatal diagnosis of brain anomalies. To provide unbiased reference data, these prospective studies should ideally compare high quality neurosonography and expert fetal MRI, include only fetuses at low risk of growth impairment or CNS anomaly (i.e. normal karyotype, normal infection screening), provide the exact definition of image quality and postnatal documentation using postnatal neurocognitive tests and mostly correlate antenatal and postnatal imaging.

Conclusion

Most published charts evaluating fetal brain biometry and growth using MRI share a low to moderate methodological quality, thus leading to potential risks of bias, particularly when focusing on concordance between ultrasound and MRI quantitative and qualitative findings. Further large

prospective studies aiming at constructing longitudinal growth charts for different fetal brain structures at MRI are needed to improve prenatal diagnosis and counseling of fetal CNS anomalies.

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REFERENCES

1. ENSO working group. Role of prenatal magnetic resonance imaging in fetuses with isolated mild or moderate ventriculomegaly in the era of neurosonography: international multicenter study. Ultrasound Obstet Gynecol. 2020; **56**:340-347
2. Di Mascio D, Sileo FG, Khalil A, Rizzo G, Persico N, Brunelli R, Giancotti A, Panici PB, Acharya G, D'Antonio F. Role of magnetic resonance imaging in fetuses with mild or moderate ventriculomegaly in the era of fetal neurosonography: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2019; **54**:164-171.
3. D'Antonio F, Sileo FG; Eurocanadian NeuroSOnography (the ENSO) working group. Role of prenatal magnetic resonance imaging in fetuses with isolated anomalies of the corpus callosum: a multinational study. Ultrasound Obstet Gynecol. 2021 Feb 17. doi: 10.1002/uog.23612.
4. Sileo FG, Di Mascio D, Rizzo G, Caulo M, Manganaro L, Bertucci E, Masmejan S, Liberati M, D'Amico A, Nappi L, Buca D, Van Mieghem T, Khalil A, D'Antonio F. Role of prenatal magnetic resonance imaging in fetuses with isolated agenesis of corpus callosum in the era of fetal neurosonography: A systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2021; **100**:7-16.
5. Prayer D, Malinger G, Brugger PC, Cassady C, De Catte L, De Keersmaecker B, Fernandes GL, Glanc P, Gonçalves LF, Gruber GM, Laifer-Narin S, Lee W, Millischer AE, Molho M, Neelavalli J, Platt L, Pugash D, Ramaekers P, Salomon LJ, Sanz M, Timor-Tritsch IE, Tutschek B, Twickler D, Weber M, Ximenes R, Raine-Fenning N. ISUOG Practice Guidelines: performance of fetal magnetic resonance imaging. Ultrasound Obstet Gynecol. 2017; **49**:671-680
6. Malinger G, Paladini D, Haratz KK, Monteagudo A, Pilu GL, Timor-Tritsch IE. ISUOG Practice Guidelines (updated): sonographic examination of the fetal central nervous system. Part 1: performance of screening examination and indications for targeted neurosonography. Ultrasound Obstet Gynecol. 2020; **56**:476-484.
7. Paladini D, Malinger G, Birnbaum R, Monteagudo A, Pilu G, Salomon LJ, Timor-Tritsch IE. ISUOG Practice Guidelines (updated): sonographic examination of the fetal central nervous system. Part 2: performance of targeted neurosonography. Ultrasound Obstet Gynecol. 2021; **57**:661-671.
8. Di Mascio D, Buca D, Rizzo G, Khalil A, Timor-Tritsch I, Odibo A, Mappa I, Flacco ME, Giancotti A, Liberati M, D'Antonio F. Reference charts of fetal brain structures for screening examination and targeted neurosonography: a systematic review. 2021

9. Ioannou C, Talbot K, Ohuma E, Sarris I, Villar J, Conde-Agudelo A, Papageorghiou AT. Systematic review of methodology used in ultrasound studies aimed at creating charts of fetal size. BJOG. 2012; **119**:1425-39.
10. Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC. How to write a Cochrane systematic review. Nephrology (Carlton) 2010; **15**:617-624.
11. NHS Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. University of York: York (UK), 2009. Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Retrieved December 3, 2016.
12. Welch V, Petticrew M, Petkovic J, Moher D, Waters E, White H, Tuqwell P. Extending the PRISMA statement to equity-focused systematic reviews (PRISMA-E 2012): explanation and elaboration. J Clin Epidemiol 2016; **70**:68-89.
13. Moher D, Liberati A, Tetzlaff J, Altman DG, and the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Ann Intern Med 2009; **151**:264–269.
14. Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, Moher D, Vohra S; PRISMA harms group. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ 2016; **352**: i157.
15. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; **283**:2008–2012.
16. Napolitano R, Dhami J, Ohuma EO, Ioannou C, Conde-Agudelo A, Kennedy SH, Villar J, Papageorghiou AT. Pregnancy dating by fetal crown–rump length: a systematic review of charts. BJOG 2014; **121**:556–565.
17. Ohadike CO, Cheikh-Ismail L, Ohuma EO, Giuliani F, Bishop D, Kac G, Puglia F, Maia-Schlussel M, Kennedy SH, Villar J, Hirst JE. Systematic review of the methodological quality of studies aimed at creating gestational weight gain charts. Adv Nutr 2016; **7**:313–322.
18. Oros D, Ruiz-Martinez S, Staines-Urias E, Conde-Agudelo A, Villar J, Fabre E, Papageorghiou AT. Reference ranges for Doppler indices of umbilical and fetal middle cerebral arteries and cerebroplacental ratio: systematic review. Ultrasound Obstet Gynecol. 2019; **53**:454-464.
19. Garel C, Chantrel E, Elmaleh M, Brisse H, Sebag G. Fetal MRI: normal gestational landmarks for cerebral biometry, gyration and myelination. Childs Nerv Syst. 2003; 19: 422-425.

20. Hatab MR, Kamourieh SW, Twickler DM. MR volume of the fetal cerebellum in relation to growth. J Magn Reson Imaging. 2008; 27:840-845
21. Parazzini C, Righini A, Rustico M, Consonni D, Triulzi F. Prenatal magnetic resonance imaging: brain normal linear biometric values below 24 gestational weeks. Neuroradiology. 2008; 50:877-883.
22. Tilea B, Alberti C, Adamsbaum C, Armoogum P, Oury JF, Cabrol D, Sebag G, Kalifa G, Garel C. Cerebral biometry in fetal magnetic resonance imaging: new reference data. Ultrasound Obstet Gynecol. 2009; 33:173-181. doi: 10.1002/uog.6276. Erratum in: Ultrasound Obstet Gynecol. 2011 Feb;37(2):254
23. Ber R, Bar-Yosef O, Hoffmann C, Shashar D, Achiron R, Katorza E. Normal fetal posterior fossa in MR imaging: new biometric data and possible clinical significance. AJNR Am J Neuroradiol. 2015; 36:795-802.
24. Jarvis D, Akram R, Mandefield L, Paddock M, Armitage P, Griffiths PD. Quantification of total fetal brain volume using 3D MR imaging data acquired in utero. Prenat Diagn. 2016; 36:1225-1232.
25. Katorza E, Bertucci E, Perlman S, Taschini S, Ber R, Gilboa Y, Mazza V, Achiron R. Development of the Fetal Vermis: New Biometry Reference Data and Comparison of 3 Diagnostic Modalities-3D Ultrasound, 2D Ultrasound, and MR Imaging. AJNR Am J Neuroradiol. 2016; 37:1359-66.
26. Kyriakopoulou V, Vatansever D, Davidson A, Patkee P, Elkommos S, Chew A, Martinez-Biarge M, Hagberg B, Damodaram M, Allsop J, Fox M, Hajnal JV, Rutherford MA. Normative biometry of the fetal brain using magnetic resonance imaging. Brain Struct Funct. 2017; 222:2295-2307.
27. Link D, Braginsky MB, Joskowicz L, Ben Sira L, Harel S, Many A, Tarrasch R, Malinger G, Artzi M, Kapoor C, Miller E, Ben Bashat D. Automatic Measurement of Fetal Brain Development from Magnetic Resonance Imaging: New Reference Data. Fetal Diagn Ther. 2018; 43:113-122.
28. Conte G, Milani S, Palumbo G, Talenti G, Boito S, Rustico M, Triulzi F, Righini A, Izzo G, Doneda C, Zolin A, Parazzini C. Prenatal Brain MR Imaging: Reference Linear Biometric Centiles between 20 and 24 Gestational Weeks. AJNR Am J Neuroradiol. 2018; 39:963-967.
29. Zhao D, Cai A, Zhang J, Wang Y, Wang B. Measurement of normal fetal cerebellar vermis at 24-32 weeks of gestation by transabdominal ultrasound and magnetic resonance imaging: A prospective comparative study. Eur J Radiol. 2018; 100:30-35.

30. Jarvis DA, Finney CR, Griffiths PD. Normative volume measurements of the fetal intra-cranial compartments using 3D volume in utero MR imaging. Eur Radiol. 2019; 29:3488-3495
31. Cai S, Zhang G, Zhang H, Wang J. Normative linear and volumetric biometric measurements of fetal brain development in magnetic resonance imaging. Childs Nerv Syst. 2020; 36:2997-3005
32. Jarvis D, Griffiths PD. Normal appearances and dimensions of the foetal cavum septi pellucidi and vergae on in utero MR imaging. Neuroradiology. 2020; 62:617-627
33. Kertes I, Hoffman D, Yahal O, Berknstadt M, Bar-Yosef O, Ezra O, Katorza E. The normal fetal Cavum Septum Pellucidum in MR imaging - New biometric data. Eur J Radiol. 2021; 135:109470.
34. Griffiths PD, Bradburn M, Campbell MJ, Cooper CL, Graham R, Jarvis D, Kilby MD, Mason G, Mooney C, Robson SC, Wailoo A; MERIDIAN collaborative group. Use of MRI in the diagnosis of fetal brain abnormalities in utero (MERIDIAN): a multicentre, prospective cohort study. Lancet. 2017; 389:538-546.
35. Rossi AC, Prefumo F. Additional value of fetal magnetic resonance imaging in the prenatal diagnosis of central nervous system anomalies: a systematic review of the literature. Ultrasound Obstet Gynecol. 2014; 44:388-93.
36. Malinger G, Paladini D, Pilu G, Timor-Tritsch IE. Fetal cerebral magnetic resonance imaging, neurosonography and the brave new world of fetal medicine. Ultrasound Obstet Gynecol. 2017; 50:679-680.
37. Di Mascio D, Buca D, D'Antonio F. Moving beyond the diatribe on ultrasound vs MRI. Ultrasound Obstet Gynecol. 2021; 57:175-176.

Figure legend

Figure 1. Prisma flow diagram

Figure 2. Quality score bar chart for the “study design” domain

Figure 3. Quality score bar chart for the “statistical and reporting methods” domain

Figure 4. Quality score bar chart for the “specific relevant MRI aspects” domain

Table 1. Methodological quality criteria for qualitative assessment of fetal brain structure growth charts

Domain	**Low risk of bias**	**High risk of bias**
1. *Study design*		
1.01 Design	Clearly described as either cross-sectional or longitudinal	Not reported
		Mixture of cross-sectional and longitudinal data
1.02 Population	Women reported as coming from population of low risk of fetal anomalies	Women from unselected population; or selected; or at high risk of fetal anomalies; or not reported
1.03 Indication for MRI	Indications clearly described	Unclear reason for MRI
1.04 Prospective data collection	Prospective study and MRI data collected specifically for purpose of constructing charts of different fetal brain structures	Retrospective study, data not collected specifically for purpose of constructing charts of different fetal brain structures, or unclear (e.g., use of routinely collected data)
1.05 Sample size	*A-priori* determination or calculation of sample size and justification	Lack of *a-priori* sample size determination or calculation and justification
1.06 Recruitment period	Reported	Not reported or unclear
1.07 Consecutive enrolment	Consecutively included patients	Did not include patients consecutively
1.08 Inclusion/exclusion criteria	Made clear that women at high risk of fetal anomalies were not included and that women with abnormal outcome were excluded, i.e. an effort was made to include as normal an outcome as possible	Study population included both low- and high-risk pregnancies, or women with abnormal outcome were not excluded

	As a minimum, the study population should exclude: multiple pregnancy; fetuses with congenital, structural or chromosomal anomaly; fetal death/stillbirth; women with disorders that may affect fetal brain growth; pregnancy complications (at least pre-eclampsia, SGA/IUGR, prematurity, diabetes mellitus); delivery prior to 37 weeks	Study population did not exclude fetuses or pregnancies with the characteristics described in the 'low risk' column
		Exclusions which would have a direct effect on fetal brain growth
1.09 Method of dating pregnancy	Clearly described known LMP and sonogram before 14 weeks' gestation demonstrating crown–rump length that corroborates LMP dates (within how many days unspecified)	Not specified or unclear
		Gestational age assessment at >14 weeks or gestational age assessment not including ultrasonographic verification
1.10 Multicenter study	Study performed with more than one center collaborating	Performed at only one hospital
2. *Reporting and statistical methods*		
2.01 Postnatal assessment	Collected and reported prospectively either by US or MRI	Not reported or unclear
2.02 Gestational age range	Reported	Not reported or unclear
2.03 MRI machines and protocols used	Clearly specified	Not clearly specified or unclear
2.04 Reported operators	Number of operators reported	Not clearly specified or unclear

2.05 Radiologist experience	Experienced or specifically trained radiologist clearly reported	Not clearly specified or unclear
2.06 Blinded measurements	Operator were blinded	Not clearly specified or unclear
2.07 Quality control measures	Should include the following: assessment of intraobserver variability; assessment of interobserver variability; image review; image scoring; image storage	No quality control measures
2.08 Number of measurements taken for each variable	At least three measures per fetus per scan	Single measure or not specified
2.09 Statistical methods	Clearly described and identified	Not clearly described and identified
2.10 Report of mean (and eventually SD) of each measurement and sample size for each week of gestation	Presented in a table or clearly described	Not presented in a table or not clearly described
2.11 Report of regression equations for mean (and SD if relevant) for each measurement	Reported	Not reported or unclear

2.12 Scatter diagram	Study included fetal brain structure charts with mean and SD or centiles (at least 5th, 50th and 95th centiles)	Fetal brain structure charts not included
3. Specific relevant MRI aspects		
3.01 Whole fetal brain assessment	All brain structures assessed and measured	Assessment related only to few fetal brain structures
3.02 US and MRI concordance	Reported concordance between US and MRI measurements	No data on concordance between US and MRI
3.03 Imaging plane concordance	Reported concordance of imaging planes taken at US and MRI	No data on concordance of imaging planes
3.04 MRI protocol	Study described sufficient and unambiguous details of measurement techniques used for fetal brain structure parameters	Study did not describe sufficient and unambiguous details of measurement techniques used for fetal brain structure parameters

SGA, small for gestational age; IUGR, intrauterine growth restriction; LMP, last menstrual period; US, ultrasound, MRI, magnetic resonance imaging; SD, standard deviation.

Table 2. General characteristics of the included studies

Author	Year	Country	Period considered	Study design	Number of fetuses	Brain districts evaluated	Reason for MRI	Data collection	Type of post natal assessment
Garel	2003	France	NR	Retrospective	225	FOD, BPD, CC length, TCD, vermis height, anteroposterior diameter of the vermis	NR	NR	US or MRI
Hatab	2008	USA	NR	Retrospective	93	Cerebellar volume	Extra-CNS disorders	NR	NR
Parazzini	2008	Italy	2001-2006	Retrospective	84	BPD, FOD, TCD, anteroposterior diameter of the pons, vermian surface area, vermian height, CC length, anteroposterior diameter of the vermis	CNS disorder in previous pregnancy or extra-CNS problems	NR	US or MRI
Tilea	2009	France	2002-2009	Retrospective	589	BPD, FOD, TCD, anteroposterior diameter of the vermis, superoinferior diameter of the vermis, laterolateral diameter of the vermis, CC length,	Increased risk of cerebral pathology (including suspicion of infectious fetopathy, suspicion of cerebral abnormality on ultrasound, positive family history, clubfoot,	NR	US or MRI

						cisterna magna width, interhemispheric distance, ventricular atria diameter, third ventricle diameter	cleft lip and/or palate, cerebral biometry at the lower limit of the norm on ultrasound, polyhydramnios, maternal disease (with possible consequences for fetal cerebral development) and decreased fetal movements)		
Ber	2015	Israel	2007-2013	Retrospective	215	TCD, anteroposterior diameter of the vermis, vermian height, vermian perimeter, vermian cross-sectional area, pontine anteroposterior diameter	Mild lateral ventricular asymmetry and/or ventriculomegaly on US, suspected anomaly on US, maternal CMV infection, extra-CNS anomalies on US, genetic disorder, disorders in the family or in previous pregnancies	NR	No postnata assessment

Jarvis	2016	United Kingdom	NR	Retrospective	132	Total brain volume	NR ("fetuses with no brain or somatic abnormalities")	NR	NR
Katorza	2016	Israel	2011-2013	Retrospective	151	Cerebellar superoinferior diameter, cerebellar anteroposterior diameter	Increased risk of suspected cerebral pathology, including suspected infectious fetopathy, suspected sonographic cerebral abnormality, positive family history, a previous pregnancy with CNS abnormality, decreased fetal movements, polyhydramnios, and extracranial anomalies such as club foot, cleft lip and or palate	Cross-sectional	NR
Kyriakopoulou	2017	United Kingdom	2007-2013	Unclear	108	Supratentorial brain tissue volume, lateral ventricles volume, cortex volume,	Healthy volunteer, previous child with confirmed disability, suspected fetal	NR	NR

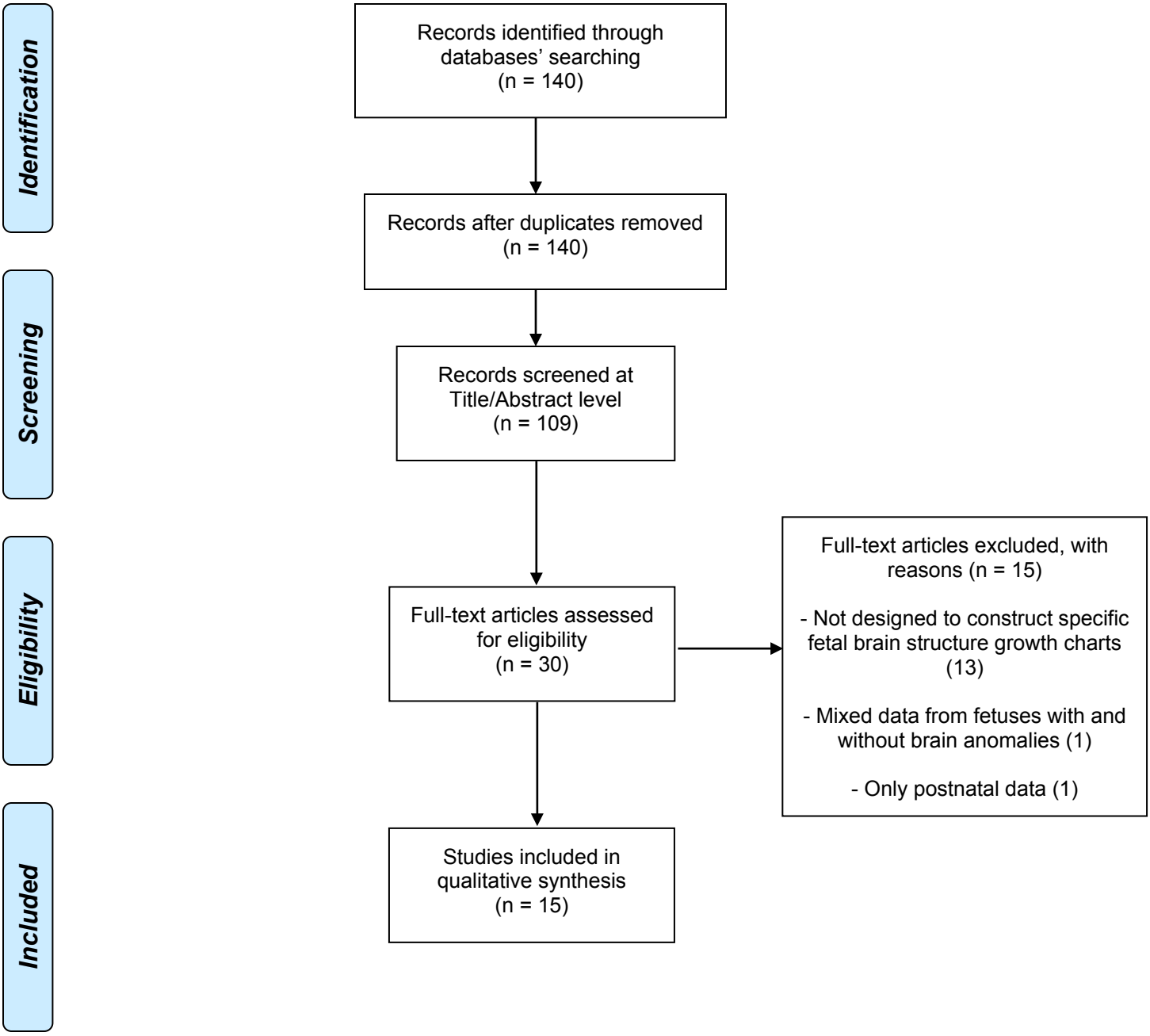
						cerebellum volume, extra-cerebral CSF	abnormality on US, mild non-CNS abnormality		
Link	2017	Israel	2012-2014	Prospective	199	Total brain volume	Family history of malformations, suspected problems unrelated to the brain, maternal CMV with no structural brain abnormalities, maternal disease with possible consequences for fetal cerebral development, suspected mild ventriculomegaly	NR	NR
Conte	2018	Italy	2005-2016	Retrospective	169	BPD, FOD, TCD, CC length, ventricular atria diameter, mesencephalic antero-posterior diameter, vermian antero-posterior diameter, vermian cranio-caudal diameter, cerebellar latero-lateral diameter,	Unclear CNS findings at US; extra-CNS disease or malformation; previous child with a confirmed CNS malformation	NR	NR

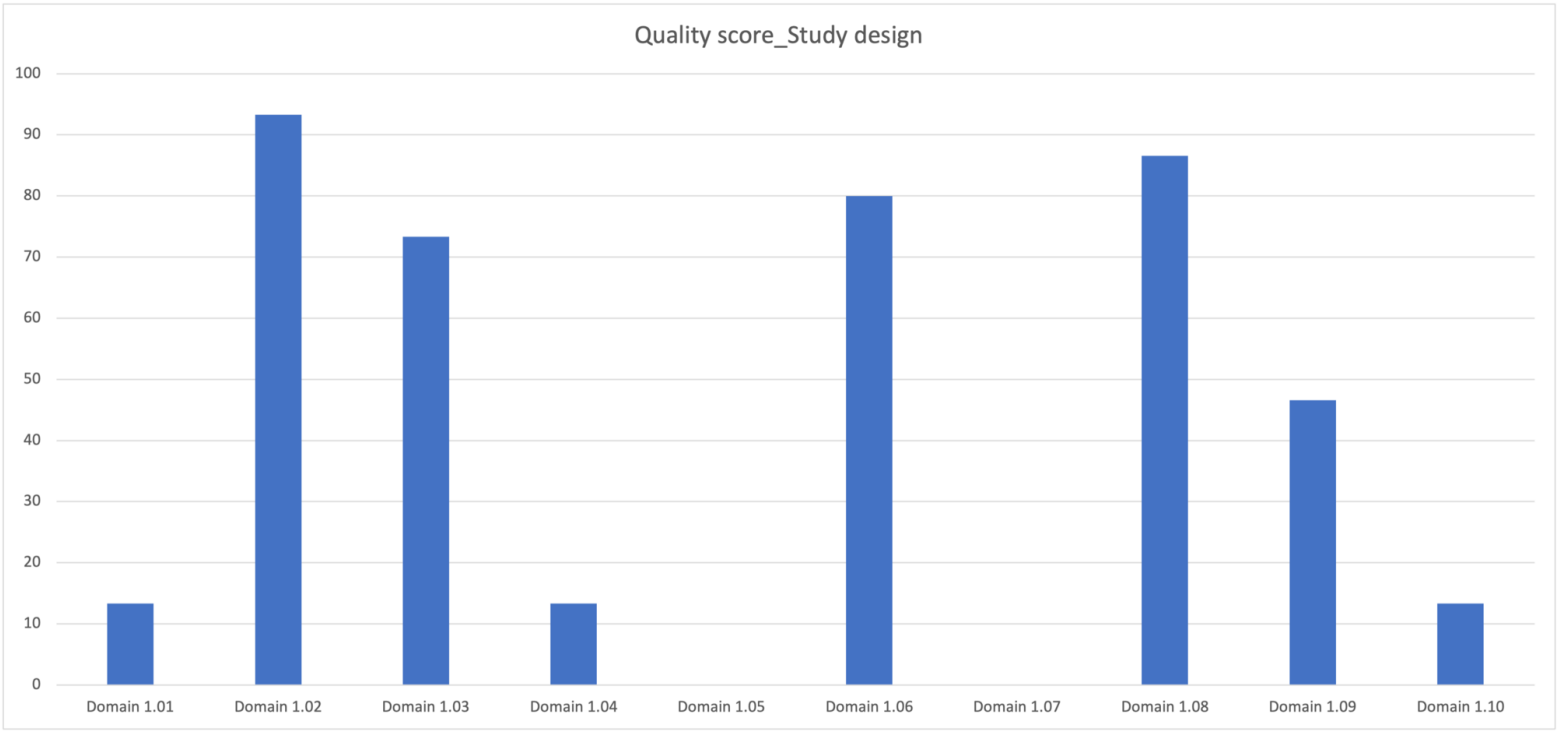
						latero-lateral diameter of the posterior cranial fossa, pontine antero-posterior diameter and pontine cranio-caudal diameter, and clivo-supraoccipital angle			
Zhao	2018	China	2014-2016	Prospective	20	Anteroposterior diameter of fetal vermis, craniocaudal diameter of fetal vermis, median surface area, brainstem-vermian angle, brainstem-tentorium angle	Suspected extra-CNS defects or increased risk of suspected CNS abnormalities	Cross-sectional	NR
Jarvis	2019	United Kingdom	NR	Retrospective	200	BPD, FOD, ventricular volume	Volunteer, low risk women	NR	NR
Cai	2020	China	2015-2018	Retrospective	98	BPD, FOD, TCD, cerebellum volume, lateral ventricle volume	NR ("normal fetuses")	NR	NR

Jarvis	2020	United Kingdom	2014-2017	Unclear	200	CSP length and width, CV width	Clinical study	NR	NR
Kertes	2021	Israel	2005-2017	Retrospective	307	CSP length, height and width	No intracranial anomalies with the exclusion of mild ventriculomegaly. Isolated extra-CNS anomalies, maternal CMV without evidence of fetal infection and normal fetuses with maternal history of anomalies in previous gestation were included	NR	NR

NR, not reported; FOD, fronto-occipital diameter; BPD, biparietal diameter; CC, corpus callosum; TCD, transverse cerebellar diameter; CNS, central nervous system; US, ultrasound; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; CSP, cavum septi pellucidi, CV, cavum vergae.

PRISMA 2009 Flow Diagram





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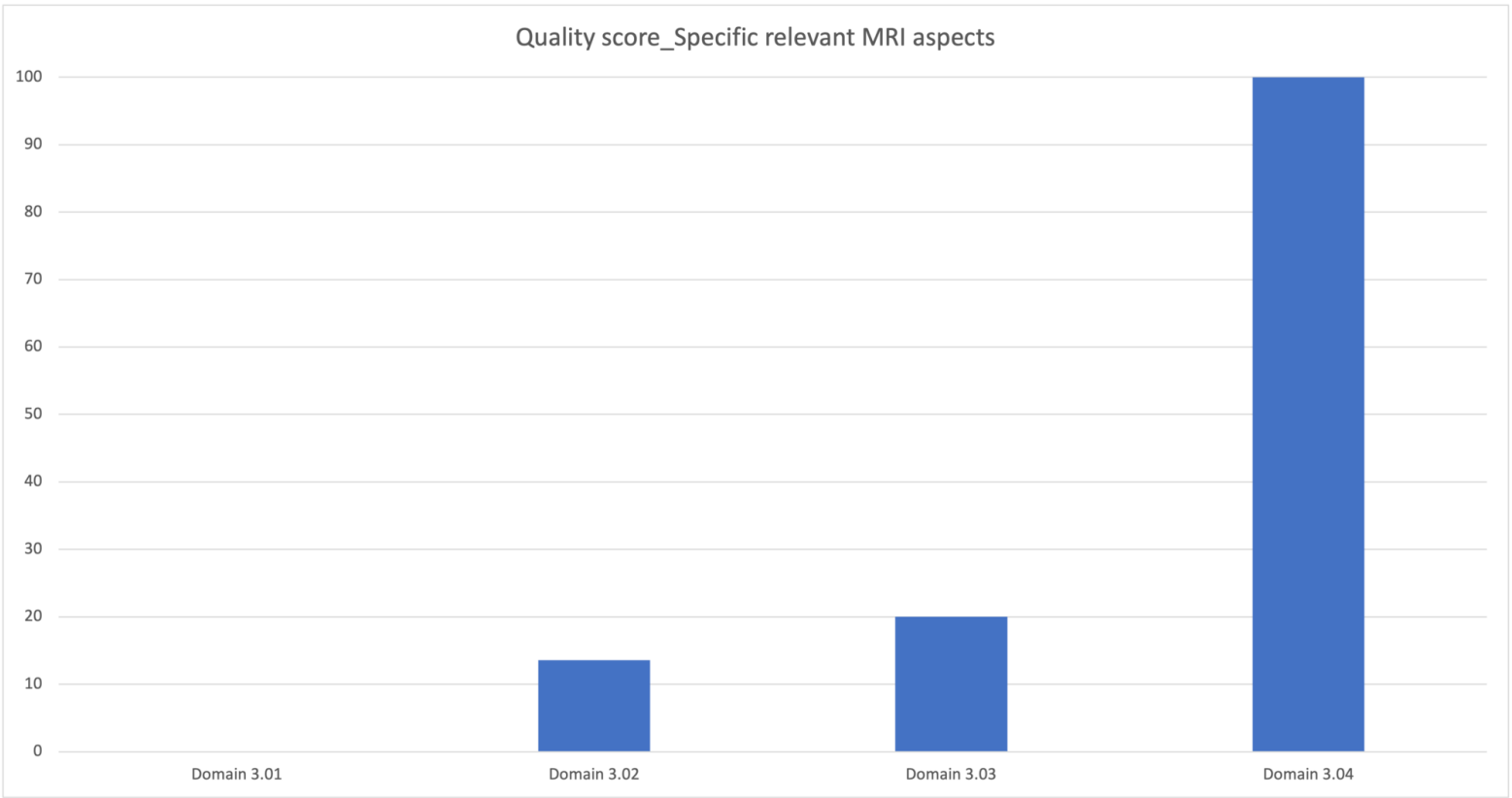

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