Assessment of Fetal Central Nervous System

Ritsuko K Pooh, KyongHon Pooh

ABSTRACT
Transvaginal high-resolution ultrasound and three-dimensional (3D) ultrasound has been establishing sonoembryology in the first trimester as well as neurosonography. Fetal brain is rapidly developing and changing its appearance week by week during pregnancy. The most important organ but it is quite hard to observe detailed structure of this organ by conventional transabdominal sonography. It is possible to observe the whole brain structure by magnetic resonance imaging in the post half of pregnancy, but it is difficult in the first half of gestation and transvaginal high-resolution 3D ultrasound is the most powerful modality. As for brain vascularization, main arteries and veins have been demonstrated and evaluated in various CNS conditions.

Keywords: Fetus, Central nervous system, Transvaginal scan, 3D ultrasound, Sonoembryology.


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INTRODUCTION
Antenatal evaluation of the fetal central nervous system (CNS) plays an important role in the field of perinatology. The brain rapidly develops in utero and remarkably changes its appearance from the primitive brain structure in early stage to the well-developed brain in late pregnancy.1 Introduction of high-frequency transvaginal transducer has contributed to establishing ‘sonoembryology’2 and recent general use of transvaginal sonography in early pregnancy enabled early diagnoses of major fetal anomalies.3 Furthermore, three-dimensional (3D) ultrasound has added accurate and objective information from early gestation till delivery, with surface anatomy, internal multidimensional analysis, volume calculation and circulatory visualization. Basic anatomical knowledge is essential, and transvaginal technique and 3D ultrasound are helpful for obtaining orientation of the brain in neuroimaging. The brain should be evaluated as a three-dimensional structure. One of reasons to make fetal neuroimaging difficult is lack of neuroanatomical knowledge. Figures 1 and 2 show basic knowledge of brain anatomy in the sagittal and coronal sections for neuroimaging diagnosis. Figure 3 shows the ventricular system.

TRANSVAGINAL APPROACH TO THE FETAL BRAIN
In the middle and late pregnancy, fetal CNS is generally evaluated through maternal abdominal wall. By transabdominal sonography, fetal brain is mostly demonstrated in transcranial axial sections. Sonographic assessment of the fetal brain in the sagittal and coronal
Fig. 4: Scheme of transvaginal sonography: Upper left: lateral view of vertex presenting fetus and transvaginal transducer. Upper right: frontal view of transvaginal approach. Clear imaging is possible by rotating and angle-changing of the transducer. Lower left: scheme of transfontanelle/trans-sutural approach of the fetal brain. Lower right: cranial bony structure from parietal direction. (AF: anterior fontanelle; S: sagittal suture; PF: posterior fontanelle). Those spaces are used as ultrasound windows.

Fig. 5: Fetal cranial structure in early gestation (3D US images). Upper left: 12 weeks, from the oblique front. Upper middle: 13 weeks, from the back. Upper right: 15 weeks, from the top of head. Lower left: 12 weeks, from the front. Lower right: 17 weeks. Oblique position. Premature shape of cranial bones, sutures and fontanelles at 12 to 13 weeks change its appearance to the neonatal shape (AF: anterior fontanelle; PF: posterior fontanelle; ALF: anterolateral fontanelle; F: frontal bone; P: parietal bone; O: occipital bone; C: coronal suture; M: metopic suture; S: sagittal suture; L: lambdoid suture).
sections, requires an approach from fetal parietal direction. Transvaginal sonography of the fetal brain opened a new field in medicine, ‘neurosonography’. Transvaginal approach to the normal fetal brain during the second and third trimesters was introduced in the beginning of 1990s. It was the first practical application of three-dimensional central nervous system assessment by two-dimensional (2D) ultrasound. Transvaginal observation of the fetal brain (Fig. 4) offers sagittal and coronal views of the brain from fetal parietal direction through the fontanelles and/or the sagittal suture as ultrasound windows. Serial oblique sections via the same ultrasound window reveal the intracranial morphology in detail. This method has contributed to the prenatal sonographic assessment of congenital CNS anomalies and acquired brain damage in utero, especially when compared with conventional transabdominal method.

THREE-DIMENSIONAL TRANSVAGINAL SONOGRAPHY

Introduction of 3D ultrasound in obstetrics has produced not only objective imaging of fetal superficial structure but also a combination of both transvaginal sonography and 3D ultrasound may be a great diagnostic tool for evaluation of three-dimensional structure of fetal CNS. 3D transvaginal sonography demonstrates bony structure such as cranial os (Fig. 5) and vertebrae (Fig. 6), multiplanar analysis of inside morphology from early till late pregnancy.

Fig. 6: Fetal back and vertebral structure of 16-week normal fetus (3D US images). Left: fetal back surface. Middle: inside of the fetus. Lamina of vertebra and ribs are clearly observed. Right: vertebral bodies and intervertebral disk spaces are seen

Fig. 7: Normal intracranial structure at 8 weeks of gestation in parallel cutting slices of three orthogonal views. Sagittal, coronal, axial sections from above. Premature sonolucent ventricular system is visible


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HYDROCEPHALUS AND VENTRICULOMEGALY

Hydrocephalus and ventriculomegaly are often used interchangeably to describe dilatation of the fetal lateral ventricles. However, they should be distinguished from each other to assess the enlargement of ventricles. Hydrocephalus is a dilatation of the lateral ventricles resulted from increased amount of cerebrospinal fluid and increased intracranial pressure, while ventriculomegaly is a dilatation of lateral ventricles with nonincreased intracranial pressure, due to hypoplastic cerebrum or other intracerebral abnormalities such as agenesis of the corpus callosum. In sonographic imaging, these two intracranial conditions can be differentiated by visualization of subarachnoid space and appearance of choroid plexus. The transvaginal oblique and coronal images demonstrate the obliterated subarachnoid space and the dangling choroid plexus in the case of hydrocephalus (Figs 12 and 13). In contrast, the subarachnoid space and choroid plexus are well preserved in the case of ventriculomegaly9 (Fig. 14). It is difficult to evaluate obliterated subarachnoid space in the axial section. Therefore, it is suggested that the evaluation of fetuses with enlarged ventricles may be evaluated by parasagittal and coronal views taken by transvaginal way. Furthermore, intracranial venous blood flow may be related to increased intracranial pressure. In normal fetuses, blood flow waveforms of dural sinuses, such as superior sagittal sinus, vein of Galen and straight sinus have pulsatile pattern23 (Fig. 15). However, in cases with progressive hydrocephalus, normal pulsation disappears and blood flow waveforms become flat pattern23 (Fig. 16). In cases with progressive hydrocephalus, there may be seven stages of progression (Fig. 17); (i) increased fluid collection of lateral ventricles, (ii) increased intracranial pressure, (iii) dangling choroids plexus, (iv) disappearance of subarachnoid space, (v) excessive extension of the dura and SSS, (vi) disappearance of venous pulsation, and (vii) enlarged skull.
**TRANSVAGINAL ASSESSMENT OF CONGENITAL CNS ANOMALIES**

**Neurulation Disorders**

**(Cranium Bifidum and Spina Bifida)**

**Cranium Bifidum**

The calvarial ossification started at 10 weeks of gestation and the hyperechogenic skull appears in sonographic image by 11 weeks in normal pregnancy. Cranium bifidum is classified into four types of encephaloschisis (including anencephaly and exencephaly), meningocele, encephalomeningocele, encephalocystocele and cranium bifidum occulatum. Encephalocele occurs in the occipital region in 70 to 80%. Many reported remarkable reduction of prevalence of NTDs after using folic acid supplementation and fortification, although some reported no decline of anencephaly rate. Acrania, exencephaly (Fig. 18) and anencephaly (Fig. 19), caused by disorder of neurulation, are not independent anomalies. It is considered that dysraphia (absent cranial vault, acrania) occurs in very early stage and disintegration of the exposed brain (exencephaly) during the fetal period results in anencephaly.

**Spina Bifida**

Spinal dysraphism is the most common abnormality of the central nervous system. Prevalence rate has been declined due to folic acid supplementation and fortification. Spina bifida aperta, manifest form of spina bifida, is classified into four types: meningocele, myelomeningocele, myelocystocele, myeloschisis. Approximately 10 to 15% of spinal dysraphic defects are closed and normal skin covers
Fig. 12: Tomographic ultrasound images of hydrocephalus at 20 weeks of gestation. Upper: sagittal images; lower: coronal images

Fig. 13: Hydrocephalus due to aqueductal obstruction at 19 weeks of gestation. Left figure: Three orthogonal views with anterior coronal (upper left) and median sagittal (upper right) and axial (lower left) slices. Bilateral ventriculomegaly and third ventriculomegaly (IIIrd V.) are seen. No enlargement of fourth ventricle indicates obstruction of the aqueduct. Right figure: Three orthogonal views with parasagittal (upper left) and posterior coronal (upper right) and axial (lower left) slices. Subarachnoid space is already obliterated and dangling choroid plexus (arrowheads) is seen. Lower right pink figure shows extracted 3D ventricular image by VOCAL mode. Ventricle in this case was tenfold size of normal 19-week ventricle
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Fig. 14: US image of ventriculomegaly at 29 weeks of gestation. Enlarged ventricle exists but subarachnoid space is well preserved and no dangling choroid plexus is seen. From those findings, nonincreased intracranial pressure (ICP) is estimated. This condition should be differentiated from hydrocephalus with increased ICP.

Fig. 15: Normal cerebral venous circulation. Left: sagittal image of color Doppler. SSS: superior sagittal sinus; ICV: internal cerebral vein; G: vein of Galen; SS: straight sinus; Right: normal blood flow waveforms of dural sinuses. In normal fetuses, venous flow always have pulsations.

Fig. 16: Disappearance of venous pulsation in cases with hydrocephalus. Normal dural sinuses have pulsatile patterns of flow waveform (Fig. 26). In cases with progressive hydrocephalus, venous pulsation disappeared (right figures) may be because of excessive extension of the dura and dural sinuses.

Fig. 17: Progressive stages of hydrocephalus. ICP: intracranial pressure; CP: choroid plexus; SAS: subarachnoid space; SSS: superior sagittal sinus.

The bony defects (spina bifida occulta). The open spina bifida with protrusion of the spinal cord mainly occur in the lumbar, thoracolumbar or lumbosacral regions. Sonographic appearance of myelomeningocele is shown in Figures 20 and 21. Chiari type II malformation is present in almost every case of myelomeningocele. This malformation is characterized by inferior displacement of the lower cerebellum through the foramen magnum with obliteration of the cisterna magna (banana sign), inferior displacement of the medulla into the spinal canal, and deformity of the frontal bone with indentation (lemon sign). Both banana
Fig. 18: Acrania at 11 weeks of gestation. Left upper: 2D coronal image. The normal appearance of amniotic membrane indicates no evidence of amniotic band syndrome. Right: 3D US occipital image of the same fetus.

Fig. 19: Anencephaly in middle gestation (same case as Fig. 24). Upper left: US sagittal image at 23 weeks of gestation. Upper right: US coronal image. Lower left: 3D US image. Lower right: external appearances of stillborn fetus at 25 weeks of gestation. It is clear that excencephalic brain tissue scattered in the amniotic space compared with this case at 10 weeks.

Disorders of Prosencephalic Development

Holoprosencephaly

Holoprosencephaly (Fig. 23) is caused by the disorder of prosencephalic development and is divided into the three subtypes: alobar, semilobar and lobar. Holoprosencephaly is frequently associated with other malformation, chromosomal aberration or Dandy-Walker malformation. A 75% of holoprosencephaly has normal karyotype, but chromosomes 2, 3, 7, 13, 18 and 21 have been implicated in holoprosencephaly. Particularly, trisomy 13 has most commonly been observed. The facial anomalies, such as cyclopia, cebocephaly, flatnose and cleft lip are often associated with holoprosencephaly. The characteristic appearance of fused ventricles is detectable from the early pregnancy.

Agenesis of the Corpus Callosum

Agenesis of the corpus callosum [(complete agenesis, partial agenesis, dysgenesis, (Fig. 24)] leads abnormal induction of medial cerebral convolution. Agenesis of the corpus callosum is associated with additional cerebral anomalies, noncerebral anomalies and chromosomal aberration. It has been described that isolated agenesis of the corpus callosum per se has little consequence on neurological development. Gupta et al. reviewed 70 reported cases of agenesis of the

sign and lemon sign are detectable by sonography until 24 weeks’ gestation (Fig. 22); and occasionally, the median section of craniovertebral junction demonstrates the medullary kink. Although the banana sign persists during pregnancy, the lemon sign may disappear in many cases with advancing gestational age.
Fig. 20: Prenatal US image of myelomeningocele, spina bifida at 20 weeks of gestation. Left: 3D bony demonstration of lumber spina bifida. 3D ultrasound shows the exact level of spina bifida. Middle: 3D surface reconstruction of large myelomeningocele (white arrows). Right: external appearance of aborted fetus at 21 weeks of gestation. Note: The central canal of the spinal cord (black arrow) in large myelomeningocele.

Fig. 21: 3D US tomographic images and 3D reconstructed image in a case of myelomeningocele at 26 weeks of gestation. Left upper: axial images; left lower: sagittal images; right: 3D image of spinal cord.

Fig. 22: Chiari type II malformation at 16 weeks of gestation. Chiari type II malformation is observed in most cases with myelomeningocele and myeloschisis. Left: typical lemon sign (arrows). Middle: typical banana sign (arrows). Right: 3D reconstruction internal image of Chiari type II malformation (arrows).
Fig. 23: Alobar holoprosencephaly at 20 weeks of gestation. Three orthogonal images of intracranial structure show complete single ventricle within a single-sphered cerebral structure. Lower right: 3D US image of fetal face and the face of aborted fetus at 21 weeks of gestation. A flat nose with median cleft lip/palate are seen.

Fig. 24: Sagittal section of AOCC (agenesis of the corpus callosum, left) and normal case (right). Lower images are 3D power Doppler images of AOCC (left) and normal (right). Note the defect of callosomarginal artery in AOCC case.
corpus callosum detected prenatally and described that 85% of fetuses without other detectable anomalies carried a normal development and 15% had a risk of handicap. Therefore, prenatal findings suggestive of agenesis of the corpus callosum should be followed by a careful search for associated anomalies and counseling parents should be prudent, if agenesis of the corpus callosum is an isolated finding. The typical findings of agenesis of the corpus callosum are the medial cerebral sulci demonstrated as a radial arrangement, enlargement of the posterior horns of lateral ventricles, steer-horn appearance of the anterior horns and upward displacement of the third ventricle. In most cases, detected prenatally by sonography, diagnosis was made by detection of indirect findings. The transvaginal median section of the brain, however, may be most reasonable to directly document the callosal lesion.

Migration Disorder

Lissencephaly

Lissencephaly is characterized by a lack of gyral development and divided into two types: type I has microcephaly and facial dysmorphism and often associated with Miller-Dierker syndrome and type II has hydrocephalus, retinal dysplasia and muscular dysplasia, associated with Walker-Warburg syndrome and Fukuyama congenital muscular dystrophy. Antenatal diagnosis of syndromes associated with lissencephaly before gyral development in families with prior affected infants has been reported by demonstration of additional abnormalities such as bilateral cataract and hydrocephalus. Sonographic detection of smooth gyral pattern at 31 to 32 weeks’ gestation has been reported. Prenatal sonographic diagnosis of lissencephaly, however, without a previous history cannot be reliably made until 26 to 28 weeks’ gestation, when the normal gyri and sulci become well defined.

Posterior Fossa Anomalies

Dandy-Walker Complex

Dandy-Walker complex is used to indicate a spectrum of anomalies of the posterior fossa. Classification of Dandy-Walker complex is as follows:

1. **Dandy-Walker malformation (Classic)—enlarged posterior fossa, complete or partial agenesis of the cerebellar vermis, elevated tentorium.**

![Fig. 25: Early stage of Dandy-Walker malformation at 11 weeks of gestation. Abnormal dilatation of the posterior fossa (arrowheads). Upper right figure is a sagittal image at the same gestational age in a normal case. Amniocentesis revealed trisomy 9 mosaicism and the fetus died in utero at 19 weeks.](image-url)
2. Dandy-Walker variant—variable hypoplasia of the cerebellar vermis with or without enlargement of the posterior fossa.

3. Megacisterna magna—enlarged cisterna magna with integrity of both cerebellar vermis and fourth ventricle.

Dandy-Walker malformation occurs as a part of recognizable syndromes such as Meckel’s syndrome and Walker-Warburg syndrome, and is frequently associated with chromosomal aberrations. There often exist additional intracerebral or extracerebral anomalies. Congenital hydrocephalus exists in 5 to 10% of cases, but hydrocephalus develops usually within 3 months after birth. Antenatal diagnosis should be performed by a careful observation of the posterior fossa in the axial, coronal and sagittal planes. The closure of the cerebellar vermis in normal fetuses is demonstrated by sonography from 14 to 18 weeks’ gestation. Bromley et al described that 56% of normal fetuses had an open vermis at 14 weeks’ gestation, 23% at 15 weeks and 6% at 17 weeks. Thus, the cerebellar vermis develops during early second trimester. The normal sonographic appearance of the open vermis should not be interpreted by developmental change of Dandy-Walker malformation and its variant, which is described as a small defect in the cerebellar vermis without dilatation of the cisterna magna. Prenatal diagnosis of Dandy-Walker variant should not be made before 18 weeks. It was described that prenatal diagnosis of Dandy-Walker malformation is possible from 14 weeks’ gestation. Although early detection of Dandy-Walker complex should be done prudently, we had a case with Dandy-Walker malformation which was strongly suspected from 11 weeks of gestation (Fig. 25) because of abnormal dilatation of the posterior fossa.

Cerebellar Hypoplasia

Cerebellar dysplasia (Fig. 26) is often associated with chromosomal abnormalities such as trisomy 18 and others. In late pregnancy, prenatal diagnosis of cerebellar dysplasia is not difficult because of conspicuous enlargement of cisterna magna. However, in the first half of pregnancy, all normal cases have large cisterna magna. In order to detect cerebellar dysplasia, therefore, it is recommended to assess the development of the cerebellum measuring the cerebellar transverse diameter in axial image or posterior coronal section.

Other Disorders

Arachnoid Cyst

Arachnoid cyst (Fig. 27) is a congenital or acquired cyst, lined by arachnoid membranes, and filled with fluid collection which is the same character as the cerebrospinal fluid. The number of cysts is mostly single, but two or more cysts can be occasionally observed. Location of arachnoid cyst is various; approximately 50% of cysts occur from the Sylvian fissure (middle fossa). Interhemispheric cysts are often associated with agenesis or hypogenesis of the corpus callosum. Postnatal prognosis is usually good.

Choroid Plexus Cyst

Choroid plexus cysts are defined as cysts with fluid collection within the choroid plexus with incidence of 0.95 to 2.8% of all fetuses scanned, which may exist unilaterally or bilaterally, associated with chromosomal anomalies such as large VSD, overlapping finger, lowset ears, etc.
Fig. 27: Fetal arachnoid cyst at 31 weeks of gestation. Upper: transvaginal US image. Sagittal (left) and coronal (middle, right) sections. Lower left: fetal MR sagittal image. The cyst occupies supra- to infratentorial space. Not only cerebrum but also cerebellum are compressed by the cyst. Lower right: fetal MR coronal image. Midline is conspicuously arcuated. Scalp and skull bone are extended due to the existence of the huge cyst. Note: The difference between right and left head size.

Fig. 28: Choroid plexus cysts (CPC) in cases of trisomy 18 (left) and normal karyotype (right). Left figures: three orthogonal views and inside 3D view of CPC in a case of trisomy 18 at 17 weeks of gestation. Various additional anomalies were detected. Right figures: three orthogonal views and inside 3D view of CPC in a case with normal karyotype at 16 weeks. No additional abnormalities. Normal postnatal course. Impossible to differentiate normal from abnormal karyotypes only by location and appearance of choroid plexus cyst. Detection of additional anomalies is important for differentiated diagnosis.
aberration such as trisomy 18. They are depicted in the second trimester and usually spontaneous resolution is observed by the 24th week. Choroid plexus cysts per se are usually asymptomatic and benign, but rarely, symptomatic and disturb CSF flow. It is impossible to differentiate normal from abnormal karyotypes only by location and appearance of choroid plexus cyst (Fig. 28). Isolated choroid plexus cysts may be normal variation. Fetal chromosomal examination should be offered if additional abnormalities are found.

**Acquired Brain Abnormalities in utero**

**Intracranial Hemorrhage**

Intracranial hemorrhage in utero may be caused by trauma, infections, asphyxia, alloimmune thrombocytopenia, intracranial tumor, cord complication, pre-eclampsia, abruptio placenta and other factors. Hemorrhage is commonly located in the subdural, periventricular and cerebellar regions. Many cases of intracranial hemorrhage detected prenatally have been reported. The outcome of fetuses with intracranial hemorrhage has ranged from fetal demise and postnatal death to a good outcome with normal development.

**Porencephaly**

Porencephaly [(porencephalic cyst, (Fig. 29)] is fluid-filled space replacing normal brain parenchyma and may or may not communicate with the lateral ventricles or subarachnoid space. Ischemic episode, trauma, demise of one twin, intercerebral hemorrhage, infection can cause porencephaly. It is easy to occur when immature cerebrum has some factors with propensity of dissolution and cavitation. Timing of ischemic injury (may be as early as second trimester) is strongly related to porencephaly.

**FUTURE ASPECTS**

The assessment of the fetal CNS plays an important role for the rest of infant’s life. Advanced sonography combined with methodology of approaching the fetal brain has improved the assessment of fetal intracranial structure and diagnosis of the prenatal brain abnormalities. Recent remarkable development of three-dimensional/four-dimensional ultrasound and advanced MRI technology will produce more accurate evaluation of the brain morphology. A functional evaluation of the intracranial condition and a prenatal prediction of neurological development after birth are also important points in a proper management for fetuses with intracranial abnormalities, but many uncertain and unknown facts still exist. Further studies on the assessment of cerebral function may be expected.

**REFERENCES**


ABOUT THE AUTHORS

Ritsuko K Pooh (Corresponding Author)
Director, Fetal Diagnosis Unit, CRIFM Clinical Research Institute of Fetal Medicine PMC, 7-3-7 Uehommachi, Tennoji, Osaka #543-0001, Japan, Phone: +81-6-6775-8111, Fax: +81-6-6775-8122
e-mail: evp-pooh@fetal-medicine-pooh.jp

KyongHon Pooh
Director, Department of Neurosurgery, Shikoku Medical Center for Children and Adults, 2-1-1, Senyucho, Zentsuji, Kagawa, Japan