ABSTRACT

Prenatal diagnosis of central nervous system (CNS) congenital anomalies is possible in the second and third trimester. Earlier diagnosis is possible for some of these as the complex acranial/exencephaly/anencephaly and alobar holoprosencephaly (HPE).

The knowledge of normal fetal brain development and its ultrasound images at the different weeks’ gestation, the expertise of operators, and high-resolution equipment are essential to obtain good results.

The diagnosis in the first trimester of some major anomalies incompatible with extrauterine life or associated with severe handicap is useful to inform the couple, to perform additional examinations, and provide them with the option of earlier and safer pregnancy termination.

For some other conditions, like agenesis of corpus callosum and hypoplasia or absence of cerebellar vermis, the diagnosis is possible only in the second trimester, so beware not to falsely reassure or scare expecting parents.

In conclusion, first trimester ultrasound could be useful for early detection of some CNS anomalies, but caution could be used for others, particularly in counseling couples about prognostic significant of ultrasound findings.

Keywords: Anencephaly, Cephalocele, First trimester, Holoprosencephaly, Ultrasound, Ventriculomegaly.


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INTRODUCTION

In the second and third trimester of pregnancy it is possible to identify fetal brain malformations by ultrasound. The first trimester scan at 11 to 13 weeks has been introduced in clinical practice to determine location of pregnancy, gestational age, number of fetuses, and ultrasound is used as a screening tool for aneuploidies by nuchal translucency (NT). With the development of ultrasound technology and increasing sonographer familiarity with scanning in early gestation, ultrasound diagnosis of several congenital anomalies is now possible. The difficulty is due to the fact that the CNS evolves considerably over gestation. For this reason, good knowledge of normal neuroembryological development and its corresponding ultrasound images is essential.

The abdominal and transvaginal approaches are both described for CNS study; moreover, the abdominal ultrasound is the most used in these years for screening programs, to measure the NT. The diagnostic potential of transvaginal scan has been described by Timor-Tritsch et al., who introduced the term “sonoembryology.” Although transvaginal probe cannot be manipulated like the abdominal one, it has better resolution and it can be a useful tool to investigate the CNS.

NORMAL FIRST TRIMESTER ANATOMY OF THE FETAL BRAIN

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 26 days after conception.

At 6 weeks’ gestation, the cephalic pole becomes visible, but no brain structures can be visualized. At 7 weeks it is possible to recognize the three cerebral vesicles: prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain). An anechogetic area corresponding to the rhombencephalon (future fourth ventricle) is easily seen in the posterior part of the head in a sagittal plane, while the mesencephalon lies at the top of the head and is smaller.

At 8 weeks’ gestation, the thalamus and cerebrum are formed from the prosencephalon, 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. An anechogetic area corresponding to the rhombencephalon (future fourth ventricle) is easily seen in the posterior part of the head in a sagittal plane, while the mesencephalon lies at the top of the head and is smaller.

At 9 weeks’ gestation, the choroid plexuses are observed as echogenic areas from 9 weeks’ gestation, and they are surrounded by a thin hypoechoic structure corresponding to brain parenchyma.
In the first trimester, the ventricular area grows more rapidly than the choroid plexus, thereby leading to a progressively decreasing plexus to ventricle ratio; so at 10 to 11 weeks’ gestation, they become more evident and the choroid plexuses measure 2 to 3 mm.

The skull ossification starts at 11 weeks, from the occipital bone.

At 12 weeks’ gestation, the cerebellar hemispheres and the thalami become visible. The cerebral cortex has a thickness of about 1 mm.

At 13 weeks the choroid plexuses are located principally in the occipital horn of the lateral ventricles and the frontal horns are sonolucent.

The corpus callosum and the cerebellum are not sufficiently developed in the first trimester, so ultrasound scan cannot allow a sonographic assessment at this stage. The cerebellar hemispheres seem to meet in the midline during weeks 11 to 12. The cerebellar diameter increases rapidly throughout the first trimester from 6 mm at 11 weeks’ gestation to 10 mm at 13 weeks.

**EARLY ANOMALIES DETECTABLE**

**Acrania/exencephaly/anencephaly**

These pathologies are incompatible with extrauterine life.

They have a prevalence of 3.68 in 10,000 births according to the EUROCAT registry (http://www.eurocat-network.eu/accessprevalencedata/prevalencetables). The aneuploidy risk is about 1 to 2% and the syndromic risk is low.

The anencephaly is the last stage of this triad. This anomaly is based on the absence of the calvarium, telencephalon, and midbrain. Due to the acrania the brain is in direct contact with the amniotic fluid (Fig. 1), so with the sagittal ultrasound scan, it is possible to detect exencephaly, like cerebral edematous tissue above the eyes (Fig. 2). Later, there is a destruction of the cerebral tissue (anencephaly) (Figs 3A to 5). Usually, anencephaly is detectable in the second trimester like the complete absence of cerebral tissue, so in the coronal scan, it is possible to see the eyes and a little hypechogenic tissue behind (the sign...

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**Fig. 1:** Sagittal scan of a fetus at 11 weeks’ gestation with cerebral tissue but there is no skull

**Fig. 2:** Another similar case at 11 weeks and 3 days

**Figs 3A and B:** (A) No more cerebral tissue is visible; and (B) by power doppler, a discrete vascularization may be seen
Central Nervous System Anomalies Detectable in the First Trimester

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of the “frog eyes” or “mickey mouse” sign). A similar appearance may be seen in the first trimester (Fig. 6).

The detection rate of these anomalies in the first trimester is about 97% and it depends in most part on the gestational age: in the late gestation, the diagnosis is easier.

Holoprosencephaly

It is the most common cerebral anomaly, although the prevalence is less than 1:10,000 live births because of the high abortion rate. The HPE is characterized by a failure of cleavage of the prosencephalon in the fifth gestational week, with incomplete division of the cerebral hemispheres and underlying structures; it is often associated with facial anomalies.

The HPE spectrum classically includes alobar, semilobar, and lobar forms (DeMyer classification).9 The most severe form is alobar HPE and it is characterized by a single ventricle, absence of interhemispheric structures, and third ventricle; the thalami are fused (Figs 7 and 8). Facial defects are frequently associated with abnormal development of the median facial structures (forehead, nose, interorbital structures, and upper lip). The differential diagnostic considerations are to make with hydranencephaly and severe hydrocephalus10 that exhibit normal thalamic cleavage, and usually at least a partially visualized falx cerebri.

The prenatal diagnosis of the semilobar and lobar forms is a challenge in the second trimester. Sometimes, the only sign is the absence of the cavum septum pellucidum at the 18–20 weeks ultrasound examination, so it cannot be diagnosed in the first trimester. The “middle interhemispheric variant” represents a more recent variant that is characterized by a mild clinical severity.

The etiology of HPE is multifactorial: chromosomal and genetic abnormalities, teratogen exposure, and/or syndromic association have all been described.

About 24 to 45% of the fetuses present anomaly of karyotype: trisomy 13 in the 75% of the cases and triploidy in 20%. At least 10% of those with a “normal” karyotype have microdeletions or duplications that can be detected with more advanced technology.11

Many reports describe the detection of alobar HPE between 11 and 14 weeks based on abnormal facial
morphology and absence of the “butterfly” sign. In a study it was reported that 20 to 33% of imaging studies failed to meet diagnostic criteria for HPE. This low rate explains the difficulty in earlier weeks. Even in the second trimester, the detection rate is reported to be nearly 86%.

Survival depends on the severity of the brain and facial malformations, the presence of chromosomal abnormalities, the involvement of other organs, and the presence of a multiple anomaly syndrome.

Cephalocele

It is due to a cranial defect with protrusion of meninges and brain. In the 37% of the cases, only the meninges protrude through the defect (meningoceles) and in 65% of the cases the brain (encephaloceles) also protrudes. The incidence is about 1:3,000 to 5,000 live births. It is often associated with other anomalies like hydrocephaly, microcephaly, and spina bifida, and it could be associated with some genetic syndrome like Meckel–Gruber syndrome (presence of polydactyly and renal dysplasia).

The aneuploidy risk is about 14 to 18%. The most common site of cephalocele is the occipital bone (75%), and another site could be the frontal or parietal bone. The lesion may differ in size and shape. The ultrasound diagnosis is possible in the first trimester, particularly in case of big protrusion, during the axial scan like a mass bulging from the fetal head (Figs 9 and 10). The first trimester detection
rate of cephaloceles is about 80%, and it depends on the location and the dimension of the defect.

**Hydrocephalus: Ventriculomegaly**

Ventriculomegaly is an increase of cerebrospinal fluid in the ventricles. Usually, it is detected in the second or third trimester of pregnancy and it is diagnosed when the liquid is more than 10 mm in the lateral ventricles in an axial scan. In the first trimester, it is possible to identify cases with severe ventriculomegaly (i.e., hydrocephalus). Ultrasound diagnosis is based on the identification of early enlargement of lateral cerebral (Figs 11 to 13). However, conclusions about diagnosing hydrocephaly should be drawn with caution before 14 weeks.

In the majority of cases, it is the consequence of an obstruction in the circulation and turnover of cerebrospinal fluid. Aqueductal stenosis is a disorder leading to hydrocephaly and it may be X-linked. The normal Sylvian aqueduct is wide throughout the first trimester.

It is conceivable that an early diagnosis of the aqueductal stenosis is possible, but we do not know when the stenosis develops. In their study, Syngelaki et al evaluated 44,859 pregnancies in the first trimester and among 11 cases of ventriculomegaly, only 1 was diagnosed before 14 weeks.

**OTHER CNS ANOMALIES**

**Open Spina Bifida**

It is due to a failure in the closure of the neural tube by the 5th to 6th week of gestation (24–27 days postconception) (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). The cerebral damage occurs in the second trimester, so it is difficult to diagnose this anomaly in the first trimester. In Syngelaki et al’s study, the detection rate was 14.3% and in other studies,
it reached 36.8% in the first trimester. A recently described marker that may improve the currently low detection rate of open spina bifida (OSB) at 11 to 13 weeks is the abnormal posterior fossa observed in the same mid-sagittal view of the fetal face for measurement of fetal NT and assessment of the nasal bone.16

Open spina bifida is associated with caudal displacement of the brain stem and compression of the fourth ventricle–cisterna magna complex within the confined space between the sphenoid and occipital bones. In normal fetuses, the fourth cerebral ventricle presents as an intracranial translucency (IT) parallel to the NT, while in fetuses with OSB there may be absence of the IT. Chaoui et al16 demonstrated an increase of the anteroposterior diameter of the IT with fetal crown–rump length (CRL) from a median of 1.5 mm at a CRL of 45 to 2.5 mm to a CRL of 85 mm at 11 to 13 weeks. In another study, some authors showed that there is an increase of the ratio brain stem/brain stem-occipital bone in all 30 fetuses with OSB analyzed.17 In a recent review, the authors conclude that most fetuses with OSB demonstrate in the first trimester positive sonographic markers in the posterior fossa, but additional prospective studies are needed to establish the best protocol for OSB screening.18 In a large meta-analysis, the purpose was to evaluate the accuracy of IT to predict spina bifida. After the analysis of nine studies (21,070 fetuses), the authors concluded that IT had low diagnostic accuracy in prediction of OSB, with a sensitivity of 53.5% [95% confidence interval (CI) 42.4–64.3], and specificity of 99.7% (95% CI 99.6–99.8),19 questioning its role as a screening marker for OSB in an unselected population.

Although the ultrasound has improved, some anomalies cannot be seen in the first trimester just because the normal conformation of the structure is not yet formed. Before 18 weeks of gestation, the cerebellar vermis is not yet complete, and it does not cover the fourth ventricle, so in some ultrasound scans it seems that there is a Vermian’s defect.8 It could be a mistake in diagnosis of Dandy Walker syndrome before the 18th week, because about 13% of fetuses before 16th week and 6% before 17th week did not complete the development.20

The corpus callosum normally develops at 14 to 19 weeks, so the ultrasound diagnosis of agenesis of the corpus callosum cannot be made at 11 to 13 weeks.21

CONCLUSION

During the first trimester scan, some major cerebral system anomalies could be diagnosed.22

In the 11–13 weeks’ scan, the pathognomonic features of acrania/exencephaly/anencephaly, alobar HPE, and cephalocele could guide for the correct early diagnosis with a high detection rate, but some pitfalls may create difficulties in early diagnosis.

Fig. 14: An axial scan having microphthalmia in fetus of 13 weeks with abnormal development of the brain: midline is not visible and an anechogenic area is present in posterior fossa. In this case chorionic villus sampling allows a diagnosis of trisomy 13

A detailed knowledge of normal ultrasonic findings, adequate equipment, and experience of the operator are mandatory in order to achieve acceptable results. The early diagnosis of some major anomalies incompatible with extrauterine life or associated with severe handicap is useful to inform the couple to perform additional examinations (Fig. 14) and provide them with the option of earlier and safer pregnancy termination. The pregnant woman must be informed that an early interruption of pregnancy is easier but it does not allow an autopic evaluation.

The diagnosis of spina bifida in the first trimester is still controversial. Although some markers have been proposed, there is lack of studies that confirm their efficiency.

For some other conditions like agenesis of corpus callosum and hypoplasia or absence of cerebellar vermis, the diagnosis is possible only in the second trimester, so beware not to falsely reassure or scare expecting parents.

In conclusion, ultrasound diagnosis is possible for some severe anomalies, such as anencephaly and alobar HPE from 11 weeks’ gestation and improves at 13 weeks, but caution must be used when the scan is performed too early.

REFERENCES


Fig. 14: An axial scan having microphthalmia in fetus of 13 weeks with abnormal development of the brain: midline is not visible and an anechogenic area is present in posterior fossa. In this case chorionic villus sampling allows a diagnosis of trisomy 13


