The Fetal Neurology Clinic – A Multidisciplinary Approach

The Edith Wolfson Medical Center Experience

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Abstract

› Fetal neurology, formerly describing observations on prematurely born babies, has become an adjunct to morphological assessment of the developing nervous system on prenatal imaging studies. A multidisciplinary approach has provided the best results.

1 Introduction

The study of fetal neurodevelopment raised interest and controversy since ancient times. As late as the first half of the twentieth century, the predominant concept was that neurological and psychological development starts after birth (deMause 1982). Following scientific observations on newborns delivered prematurely, the notion of fetal neurological function gained quick acceptance (Vaughn 1975). In the 1980s, the group led by Professor Prechtl used ultrasound to study fetal behavioral states (Nijhuis et al. 1982; de Vries et al. 1982) and fetal eye movements (Bots et al. 1981) and founded the basis of a new field of research: Fetal Neurology (Prechtl 1988).

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Advances in the field of Fetal Neurology were possible due to two separate but interacting factors: (a) the improvement in fetal imaging due to the development of high frequency ultrasound probes, the use of the transvaginal approach, and the introduction of magnetic resonance as a complementary imaging technique; (b) the creation of multidisciplinary groups of experts from different fields that were able to integrate their knowledge for the benefit of the unborn patients and their families.

The Fetal Neurology Clinic at Wolfson Medical Center in Israel represents one example of such an approach. Similar clinics are now actively working in many countries (Italy, France, Spain, Colombia, Chile, and the USA).

The purpose of this chapter is to present the clinical approach of The Fetal Neurology Clinic at Wolfson Medical Center to the fetus with suspected neurological pathology and the methods we use for accurate parental counseling.

2 Early Steps Toward the Opening of a New Fetal Neurology Clinic

2.1 The Team

The success of a new FNC depends on the commitment and dedication of the participants. The initial team should include a specialist in fetal imaging, a geneticist, and a pediatric neurologist. We consider the participation of a social worker or a psychologist extremely important to help families cope with the serious dilemmas they are confronted with during and following counseling. Other specialists (Table 1) can participate on a routine basis, but more often will be invited to participate according to the specific findings on fetal imaging.

A reliable database that includes image files as well as demographic and, clinical information should be created from the beginning – for research and follow-up purposes.

It is also important that the pediatric neurologist who participates in the Fetal Neurology Clinic be able to follow the patients after birth and offer early intervention when needed.

In countries where termination of pregnancy is allowed, it is imperative to do an autopsy and study the brain by a pediatric pathologist with special expertise in fetal brain development.

Table 1 The fetal neurology clinic-participating disciplines

Initial team
Dedicated neurosonography
Pediatric neurology
Genetics
Clinic coordinator
Additional disciplines
Social service or psychology
Perinatology
Neonatology
Pediatric neuradiology
Pediatric neurosurgery
Perinatal pathology
Pediatric cardiology

2.2 Training in Fetal Neuroimaging

Currently we are not aware of any fellowship programs dedicated to fetal neuroimaging. Obstetric programs provide training in prenatal diagnosis based mainly on the use of ultrasound, and radiology programs usually concentrate on Pediatric imaging with little or no emphasis on fetal neurosonography and fetal MRI.

Historically, training in fetal neuroimaging developed on an individual, self-learning basis. During the last 10 years, dedicated courses on Fetal Neuroimaging have been available at different venues but self-training based on trial and error continues to be important. Articles and textbooks are useful in the process of understanding normal and pathologic fetal anatomy (Naidich et al. 1986; Volpe 2008a; b) and can enable learning from the experience of other centers in order to supply accurate counseling. In order to achieve proficiency in fetal neuroimaging, the ultrasonographers and pediatric neuroradiologists who work in the field of fetal neurology should study in established centers with a good work volume for a period of at least 6 months, and receive hands-on experience.

Fetal dedicated neurosonography (Malinger et al. 1993; Timor-Tritsch and Monteagudo 1996; Malinger et al. 2003; Malinger et al. 2006; Malinger and Pilu 2009; ISUOG guidelines 2007) relies on the multiplanar approach of the brain, and it should be clear that the use of standard axial planes is inadequate for the diagnosis of complex pathologies (Malinger et al. 2002, 2007). Furthermore, the dynamic maturation of the fetal brain

throughout pregnancy, particularly the formation of the cortex, corpus callosum, and cerebellum should be understood and kept in mind in order to avoid possible diagnostic errors (Fong et al. 2004; Cohen-Sacher et al. 2006; Malinger et al. 2009).

2.3 Fetal Neurology Clinic Setup

Almost from the start, 15 years ago, the FNC is conducted on a weekly basis with active participation of staff from the Prenatal Diagnosis and Pediatric Neurology Units, and the Genetics Institute. The participants are exclusively committed to the task. The appointments are usually scheduled by the patients or their treating physicians and they are asked to send all the relevant information to the program's coordinator. A list of the scheduled patients with a short history indicating the reason for the consultation and the data regarding imaging findings and or familiar history is e-mailed, two or three days in advance to all the FNC members, including those that do not participate on a regular basis. This allows the physicians to prepare themselves and have the opportunity to review the relevant literature. In urgent cases, an ad hoc meeting may be summoned without delay.

Upon arrival, the patients fill a form that includes demographic and pregnancy-related data, thereafter an introductory talk with the family and a complete medical intake are conducted.

The US examination includes biometry measurements and the performance of a detailed multiplanar neurosonographic examination. When indicated and technically possible, an anatomical full body scan is also performed. It should be mentioned that more than 50% of the examinations are performed during the third trimester with the well-known limitations of US at that time.

A tentative diagnosis is usually given after the initial examination and compared with the referral diagnosis. It is important to mention that currently 30% of the referrals are evaluated following the performance of fetal brain MRI.

The presence of all the relevant specialists in situ enables to provide the family with a unified diagnosis, and counseling regarding prognosis and management including recommendations for further tests (i.e., fetal echocardiography, TORCH, amniocentesis, genetic tests) and follow-up. When considered necessary, the social worker is asked to participate in this part of the discussion. The social worker will accompany the family during the stressful pregnancy until after delivery.

A complete and detailed report including annexed images is provided to the family and in most cases a follow-up visit is scheduled. During these visits new information and results of pertinent tests are obtained, a full neurosonographic examination is performed and compared to the previous US or when available to the MRI. The parents are counseled according to the new findings and test results.

When the patients are referred for either fetal MRI or neurosurgical consultations, the referral is usually done by physician to physician direct communication by phone or e-mail. Following termination of pregnancy, the fetus is delivered to a pediatric pathologist with special expertise in fetal brain development after discussion of the relevant findings and full documentation.

Delivered babies are first examined close to birth by the pediatric neurologist and geneticist and then followed routinely in the pediatric neurology clinic. When the family opts for termination of pregnancy the team reconvenes with the parents, after the autopsy results have been received and provides genetic counseling and recommendations regarding future tests and pregnancies.

3 Fetal Neurosonography

The fetal neurosonography technique has been extensively reported (Malinger et al. 1993; Timor-Tritsch and Monteagudo 1996; Malinger et al. 2003; Malinger et al. 2006; ISUOG guidelines 2007; Malinger and Pilu 2009), we will present a short description accompanied by demonstrative images.

A complete fetal neurosonographic examination depicts the brain in three orthogonal planes: axial, coronal, and sagittal. The examination is performed using transabdominal probes, when the fetus is in breech presentation and a combination of transabdominal and transvaginal probes for fetuses in vertex presentation. Although the use of 3D volume acquisitions has been proposed as an alternative (Pilu et al. 2006) we believe that at present in cases with suspected brain pathologies, the study should be done using the 2D technique.

The axial planes are the same as used for the basic examination of the brain: transventricular, transthalamic, and transcerebellar (Fig 1).

The transventricular plane enables visualization and measurement of the distal lateral ventricle width (LVW). LVW should be measured by positioning the calipers (in–in) at the level of the atrium and perpendicular to the median wall of the ventricle (ISUOG guidelines 2007). We also recommend obtaining an image of the proximal ventricle, when it is of normal size we do not measure the LVW of this ventricle.

The transthalamic plane is used to measure the HC and BPD and to depict the cavum septi pellucidi and the zone of the third ventricle.

The transcerebellar plane focuses on the visualization of the cerebellum and cisterna magna with the measurement of the transcerebellar diameter and the width of the cisterna magna.

Coronal planes are depicted by moving the transducer in a ventro-dorsal direction through the anterior fontanel, the sagittal suture, and the posterior fontanel. In this way, parallel views of each of the planes are obtained. Although the whole brain is scanned, four main planes have been described: transfrontal, transcaudal, transthalamic, and transcerebellar (Fig. 2). The transfrontal plane enables visualization of the frontal horns, the interhemispheric fissure, and during the third trimester depiction of the main frontal sulci. The transcaudal plane shows the presence of the anterior part of the CC and the CSP and its relationship with the lateral ventricles. The transthalamic plane is useful for the visualization of the 3rd ventricle and the insula; the lateral ventricles, CC, and CSP are also visualized. The transcerebellar plane depicts the occipital horns of the lateral ventricles, the tentorium, and the cerebellar hemispheres with the usually more echogenic vermis in the midline. Special attention should be given to the echogenicity of the periventricular zone, looking specifically for the presence of echogenicities, cystic changes, or an irregular ventricular wall. The coronal planes are also useful in the demonstration of the middle cerebral arteries and the presence of the optic chiasm (Fig. 3).

The sagittal planes are obtained while rotating the transducer 90° from any of the coronal views. The depiction of the brain is best when obtaining these planes through the anterior fontanel, but all the other placements, through the metopic suture, sagittal suture, or posterior fontanel also produce good quality pictures. Failure to visualize the brain structures through these points should raise the suspicion of craniosynostosis. We generally obtain a midsagittal and two parasagittal views, one for each ventricle.

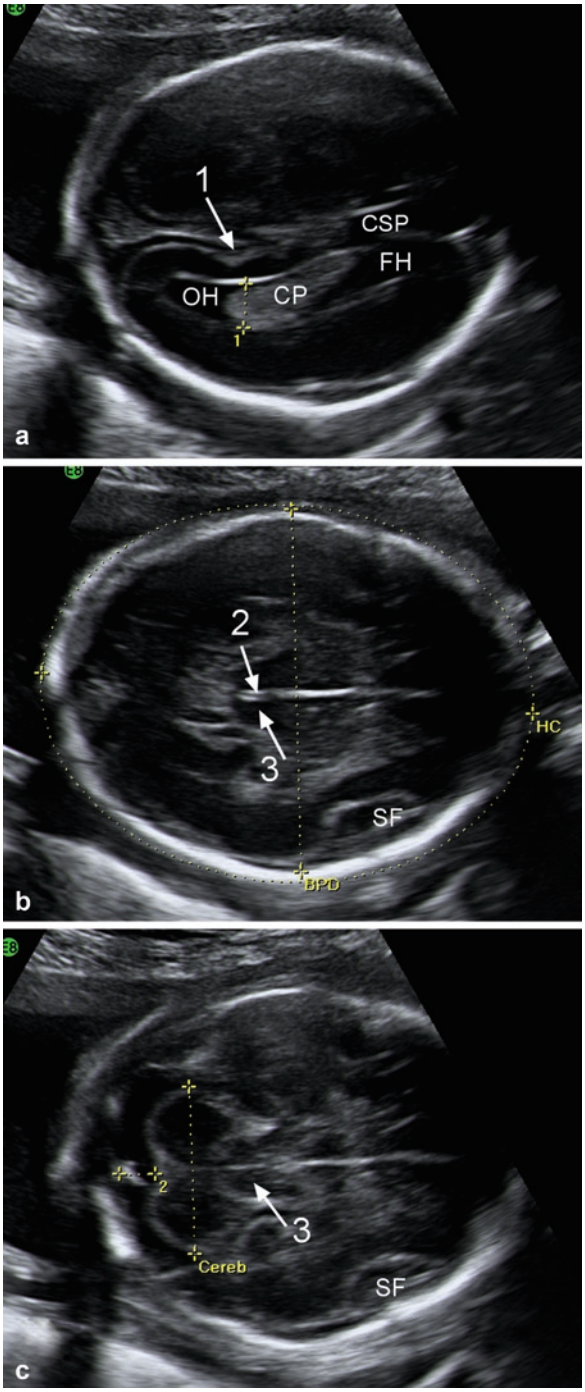

Fig. 1 Transabdominal axial planes at 23 weeks of gestation. (**a**) Transcentricular, (**b**) transthalamic,and (**c**) transcerebellar. Parieto-occipital fissure (1), aqueduct (2), middle cerebellar peduncles (3). Frontal (FH) and occipital OH lateral ventricle horns; choroid plexus (CP); cavum septi pellucidi (CSP); Sylvian fissure (SF). The yellow calipers are measuring the LVW (1 in (**a**)); the biparietal diameter (BPD) and head circumference (HC) (**b**) and the transverse cerebellar diameter (cereb) and cisterna magna width (2 in (**c**)) Note the poor visualization of the proximal cerebral hemisphere

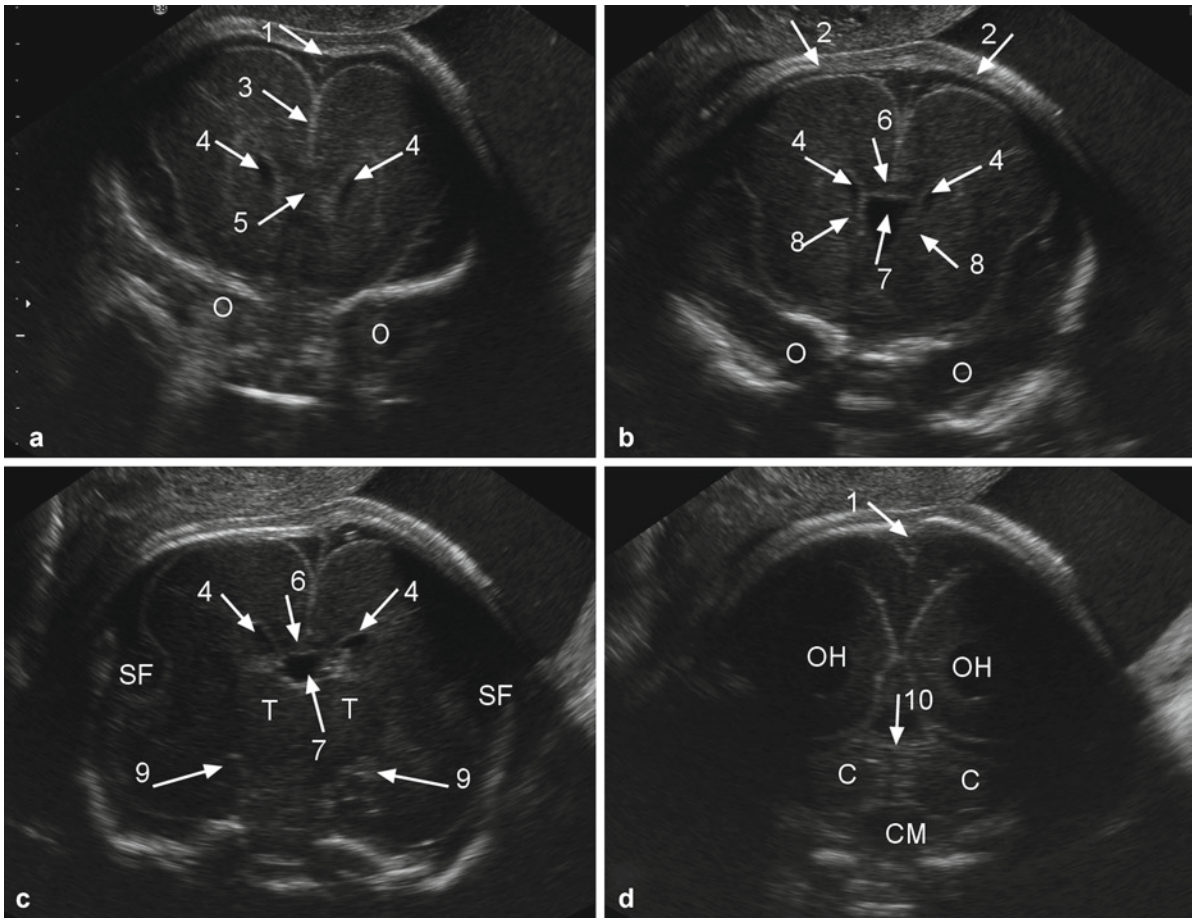

Fig. 2 Transvaginal coronal planes at 23 weeks of gestation. (**a**) Transfrontal, (**b**) transcaudate, (**c**) transthalamic, and (**d**) transcerebellar. Superior sagittal sinus (1), parietal bones and anterior fontanel (2), interhemispheic fissure (3), frontal horns of the lateral ventricles (4), genu (5) and body (6) of the corpus callosum, cavum septi pellucidi (7), caudate nucleus (8), hippocampus (9), cerebellar vermis (10). Orbits (O), Sylvian fissure (SF), occipital horns (OH), cerebellar hemispheres (C), cisterna magna (CM)

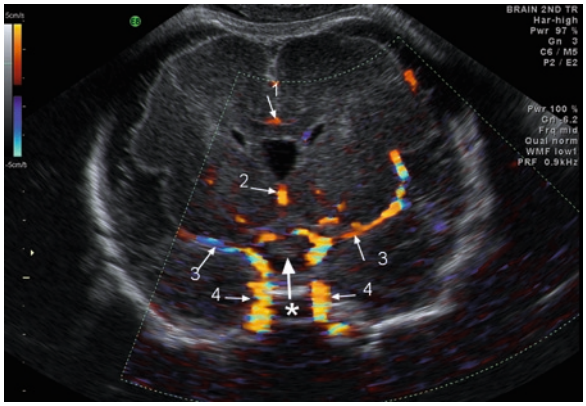

Fig. 3 Transvaginal transthalamic coronal plane at 26 weeks of gestation showing the optic chiasm (*). Callosal arteries (1), anterior cerebral artery (2), middle cerebral arteries (3), carotid arteries (4)

The midsagittal view depicts the midline structures: the corpus callosum, with the CSP and the cavum vergae and the cerebellar vermis, 4th ventricle, pons and surrounding cisterns (Fig. 4).

The parasagittal views show the lateral ventricle and the surrounding basal ganglia and brain parenchyma (Fig. 5).

4 Indications for Referral to Wolfson FNC

The indications for referral to the FNC can be divided into two groups (Table 2): screening of patients with a family history of congenital neurological disease, or exposure to possible teratogens; and evaluation of

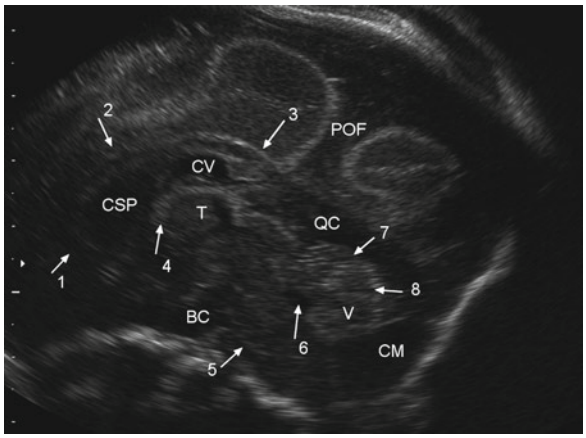

Fig. 4 Transvaginal median plane obtained through the sagittal suture at 23 weeks of gestation. Genu (1), body (2), and splenium (3) of the corpus callosum, choroid plexus of the 3rd ventricle (4), pons (5), 4th ventricle (6), primary (7) and secondary (8) vermian fissures. Cavun septi pellucidi (CSP), cavum vergae (CV), basal (BC), quadrageminal (QC) and magna (CM) cisterns; cerebellar vermis (V) and parieto-occipital fissure (POF)

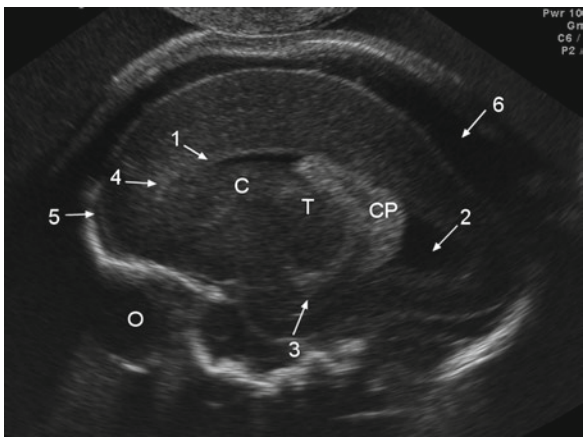

Fig. 5 Transvaginal parasagittal plane at the level of the lateral ventricles at 23 weeks of gestation. Frontal (1), occipital (2) and temporal (3) horns of the lateral ventricle; hyperechogenic normal periventricular zone (4); subarachnoid space, note the normal differences in cerebrospinal fluid between the frontal (5) and occipital (6) regions. Orbit (O), caudate (C), thalamus (T), choroid plexus (CP)

fetuses with suspected anomalies, either involving the CNS or other organs.

In the first group, it is particularly important to have maximal information regarding the affected family member or the possible teratogenic agent before starting the US examination. In cases with a known diagnosis in a family member, it is mandatory to know the inheritance of the disease and to obtain a detailed clinical synopsis of the expected findings. It is sometimes necessary for the pediatric neurologist/geneticist to evaluate the affected child. It should be remembered that some important signs of the disorder may not always be present or amenable to diagnosis during pregnancy (examples: postnatal microcephaly or brain findings associated with tuberous sclerosis).

The second group of indications includes fetuses with suspected anomalies usually diagnosed during routine or targeted examinations at referring centers.

The more frequent diagnoses evaluated at the FNC include: mild ventriculomegaly, either symmetric or asymmetric; fetuses with small or large head circumferences; suspicion of callosal or vermian anomalies. Cases of serious early developing malformations such as anencephaly, holoprosencephaly, and open neural tube defects are rarely seen.

Table 2 Indications for referral to the fetal neurology clinic

Family history of potentially recurrent CNS anomaly
Family history of an undiagnosed CNS malformation
Fetus at risk of intrauterine infection involving the CNS
Follow-up of maternal abdominal trauma (3 weeks after trauma)
Maternal epilepsy
Medications or drug consumption of substances known to produce CNS anomalies
Suspected CNS anomaly
Patient with apparently isolated non-CNS anomaly
Fetal growth restriction (below 5th percentile)
Hydramnios (AFI > 30)
Fetuses with known chromosomal aberrations
Fetuses with known anemia
Twin to twin transfusion
Single twin demise

5 Indications for Fetal MRI

Our indications for referral to Fetal MRI are not based on a routine protocol; we try to individualize our decisions taking into consideration:

1. The degree of diagnostic certainty reached by the US examination.
2. The willingness of the family to modify the proposed management in case of a different MRI diagnosis.
3. When it is obvious that the US examination cannot provide a diagnosis (due to a specific etiology or due to technical difficulties).
4. When the families need confirmation of the dire finding by another modality in order to make decisions regarding the continuation of pregnancy.
5. When MRI can give additional information regarding cortical malformations.

We believe that the option to perform a full body MRI examination late in pregnancy, following the diagnosis of an apparently isolated malformation, will become in the future one of the main indications for fetal MRI, particularly in countries that permit late termination of pregnancy.

References

deMause L (1982) The Fetal Origins of History In *Foundations of Psychohistory*. Creative Roots, Inc, New York, p 247

Vaughn HG Jr (1975) Electrophysiological analysis of regional cortical maturation. Biol Psychiatry 10:513–526

Nijhuis JG, Prechtl HF, Martin CB Jr, Bots RS (1982) Are there behavioural states in the human fetus? Early Hum Dev 6:177–195

de Vries JI, Visser GH, Prechtl HF (1982) The emergence of fetal behaviour. I. Qualitative aspects. Early Hum Dev 7:301–322

Bots RS, Nijhuis JG, Martin CB Jr, Prechtl HF (1981) Human fetal eye movements: detection in utero by ultrasonography. Early Hum Dev 5:87–94

Prechtl HF (1988) Developmental neurology of the fetus. Baillières Clin Obstet Gynaecol 2:21–36

Naidich TP, Yousefzadeh DK, Gusnard DA (1986) Sonography of the normal neonatal head. Supratentorial structures: state-of-the-art imaging. Neuroradiology 28:408–427

Volpe JJ (2008a) Neural tube formation and prosencephalic development. In: Neurology of the newborn. Saunders, Philadelphia, pp 3–50

Volpe JJ (2008b) Neuronal proliferation, migration, organization, and myelinization. In: Neurology of the newborn. Saunders, Philadelphia, pp 51–118

Malinger G, Katz A, Zakut H (1993) Transvaginal fetal neurosonography. Supratentorial structures. Isr J Obstet Gynecol 4:1–5

Timor-Tritsch IE, Monteagudo A (1996) Transvaginal fetal neurosonography: standardization of the planes and sections by anatomic landmarks. Ultrasound Obstet Gynecol 8:42–47

Malinger G, Lev D, Lerman-Sagie T (2003) Assessment of fetal intracranial pathologies first demonstrated late in pregnancy: cell proliferation disorders. Reprod Biol Endocrinol 1:110

Malinger G, Lev D, Lerman-Sagie T (2006) Normal and abnormal fetal brain development during the third trimester as demonstrated by neurosonography. Eur J Radiol 57:226–232

Malinger G, Pilu G (2009) Sonography of the central nervous system. In: Rodech CH, Whittle MJ (eds) Fetal medicine. Basic science and clinical practice. Elsevier, London

ISUOG guidelines (2007) Sonographic examination of the fetal central nervous system: guidelines for performing the basic examination and the fetal neurosonogram. Ultrasound Obstet Gynecol 29:109–116

Malinger G, Lerman-Sagie T, Watemberg N, Rotmensch S, Lev D, Glezerman M (2002) A normal second-trimester ultrasound does not exclude intracranial structural pathology. Ultrasound Obstet Gyneco 20:51–56

Malinger G, Kidron D, Schreiber L, Ben-Sira L, Hoffmann C, Lev D, Lerman-Sagie T (2007) Prenatal diagnosis of malformations of cortical development by dedicated neurosonography. Ultrasound Obstet Gynecol 29:178–191

Cohen-Sacher B, Lerman-Sagie T, Lev D, Malinger G (2006) Developmental milestones of the fetal cerebral cortex. A longitudinal sonographic study. Ultrasound Obstet Gynecol 27:494–502

Fong KW, Ghai S, Toi A, Blaser S, Winsor EJ, Chitayat D (2004) Prenatal ultrasound findings of lissencephaly associated with Miller–Dieker syndrome and comparison with pre- and postnatal magnetic resonance imaging. Ultrasound Obstet Gynecol 24:716–723

Malinger G, Lev D, Lerman-Sagie T (2009) The fetal cerebellum. Pitfalls in diagnosis and management. Prenat Diagn 29:372–380

Pilu G, Segata M, Ghi T, Carletti A, Perolo A, Santini D, Bonasoni P, Tani G, Rizzo N (2006) Diagnosis of midline anomalies of the fetal brain with the three-dimensional median view. Ultrasound Obstet Gynecol 27:522–529