Added value of fetal MRI in fetuses with suspected brain abnormalities on neurosonography: a systematic review and meta-analysis

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Added value of fetal MRI in fetuses with suspected brain abnormalities on neurosonography: a systematic review and meta-analysis

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Abstract

Purpose: To evaluate the additional diagnostic value of fetal Magnetic Resonance Imaging (MRI) in fetuses with suspected brain abnormalities identified with advanced neurosonography (NS).

Methods: A systematic literature search was performed for studies reporting on a comparison between diagnosis with NS and MRI, in fetuses suspected for brain abnormalities. Abnormalities detected on NS were compared with those detected on MRI as well as with postnatal imaging findings to assess the added value of fetal MRI.

Results: We included 27 articles, reporting on 1184 cases in which NS and MRI diagnosis were compared. In 65% of cases [773/1184] fetal NS and fetal MRI diagnosis agreed completely. In 23% [312/1184], MRI showed additional or different pathology. In 8% [99/1184], MRI rejected the NS diagnosis with normal brain as conclusion. For 454 cases a comparison with postnatal imaging could be made. Compared to the postnatal diagnosis, fetal MRI diagnosis agreed completely in 80% [364/454] and fetal NS in 54% [243/454] (difference 27%, 95% CI 21–33%). Additional abnormalities were found on postnatal imaging in 36% [164/454] after NS and in 14% [61/454] after fetal MRI.

Conclusions: This meta-analysis shows that fetal MRI in addition to NS improves diagnostic accuracy in detecting brain abnormalities.

Keywords

Brain, fetal, MRI, sonography

History

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Introduction

Central nervous system (CNS) abnormalities can have a great effect on clinical outcome and the development of a child. Since the impact varies strongly between diagnoses, accurate information on the diagnosis and prognosis of fetal abnormalities is crucial, both for clinicians when counseling parents about the prognosis, as for parents in their decision making on continuation or termination of pregnancy. The correct diagnosis also allows for optimal monitoring of pregnancy and planning of delivery.

Often, the first suspicion of a cerebral abnormality arises during a routine prenatal ultrasound examination in the second trimester of pregnancy. When a cerebral abnormality is suspected on ultrasound, patients are generally referred to a dedicated fetal medicine unit for neurosonography (NS). Additionally, fetal magnetic resonance imaging (MRI) may be performed, either to confirm or reject a suspected abnormality on prenatal NS, or to determine the exact nature of the lesion, or when NS is inconclusive. The most common indications for fetal MRI are the detection of ventriculomegaly, suspected agenesis of the corpus callosum or posterior fossa abnormalities at NS [1,2].

For 30 years, many descriptive review articles have been published elaborating on the technical aspects of fetal MRI and imaging characteristics of various CNS malformations and their outcomes. Moreover, numerous case reports and case series and only one review [3] have been published about the complementary role of fetal MRI to NS. Most studies found that MRI is more accurate than NS in detecting brain abnormalities, sometimes concluding even without descriptions of the type of anomaly. Therefore, we systematically evaluated the added value of fetal MRI in fetuses with suspected brain abnormalities identified and described by sonography.

Methods

Data sources

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. We performed a search on 30 March 2014 in Medline and
Postnatal follow up, and its agreement with prenatal diagnosis; (g) performance and type of brain abnormalities on NS; (f) type of brain abnormalities on fetal MRI; (e) type of brain abnormalities on fetal MRI at the time of the index test; (d) time between NS and MRI. For each study, we extracted data on (a) the duration of the study; (b) the number of patients included; (c) gestational age at the time of the index test; (d) time between NS and MRI; (e) type of brain abnormalities on NS; (f) type of brain abnormalities on fetal MRI; (g) performance and type of postnatal follow up, and its agreement with prenatal diagnosis; (h) number and training of assessors; (i) retrospective or prospective study design; (j) comparison of NS and MRI diagnosis.

Data extraction was done by two reviewers independently (MvD, EN) using a standardized form (Appendix 2). The comparison of the NS diagnosis with fetal MRI diagnosis was made for each fetus by two reviewers (MvD and EP, fetal medicine specialist). Moreover, in those cases either autopsy or postnatal imaging (sonography, CT or MRI) was available, both the NS and the MRI diagnosis were compared with the postnatal diagnosis. Each case was scored by two reviewers (MvD and EP). Disagreements about data extraction were resolved by discussion until consensus was reached. Furthermore, we reviewed for each included study if a dedicated neurosonographical examination had been performed and the method used to obtain fetal MRI scans (field strength and scan sequences).

**Data synthesis and analysis**

To compare NS with MRI, we created three main groups consisting of the following subgroups:

- Prenatal NS diagnosis confirmed by fetal MRI with (1a) or without (1b) additional pathology
- Prenatal NS diagnosis partially confirmed by fetal MRI with (2a) or without (2b) additional pathology
- Prenatal NS diagnosis rejected by fetal MRI with (3a) or without (3b) additional pathology

For example, if on NS ventriculomegaly and partial agenesis of corpus callosum is suspected, and fetal MRI diagnosed isolated ventriculomegaly, the NS diagnosis is partially confirmed (2b). However, in case of isolated ventriculomegaly on NS as compared to ventriculomegaly with intraventricular bleeding on MRI, this is scored as partially confirmed with an additional pathology (2a).

If an article also described postnatal outcome, the diagnosis following both prenatal NS and MRI was compared with postnatal diagnosis (PN). We created three main groups for both comparison between: (a) prenatal NS and postnatal diagnosis and (b) prenatal MRI versus postnatal diagnosis:

- Prenatal NS/MRI diagnosis is confirmed by PN diagnosis with (1a) or without (1b) additional pathology
- Prenatal NS/MRI diagnosis is partially confirmed by PN diagnosis with (2a) or without (2b) additional pathology
- Prenatal NS/MRI diagnosis is rejected by PN diagnosis with (3a) or without (3b) additional pathology

We tested for differences between the percentage correct diagnosis using NS and the percentage correct diagnosis using MRI, with the chi-square test.

Because in more than half of the cases, the reason for referral was isolated mild ventriculomegaly by NS, we analyzed the subgroup with ventriculomegaly separately. Ventriculomegaly is defined as an atrial diameter ≥10 mm. The atrium of the lateral ventricle is the portion where the body, posterior horn and temporal (inferior) horn converge. Ventriculomegaly is generally considered mild if the atrial diameter is between 10 and 15 mm and severe if >15 mm, although some authors use the categories of mild (10–12 mm), moderate (13–15 mm) and severe (≥16 mm) [5]. In this study, mild ventriculomegaly was defined as 10–12 mm.
Results

Literature search and studies included

In Appendix 3, the flowchart of the articles retrieved by the literature search is shown. Of the 2748 unique publications identified, 2577 articles were excluded based on title and abstract. After reading the full text of 171 articles, we excluded 144 articles. Twenty-seven publications could be included for meta-analysis [2,5–30], reporting on 1445 patients of which 1184 had brain abnormalities detected on NS and could be included.

Characteristics of included studies

All studies were cohort studies, eight prospective [5,7,17,23,24,26,28], nine retrospective studies [2,8,9,11,13,15,19,21,29], and 10 studies [6,12,14,16,18,20,22,25,27,30] did not report on this. The articles reported on an average of 54 patients (range 21–185). The average study duration was 4 years (range 2–7), nine studies did not report on its duration [6,7,10,12,14,15,19,22,28]. Gestational age during NS was described in 16 studies [2,6,7,10–15,17–21,24,27] ranging from 15 to 39 weeks. Gestational age during MRI was described in 13 studies [2,5,8,9,11,16,18,21–23,27,29] ranging from 16 to 39 weeks. The average time interval between NS and MRI was 5 days (range 0–29) described in 13 articles [9,11,15–19,22–24,28,29].

Almost all studies performed fetal MRI on a 1.5 Tesla (T) MRI scanner, three studies [7,13,14] used 0.5 T system and two studies [14,20] used a 1.0 T system, only one article [27] did not mention which field strength was used. T2 weighted images (half Fourier) single shot fast spin echo sequences in three planes were performed in all studies except in two which only performed T1 weighted images in three planes [7,13]. T1 weighted images, (fast) spin echo or (fast) gradient echo, were made as additional sequence in the scan protocol or when necessary in 15 articles [2,5,6,8–10,12,16,19–21,23,26,29,30]. Diffusion weighted images (DWI) was performed in seven studies [8,9,12,23,26,29,30], with b-values of 0 and 500, 600, 700 or 1000 s/mm².

Five studies [2,11,16–18] described the number of sonographers with a maximum of 3. If a dedicated neurosonographical examination had been performed was not mentioned. A few articles described that the examination had been performed by experienced or dedicated sonographers or gynecologists or had been made in a specialized fetal medicine unit [2,7,9,11,14–18,21–24,28–30]. Fifteen articles [2,5,8,9,11,13,14,16–20,22,24,29] described the number of assessors for the MRI, with a maximum of 3. Experience of assessors was described in 19 articles as board certified, experienced or specialized radiologists, (staff) perinatologists or pediatric neuroradiologists, or described as >5 or >10 years of experience. Eight articles did not describe experience [6,10,12,13,22,24,26,27].

In 8 articles [2,5,8,9,15,25,28,29] consisting of 482 patients, no autopsy or postnatal imaging had been performed (our reference standard). In the remaining 19 studies, autopsy or postnatal imaging was performed in 454 of 702 patients.

Mild ventriculomegaly was defined by measurement in 10 articles as >10 mm [30], 10–15 mm (mild/moderate) [15,18], 10–12 mm [2,5,10,16,23,29], 11–13 mm [25].

Quality assessment

Study quality was assessed using the Quadas criteria [4] with an addition of specific study related items, shown in Appendix 4. We noted that all articles described patient selection criteria and the index test. The time period between the tests was described in nearly 80% of the articles. Most articles gave no description of their postnatal reference test, or no postnatal reference test had been performed at all. In 22 out of 27 articles, binding of the reference test was not reported. Also not reported in almost half of the articles was the use of sedation, training of test operators, instrumentation variation, whether there was commercial funding.

Fetal NS versus fetal MRI diagnosis

Table 1 shows the comparison of diagnoses between NS and MRI of 1184 patients with suspected brain abnormalities on NS. Appendix 5 shows the type and frequency of additional pathology found on fetal MRI.

In 65% of cases [773/1184], fetal NS completely agreed with fetal MRI; in 26% [312/1184], MRI did provide additional or different pathology and in 12% [141/1184], NS diagnosis was rejected by MRI, with 8% [99/1184] being diagnosed as normal by MRI.

For the subgroup isolated mild ventriculomegaly 657 fetuses were described. In 70% of cases [459/657], fetal NS completely agreed with fetal MRI; in 20% [134/657], MRI showed additional or different pathology while in 10% [67/657], NS diagnosis was rejected by MRI; of which in 64 cases MRI showed a normal brain.

Fetal NS and MRI versus postnatal diagnosis

In Table 2, the additional value of MRI after suspicion of brain anomalies on NS is described, related to the postnatal findings. Appendix 5 shows the additional pathology found postnatally. Overall, in 38% of cases [454/1184], a
Table 2. MRI and NS diagnosis compared to postnatal diagnosis in total group (a) and subgroup mild ventriculomegaly (b).

<table>
<thead>
<tr>
<th>Total group</th>
<th>MRI versus postnatal diagnosis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Confirmed</td>
</tr>
<tr>
<td></td>
<td>No addition</td>
</tr>
<tr>
<td>NS vs postnatal</td>
<td></td>
</tr>
<tr>
<td>Confirmed</td>
<td>No addition</td>
</tr>
<tr>
<td></td>
<td>Addition</td>
</tr>
<tr>
<td>Partly confirmed</td>
<td>No addition</td>
</tr>
<tr>
<td></td>
<td>Addition</td>
</tr>
<tr>
<td>Rejected</td>
<td>No addition</td>
</tr>
<tr>
<td></td>
<td>Addition</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

Comparison between totals NS (row total) and totals MRI (column total) versus postnatal diagnosis

NS postnatally confirmed 243 (54%) 113 (25%) 9 (2%) 34 (7%)
MRI postnatally confirmed 364 (80%) 35 (8%) 16 (4%) 17 (4%)
Difference in % (95% CI) 26 (21;33) 17 (12;22) 2 (1;4) 6 (2;9) 4 (1;8)

p Value chi-square <0.002 <0.002 0.156 0.111 <0.001 0.014

NS vs postnatal Mild ventriculomegaly (N = 115)

<table>
<thead>
<tr>
<th>MRI versus postnatal diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed</td>
</tr>
<tr>
<td>No addition</td>
</tr>
<tr>
<td>Addition</td>
</tr>
<tr>
<td>Partly confirmed</td>
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<tr>
<td>Addition</td>
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<tr>
<td>Rejected</td>
</tr>
<tr>
<td>Addition</td>
</tr>
</tbody>
</table>

Comparison between totals NS (row total) and totals MRI (column total) versus postnatal diagnosis

NS postnatally confirmed 53 (46%) 41 (36%) 3 (3%) 4 (3%)
MRI postnatally confirmed 89 (77%) 10 (9%) 3 (3%) 7 (6%) 3 (3%)
Difference in % (95% CI) 31 (18;43) 27 (16;38) 3 (2;1) 0 (6;16) 1 (5;7)

p Value Fisher exact <0.002 <0.002 0.081 1 0.109 0.701

Comparable agreement between NS/MRI and postnatal diagnosis, with * meaning perfect diagnosis
MRI diagnosis closer to postnatal diagnosis
NS diagnosis closer to postnatal diagnosis.
comparison with postnatal imaging or postnatal pathology was made. For the subgroup of fetuses with mild ventriculomegaly this was made in 18% of cases [115/657].

As shown in Table 2, in 49% of cases [223/454] both NS and MRI are in perfect agreement with the postnatal findings. MRI diagnosis agreed more often with autopsy or postnatal imaging than ultrasound, 80% [364/454] for MRI (total column 1) and 54% [243/454] for NS (total row 1) (difference 26%, 95% CI 21–33%), respectively. Postnatal imaging showed an additional pathology in 14% [61/454] of MRI diagnoses and in 36% [164/454] of NS diagnoses.

In 16% [72/454], NS diagnosis was rejected postnatally versus 6% [30/454] of MRI diagnosis. In 50 of these 72 cases (69%), in which the NS diagnosis was rejected by the postnatal imaging or autopsy findings, prenatal MRI had a correct diagnosis. In 2% [8/454], both the prenatal NS and MRI were rejected as additional CNS anomalies were diagnosed postnatally. In a further 9 cases [2%], postnatal imaging proved to be completely normal and rejected both the prenatal NS and MRI diagnosis. In 2% [7/454], a correct diagnosis was made by NS but not by MRI.

In 36% [164/454] of cases, postnatal imaging indicated that one or more diagnoses were missed on NS, of which 114 (70%) had been correctly diagnosed on prenatal MRI.

In the subgroup of patients with mild ventriculomegaly in 43% of cases [49/115], both NS and MRI are in total agreement with the postnatal findings. MRI diagnosis agreed more often with autopsy or postnatal imaging diagnosis than ultrasound; 77% [89/115] for MRI and 46% [53/115] for NS (difference 31%, 95% CI 18–43%). Postnatal imaging or autopsy showed additional pathology in 15% [16/115] of MRI diagnoses and in 42% [47/115] of NS diagnoses.

In 15% [18/115], NS diagnosis was rejected postnatally versus 9% [10/115] of MRI diagnosis. In 56% [10/18] of these cases, in which the NS diagnosis was rejected by the postnatal diagnosis, prenatal MRI had a correct diagnosis. In 2% [2/115], both the prenatal NS and MRI were rejected as additional CNS anomalies were diagnosed postnatally. Further, in 6 cases [5%], postnatal imaging proved to be completely normal and rejected both the prenatal NS and MRI diagnosis. In 1% [1/115], a correct diagnosis was made by NS, but not by MRI.

In 42% [48/115] of cases, postnatal imaging indicated that one or more diagnoses were missed on NS, of which 69% [33/48] had been correctly diagnosed on prenatal MRI.

**Discussion**

Our systematic review on 27 articles reporting on 1184 fetuses shows that fetal MRI changed diagnosis in 35% of cases when compared to NS. However, MRI still failed to detect abnormalities in 14% of cases when compared to the postnatal imaging findings. The most likely explanation for this failure is the gestational age at the time of fetal scanning. Fetal MRI scans were performed from 17 weeks up to 39 weeks’ gestation. Interpretation of anatomy of the fetal brain is much more difficult at early gestation, because brain structures might not be developed to an extent that congenital abnormalities can be detected. For instance, the posterior fossa structures or the corpus callosum forms between 8th and 20th week of gestation [25]. In only 2% of cases, a normal brain was seen postnatally, whereas fetal MRI suggested brain abnormalities. This discrepancy is probably related to the normal course of a disease, rather than misinterpretation by the assessors, as for example intraventricular hemorrhage or ventriculomegaly may resolve over time.

It was not possible to extract the exact time interval between NS and MRI, because this was not reported in most studies. Therefore, it is unknown what the influence of the timing interval is and even the gestational age at which MRI was performed. There is a large chance that minor findings could have resolved spontaneously in a large time interval or that additional findings (such as malformations of cortical development) could have become more apparent.

A strength of this first systematic review is the extended search performed, and scoring of the articles by two experienced reviewers, a radiologist and fetal medicine specialist. Another strength is the comparison with postnatal diagnosis made on postnatal imaging or autopsy, which allows comparison with the reference standard. Furthermore, the subgroup referred with isolated ventriculomegaly is of great interest in this review, whereas this is the largest group of patients referred for MRI. We observed that the added value of fetal MRI in this group is 30%, comparable to the added value in the total group of analyzed cases (35%).

There are also several potential weaknesses of our review that should be mentioned. We had to rely upon the way in which results are interpreted by the authors of the included studies. Only in a few articles, MRI assessors were blinded for index test (NS) results. It is therefore possible that interpretation of MRI study depended on knowledge of NS results, and thereby improves the concordance between MRI results and postnatal imaging, when compared to NS and postnatal imaging. However, this resembles clinical practice and does not interfere with our aim to determine additional value of fetal MRI to NS. Most articles gave no description of their postnatal reference test, or no postnatal reference test is performed at all, and thus lack a gold standard. Training of neurosonographers and MRI assessors is not reported very well in most articles, while it is well known that experience in fetal NS and fetal MRI is of the utmost importance to make a correct diagnosis. It is difficult to judge if any bias occurred in interpretation when NS and MRI are performed by multiple assessors. Repeating the NS by a second assessor will probably lead to more accurate diagnostic information. The diagnostic capacity of NS is limited in case of obesity and oligohydramnios. However, these conditions were not standard reported in the literature reviewed. Improvement of NS and MR technology and expertise in fetal NS and MRI will increase diagnostic performance and therefore influence the results. We did not analyze the effect of gestational age on fetal MRI diagnosis, as this information was not available per case. Finally, several articles reported a mixture of diagnostic tools to acquire final outcomes, such as postnatal NS, MRI or CT, postnatal clinical follow up, or autopsy reports. We only used postnatal NS, MRI, CT or autopsy reports. However, MRI and autopsy are considered to be the gold standard, and MRI may even be more sensitive than autopsy, because of the rapid deterioration of brain tissue and fixation artifacts postmortem.
In summary, the selected articles in this review show that fetal MRI is a complementary modality to NS in the diagnostic workup providing additional information in 35%. However, the available literature leaves many gaps in the knowledge to allow interpolation of the data, and a few well designed prospective studies are needed to finally clarify the topic of whether, and in which cases, MRI adds to the value of fetal neurosonography, in which cases a repeat neurosonography is necessary and in which cases other diagnostic modalities (such as DNA analysis) should be considered.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References

22. Whitby EHP. Comparison of ultrasound and magnetic resonance imaging in 100 singleton pregnancies with suspected brain abnormalities. BJOG 2004;111:784–92.

Appendix 1: Search strategy for Medline and Embase through Ovid

1. exp Magnetic Resonance Imaging/ or (mri or magnetic resonance imaging).tw.
2. exp Ultrasonography/ or (ultraso* or sonogr*).tw. or echogr*.sh.tw.
3. 1 and 2
4. fetus.sh.tw. or (foetus or fetuses or foetuses or fetal or foetal or prenatal).tw.
5. exp congenital abnormalities/ or (congenital abnormalit* or malformation*).tw.
6. exp central nervous system/ or central nervous system.tw.
7. brain/ or (brain* or spinal cord* or cereb* or encephal* or mening*).tw. or cranium*.sh.tw.
8. or/5-7
9. 4 and 8
10. 3 and 9
Appendix 2: Data extraction form

<table>
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<tr>
<td></td>
<td></td>
<td>2. Martine van Doom</td>
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<tr>
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<td></td>
<td>3. Eva Pajkr</td>
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<thead>
<tr>
<th>3. First author: Author</th>
<th>4. Publication year: PubYear</th>
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<tr>
<td>108</td>
<td>88</td>
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<tr>
<th>3a. Profession of the authors: proAuth</th>
<th>1. Radiologist</th>
<th>2. Sonographist/Gynaecologist</th>
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<tbody>
<tr>
<td></td>
<td>3. Other, please describe:</td>
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<tr>
<th>5a. Setting: secCare</th>
<th>2. ternary Care</th>
<th>3. mixed care</th>
<th>5 other</th>
<th>6. not reported</th>
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<tr>
<th>5b. Number of participating centers: Centers</th>
<th>56 not reported</th>
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<tr>
<td>(single/ multi)</td>
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<tr>
<th>5c. Country of investigation: Country</th>
<th>56 not reported</th>
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<tr>
<th>6. Eligibility/ in-/ exclusion criteria</th>
<th>56 not reported</th>
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</thead>
<tbody>
<tr>
<td>6a. Did all patients undergo both fetal US and fetal MRI? FetalUSMRI</td>
<td>yes</td>
</tr>
<tr>
<td>6b. Did all patients have singleton pregnancies? Single</td>
<td>yes</td>
</tr>
<tr>
<td>6c. Were all fetuses alive during US and MRI investigation? Fetal alive</td>
<td>yes</td>
</tr>
<tr>
<td>6d. Are fetal brain abnormalities described? FetalBrain</td>
<td>yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6d1. Which fetal brain abnormalities are described? FetalBrain</th>
<th>1. Ventriculomegaly</th>
<th>66 not reported</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>2. Corpus callosum agenesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Posterior fossa abnormalities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Other, please describe:</td>
<td></td>
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</tbody>
</table>


6d2: If ventriculomegaly is checked at 6d1, please report the degrees and sizes of ventriculomegaly:  
- mild, moderate, severe: 10-12, 13-15, >16 mm
☐ □ mild not reported
☐ □ moderate not reported
☐ □ severe not reported

6e. Are other fetal abnormalities described?  
☐ □ yes  ☐ □ no

6e1. If ‘yes‘ at item 6e, do the fetuses have abnormalities?  
☐ □ yes  ☐ □ no

6e2. If ‘yes‘ at item 6e1, describe which abnormalities:  
Specify

6e3. In how many cases were the abnormalities parts of a chromosomal syndrome?  
☐ □ yes  ☐ □ no

6e4. In how many cases were the abnormalities parts of a genetic syndrome?  
☐ □ yes  ☐ □ no

6f. Were patients with the following disorders included/ not included?  

6f1. Twin-to-twin transfusion syndrome  
☐ □ yes  ☐ □ no

6f2. Fetal chromosomal abnormalities  
☐ □ yes  ☐ □ no

6g. Other eligibility/ inclusion criteria:  
e.g. healthy fetuses

7. Study population: describe the following data:  
Describe for whole group! If only data can be described for subgroups, describe for subgroups

7a. Total number of fetuses

7b. Gestational age at ultrasound

7c. Gestational age at MRI

7. Study population: describe the following data:  
Describe for whole group! If only data can be described for subgroups, describe for subgroups

7a. Total number of fetuses

7b. Gestational age at ultrasound

7c. Gestational age at MRI
8. Start inclusion patients (year): not reported

9. End inclusion patients (year): not reported

10a. Study design: StudyDes
   - □ cohort
   - □ case control
   - □ cross sectional
   - □ other

10b1. Case control design: CaseDes
   - □ nested in
   - □ matched
   - □ both, nested and matched
   - □ other
   - □ not applicable

10b2. How was the control group composed? Control
   - □ differential diagnosis
   - □ healthy controls sample
   - □ not applicable

11a. Consecutive series of patients (selection): Consecutive
   - □ yes
   - □ no, random
   - □ no, neither consecutive, nor random sample (e.g., matched cohort)
   - □ not reported

11b. If 'no' at item 13a, number(s) of patients missed: not reported

12. Details of fetal ultrasound measurement
   Index test under review: USDet
   - (1) Type of measurement device
   - (2) Manufacturer
   - (3) Transducer
   - (4) Frequency
   - (5) Gestational age (mean)
   - (6) Where is the US performed
   - (7) How is the US performed
   - (8) Duration of examination
   - (9) other relevant details

13. Details of fetal MRI measurement
   Reference test under review: MRIDet
   - (1) Type of measurement device
   - (2) Manufacturer
   - (3) Scanner
   - (4) Sequence
   - (5) number of slices
   - (6) Thickness of slices
   - (7) Position body of pregnant woman
   - (8) Sedation, specify
   - (9) Contrast, specify
   - (10) Gestational age (mean)
   - (11) Duration of examination
   - (12) other relevant details
<table>
<thead>
<tr>
<th>Question</th>
<th>Option 1</th>
<th>Option 2</th>
<th>Option 3</th>
<th>Option 4</th>
<th>Option 5</th>
<th>Option 6</th>
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<tbody>
<tr>
<td>14. Flow: was fetal ultrasound executed first? (infrag)</td>
<td>yes, not applicable</td>
<td>no, fetal MRI first</td>
<td>no, at random</td>
<td>no, mixed</td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td>15. Prospective data collection:</td>
<td>yes</td>
<td>no, retrospective</td>
<td>no, ambispective</td>
<td>not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Were there any adverse events when performing ultrasound or MRI? (AdEv)</td>
<td>yes, specify</td>
<td>no</td>
<td>not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. Were MRI results blind for ultrasound results? (MRIB)</td>
<td>yes, not applicable</td>
<td>no</td>
<td>not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. Were ultrasound results blind for MRI results? (USBlind)</td>
<td>yes, not applicable</td>
<td>no</td>
<td>not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19a. Did ultrasound assessors have had training? (TrainAssUS)</td>
<td>yes</td>
<td>no</td>
<td>not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19b. Number of ultrasound assessors: (NAssUS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td>20a. Did MRI assessors have had training? (TrainAssMRI)</td>
<td>yes</td>
<td>no</td>
<td>not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20b. Number of MRI assessors: (NAssMRI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td>21a. Number of not interpretable, indeterminate, intermediate ultrasound results: (USMes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21b. Number of non-interpretible, indeterminate, intermediate MRI results: (MRIMes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21c. Number of non-interpretible, indeterminate, intermediate test results overall: (TotMes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21d. Are drop-outs reported? (DropOut) Drop-outs should not have been scored at any previous item!</td>
<td>yes</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21e. If 'yes' at item 25f, state number of drop-out: (NfDrop)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21f. Total number of patients excluded from analysis: (NfExcl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22. Are subgroup effects reported? (Sub#)</td>
<td>yes</td>
<td>no</td>
<td>not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. Does the reported estimate of diagnostic accuracy vary between subgroups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23a. Normal posture vs obese posture: (Posture)</td>
<td>yes</td>
<td>no</td>
<td>not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23b. Between centers: (Center)</td>
<td>yes</td>
<td>no</td>
<td>not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23c. Other subgroups: (Other) specify</td>
<td></td>
<td></td>
<td></td>
<td>85</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 24a. Gestational age(s) of patients at time(s) of index test measurement(s): GestAge

<table>
<thead>
<tr>
<th>Ultrasound</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
<td>Range</td>
</tr>
</tbody>
</table>

24b. How much time was there between ultrasound and MRI? Time

<table>
<thead>
<tr>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
</table>

25a. Describe type of brain malformations seen on fetal ultrasound: BMUS

25b. Describe type of brain malformations seen on fetal MRI: BMMRI

26. Prevalence of brain malformation in study population (%): PpMM

NB: In case control studies based on the cohort

27. Table

<table>
<thead>
<tr>
<th>Table</th>
<th>MRI does find additional / other pathology</th>
<th>MRI finds no additional / other pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI confirms US</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI partly confirms/rejects US</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI rejects US</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

28. Has postnatal follow up been done? PostNU

- Yes
- No

28a. If ‘yes’ at 28, what kind of follow up has been done? KindNU

- Cerebral ultrasound
- Cerebral MRI
- Neurological examination
- Other, please describe:

28b. If ‘yes’ at 28, was the prenatal diagnosis confirmed by postnatal follow up? ConfNU

- Yes, confirmed
- No, rejected

29. Financial support of industry: FinInd

- Yes
- No
Appendix 3: Flowchart showing selection of publications eligible for analysis or analysis

Records identified through Embase (n=2625)

Records after duplicates removed (n=2748)

Records identified through Medline (n=1416)

Records excluded (n=2577)

- Review/editorial/commentary/letter/case report
- No cerebral pathology
- No fetal US and MR
- No comparison 2D US and MR
- Not human
- Article published before 1990
- Deceased fetus during US or MRI examination

Records screened (n=2748)

Full-text articles assessed for eligibility (n=171)

Studies included in meta-analysis (n=27)

Full-text articles excluded (n=144)

- Review/Case report (n=43)
- No cerebral pathology (n=4)
- No fetal US and MR (n=6)
- No comparison 2D US and MR (n=29)
- No useful tables (n=25)
- Patient group <20 (n=26)
- No article available (n=7)

Appendix 4: Quality assessment

*If postnatal imaging or autopsy was performed in 75% of cases or more, we scored ‘reference test performed’ as positive.
Appendix 5: Additional findings fetal MRI and postnatal diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Additional fetal MRI diagnosis (n=267)</th>
<th>Additional postnatal diagnosis (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCA, CC hypoplasia</td>
<td>24% (64)</td>
<td>9% (7)</td>
</tr>
<tr>
<td>Parenchymal abnormalities</td>
<td>21% (55)</td>
<td>21% (16)</td>
</tr>
<tr>
<td>Gyral/sulcal abnormalities</td>
<td>15% (41)</td>
<td>9% (7)</td>
</tr>
<tr>
<td>Posterior fossa abnormalities</td>
<td>13% (36)</td>
<td>11% (8)</td>
</tr>
<tr>
<td>Biometric parameters</td>
<td>10% (27)</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Aqueduct stenosis</td>
<td>5% (13)</td>
<td>1% (1)</td>
</tr>
<tr>
<td>AVM, vein of Galen malformation, sinus thrombosis, SAB</td>
<td>2% (5)</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Tumor, teratoma</td>
<td>1% (3)</td>
<td>-</td>
</tr>
<tr>
<td>Absent septum pellucidum</td>
<td>1% (2)</td>
<td>3% (2)</td>
</tr>
<tr>
<td>Partially fused thalami</td>
<td>-</td>
<td>4% (3)</td>
</tr>
<tr>
<td>Fused coronal sutures</td>
<td>-</td>
<td>1% (1)</td>
</tr>
</tbody>
</table>

AVM arteriovenous malformation, CC corpus callosum, CCA corpus callosum agenesis, CM cisterna magna, DWM Dandy Walker Malformation, DWV Dandy Walker Variant, HC hydrocephalus, IVH intraventriculair hemorrhage, PF posterior fossa, SAB subarachnoidal bleeding, VM ventriculomegaly, WM white matter