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Should MRI be performed on all fetuses with mild ventriculomegaly ?

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* Discussants are listed in the order they debated.

Key points:

What is already known on this subject?

- Mild ventriculomegaly may be associated with a poor outcome, though in the vast majority of cases outcome is good.
- Whether upon diagnosis second line MRI should be done, remains controversial.

What does this study add?

- Each of these examinations is only as good as the operator's expertise
- Expert neurosonography can detect many anomalies being described on MRI in the context of mild ventriculomegaly
- In some settings, there may be medicolegal reasons to complement ultrasound with fetal MRI

Abstract:

A ventricular diameter of 10 mm correlates with more than two standard deviations of the normal, hence is qualified as ventriculomegaly. The relevance of it is dependent on whether there are associated infectious, genetic or structural problems. The chance for neurodevelopmental delay in isolated ventriculomegaly less than 15mm is 7.9% (4.7-11.1), and less if it is unilateral. It can be further divided in mild (10-12) or moderate (13-15), though this is not widely accepted.

As part of the work-up, structural assessment today may include ultrasound or magnetic resonance imaging, or both. Discussants agreed that the diagnostic performance of both methods is as good as the expertise with which the images are acquired and interpreted. Discussants agreed that when the initial neurosonogram is normal, the likelihood of finding significant findings on MRI is low. Nevertheless, some anomalies may only be picked up or better worked out by fetal MRI. In utero follow up is advocated, as progression may indicate a poorer outcome, and some conditions are only obvious late in pregnancy. Most benefit for future patients is expected from appropriate training in prenatal neuro-imaging.

Introduction (Jan Deprest)

International and most national guidelines make measurement of the atrial width of the lateral ventricle on occasion of the second trimester ultrasound (US) mandatory [1]. That obviously requires an accurate measurement of the atrium of the lateral ventricles on an axial transventricular plane, including the frontal horns and cavum septi pellucidi, with symmetrical hemispheres. The measurement is done there where the body, posterior horn and temporal horn converge. The calipers should be positioned on the internal margins of the atria, at the level of the parietal-occipital groove and glomus of the choroid plexus, on an axis perpendicular to the long axis of the lateral ventricle [1] (Figure 1). Fetal ventricular diameters remain stable between 15 and 40 weeks and their normal range is between 5.4 – 7.6 mm [2].

A diameter of 10 mm or more correlates with at least 2.5 standard deviations above the normal, therefore abnormal and referred to as ventriculomegaly [1-3]. Fetal ventriculomegaly is a descriptive term and, like fetal hydrops, not a diagnostic entity with an unequivocal prognosis, yet it may be a sign of underlying problems. Once ventriculomegaly has been diagnosed, it should prompt a number of additional diagnostic procedures to determine its clinical relevance (summarized in [4]). The differential diagnosis is wide, and it may be challenging to identify an exact etiology during the prenatal period.

Ventriculomegaly is for prognostic reasons divided based on the ventricular diameter and the presence or absence of additional problems. For *non-isolated* cases, the prognosis in essence depends on the nature of the associated findings. *Isolated* ventriculomegaly is used when no additional structural, genetic or acquired anomalies are present. The other major prognostic factor is ventricular size. When the ventricles measure more than 15 mm, it is referred to as severe. The prevalence of severe ventriculomegaly at birth is around 0.3-1.5/1,000 [5] and only 42.2% (CI: 27.5-57.6) of cases will have normal neurodevelopment [6].

When the ventricles measure between 10 to 15 mm, the likelihood of abnormal neurodevelopment is around 7.5%, which is two to three times higher than in the general population [7, 8]. Such ventriculomegaly has a prevalence of 0.7-1% [1, 9, 10] and it is more common in male fetuses [11, 12]. The likelihood to identify in mild ventriculomegaly associated structural abnormalities in a systematic review on 20 studies on 770 patients, was 4.5% for genetic abnormalities and one in three for structural anomalies [7]. Unilateral mild ventriculomegaly (50-60%) is more frequent than bilateral [13, 14], has less associated problems and a better prognosis [15]. Further subcategorization is possible as either *mild* (10.0-12.0 mm, both included) or *moderate* (12.1-15.0 mm) ventriculomegaly, because of the difference in outcome [4, 16, 17]. The latter subdivision is however controversial because of the moderate quality evidence on the different prognosis [10, 18].

This debate assumes that fetal infection and genetic problems have been ruled out as causative of the ventriculomegaly [4, 19] and focuses on what *imaging methods* should be used to further explore what seems an isolated finding on US. Magnetic Resonance Imaging (MRI) is increasingly used and accessible and the question is whether MRI should be routinely performed when isolated mild ventriculomegaly has been diagnosed.

FOR (Daniela Prayer)

While ultrasound may recognize most abnormalities described with mild ventriculomegaly, certainly when performed by a dedicated and experienced neurosonographer, fetal MRI provides additional information in 5.7 % of fetuses with normal ultrasound findings [13], even when using only a basic protocol consisting of T1 and T2 weighed sequences. In the Meridian cohort, MR findings included

agenesis of the corpus callosum, absent septum pellucidum, disorders of cortical development and cerebrovascular conditions [13]. It is correct that not all the additional findings were associated with a poor prognosis. For instance, isolated septal agenesis typically has no impact on neuropsychological development [20]. In some cases, however, mild ventriculomegaly can also be the peak of the iceberg and be a sign of clinically relevant problems. Therefore, when detected on routine mid-trimester ultrasound, the finding should initiate follow up examination by a dedicated neurosonographer or MRI-examination [21]. Though basic sequences are already of added value, exploiting all the possibilities of fetal MRI, including sequences sensitive for ischemic lesions and haemorrhage, tractography, spectroscopy, and, in the future also resting state MRI [22], will add information. Pathologies associated with mild ventriculomegaly that may only be visualized by MRI or for which MRI is more sensitive than US, are displayed in Table 1. Given the relevance of excluding some of these findings, it is fair to say that the main role for MRI in this situation is that it may reassure pregnant woman that the prognosis is good (Figure 2).

The suspicion of ventriculomegaly very often is raised at the time of mid-trimester screening ultrasound. This is relatively early in pregnancy. MR assessment of the fetal brain *before* 24 weeks may be impaired by fetal movement which by the third trimester is less. In addition, post-migratory changes may not yet be present. However, pathological changes that may be associated with ventriculomegaly, such as haemorrhagic residuals at the ependymal, or lissencephaly associated with a dysplastic brainstem or disorders of lamination respectively may already be visible before 24 weeks[23].

Often cost issues and availability are called in to a debate like this one. These may indeed be factors determining the use of either ultrasound or MRI for further assessment. The cost of an expert neurosonography and fetal MRI indeed vary between countries and health systems. In some places, costs are comparable, hence MRI should be offered, but we acknowledge the situation may be different elsewhere. Whereas availability of MRI, and of its expert interpretation, may be an issue in places, one needs to admit that both imaging modalities are subject to similar limitations. As to MR, reassurance is only warranted if an appropriate image acquisition protocol has been used and the images are read by a skilled reader. Therefore, as for US, suboptimal MRI may not provide any diagnostic advantages to US done by a dedicated neurosonographer. However, the opposite is also true. To date and in every day practice, comprehensive education in both fetal neurosonography as well as fetal MRI is unfortunately still limited. Courses and visiting fellowships are increasingly available, yet experience with MRI is still not widespread, and candidate subspecialists, or even residents should therefore be encouraged to obtain hands-on education in both fetal neuro-ultrasound as well as fetal MRI.

In conclusion indications for fetal MRI are:

- Suboptimal conditions for ultrasound in the widest sense of the word
- Potential medicolegal consequences for those countries where not offering MRI may lead to litigation
- History of cerebral malformations in former pregnancies or in the family
- Suspicion of ischemic lesion or haemorrhagic residuals

And as pregnancy progresses:

- Increasing ventricular width at ultrasound follow up
- De novo detection of mild ventriculomegaly in the third trimester

Also, fetal MRI should be performed when the pregnant woman asks for it, or when the obstetrician seeks for reassurance that the ventriculomegaly is truly isolated.

AGAINST (Daria Paladini).

Even though I agree with the further subdivision of mild and moderate ventriculomegaly, most papers discussed below are not considering these subgroups. Therefore, in this debate, I refer to isolated ventriculomegaly with atrial widths between 10.0 and 15.0 mm.

Whereas MRI was introduced several years ago to further explore intracranial anomalies [33], it has now gained popularity in the evaluation of a rather uncomplicated condition such as isolated mild ventriculomegaly. However, considering that ventriculomegaly represents the most common brain abnormality in the fetus, with an incidence of 0.3-1.5/1000 livebirths [12], and that normal neurodevelopmental outcome is expected in the overwhelming majority [11], carrying out an MRI on all these fetuses does represent an economic and logistic nightmare. In my opinion, there are two important errors significantly contributing to the perceived need for recommending an MRI.

The first one is that, in several cases, the measurement of the atrial width was not adequately done. Again, ISUOG guidelines [1] and most fetal neurology experts[34], recommend measurement of the atrial width (a) in a correct axial plane; (b) at a correct anatomic level; (c) on a magnified image; and (d) with correct IN-IN positioning of the calipers. Despite precise guidelines and a significant effort to teach these in all good quality basic courses in obstetric ultrasound, it is all but common to see printed or archived images with suboptimal size of the proper axial view of the fetal head and/or wrong placement of the calipers. This underscores how critical an adequate theoretical and practical training in obstetric ultrasound is before moving to clinical practice [1, 34] and should not be solved by doing additional second line investigations like MRI. In addition, the natural history of ventriculomegaly should be taken into account. It has been well established that mild ventriculomegaly regresses to normal in 13% to 83% of cases, with a median value of 34% [11]. These two issues explain why in a significant proportion of cases an MRI carried out after mild ventriculomegaly is suspected/diagnosed on ultrasound, will obviously be reassuring. Given that in one third of the cases, regression will occur, repeated sonographic assessment should be sufficient, hence eliminate the need for a costly MRI, which may require extensive travel for the patient. Because of the above, many false positive or transient cases are inappropriately included in series supporting the diagnostic role of MRI.

However, we think that, on the top of the two issues mentioned above, the core of the problem lies elsewhere. We carried out a careful review of the pertinent literature, retrieving 1520 cases of mild ventriculomegaly that were assessed with both US and MRI. In this pooled set of cases, MRI added “clinically relevant *additional* information/malformations” in 127 cases (= 8.3%). However, at closer look, a number of critical issues were found that question that number, as itemized below.

- *Quality of the initial ultrasound.* In several series, there is no detail on whether the findings were made by fetal neurosonography, i.e. second line scan as recommended for suspected CNS fetal abnormalities [1], or on simple US screening. In addition, in some series the performance was obviously of very low quality, since basic abnormalities easily detectable at the screening level, were repeatedly missed [13, 16] (Table 2).
- *Quality of the neurosonography.* In most cases, the neurosonography was performed only transabdominal. This is not the recommended approach for neurosonography [1, 35]. The high frequency vaginal transducer is more performant, especially for subtle anomalies such as periventricular heterotopias, periventricular cysts or small hemorrhages. In the few papers in which transvaginal three-dimensional neurosonography was performed, the added value of MRI was only in 1.2% (3/245 cases), including one in a morbidly obese woman [35-37]. We acknowledge that there are rare circumstances in which it is impossible to carry out

transvaginal ultrasound, such as persistent breech, but one paper [13] states that “*the reduced accuracy of ultrasound in older gestational age fetuses can be attributed to several factors including ... the descent of the fetal head into the maternal pelvis*”! Given this seems rather an ideal situation for carrying out a successful transvaginal neurosonography, it can be easily imagined how inadequate was the scanning.

- *Experience of the operator.* In 87/127 (68.5%), the anomaly only detected by MRI should have been *easily* detected at neurosonography, at times even on screening ultrasound (Table 2). The above number is a cautious estimate, as another 31/127 (24.4%) diagnoses might be picked up by US if their size or subtype would allow, yet details were not provided by the authors (Table 3). In none of these cases, acceptable limitations such as maternal obesity or multiple pregnancy were mentioned by the authors.
- *Questionable diagnoses and inadequate terminology.* In 31/127 (24.4%), the terminology used to describe the additional information provided by the MRI was not matching any official classification of CNS malformations (Table 4). In addition, some diagnoses were MRI findings without clinical counterpart (e.g. white matter T2 hyperintensity). This adds to the observation that in some cases no post-mortem or post-natal confirmation was available [38-41].
- *Accuracy of the MRI.* In 15/127 (11.8%), the MR diagnosis was either incorrect (while the US was correct; n=2), incomplete (n=10), while in 3 cases both ultrasound and MR did not detect the malformation diagnosed postnatally (hence being false negative) [13, 19, 36, 41-43].

Therefore, in *our brave new world* – quoting a recent editorial by Malinger [44] – when mild ventriculomegaly (or even other intracranial findings) is diagnosed, women should be referred primarily for neurosonography, i.e. by transvaginal route; with three-dimensional and multiplanar image correlation carried out by an expert in fetal central and peripheral nervous system malformations. In such setting [35-37] one can expect that in 1.2% there will be added value of MRI for as long as image acquisition and interpretation is done as well by an expert. This means 100 MRI scans should be performed to add clinically relevant information in one patient. Under the assumption one fetal MRI costs 200 €, while fetal neurosonography in most European countries costs less than 100 €, 20.000 € will be spent on any single case with additional clinically relevant information. I acknowledge that this is not necessarily a personal cost and that non-monetary arguments play a role as well. That money could for instance be invested in adequate training in fetal neurology and transvaginal neurosonography.

Discussion (Jan Deprest)

Debates on purpose pin discussants to a black and white situation. Discussants agreed that the finding of isolated ventriculomegaly should prompt follow up to assess for progression of the finding. Progression may occur and should be considered as a poor prognostic sign, while resolution is reassuring [11, 12]. When stable, there seems to be no need to modify timing and mode delivery [4]. There is neither any doubt that MRI has the potential of diagnosing abnormalities not visible (or missed) on ultrasound such as cortical folding and migrational disorders, some of them very relevant to ventriculomegaly ([35, 45] [46]), hence changing the prognosis, yet for other abnormalities the clinical relevance may be minimal. MRI is also the modality of choice in specific conditions, such as body habitus, non-vertex presentation or placenta previa, and twins.

There is also a non-medical argument in the discussion. Even when complete work-up suggests that the mild ventriculomegaly is truly isolated, whether that conclusion is reached based on advanced neurosonography, MRI or both, the postnatal occurrence of neurodevelopmental problems may in the current medico-legal climate lead to legal consequences. In some countries, judges may rule that fetal MRI should have been offered, as it *might* have provided additional information. Though such decision by a judge may not at all be evidenced based, the consequences of it may be dramatic for the physician. Therefore many clinicians may feel obliged to complete a negative work-up with an additional MR examination, certainly if national societies like the Society of Maternal-Fetal Medicine seem to advocate to do so[4]. However, one should read its recommendation in detail, stating this should *only* be done provided such “experience and expertise is available”. One should keep in mind, that in court, experts will also look at the quality of the images (either US or MRI) and their appropriate interpretation.

It seems fair to conclude that the overall outcome of mild ventriculomegaly is in most cases good, and women should be reassured after appropriate and comprehensive work up [4, 7]. In that process, prenatal imaging is key. Any imaging method is only as diagnostic as the quality and scrutiny with which it is performed. Whether it is ultrasound or MRI, mediocre quality assessment will be falsely reassuring. Therefore the best available advanced neuro-imaging should be offered. Expert neurosonography can rule out most intracranial abnormalities, yet others may only be diagnosed by MRI. Finally, further follow up is advocated, as progression is a poor prognostic sign and some anomalies only become obvious later on. We acknowledge that in some countries both examinations may be required for medicolegal reasons, yet even reassuring findings do not exclude postnatal problems. The rate of newly discovered anomalies reportedly is as high as 6-10% [11](8.3% in the critical review carried out by the opponent), while in other series it is even higher, yet this may be an overestimation [17, 19]. Discussants felt that this should be much lower if expert neuro-imaging would have been performed. Apparently that required high level of neurosonography is not widely available, yet the problem may not be solved by routinely offering MRI, as the same quality and expertise limitations apply to MRI. Appropriate training and multidisciplinary approach is recommended.

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Figure 1: Accurate measurement of the ventricles on ultrasound. Trans-ventricular view of a 23 gestational weeks old fetus. The correct approach for measuring the atrial width on screening ultrasound is based on: A) perfect symmetric axial trans-ventricular view (insert bottom left); B) adequate magnification, to ensure that both the proximal and the distal walls of the lateral ventricle are clearly visible; C) Inner-to-inner diameter measurement; D) according to most experts, the measurement should be taken at the level of the parieto-occipital fissure (arrow). In the image displayed, the measurement of 8.83 mm on the left is the correct one. The second measurement, on the right, is a wrong measurement, as it is taken as an outer-to-outer diameter, which leads to a false positive diagnosis of mild ventriculomegaly (10.02 mm). To avoid this inaccuracy, the most important step is an adequate magnification of the image (Courtesy: D Paladini).

Figure 2: Axial T2-weighted image at 24 weeks of pregnancy in a fetus with bilateral mild ventriculomegaly (courtesy D Prayer). The bar indicates the actual measurement.

Figure 3: Subtle cerebral abnormalities missed at trans-abdominal scanning and detectable at trans-vaginal neurosonography. A) Coronal view of the frontal horns at 24 gestational weeks. Evidence of bilateral germinal matrix multi-locular cysts (arrows); B) Grade I cerebral hemorrhage. The presence of bilateral hyperechoic areas, consistent with hemorrhage of the germinal matrix (arrows), is visible on the coronal view of the frontal horns; C) parasagittal view of the lateral ventricle showing irregular ependymal lining consistent with sub-ependymal heterotopias at 21 weeks (arrowheads); D) Parasagittal view of the lateral ventricle showing an abnormally deep parieto-occipital sulcus (arrowhead) at 26 gestational weeks. A large choroid plexus cyst (asterisk) was also present. Courtesy: D Paladini.

Table 1: Fetal brain pathologies that may be associated with mild ventriculomegaly, and under what circumstances they can be detected by US or MRI.

Pathology	Circumstances in which the pathology may be visible on US	Circumstances in which the pathology may be visible on MRI	Reference
Infarction	Chronic stage, when being cystic	Diffusion weighted MRI very sensitive to acute lesions	[24] [25]
Blood breakdown products	Accumulation detectable	Blood-sensitive sequences detect smaller bleeds	[24] [25]
Failure of white matter track formation	Difficult before 24 weeks, detection rate higher with increasing ventricular width	MRI very reliable, even on basic protocol	[26] [13]
Subependymal heterotopia	Will not be picked-up in average hands	MRI more reliable, maternal brain can be scanned in same session as this may be a X-linked condition	[27] [28]
Persistence of ganglionic eminence	Not yet reported	May be associated with micro-lissencephaly	[29]
Lamination abnormalities	May be visualized	MRI more reliable, and can predict gyration abnormalities later on	[30] [31]
Postmigratory changes of cortical development	Difficult to visualize due to skull ossification	MRI very sensitive	[32]

Table 2. Central nervous system malformations unquestionably diagnosable at neurosonography, or even on screening ultrasound, but that were missed at ultrasound in a pooled set of 127 cases out of a literature search made for this debate.

Type of Malformation	Number of cases	Authors, reference number
Corpus Callosum Agenesis	20 ¹	[16]Griffiths 2010 and [13]2017, [47]Morris 2007, [46]Whitby 2004 ²
Migration anomalies	10 ³	[13]Griffiths 2017, [48]Huang 2013, [49]Kandula 2015, [41]Salomon 2006, [40]Simon 2000, [50]Tonni 2016
Cerebellar and vermian anomalies	8 ⁴	[39]Benacerraf 2007, [16]Griffiths 2010 and [13]2017, [48]Huang 2013, [42]Ouahba 2006, [19]Pasquini 2014, [50]Tonni 2016
Septum Pellucidum agenesis	7 ⁵	[16]Griffiths 2010, [49]Kandula 2015, [42]Ouahba 2006, [36]Parazzini 2012, [46]Whitby 2004
Aqueductal stenosis	7 ⁶	[43]Baffero 2015, [47]Morris 2007, [42]Ouahba 2006, [19]Pasquini 2014
Severe clastic lesions	5 ⁶	[43]Baffero 2015, [16]Griffiths 2010 and [13]2017, [38]Mehlhorn 2017, [40]Simon 2000
Other major anomalies	9 ⁸	[48]Huang 2013, [47]Morris 2007, [46]Whitby 2004
Others	4 ⁹	[48]Huang 2013, [38]Mehlhorn 2017, [47]Morris 2007, [19]Pasquini 2014

In *italics*, the descriptive terms as used in the papers, not matching any official classification of central nervous system malformations or inadequately describing the lesion

¹ : 4 cases associated with gyration abnormalities, one of which was Aicardi syndrome (with microphthalmia and ocular coloboma); 1 case of *hypogenesis* of corpus callosum and gyration abnormalities

² : All studies from the same multicentre group, in different periods

³ : including: abnormal gyration, subependymal heterotopia, hemimegalencephaly, microlissencephaly

⁴ : including: cerebellar hypoplasia, vermian agenesis, Dandy-Walker malformation, vermian hypoplasia, megacisterna magna; one case associated with corpus callosum hypoplasia

⁵ : one case associated with schizencephaly (unknown if open or closed lipped)

⁶ : including five cases defined as *dilatation of the 3rd ventricle* (and not openly as aqueductal stenosis)

⁷ : including: schizencephaly + septo-optic dysplasia, brain atrophy, periventricular leukomalacia, *encephalomalacia*, *reduced brain volume*

⁸ : including: holoprosencephaly (semilobar + 1 not subclassified), encephalocele, arachnoid cyst, vein of Galen aneurysm

⁹ : including findings but not conclusive diagnoses (*Chiari* malformation, without specification of type; *colpocephaly*, without diagnosis of corpus callosum agenesis), *hypotrophy of periventricular white matter*, and *thickened nuchal fold* leading to a diagnosis of Down syndrome

Table 3. Central nervous system anomalies that can potentially be diagnosed at neurosonography, depending on the subtype and size (information not provided by authors) but were missed at ultrasound in a pooled set of 127 cases out of a literature search made for this debate.

Type of anomaly	Circumstances under which this can be picked up by ultrasound
Periventricular leucomalacia	when cysts are large enough
Gyration abnormalities	depending on location and extent of sulcation anomaly
Corpus callosum hypoplasia	when significantly hypoplastic
Connatal cysts	when in the usual location at the frontal horns
Germinal matrix hemorrhage	depending on the interval between event and scan and size
Heterotopia	if subependymal, not if band heterotopia
Monro hamartoma	depending on size
Schizencephaly	when open lipped
Sinus thrombosis	when extensive

Table 4. Central nervous system malformations missed at ultrasound and detected on MR in a pooled set of 127 cases out of a literature search made for this debate, with inadequate terminology or incomplete diagnosis.

Type of Malformation	Comment
3 rd ventricular enlargement	finding only, no final diagnosis (e.g. aqueductal stenosis?)
Absent septum pellucidum	incorrect terminology, should read: septum pellucidum agenesis
Corpus callosum hypogenesis	incorrect terminology, should read: corpus callosum hypoplasia
Chiari malformation	incomplete diagnosis. Unclear if Chiari I or Chiari II
Colpocephaly	finding only, no final diagnosis (e.g. corpus callosum agenesis)
Decreased volume posterior white matter	incorrect terminology and unclear diagnosis
Encephalomalacia	incomplete diagnosis and no etiology
Frontal parenchymal thinning	incorrect terminology, should read: microcephaly?
Holoprosencephaly	incomplete diagnosis, no subtype
Hypotrophy periventricular white matter	incorrect terminology
Irregular ventricular walls	finding only, no final diagnosis (e.g. hemorrhage postnatal MR)
Periventricular cyst	incomplete diagnosis; no location and no etiology
Reduced brain volume	incorrect terminology; should read: brain atrophy
White matter cavitations	finding only, no final diagnosis
Thin, short corpus callosum	incorrect terminology; should read: corpus callosum hypoplasia
Undergyration	incorrect terminology, should read: pachygyria, microgyria
T2 hyperintensity	MR finding, unrelated to clinical counterpart