
Clinical Standards Committee

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INTRODUCTION

Central nervous system (CNS) malformations are some of the most common congenital abnormalities. Neural tube defects are the most frequent CNS malformations and amount to about one to two cases per 1000 births. The incidence of intracranial abnormalities with an intact neural tube is uncertain, as most of these abnormalities probably go undetected at birth and manifest only in later life. However, long-term follow-up studies suggest that the incidence may be as high as one in 100 births1.

Ultrasound has been used for nearly 30 years as the main modality to help diagnose fetal CNS anomalies. The aim of these Guidelines is to review, describe and update the technical aspects of the screening evaluation of the fetal brain to be performed as part of the midtrimester anomaly scan, which is referred to in this document as a 'screening examination'. This Guideline also presents the indications for the detailed evaluation of the fetal CNS, which constitutes ‘targeted fetal neurosonography’, a dedicated examination of the fetal brain and spine that requires specific expertise and sophisticated ultrasound equipment. This examination is described in Part 2 of this Guideline, in which we also discuss the indications for fetal brain magnetic resonance imaging (MRI). Details of the grades of recommendation and levels of evidence used in this Guideline are given in Appendix 1.

GENERAL CONSIDERATIONS

Gestational age

Recommendation

- Examiners involved in screening for CNS abnormalities should be familiar with normal CNS appearance at different gestational ages (GOOD PRACTICE POINT).

The appearance of the brain and the spine changes throughout gestation. To avoid diagnostic errors, it is important to be familiar with normal CNS appearance at different gestational ages (Figure 1), although most efforts to diagnose CNS anomalies are focused around midgestation2. Hence, it is recommended that this Guideline is applied during the midtrimester anomaly scan.

However, during the last decade, it has become evident that an increasing number of CNS and neural tube abnormalities, mainly dorsal and rhombencephalic induction defects, may be visible from the end of the first trimester3–9. Although these are in the minority, they are usually severe and therefore deserve special consideration. While early examination of the CNS requires certain skills, it is always worthwhile paying particular attention to the fetal head and brain at early gestational ages. The advantage of early fetal neurosonography at 12–15 weeks is that the bones are thin and the brain may be evaluated...
### Technical factors

#### Ultrasound transducers

High-frequency ultrasound transducers increase spatial resolution but decrease the penetration of the sound beam. The choice of optimal transducer and operating frequency is influenced by a number of factors, including maternal habitus, fetal position, gestational age and the approach used. Most screening examinations are performed satisfactorily with a 3–5-MHz transabdominal transducer, although recent wideband transducers can also be employed advantageously.

#### Imaging parameters

The examination is performed with grayscale two-dimensional ultrasound. Harmonic and crossbeam imaging, as well as speckle-reduction filters, may enhance visualization of subtle anatomic details and in patients who scan poorly, for example those with increased body mass index or abdominal scarring.

### Screening examination of fetal brain after 18 weeks

#### Qualitative evaluation

**Recommendation**

- Transabdominal sonography is the technique of choice for the screening examination of the fetal CNS during the midtrimester scan in low-risk pregnancies. This examination should include evaluation of the fetal head and spine (GOOD PRACTICE POINT).

The fetal CNS screening examination during the midtrimester scan in low-risk pregnancies should include evaluation of the fetal head and spine, using transabdominal sonography. Evaluation of two axial planes allows visualization of the relevant cerebral structures to assess the anatomic integrity of the fetal brain. These planes are commonly referred to as the transventricular (Figure 2a) and transcerebellar (Figure 2b) planes. A third plane, the

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**Figure 1** Normal morphological changes of fetal brain throughout gestation, as visualized on sonographic examination in axial planes: views in transventricular, transthalamic and transcerebellar planes at 12, 21 and 32 gestational weeks. Note significant structural change of lateral ventricles and choroid plexus from late first trimester to midgestation, along with appearance of cavum septi pellucidi only from early second trimester onwards. Nevertheless, ventricular atrial width remains relatively stable during second and third trimesters.
Figure 2 Fetal central nervous system screening examination (normal 21-week fetus) in three axial planes. (a) Transventricular plane, showing anterior and posterior portions of lateral ventricles. Comma-shaped anterior horns are separated centrally by cavum septi pellucidi (CSP). Atrium and posterior horn of ventricle distal to transducer are also demonstrated, along with choroid plexus (CP), as anatomic reference for measurement of atrial width, and parieto-occipital fissure (*). (b) For transcerebellar plane, transducer is tilted posteriorly in order to depict middle and posterior fossa structures: thalami (Th), cerebellar hemispheres and cerebellar vermis, demonstrated as butterfly shape, and retrocerebellar anechoic space corresponding to cisterna magna (CM). (c) Transthalamic plane is frequently used for biometry of fetal head (biparietal diameter, occipitofrontal distance and head circumference) and is inferior and parallel to transventricular plane. In this plane, falx, anterior horns of lateral ventricles and CSP are also observed, as well as thalami (Th) and hippocampal gyri bilaterally. Line diagram (top left) illustrates positions of axial planes.

so-called transthalamic plane (Figure 2c), is frequently added, mostly for the purpose of biometry. Structures that should be noted in the routine examination include the lateral ventricles, the cerebellum and cisterna magna, and the cavum septi pellucidi (CSP). Head shape and brain texture should also be noted on these views (Table 1).

Table 1 Structures usually noted on screening ultrasound examination of fetal central nervous system

<table>
<thead>
<tr>
<th>Structure</th>
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<tbody>
<tr>
<td>Head shape</td>
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<tr>
<td>Lateral ventricles</td>
</tr>
<tr>
<td>Cavum septi pellucidi</td>
</tr>
<tr>
<td>Thalami</td>
</tr>
<tr>
<td>Cerebellum</td>
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<tr>
<td>Cisterna magna</td>
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<tr>
<td>Spine</td>
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Transventricular plane (Figure 2a)

Recommendation

- In the transventricular plane, the aspect of the atrium distal to the transducer and the presence of the CSP should be assessed and documented (GOOD PRACTICE POINT).

The transventricular plane demonstrates the anterior and posterior portions of the lateral ventricles. The anterior portion (frontal or anterior horns) appears as...
two comma-shaped, fluid-filled structures. They have a well-defined lateral wall and are separated medially by the CSP. The CSP is a fluid-filled cavity between two thin membranes. In late gestation or the early neonatal period, these membranes usually fuse to become the septum pellucidum. The CSP becomes visible between 17 and 20 weeks and disappears near term. Using transabdominal ultrasound, it should always be demonstrable between 17–20 and 37 weeks, or at a biparietal diameter (BPD) of 44–88 mm. Failure to demonstrate the CSP prior to 16 weeks or later than 37 weeks is a normal finding; rarely, absence of fluid in the CSP is seen in completely normal fetuses. The importance of visualizing the CSP between 17 and 37 gestational weeks is due to the fact that its non-visualization or an abnormal appearance is associated with commissural anomalies, which may be an indirect sign of corpus callosal agenesis on screening views (usually in conjunction with a tear-shaped appearance of the lateral ventricles, known as colpocephaly). Failure to visualize the membranes of the septum pellucidum is highly suspicious for the presence of a number of severe cerebral malformations, such as holoprosencephaly, severe hydrocephaly and septo-optic dysplasia. Recently, an abnormal shape of the CSP has been described as a relatively reliable marker of partial agenesis of the corpus callosum.

From about 16 weeks, the posterior portion of the lateral ventricles (also referred to as occipital horns) is, in reality, a complex formed by the atrium that continues posteriorly into the occipital horn. The atrium is characterized by the presence of the glomus of the choroid plexus, which is highly echogenic, while the occipital horn is filled with cerebrospinal fluid. Particularly in the second trimester of gestation, both medial and lateral walls of the ventricle are parallel to the midline and are therefore well-depicted sonographically as well-demarcated echogenic lines. Under normal conditions, the glomus of the choroid plexus completely fills the cavity of the ventricle at the level of the atrium, being in close contact with the medial and lateral walls, although in some normal cases a small amount of fluid may be present between the medial wall and the choroid plexus.

It should be noted that, due to artifacts in the near field of the image, caused by shadowing from the proximal parietal bone, in the standard transventricular plane, only the hemisphere and the lateral ventricle on the far side of the transducer are usually visualized clearly. However, most severe cerebral lesions are bilateral or associated with a significant deviation or distortion of the midline echo, and it has been suggested that, in screening examinations, symmetry of the brain can be assumed.

Transcerebellar plane (Figure 2b)

Recommendation

- In the transcerebellar plane, the presence and shape of the cerebellum, as well as the presence of cerebrospinal fluid in the cisterna magna, should be assessed and documented (GOOD PRACTICE POINT).

The transcerebellar plane is slightly caudal to the transventricular one, and it is usually obtained with slight posterior tilting of the transducer. It is used to visualize the thalamus, cerebellum and cisterna magna. The cerebellum appears as a butterfly-shaped structure formed by the round cerebellar hemispheres joined in the middle by the slightly more echogenic cerebellar vermis. The cisterna magna, or cisterna cerebellomedullaris, is a fluid-filled space posterior to the cerebellum. It normally contains thin septations, which are not usually demonstrated in the presence of pathology. In the second half of gestation, the antero-posterior diameter of the cisterna magna remains stable and should not exceed 10 mm. Before 19–20 gestational weeks, the cerebellar vermis has not yet completely covered the fourth ventricle, and this unusual appearance may give the false impression of a defect of the vermis. As a rule of thumb, by 19 gestational weeks, there should be no midline fluid-filled space between the two cerebellar hemispheres; should this finding, referred to as ‘keyhole sign’, be detected, it may be associated with an anomaly of the cerebellar vermis and the fetus should be referred for neurosonography. Care should be taken to avoid ‘over-tilting’ of the probe, since this will increase the likelihood of false-positive diagnosis of a vermic anomaly.

Transthalamic plane (Figure 2c)

Commonly referred to as the transthalamic or BPD plane, a third scanning plane, obtained parallel but caudal to the transventricular plane, is also frequently used in the sonographic assessment of the fetal head. The anatomic landmarks include, from anterior to posterior, the frontal horns of the lateral ventricles, the CSP, the thalami and the hippocampal gyri. This plane is used for biometry of the fetal head. It is easier to identify in late gestation and allows more reproducible measurements than does the transventricular plane.

Fetal spine

Recommendation

- When technically feasible, a longitudinal section of the fetal spine should be obtained, in order to screen for open and closed spinal dysraphism (GOOD PRACTICE POINT).

Technical advice

- Up to 97% of cases of open spina bifida present with the so-called ‘banana sign’, which is due to Chiari-II malformation (GRADE OF RECOMMENDATION: C).

Detailed examination of the fetal spine requires expertise and meticulous scanning, and the results are heavily dependent on the fetal position. Therefore, a full and detailed evaluation of the fetal spine in every plane is not part of the screening examination. One of the most frequent severe spinal abnormalities, open spina
bifida, is usually associated with abnormal intracranial anatomy: up to 97% of cases present with the so-called ‘banana sign’, which is due to Chiari-II malformation\(^2\). However, a longitudinal section of the fetal spine should be sought\(^4\) if technically feasible, because it may reveal, at least in some cases, other spinal malformations, including vertebral abnormalities and sacral agenesis, although the latter diagnosis may be challenging even for experts, due to the physiological non-ossification of the caudal spine in the mid trimester\(^2\). Under normal conditions, a sagittal section of the spine at 18–24 gestational weeks demonstrates the three ossification centers of the vertebrae (one inside the body and one on each side at the junction between the lamina and pedicle) that surround the neural canal, and that appear as either two or three parallel lines, depending on the orientation of the ultrasound beam (Figure 3). The three ossification nuclei are best visualized on an axial view of individual vertebrae (Figure 4). In addition, an attempt should be made to demonstrate the intactness of the skin overlying the spine, on either a transverse or a longitudinal view.

**Quantitative evaluation**

**Recommendation**

- The following measurements represent an integral part of sonographic screening for CNS malformations: atrial width and transverse cerebellar diameter. Additional measurements usually performed for general biometry purposes (BPD and head circumference (HC)) are also part of the examination, since they may, in some cases, reveal proliferation abnormalities (e.g. microcephaly or macrocephaly) (GOOD PRACTICE POINT).

**Technical advice**

- The atrial width should be measured inner-to-inner and should be <10 mm throughout pregnancy (GRADE OF RECOMMENDATION: 1).

Biometry is an essential part of sonographic examination of the fetal head. In the second-trimester anomaly scan, a standard examination includes measurement of the BPD, HC, internal diameter of the atrium and transverse cerebellar diameter. The cisterna magna depth should be measured if this structure is visually thinner or wider than normal on qualitative assessment of the posterior fossa.

BPD and HC are commonly used for assessing fetal age and growth and may also be useful to identify some cerebral anomalies. They may be measured either in the transventricular plane or in the transthalamic plane. There are various techniques for measuring BPD. Most frequently, the calipers are positioned outside the fetal calvarium (so-called ‘outer-to-outer’ measurement)\(^2\). However, some commonly used charts were produced using an outer-to-inner technique, to avoid artifacts generated by the distal echo of the calvarium, an issue that is less relevant now, with modern transducers, than it was several years ago\(^2\). These two approaches to measurement result in a difference of a few millimeters, which may be clinically relevant in early gestation. It is important, therefore, to know the technique that was used to construct the reference charts that one uses. HC can be measured directly, with the ellipse method, by placing the ellipse around the outer outline of the calvarium echoes. Alternatively, it can be calculated after measuring the BPD and occipitofrontal diameter (OFD), using the equation: $\text{HC} = 1.62 \times (\text{BPD} + \text{OFD})$. The BPD/OFD ratio is usually 70–85%. However, molding of the fetal head, particularly in early gestation, is frequent, and fetuses in breech presentation may show some degree of dolicocephaly. It is not appropriate to use HC nomograms intended for

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fetal weight estimation if the endpoint of the measurement is to exclude microcephaly.

Measurement of the atrium is recommended because several studies suggest that this is the most effective approach for assessing the integrity of the ventricular system, and ventriculomegaly is a frequent marker of abnormal cerebral development. Measurement is performed at the level of the glomus of the choroid plexus, perpendicular to the ventricular cavity, positioning the calipers inside the echoes generated by the lateral walls (Figure 5). This measurement remains stable in the second and early third trimesters, with a mean diameter between 6 and 8 mm. Although this cut-off was determined several years ago, it remains valid even with more modern equipment, particularly at midgestation. Therefore, an atrial width ≥ 10 mm should be considered suspicious. It is useful to emphasize here that: (1) the atrial width may change during gestation, either increasing or decreasing, and (2) moderate asymmetry in atrial width between the two sides should be considered normal, if both atria measure <10 mm.

The transverse cerebellar diameter increases by about 1 mm per week of pregnancy between 14 and 21 gestational weeks. This measurement, along with the HC and BPD, is helpful to assess fetal growth. In cases in which the anteroposterior diameter of the cisterna magna should be measured (because it is subjectively considered abnormal), the calipers should be positioned in a correct transcerebellar plane, between the outer edge of the most dorsal point of the cerebellar vermis and the internal side of the occipital bone. A normal measurement is 2–10 mm. With dolicocephaly, measurements slightly larger than 10 mm may be encountered.

In a low-risk midtrimester pregnancy, if the transventricular and transcerebellar planes are obtained satisfactorily, the head measurements (HC in particular) are within normal limits for gestational age, the atrial width is <10 mm and the cisterna magna width is between 2 and 10 mm, many cerebral malformations are excluded, the risk of a CNS anomaly that can be diagnosed at this gestational age is exceedingly low and further examinations are not indicated.

**SCREENING EXAMINATION OF FETAL BRAIN BEFORE 18 WEEKS**

**Recommendation**

- If a screening ultrasound examination is carried out before 18 gestational weeks, efforts should be made to visualize and document the transventricular and transcerebellar planes (GOOD PRACTICE POINT).

Fetal ultrasound examinations are being performed increasingly during the last few weeks of the first trimester and the early second trimester. These examinations include evaluation of the brain, but, until now, there have been no clinical guidelines for its examination. In our opinion, every fetal brain examination should include, at the very least, visualization of the transventricular and transcerebellar planes (Figure 6). Due to the rapid and dynamic developmental changes of the brain that occur both during pregnancy and after delivery, the patient should be informed not only of the technical limitations of these examinations but also of those related to temporal issues.
Figure 6 Transventricular (a) and transcerebellar (b) planes of fetal brain at 16 weeks. (a) In transventricular plane, lateral ventricles are large in relation to surrounding thin brain parenchyma. Frontal horns (*) are round and filled with cerebrospinal fluid. Choroid plexuses (CP) fill body, atria, occipital and temporal horns of lateral ventricles and may present irregular external boundaries. (b) In transcerebellar plane, in early second trimester, cerebellum (C) has dumbbell shape and superior vermis is present and isoechogetic relative to hemispheres (whereas it becomes weakly hyperechogetic later in gestation). Anterior horns (*), thalami (th), part of occipital horns of lateral ventricles and choroid plexuses (CP) are observed.

**Table 2 Indications for targeted fetal neurosonography**

- Suspicion of CNS or spinal malformation at routine screening ultrasound
- Suspicion of CNS or spinal malformation at nuchal translucency scan
- Family history of inheritable CNS or spinal malformations
- Previous pregnancy complicated by fetal brain or spinal malformation
- Fetus with congenital heart disease
- Monochorionic twins
- Suspected congenital intrauterine infection
- Exposure to teratogens known to affect neurogenesis
- Chromosomal microarray findings of unknown significance

CNS, central nervous system.

The introduction of MRI for evaluation of the fetal brain has provided a new and important diagnostic tool and has boosted research into and education on the complexities of the developing brain. ISUOG Guidelines for the performance and reporting of fetal MRI have been published recently and provide important information on this technique. However, stricter adherence to standard referral protocols is mandatory in order to avoid requests for fetal brain MRI directly from the operator performing a screening examination or a scan that is marginally more advanced than screening. Inappropriate referrals have resulted in both a falsely high rate of clinically relevant malformations being detected only by MRI (and published as such) and an exponential rise in fetal brain MRI examination. It is not appropriate to request MRI based only on suspicion of brain abnormality raised at screening ultrasound (GOOD PRACTICE POINT).
requests for questionable sonographic findings. In fact, when the results of these publications are analyzed carefully, the clinical usefulness of MRI in fetuses with suspicion of a CNS anomaly is much lower.\(^{40,41}\) Furthermore, the issue of high rates of false-positive MRI findings has been raised recently.\(^{42}\) It is therefore important that fetal brain MRI is performed only after, and to complement, a neurosonographic examination, and only if indicated by an expert.

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**REFERENCES**


APPENDIX 1 Grades of recommendation and levels of evidence used in ISUOG Guidelines

Classification of evidence levels

1++ High-quality meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with very low risk of bias
1+ Well-conducted meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with low risk of bias
1– Meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with high risk of bias
2++ High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with very low risk of confounding, bias or chance and high probability that the relationship is causal
2+ Well-conducted case-control or cohort studies with low risk of confounding, bias or chance and moderate probability that the relationship is causal
2– Case-control or cohort studies with high risk of confounding, bias or chance and significant risk that the relationship is not causal
3 Non-analytical studies, e.g. case reports, case series
4 Expert opinion

Grades of recommendation

A At least one meta-analysis, systematic review or randomized controlled trial rated as 1++ and applicable directly to the target population; or a systematic review of randomized controlled trials or a body of evidence consisting principally of studies rated as 1+ applicable directly to the target population and demonstrating overall consistency of results
B Body of evidence including studies rated as 2++ applicable directly to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C Body of evidence including studies rated as 2+ applicable directly to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D Evidence level 3 or 4; or evidence extrapolated from studies rated as 2+
Good practice point Recommended best practice based on the clinical experience of the guideline development group

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