REVIEW

Sonographic detection of central nervous system defects in the first trimester of pregnancy

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ABSTRACT

The fetal central nervous system can already be examined in the first trimester of pregnancy. Acrania, alobar holoprosencephaly, cephaloceles, and *spina bifida* can confidently be diagnosed at that stage and should actively be looked for in every fetus undergoing first-trimester ultrasound. For some other conditions, such as vermian anomalies and agenesis of the *corpus callosum*, markers have been identified, but the diagnosis can only be confirmed in the second trimester of gestation. For these conditions, data on sensitivity and more importantly specificity and false positives are lacking, and one should therefore be aware not to falsely reassure or scare expecting parents based on first-trimester findings. This review summarizes the current knowledge of first-trimester neurosonography in the normal and abnormal fetus and gives an overview of which diseases can be diagnosed. © 2016 John Wiley & Sons, Ltd.

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INTRODUCTION

In many countries, the 11 to 13 weeks' ultrasound scan has been introduced in routine screening programs as it allows to determine gestational age and confirm number and location of pregnancies and is used as a screening for aneuploidies.[1] Because of advances in ultrasound technology and increasing sonographer familiarity with scanning in early gestation, many fetal malformations can now be detected in the first trimester.[2–4]

First-trimester evaluation of the fetal central nervous system is difficult, as this organ system evolves considerably over gestation. Nevertheless, with good knowledge of normal neuroembryology, early markers of disease can already be seen that early in pregnancy and some major abnormalities can be diagnosed or at least suspected in the first trimester. Both transabdominal and transvaginal approaches have been described to assess the fetal brain.[5,6] Although the transabdominal approach is most frequently used in routine screening, complementing it with a transvaginal scan is often useful in early pregnancy. Indeed, even though transvaginal probes cannot be manipulated with as many freedom as transabdominal probes, they are closer to the fetus and have better resolution,[7,8] thereby allowing a more detailed evaluation in cases of suspected anomalies.

The aim of this article is to summarize which anomalies of the fetal central nervous system can be suspected and/or diagnosed in the first trimester of pregnancy.

NORMAL FIRST-TRIMESTER ANATOMY OF THE FETAL BRAIN AS SEEN BY ULTRASOUND

To detect fetal brain abnormalities during the first trimester of pregnancy and avoid high numbers of false positives, it is necessary to understand the normal neurodevelopment in early pregnancy. In a process called neurulation, the initially formed neural plate transforms into the neural tube. This process starts at around 19 days of embryonic life and finishes around day 26. The neural tube then further develops into prosencephalon (forebrain), mesencephalon (midbrain), rhombencephalon (hindbrain), and the spinal cord. The primary brain vesicles can be identified by ultrasound as early as 5 to 6 weeks of gestation,[9] and their volume increases rapidly in the next few weeks[10] (Figure 1). At 8 weeks' gestation, the thalamus and cerebrum are formed from the forebrain, and the brain splits into the left and right cerebral hemispheres. The midbrain further develops into the tectum and cerebellar peduncles. The hindbrain develops into medulla oblongata, pons, and cerebellum. At the time of the first-trimester scan (11–13 weeks), rudimentary brain structures are present and can be assessed by ultrasound.[11]

The thickness of the brain cortex at that stage is about 1 to 2 mm. The insula appears as a slight depression on the lateral surface of the hemispheres. The hemispheres should appear symmetrical and should be separated by the interhemispheric fissure and falx[12] (Figure 2).

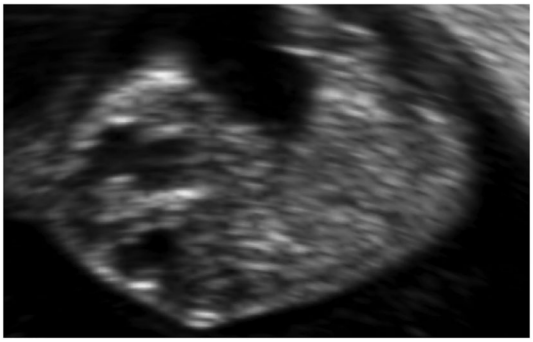

Figure 1 Normal neurosonographic image at 8–9 weeks in the sagittal plane

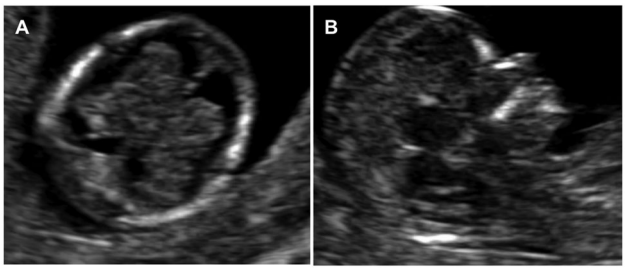

Figure 2 Transverse (A) and mid-sagittal (B) views of a healthy fetus at the time of the first trimester scan

The fluid-filled cerebral ventricles are almost completely filled by the choroid plexus and are clearly visible. The lateral walls of the anterior part of the ventricles can be visualized as two lateral echo's running parallel to the midline. The posterior parts of the lateral ventricles are filled with the echogenic choroid plexuses.[13,14] In the first trimester, the ventricular area grows more rapidly than the choroid plexus, thereby leading to a progressively decreasing plexus to ventricle ratio.[15] Of note also, the choroid plexus develops asymmetrically, with greater measurements on the left side.[16]

The cerebral subarachnoid space can be seen surrounding the brain parenchyma. The amount of fluid that this space contains can vary significantly.

The *corpus callosum* and the cerebellum are not sufficiently developed in the first-trimester ultrasound to allow complete sonographic assessment at this stage. However, the cerebellar hemispheres can already be seen, meeting in the midline, at 11 to 12 weeks' gestation. The cerebellar diameter increases rapidly throughout the first trimester from 6 mm at 11 weeks' gestation to 10 mm at 13 weeks.[17] The pericallosal artery can be evaluated with color Doppler ultrasonography in a mid-sagittal view.[18,19]

In the same mid-sagittal view, the brain stem, fourth ventricle, and *cisterna magna* can be seen (Figure 3). The fourth ventricle (which has also been called the 'intracranial translucency' because of its resemblance with the nuchal translucency) increases linearly over the first-trimester parallel to the fetal crown-rump length.[20,21]

Ossification of the skull should be visible from the 11th week onwards, and also the shape of the skull should be well assessable at that stage.[22] Ossification of the spine is visible

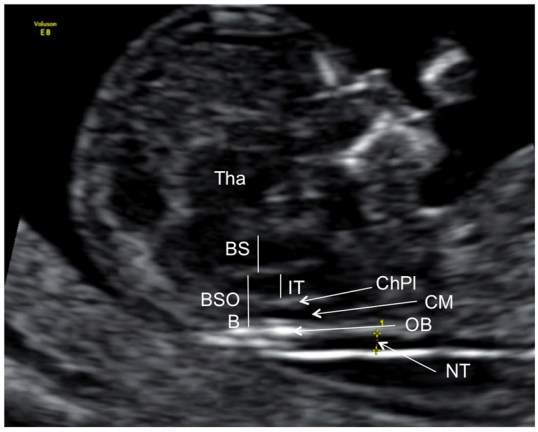

Figure 3 Normal mid-sagittal view at the first trimester. Possible measurements and anatomical structures of the posterior fossa are indicated: Tha, thalamus; BS, brainstem; IT, intracranial translucency; ChPl, choroid plexus; CM, *cisterna magna*; OB, occipital bone; BSOB, brain stem to occipital bone diameter; NT, nuchal translucency; adapted from Chaoui *et al.* 2011[63]

from 11 to 12 weeks onwards, and usually by 16 weeks, the cervical, thoracic, and lumbar vertebral bodies are well ossified. From 16 weeks onwards, an additional sacral level ossifies every 2 to 3 weeks.[23] The biparietal diameter (BPD) is usually measured during the first-trimester scan, although the *cavum septum pellucidi* is not visible as a landmark during this stage. Therefore, BPD measurements are often performed at varying levels of the fetal cranium. To avoid interobserver variability and intraobserver variability, they should be measured on the largest true symmetrical axial view of the fetal head. At about 10 weeks of gestation, landmarks such as midline and choroid plexus should be visible. Toward week 13, the thalamus and third ventricle provide good landmarks, too. Correct axial orientation will include both anterior horns and low occipital lobes of the cerebral ventricles.[12] Several direct and indirect signs have been described to identify malformations of the CNS at the 11 to 13 weeks' scan (Table 1).

ANOMALIES OF THE FETAL CENTRAL NERVOUS SYSTEM

Acrania–exencephaly–anencephaly sequence

Anencephaly is the endstage of the acrania–exencephaly–anencephaly sequence, which consists in the absence of skin and skull bones covering the brain. The brain, which is then directly exposed to the neurotoxic amniotic fluid and to direct trauma, will dissolve progressively.[24] The reported prevalence is 3.68 in 10 000 births according to the EUROCAT registry of congenital anomalies (http://www.eurocat-network.eu/accessprevalencedata/prevalencetables). Anencephaly is associated with other fetal malformations in about 12% of the cases and with chromosomal anomalies in 1 to 5%.[25] Exencephaly is typically described on ultrasound as the 'Mickey Mouse sign',[26] reflecting the two split cerebral hemispheres dangling freely in the amniotic fluid (Figure 4). After the progression to anencephaly, the characteristic 'frog eyes' appear, yet this is usually only in the second trimester. Although the abnormal brain may be the most striking sign,

Table 1 **Table indicating the different direct and indirect signs for the described malformations**

Malformation	Direct signs	Indirect signs	Sensitivity	False-positive rate
Open *spina bifida*	U-shaped spine	Brain stem/brain stem occipital bone ratio[71]	100%	n.s.
	Dorsal cyst (myelomeningocele)	Brain stem diameter >95th percentile[71]	96.7%	n.s.
	Kyphoscoliosis	Frontomaxillary angle <5%[57]	90%	n.s.
		Four-line view observed[68]	88%	n.s.
		BSOB diameter <5th percentile[71]	86.7%	n.s.
		Absent *cisterna magna*[53]	73%	n.s.
		BPD + biomarkers[62]	70%	10%
		Ratio BPD/TAD ≤ 1[60]	69.2%	5.1%
		BPD <5th percentile[58]	50–55.6%	n.s.
		IT[53]	45%	n.s.
		Lemon sign[54]	n.s.	n.s.
		Absence of 1 of 3 posterior brain spaces[46]	n.s.	n.s.
Dandy–Walker malformation	Enlarged posterior fossa with cyst	IT[77]	100%	n.s.
		BSOB diameter >95%[77]	100%	n.s.
		Brainstem to vermis angle[78]	n.s.	n.s.
Agenesis of *corpus callosum*	—	Pericallosal artery[18]	100%	n.s.
		Midbrain/falx diameter ratio[91]	85%	n.s.
Holoprosencephaly	—	Butterfly sign absent[35]	100%	n.s.
Encephalocele	Protruding brain	Absence of 1 of 3 posterior brain spaces[46]	n.s.	n.s.
	Chiari type III			
Anencephaly	Absence of skull	—	—	—
	Defromity of brain			
Ventriculomegaly	Increased ventricle size	—	—	—

Sensitivity and false-positive rate are indicated where applicable. Indirect markers with high sensitivity have to be taken with caution as they are often resulting from studies with very low case numbers.
BSOB, brain stem to occipital bone; BPD, biparietal diameter; TAD, transabdominal diameter; IT, intracranial translucency.

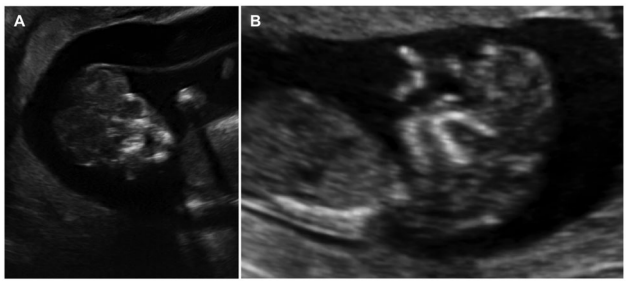

Figure 4 **Images of an acrania–exencephaly sequence at 11 weeks. The characteristic 'Mickey Mouse sign' can be seen (A). In the mid-sagittal view, the acrania and exencephaly can be identified (B)**

the primary marker of acrania is the absence of the skull bones, which should be ossified after 11 weeks' gestation. Although the prenatal detection rate of anencephaly is nearly 100%,[26–30] a recent study has shown that, in the Netherlands, only about 69% are diagnosed before 18 weeks of gestation and that this was strongly related to sonographer training.[31] However, even trained and accredited sonographers only reached an 86% detection rate, partly because some ultrasounds were performed prior to 11 weeks' gestation, thereby making assessment of skull ossification difficult.

Holoprosencephaly

Holoprosencephaly is characterized by maldevelopment of the prosencephalon into two hemispheres.[32] The result is a single-lobed brain structure and is often associated with severe skull and facial defects[33] (Figure 5). A prevalence of 1 : 1298 is reported, and over two thirds of cases are associated with

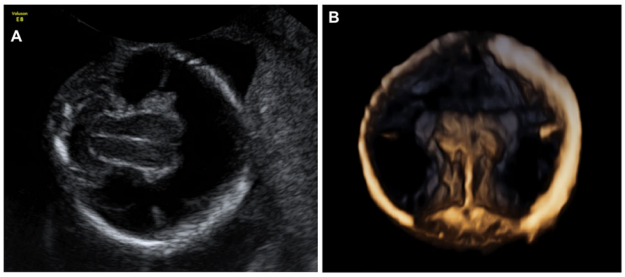

Figure 5 **A single-lobed brain structure can be identified in the 11 to 13 weeks' scan in this case of holoprosencephaly**

chromosomal abnormalities, mainly trisomies 13 and 18.[34] In the first trimester, the visualization of both choroid plexuses in an axial plane has been described as the so-called butterfly sign,[35] and the absence of this sign has very high sensitivity and specifity for alobar holoprosencephaly. As a consequence, early screening and diagnosis for this severe malformation are possible from early pregnancy onwards.[36,37] Lobar or semilobar holoprosencephaly, however, are more subtle to diagnose and will usually not be detected in the first trimester. Three-dimensional ultrasound has been investigated as a tool to detect holoprosencephaly, but, although very illustrative, its added value is questionable.[38,39]

Cephalocele

Cephaloceles are neural tube defects characterized by protrusions of intracranial structures through a defect in the skull. The incidence is around 1 in 5000 live births. Additional fetal malformations are seen in 65%.[40,41]

Most cases can be detected on axial or sagittal ultrasound views showing a cystic cranial lesion in continuity with the brain (Figure 6). This finding has often already preceded by an enlarged rhombencephalic cavity.[42,43] By visualization of the defect in the axial plain, a differentiation can be made between cranial meningoceles (only protrusion of meninges – 37% of cases) and encephaloceles (protrusion of brain tissue into the cephalocele[44]; 63% of cases).[45] In the mid-sagittal view, the absence of one of the three posterior brain spaces can be helpful to identify fetuses with cephalocele.[46] Three-dimensional ultrasound can be helpful to clearly image the defect.[43] The first-trimester detection rate of cephaloceles is 80%.

Open *spina bifida*

Open *spina bifida* (OSB) has a prevalence of about five per 10 000 pregnancies in Europe.[47] The phenotype seen postnatally is caused by a failure in the closure of the neural tube by the fifth to sixth week of gestation (24–27 days post conception) (first hit), which is subsequently followed by secondary brain changes and damage of the developing spinal cord and nerves due to direct trauma and neurotoxic agents in the amniotic fluid (second hit).[48–50] In the first trimester of pregnancy, these secondary changes will not have fully developed. As a consequence, the clinical picture is often more subtle, and OSB is difficult to diagnose.[48] Looking directly for the spinal defect in the first trimester will only allow to diagnose about half of all OSB cases (Figure 7). Especially lower level defects, without a large sac, are more difficult to detect as the spine is not yet fully ossified. The cases that are diagnosed in this way in the first trimester are usually severe and frequently associated with other major defects.[51,52]

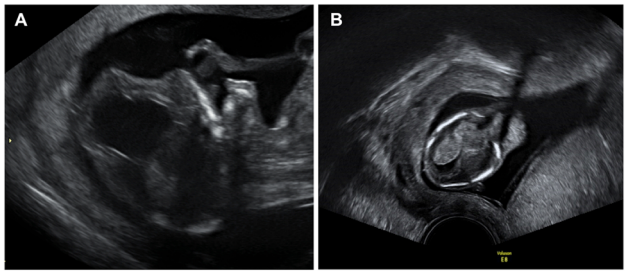

Figure 6 A cystic cranial lesion in continuity with the brain can be identified in cases of encephalocele in the axial (A) and sagittal (B) views

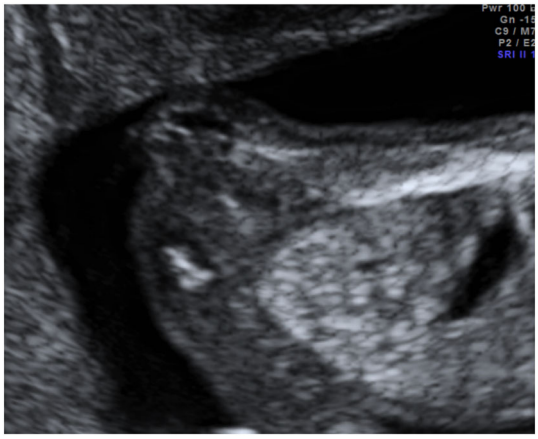

Figure 7 Visualization of a *spina bifida* defect in the first trimester in the sagittal view

To improve the detection rate of OSB in the first trimester, different ultrasound markers have been proposed, including an abnormal skull shape and size and abnormalities of the posterior fossa.[53] Similar with what is seen in the second trimester of pregnancy, many OSB fetuses will demonstrate scalloping of the frontal bones (the so-called lemon-sign) at 10 to 14 weeks' gestation.[54,55] This is probably already an early sign of cerebrospinal fluid leakage as fetuses with OSB have been shown to have decreased intracranial fluid spaces ('dried up brain') already from the first trimester of gestation on.[56]

The abnormal skull shape is also reflected in a sharper facial angle that, when corrected for crown-rump length, is about 10° lower than in controls, and it is below the fifth percentile in 90% of cases (Table 2).[57] Moreover, about 50% to 55% of OSB fetuses will have a BPD below the fifth percentile.[58,59] A ratio between the BPD and the transverse abdominal diameter lower than 1 is more practical to use in clinical practice as it obliviates the need for nomograms and will detect 69% of OSB cases for a similar 5% false-positive rate. The use of the BPD/abdominal diameter ratio in combination with a BPD less than the fifth percentile has the advantage of increasing the specificity (false positive 0.6%) but results in a lower detection rate (39%).[60] Combining BPD measurements with first-trimester maternal serum alpha-fetoprotein and free beta-hCG improves detection rates only marginally and has not gained widespread acceptance (70% sensitivity for 10% false positives).[61]

Another method for screening for OSB at the cranial level is by imaging the posterior brain. Indeed, posterior fossa abnormalities, which are omniprevalent in second-trimester OSB fetuses, already find their origin in the first trimester of pregnancy. At 11 to 13 weeks' gestation, the fourth ventricle or intracranial translucency can be visualized as an echolucent region in a mid-sagittal view of the fetal head and is delineated by the posterior border of the brain stem and the choroid

Table 2 Studies about intracranial translucency in regard to the identification of malformations

Study authors	Study design	Number of cases		Application	Main outcome
		Total no. of cases	malformations		
Volpe *et al.*,[75]	Retrospective	233	4	Dandy–Walker malformation	IT increased in study group
			10	Chromosomal anomalies	
Chen *et al.*,[53]	Prospective	15.526	11	*Spina bifida*	Screening for OSB feasible with CM and IT
Kappou *et al.*,[93]	Prospective	2.491	3	*Spina bifida*	IT and CM can identify OSB
Karl *et al.*,[67]	Retrospective	220	21	*Spina bifida*	PFF and IT decreased in OSB
Liu *et al.*,[94]	Prospective	3087	7	*Spina bifida*	IT useful for screening of *spina bifida*
Yuksel *et al.*,[95]	Prospective	596	3	*Spina bifida*	IT is gestational age dependent
Mangione *et al.*,[70]	Retrospective	260	52	*Spina bifida*	CM sensitivity > IT sensitivity
Kavalakis *et al.*,[96]	Prospective	1.330	2	Open neural tube defects	CM sensitivity > IT sensitivity
Fong *et al.*,[65]	Retrospective	199	8	*Spina bifida*	Sensitivity of absent IT = 50%
Chaoui *et al.*,[21]	Retrospective	204	4	*Spina bifida*	IT can be visualized in mid-sagittal view

Case reports and case series were excluded.
IT, intracranial translucency; OSB, open *spina bifida*; CM, *cisterna magna*; PFF, posterior fossa fluid.

plexus of the fourth ventricle (Figure 3).[21,63] The intracranial translucency (IT) can be identified in 96% of normal fetuses by trained sonographers,[64] and non-visualization of the IT has a sensitivity of 50% and specificity of 99% for OSB.[65] In some rare cases, the fourth ventricle, although abnormal in appearance, will still be present, thereby leading to a false-negative diagnosis. To solve this issue, other posterior brain markers have been proposed.[66] These include measurements of the *cisterna magna*, the brain stem and the brain stem occipital bone distance (BSOB), the posterior fossa fluid area, and the four-line view (Figure 3).[67,68] The anterior–posterior diameter of the *cisterna magna* can be measured in a mid-sagittal view.[69] Non-visualization of the *cisterna magna*, or a *cisterna magna* width below the fifth percentile, achieves sensitivity for OSB of 50% to 73%.[70] Absence of one of the three posterior brain spaces can be a useful marker for OSB.[46] On the same image, one can assess the brain stem diameter and brain stem to occipital bone distance.[63,64] A brain stem diameter above the 95th percentile, a BSOB diameter below the fifth percentile, and a brain stem to BSOB ratio above the 95th percentile have a sensitivity of 96.7%, 86.7%, and 100% for OSB, respectively.[71] When combining all three parameters for posterior brain evaluation in the first trimester (non-visualization of the IT, caudal displacement of the brainstem, leading to a short BSOB distance or non-visualization of the *cisterna magna*), most cases of OSB should be detectable from early gestation on as shown by the Multicenter Berlin IT study, which included 15 526 patients prospectively.[53]

Dandy–Walker malformation

Dandy–Walker malformation occurs in about one out of 30 000 live births.[72] Cardinal features of this condition at the second-trimester ultrasound include agenesis or hypoplasia of the cerebellar vermis, enlargement of the *cisterna magna*, atresia of the median and lateral foramina, and variable degrees of resulting obstructive hydrocephaly.[73] In the first trimester of pregnancy, direct assessment of the cerebellar vermis is not yet possible as it develops only later on. Fetuses who are later on diagnosed with vermian anomalies may, however, present with a markedly enlarged intracranial translucency and BSOB.[74–77] The absence of the dividing septum between the future fourth ventricle and the *cisterna magna* makes this sign even more sensitive and can also be seen in chromosomal aberrations and some other fetal abnormalities.[75] At 14 weeks of gestation, an increased brainstem-vermis angle was described in one case as an eventual marker for Dandy–Walker malformation,[78] and craniomegaly may sometimes be present.[79] The final diagnosis of vermian anomalies, however, can and should not be made prior to 16 weeks' gestation, given the incomplete development of this organ earlier on in gestation, and also in later gestation, such diagnosis can be difficult. First-trimester markers, however, could trigger an earlier second-trimester ultrasound (around 16 weeks' gestation) to not unnecessarily postpone diagnosis.[5,80,81] In fetuses with trisomy 18, trisomy 13, and triploidy, larger fourth ventricle diameters have been documented, and this should not be mistaken for a Dandy–Walker malformation.[82,83] However, Dandy–Walker malformation is often associated with these types of chromosomal abnormalities, so an underlying cerebellar anomaly in fetuses with trisomy 18, trisomy 13, and tryploidy cannot be excluded. Also, the rare case of an early detectable arachnoid cyst must be considered as differential diagnosis for Dandy–Walker malformation.[84] Also, false-positive values of IT and BSOB diameters need to be kept in mind.[75]

Agenesis of the *corpus callosum*

The *corpus callosum* is the most important brain commissure. Agenesis of the *corpus callosum* (ACC) occurs in 0.3–0.7% of the general population[85] yet is often part of a syndrome.[86] The pericallosal artery runs sagittally over the *corpus callosum* and can be assessed in the diagnosis of ACC.[19] The earliest direct sonographic visualization of the *corpus callosum* is possible from 16 weeks of gestation onwards and can be about

1 week earlier in female compared with male fetuses.[85] However, a non-detection of the *corpus callosum* should not be taken as a sign for ACC that early in pregnancy. The *corpus callosum* should be visible in most fetuses between 18 and 25 weeks' gestation.[87,88] The condition of ACC is usually suspected by absence of the *cavum septum pellucidum* and the teardrop configuration of the lateral ventricles with enlargement of the posterior horns[89] in the second or third trimester of pregnancy. These findings, however, are not yet present in the first trimester. An indirect marker of the presence or absence of the *corpus callosum*, however, is the course of the pericallosal artery. This vessel can be detected in >95% of normal fetuses at the 11 to 13 weeks' scan[18] and should be visible in all fetuses when the BPD is over 20 mm.[19] The use of three-dimensional ultrasound may help in improving detection rates.[90] An abnormal course of the pericallosal artery in the first trimester has been seen in fetuses diagnosed with ACC later on,[18] but given the rarity of the condition, data on sensitivity and specificity are lacking. Another marker for ACC is the 'midbrain/falx diameter ratio', which is measured in a mid-sagittal view at 11 to 13 weeks.[91] In a case–control study, Lachman *et al.* showed that this ratio is increased in more than 85% of fetuses with ACC.[91] Again, however, as with vermian anomalies, the diagnosis of ACC cannot be made in the first trimester, and early findings can only trigger an earlier second-trimester scan. Further data on false-positive rates are needed before such assessment is introduced in routine screening.

Ventriculomegaly

Most cases of ventriculomegaly will only present in the second and third trimesters of gestation. Reference values for the fetal ventricular system in the first trimester are available[56] but should be interpreted with care as brain formation is still ongoing and mild ventriculomegaly may still be a variation of normal. Nevertheless, first-trimester enlargement of the lateral ventricle has been described in fetuses with aneuploidy.[15,83] However, the type of chromosomal anomaly has an influence on the ventricle size in the first trimester as the ratio of choroid plexus area to lateral ventricles area is smaller in cases with trisomies 18 and 13 but remains unchanged in trisomy 21 compared with euploid fetuses.[15] Aquaductal stenosis can, in some rare cases, already present in the first trimester as severe ventriculomegaly. An abducted thumb may guide the sonographer to X-linked hydrocephalus.[92]

CONCLUSION

Acrania, alobar holoprosencephaly, cephaloceles, and *spina bifida* can be diagnosed in the first trimester of pregnancy and should actively be looked for in every fetus undergoing first-trimester ultrasound. For some other conditions, such as vermian anomalies and agenesis of the *corpus callosum*, markers have been identified, but the diagnosis can only be confirmed in the second trimester of gestation. For these conditions, data on sensitivity and more importantly specificity and false positives are lacking, and one should therefore beware not to falsely reassure or scare expecting parents based on first-trimester findings. Finally, as the brain grows and matures rapidly throughout gestation and even postnatally, it is not surprising that many anomalies cannot be diagnosed in early gestation (gyration anomalies, tumors, mild ventriculomegaly, schizencephaly, infectious sequellae, and so on). Careful examination throughout pregnancy remains warranted.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Several indirect and direct signs to diagnose malformations of the central nervous system (CNS) have been described for the 11 to 13 weeks' scan.
- However, to identify the best markers remains difficult.

WHAT DOES THIS STUDY ADD?

- Overview of the different markers that can be used to identify CNS malformations in the first trimester.
- How to use and interpret the early signs of those malformations.
- Overview of which CNS malformations can be at all diagnosed during the 11 to 13 weeks' scan and which measurement should be taken with caution.

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