

A normal second-trimester ultrasound does not exclude intracranial structural pathology

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ABSTRACT

Objective To report the prenatal diagnosis and management of 34 fetuses with various intracranial structural pathologies diagnosed following a normal second-trimester ultrasound examination.

Methods We retrospectively reviewed the images of 203 abnormal central nervous system ultrasound examinations performed between 13 and 37 weeks of gestation at our prenatal diagnosis unit. In 34 (16.7%) of them at least one previous second-trimester ultrasound examination had been performed and considered normal. These 34 fetuses represent the study group.

Results The following intracranial pathologies were diagnosed: dysgenesis of the corpus callosum, ventriculomegaly, cerebral cysts or hemorrhage, migrational disorders, vermian dysgenesis, arachnoid cysts, macrocephaly, enlarged sub-arachnoid space, brain calcifications and microcephaly.

Conclusion A normal second-trimester ultrasound scan does not rule out significant intracranial anomalies. Parents and physicians should be informed about the limitations of second-trimester sonography as far as brain diagnosis is concerned. A repeat third-trimester scan may enable more accurate diagnosis and counseling.

INTRODUCTION

The human fetal brain develops throughout pregnancy. Major developmental events occur during the second half of gestation and include neuronal proliferation, migration and organization¹. Therefore, a second-trimester ultrasound examination, routinely performed between 19 and 22 weeks, may fail to detect pathological conditions associated with later events. Often, neither the patient nor the physician is

aware of the fact that a normal second-trimester ultrasound examination of the fetal brain does not necessarily signify that the newborn will be free of an intracranial anomaly.

Although the prenatal diagnosis of some of these intracranial pathologies has been reported, there are no published studies encompassing prenatal diagnosis of late developing brain events. We performed a retrospective study of all intracranial pathologies seen at our prenatal diagnosis unit in which at least one of the previous ultrasound examinations, performed during the second trimester, had been considered normal. Thirty-four fetuses fulfilled this criterion and they constitute the study group.

METHODS

The prenatal diagnosis unit at the Edith Wolfson Medical Center is a referral ultrasound laboratory that provides consultation to community-based ultrasound services and provides second-opinion consultation in the field of fetal neurosonography. The referring physicians are all board-certified obstetricians with special training in obstetric ultrasound.

Between January 1990 and January 2000, central nervous system anomalies were diagnosed in 203 fetuses (Table 1). Most abnormalities were identified at the time of the second-trimester ultrasound examination. In 34 fetuses (16.7%) the diagnosis of a major intracranial abnormality was only made in a subsequent examination. This group of fetuses is the subject of this report. The findings in two of these patients have been reported previously².

In 25 fetuses the second-trimester ultrasound was completely normal according to the written report and/or review of the ultrasound images and the cause of referral was either an abnormality detected in a subsequent, routine, follow-up scan ($n = 21$) or poor visualization of the fetus due to maternal obesity or fetal position ($n = 4$). Eight patients were referred because of some form of variant of the norm which

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Table 1 Main diagnosis in 203 fetuses with central nervous system pathology

Main diagnosis	Total (n (%))	Late diagnosis (n)
Hydrocephalus—ventriculomegaly	55 (27.1)	6
Open neural tube defect	42 (20.7)	—
Anencephaly	34 (16.6)	—
Posterior fossa anomaly*	23 (11.3)	2
Corpus callosum anomaly	13 (6.4)	10
Holoprosencephaly	11 (5.4)	—
Signs of intrauterine infection†	7 (3.5)	4
Cerebral cysts	4 (2.0)	4
Hemorrhage‡	3 (1.5)	2
Macrocephaly	3 (1.5)	3
Microcephaly	3 (1.5)	1
Craniosynostosis	3 (1.5)	—
Migration disorder	1 (0.5)	1
Brain atrophy	1 (0.5)	1

*Posterior fossa anomalies include: vermian dysgenesis, cerebellar hypoplasia, cerebellar agenesis, mega cisterna magna, and arachnoid cyst. †Signs of intrauterine infection include: parenchymal calcifications, intraventricular adhesions, and striatal artery hyperechogenicity.

‡Hemorrhage includes: intraventricular and cerebellar hemorrhage.

was observed in the second-trimester ultrasound. These findings included: asymmetrical lateral ventricles ($n = 4$), lateral ventricle size at the upper range of the normal ($n = 3$) and bilateral choroid plexus cysts ($n = 1$). One patient was referred because of oligohydramnios.

Twenty-two patients were diagnosed among our own patients and 12 were referred from other hospitals for a second-opinion consultation.

The sonographic equipment used included an Elscint 1000 (Elscent, Haifa, Israel) and an HDI 3000 (ATL, Bothell, WA, USA) with 3.5- and 5-MHz transabdominal probes and 6.5- and 4–8-MHz transvaginal probes. The same examiner (G.M.) performed all the examinations.

All patients underwent a transabdominal targeted ultrasound examination. The brain was studied using axial and coronal planes. In 32 patients a transvaginal examination of the fetal brain was possible and coronal and sagittal planes were obtained.

Gestational ages at the time of the last normal examination ranged from 15 to 28 (mean, 21.5) weeks, and at diagnosis of the intracranial pathology from 22 to 37 (mean, 29) weeks.

The patients received counseling by a team that included a perinatologist, a geneticist and a pediatric neurologist and in selected cases a pediatric neurosurgeon. Maternal TORCH screen, fetal karyotype and polymerase chain reaction for cytomegalovirus (CMV) were performed when relevant.

In Israel, termination of second- and third-trimester pregnancies is permitted by law, pending approval by one of 12 special ethics committees accredited by the Ministry of Health. Patients wishing to terminate the pregnancy were referred to one of these committees. Pathological examination was obtained after fetal or neonatal death upon parental consent.

Postnatal evaluation and brain imaging were performed in all surviving infants. Periodic follow-up was carried out at the child neurology clinic.

RESULTS

Of the study group, isolated intracranial pathology was identified in 22 fetuses, while multiple intracranial abnormalities were present in 12. The main diagnosis of intracranial pathologies at the index scan is presented in Table 1 and the overall pathologies at the index scan included: dysgenesis of the corpus callosum ($n = 11$), severe ventriculomegaly ($n = 5$) and mild ventriculomegaly ($n = 6$), cerebral cyst or hemorrhage ($n = 6$), migration disorders ($n = 6$), vermian dysgenesis ($n = 5$), arachnoid cysts ($n = 3$), macrocephaly ($n = 3$), enlarged subarachnoid space ($n = 2$), brain calcifications ($n = 4$), microcephaly ($n = 1$) and brain atrophy ($n = 1$) (Table 2).

A diagnosis of migration disorder was made based on the finding of an abnormal sulcation pattern related to the gestational age and/or the presence of a thickened, irregular cortical ribbon. Brain atrophy was diagnosed based on an enlarged subarachnoid space with a normal head circumference².

Nine fetuses had associated malformations of other organs: cleft lip ($n = 1$), clubfoot ($n = 2$), micrognathia ($n = 1$), skeletal dysplasia ($n = 2$), hepatic abnormality ($n = 2$) and cardiac anomaly ($n = 1$). Intrauterine growth restriction was observed in five fetuses.

The maternal TORCH screen was positive in four patients including elevated IgM for CMV ($n = 3$) and syphilis ($n = 1$). The fetal karyotype was obtained in 14 cases and found to be normal. In two patients CMV infection was confirmed by polymerase chain reaction of the amniotic fluid.

The option for termination of pregnancy was offered to 20 patients. Two of these, one whose fetus had enlarged subarachnoid spaces due to brain atrophy and one whose fetus had incomplete vermian agenesis, decided to continue the pregnancy for religious reasons. The ethics committee denied pregnancy termination in the fetus with microcephaly. In two patients intrauterine fetal death occurred before termination. Selective feticide was proposed in one case but the family elected to continue the pregnancy.

In 15 patients termination of pregnancy was performed: four cases with severe hydrocephalus, six of the cases with corpus callosum pathologies, one of the cases with incomplete vermian agenesis, three cases with CMV, and one case with hemimegalencephaly and polymicrogyria.

Intrauterine fetal death occurred in five cases: two cases with corpus callosum pathologies and three cases with fetal intracranial hemorrhage.

Fourteen patients delivered live neonates. Early neonatal death occurred in the patient with congenital syphilis and in the patient with a suprasellar cyst, germinolysis and micrognathia.

The 12 survivors included two infants with isolated corpus callosum pathology, one with isolated incomplete vermian agenesis, two with nodular heterotopia, one with microcephaly, three with macrocephaly, one with enlarged subarachnoid spaces, one with fetal periventricular hemorrhage and one with a prenatal stroke who later developed a simple porencephalic cyst.

At the time of writing, seven infants were developing normally, at ages ranging from 1 to 10 (mean, 5) years. The child who had had a prenatal stroke suffers from left hemiparesis and one of the children with nodular heterotopia suffers from

Table 2 Clinical data of 34 cases of intracranial structural pathologies diagnosed late in pregnancy

Case	First scan		Index scan		Follow-up	Postnatal evaluation
	GA (weeks)	Findings	GA (weeks)	Findings		
1	21	Normal	28	Ventriculomegaly, third vent dilatation, cleft lip	TOP	PM: aqueductal stenosis, cleft lip
2	22	Normal	26	Ventriculomegaly, hypoplastic vermis, clubfoot	TOP	PM: hydrocephalus, hypoplastic vermis, clubfoot
3	21	Normal	31	Ventriculomegaly, third vent dilatation, clubfoot	TOP	PM: aqueductal stenosis, clubfoot
4	21	Bilateral choroid plexus cysts	32	ACC	IUFD	PM: ACC, craniosynostosis
5	23	Normal	32	ACC, intrahemispheric cyst	TOP	PM: ACC
6	19	Normal	24	ACC	TOP	PM: ACC
7	15	Normal	23	ACC	TOP	PM: ACC
8	22	Normal	28	ACC	Delivered	ACC confirmed by ultrasound, normal development at 20 months
9	23	Normal	34	ACC	TOP	PM: ACC
10	22	Normal	30	Partial ACC, intrahemispheric cyst, lissencephaly, AV canal	IUFD	PM: partial ACC, lissencephaly, AV canal, micrognathia, megaureter
11	22	Normal	28	ACC	TOP	PM: ACC
12	21	Normal, LVW = 9 mm	24	Hypoplastic CC, ventriculomegaly	TOP	PM: hypoplastic CC
13	20	Normal	32	Hypoplastic CC	Delivered	CT: hypoplastic CC, psychomotor impaired development
14	21	Asymmetrical ventricles	25	Incomplete vermian agenesis	TOP	PM: incomplete vermian agenesis
15	22	Normal	27	Incomplete vermian agenesis	Delivered	Incomplete vermian agenesis, normal development at 5 years
16	23	Normal, LVW = 9 mm	28	Asymmetrical ventricles, left = 15 mm, hyperechogenic cortex	Delivered	Epilepsy from 8 months, MRI: heterotopia
17	22	Asymmetrical ventricles	24	Asymmetrical ventricles, left = 15 mm, hyperechogenic cortex	Delivered	MRI: heterotopia, normal development at 2 years
18	22	Normal	26	Suspected microcephaly	Delivered	Microcephaly vera, severe developmental delay
19	22	Normal	30	Microcephaly	Delivered	Hypochondroplasia
20	21	Normal	32	Macrocephaly, suspected skeletal dysplasia	Delivered	Spondyloepiphyseal dysplasia
21	23	Normal, LVW = 9.8 mm	36	Macrocephaly, suspected skeletal dysplasia	Delivered	Macrocephaly, normal development
22	21	Normal	31	Macrocephaly, large subarachnoid space (1.2–0.8 mm)	Delivered	Trisomy 21
23	20	Normal	33	Enlarged subarachnoid space, suspected brain atrophy	Delivered	Bilateral IVH Grade IV
24	28	Normal	37	Bilateral IVH Grade IV	IUFD	Large porencephalic cyst, left parietal lobe
25	23	Normal	30	Large porencephalic cyst (53 mm), left parietal lobe	IUFD	Maternal homocystinuria, no PM
26	22	Normal	33	Periventricular cyst with septations in the caudate nucleus (6 mm)	IUFD	IVH Grade I developing into Grade III, normal development
27	20	Normal	34	IVH Grade I, spontaneous fetal bradycardia	Delivered	MRI: leukomalacia, small porencephalic cyst, mild hemiparesis
28	18	Severe oligohydramnios	23	Suspected fetal stroke, porencephalic cyst	Delivered	PM: disseminated CMV infection
			22	Ventriculomegaly, periventricular calcifications, hepatic calcifications, IUGR	TOP	

Table 2 Continued

Case	First scan		Index scan		Findings	Follow-up	Postnatal evaluation
	GA (weeks)	Findings	GA (weeks)	Findings			
29	22	Normal	29	Ventriculomegaly, dysplastic CC, hypoplastic vermis, polymicrogyria, IUGR	CMV amnio, TOP	PM: disseminated CMV infection	
30	19	Normal	25	Intraventricular adhesions, diffuse focal intracerebral calcifications, IUGR	CMV amnio, TOP	PM: disseminated CMV infection	
31	22	Normal, suspected VSD (ruled out)	34	IUGR, asymmetrical ventricles, intraventricular adhesions, striatal artery vasculopathy, pachygyria, hepatosplenomegaly	Delivered	PPND PM: syphilis	
32	22	MRI: asymmetrical ventricles	25.5	Thick and irregular occipital parenchyma, focally abnormal gyri, suspected hemimegalencephaly	TOP	MRI: migrational disorder, hypoplastic CC	
33	22	Asymmetrical ventricles	26	Thin occipital cortex, left calcarine asymmetry	TOP	PM: hemimegalencephaly, polymicrogyria	
34	22	Normal twins	28	Unilateral ventriculomegaly, large CM	Delivered	PM: unilateral hydrocephalus, mega cisterna magna	
			33	Suprasellar cyst, germinolysis, micrognathia, IUGR		PPND	
GA, gestational age; LVW, lateral ventricle width; VSD, ventricular septal defect; ACC, agenesis of the corpus callosum; AV, atrioventricular; CC, corpus callosum; IVH, intraventricular hemorrhage; IUGR, intrauterine growth restriction; CM, cisterna magna; TOP, termination of pregnancy; IUFD, intrauterine fetal death; CMV, cytomegalovirus; amnio, amniotic fluid diagnosis; PM, post mortem examination; CT, computed tomography; MRI, magnetic resonance imaging; PPND, post partum neonatal death.							

GA, gestational age; LVW, lateral ventricle width; VSD, ventricular septal defect; ACC, agenesis of the corpus callosum; AV, atrioventricular; CC, corpus callosum; IVH, intraventricular hemorrhage; IUGR, intrauterine growth restriction; CM, cisterna magna; TOP, termination of pregnancy; IUFD, intrauterine fetal death; CMV, cytomegalovirus; amnio, amniotic fluid diagnosis; PM, post mortem examination; CT, computed tomography; MRI, magnetic resonance imaging; PPND, post partum neonatal death.

epilepsy; both have normal intelligence. The remaining three have moderate to severe developmental delay: one with corpus callosum dysgenesis, one with Down syndrome and the third with microcephaly (Table 2).

DISCUSSION

The detection of fetal intracranial pathologies poses a challenge for the sonographer. Misdiagnosis of a major malformation or anomaly may lead to a burden on the family and/or society. Maternal alpha-fetoprotein and ultrasound screening are expected to detect most of these anomalies, but the relatively large number of children with brain anomalies only diagnosed postnatally and followed up in pediatric neurology and developmental clinics prove that often prenatal diagnosis is not satisfactory.

We identified major brain pathologies during ultrasound examinations performed after a second-trimester ultrasound examination had been considered normal or had only revealed some form of variant of the norm. These findings enabled accurate counseling and termination of pregnancy in the severely affected fetuses.

In Israel, as in most countries, according to established guidelines, the second-trimester systematic survey of the fetal brain for the detection of anomalies requires the inclusion of standard axial planes at the level of the thalami, lateral ventricles and posterior fossa³. Therefore, a possible explanation for the misdiagnosis of some of the intracranial pathologies at the first scan may be that most sonographers put emphasis on size and content of ventricles and cisterna magna rather than on the brain itself. This has become the standard approach since the 1989 study by Filly *et al.*⁴ on 112 fetuses with sonographically diagnosed brain anomalies. They found that most of the prenatally diagnosed central nervous system anomalies could be diagnosed by examining the atrium of the lateral ventricle and the cisterna magna. However, the authors did not state the week of pregnancy in which malformations were detected and did not provide data on the number of children with brain anomalies in whom prenatal diagnosis had not been performed and diagnosis was only made postnatally. Reece and Goldstein⁵ described similar results in 131 cases of intracranial pathologies diagnosed between 14 and 24 weeks of gestation but did not present data on postnatal diagnosis. Our study demonstrates that most but not all of the prenatally detectable brain pathologies are accompanied by abnormal amounts of cerebrospinal fluid.

Our study group may be influenced by a selection bias, since 12 patients were referred from other hospitals in Israel for a second opinion. Even when these cases are excluded, a considerable number of fetuses (11.5%) were only diagnosed late in pregnancy.

There are two groups of abnormalities that can only be identified in the third trimester. The first group consists of acquired lesions that develop only during this time period, for example stroke, hemorrhage, infection and tumors. The second group includes developmental anomalies which become evident after the end of the proliferation and migration period (2–5 months of gestation) during rapid brain enlargement,

for example lissencephaly, heterotopia, microcephaly/macrocephaly and hemimegalencephaly.

Fetal intracerebral hemorrhage has been increasingly recognized in recent years. Although subdural, intraparenchymal, and subarachnoid hemorrhages have been described, intraventricular hemorrhage (IVH) constitutes the single most common type of antenatal intracranial bleeding⁶. Antenatal cases have been described from 20 weeks of gestation. Maternal predisposing factors for all types of intracranial hemorrhage include alloimmune and idiopathic thrombocytopenia, Von Willebrand disease, maternal warfarin use, maternal seizures, cocaine abuse, trauma, amniocentesis and maternal fever. Fetal risk factors are coagulation disorders, thrombophilia (in particular factor V Leiden mutation), twin–twin transfusion, fetomaternal transfusion, fetal distress and bleeding into an intracranial tumor⁷. Two cases in our series developed IVH in later pregnancy. In Case 23 (Table 1) there was intrauterine fetal demise following bilateral Grade IV IVH at 37 weeks of gestation. In Case 26 a Grade I IVH was detected following spontaneous fetal bradycardia at 34 weeks.

Antenatal ischemic stroke has also been recognized in recent years. The main causes include thrombophilic states, supraventricular tachycardia, cocaine abuse, intrauterine infections and middle cerebral artery occlusion^{8,9}. However, in many cases an etiology cannot be discerned. One of our patients (Case 24) had a normal ultrasound scan at 28 weeks, but a repeat examination 2 weeks later showed a large porencephalic cyst in the left parietal lobe giving rise to the possibility that the cyst had been present but was not diagnosed at 28 weeks. Another fetus (Case 27) had a normal sonogram at 20 weeks, but a repeat one at 23 weeks demonstrated a small parietal hypoechoic lesion with peripheral echogenic enhancement that developed into a porencephalic cyst by 27 weeks. The neonate was delivered successfully and went on to suffer from mild hemiparesis. Some thrombophilic states, such as factor V Leiden mutation and antiphospholipid antibodies, may also cause late pregnancy strokes¹⁰.

Among intrauterine infections, CMV¹¹, syphilis¹² and toxoplasmosis¹³ show a progressive course as pregnancy continues. Cases 28–31 in our series exemplify this situation.

There are single case reports in the literature describing the identification of migrational disorders prenatally by ultrasound. In most of them the brain anomaly was only diagnosed in the third trimester. We found three case reports on hemimegalencephaly^{14–16}; two of the cases were discovered after the 22nd week. We identified incipient hemimegalencephaly based on the visualization of thickened, sausage-like occipital brain parenchyma, focal abnormal sulcation and enlargement of the ventricle (Case 32) at 25.5 weeks (Figure 1). A magnetic resonance image obtained 2.5 weeks previously showed asymmetrical ventricles but did not identify the parenchymal abnormalities (Figure 2).

Lissencephaly has been described in one case at 24 weeks¹⁷ and in two others at 32 weeks¹⁸. We diagnosed lissencephaly with associated anomalies (Case 10) at 30 weeks, based on generalized abnormal sulcation with partial agenesis of the corpus callosum. Schizencephaly has been described at 29 weeks¹⁹ and at 32 weeks²⁰. The prenatal diagnosis of heterotopia has been previously diagnosed at 23 weeks^{21,22}.



Figure 1 Case 32 at 25.5 weeks: parasagittal view (a) showing thick and irregular occipital parenchyma (arrows) with ventriculomegaly, and modified coronal view (b) showing abnormal gyri and sulci (arrows). The calipers indicate the subarachnoid space.

In our two cases, the heterotopia was missed during the second-trimester ultrasound examination.

Our study also demonstrates that dysgenesis of the corpus callosum cannot be diagnosed accurately in the second trimester by standard ultrasound. We diagnosed 11 cases of callosal dysgenesis that were missed on previous examinations. This pattern has been previously reported by Bennett *et al.*²³ who compared initial scans obtained at or before 22 weeks of pregnancy and follow-up scans obtained in the third trimester. Among 15 fetuses with callosal agenesis confirmed by means of third-trimester scans, 10 had completely normal ultrasound scans at 16–22 weeks and five had other ultrasound abnormalities.

Congenital intracranial tumors were not found among our series, probably due to their extreme rarity; however, it is important to remember that they too may not be diagnosed during a routine second-trimester ultrasound examination²⁴.



Figure 2 Fetal magnetic resonance image of the same patient as in Figure 1 at 23 weeks: coronal view showing asymmetrical ventricles.

The diagnosis of intracranial abnormality was made in ten fetuses in our study following demonstration of some deviation from the norm at the second-trimester examination. Alertness on the part of the sonographer to subtle abnormal findings during the second-trimester scan, such as lateral ventricular width in the upper range of the norm, asymmetrical lateral ventricles, the presence of choroid plexus cysts and the presence of oligohydramnios or polyhydramnios, should be the basis for a specifically directed follow-up.

Our study demonstrates that a 'routine' third-trimester ultrasound examination contributes to the diagnosis of some rare intracranial structural pathologies. A third-trimester ultrasound scan may also contribute to the diagnosis of malformations of other systems, particularly congenital heart defects, that may remain undiagnosed during the second-trimester ultrasound examination. However, most of these malformations will be amenable to surgery. Yagel *et al.*²⁵ found that 6.5% of cardiac malformations were detected only during the third trimester and 14.9% were only diagnosed after delivery.

Clearly, fetal biometry, assessment of the placenta and the biophysical profile are not sufficient to detect all intracranial anomalies. Parents and physicians should be informed about the limitations of second-trimester ultrasound scans in general, and particularly as far as brain diagnosis is concerned, with an understanding of the rarity of these anomalies.

REFERENCES

- Volpe JJ. *Neurology of the newborn*. Philadelphia: WB Saunders, 1995: 43–90
- Malingier G, Lerman-Sagie T, Achiron R, Lipitz S. The subarachnoid space: normal development as demonstrated by transvaginal ultrasound. *Prenat Diagn* 2000; 20: 890–3
- American College of Obstetricians and Gynecologists. *Ultrasound in Pregnancy*. Technical bulletin no. 116, 1988
- Filly RA, Cardoza JD, Goldstein RB, Barkovich AJ. Detection of fetal central nervous system anomalies: a practical level of effort for a routine sonogram. *Radiology* 1989; 172: 403–8
- Reece EA, Goldstein I. Three-level view of fetal brain imaging in the prenatal diagnosis of congenital anomalies. *J Matern Fet Med* 1999; 8: 249–52
- Catanzarite VA, Schrimmer DB, Maida C, Mendoza A. Prenatal sonographic diagnosis of intracranial hemorrhage: Report of a case with a sinusoidal fetal heart rate tracing, and review of the literature. *Prenat Diagn* 1995; 15: 229–35
- Sherer DM, Anyaegbunam A, Onyeije C. Antepartum fetal intracranial hemorrhage, predisposing factors and prenatal sonography: a review. *Am J Perinatol* 1998; 15: 431–41
- Kraus FT, Acheen VI. Fetal thrombotic vasculopathy in the placenta, cerebral thrombi and infarcts, coagulopathy, and cerebral palsy. *Hum Pathol* 1999; 30: 759–69
- Schade RP, Stoutenbeek P, deVries LS, Meijboom EJ. Neurological morbidity after fetal supraventricular tachyarrhythmia. *Ultrasound Obstet Gynecol* 1999; 13: 43–7
- Akanli LF, Trassi SS, Thuraishamy K, Bergtraum MP, Thantun A, Fischer RF, Cohen Addad N. Neonatal middle cerebral artery infarction: association with elevated maternal anticardiolipin antibodies. *Am J Perinatol* 1998; 15: 399–402
- Brown HL, Abernathy MP. Cytomegalovirus infection. *Semin Perinatol* 1998; 22: 260–6
- Sheffield JS, Wendel GD. Syphilis in pregnancy. *Clin Obstet Gynecol* 1999; 42: 97–106
- Alford CA, Stagno S, Reynolds DW. Congenital toxoplasmosis. Clinical, laboratory, and therapeutic considerations, with special reference to subclinical disease. *Bull N Y Acad Medical* 1974; 50: 160–81
- Sandri F, Pilu G, Dallacasa P, Foschi F, Salvioli GP, Bovicelli L. Sonography of unilateral megalencephaly in the fetus and newborn infant. *Am J Perinatol* 1991; 8: 18–20
- Ramirez M, Wilkins I, Kramer L, Slopis J, Taylor SR. Prenatal diagnosis of unilateral megalencephaly by real-time ultrasonography. *Am J Obstet Gynecol* 1994; 170: 1384–5
- Hafner E, Bock W, Zoder G, Schuchter K, Rosen A, Plattner M. Prenatal diagnosis of unilateral megalencephaly by 2D and 3D ultrasound: a case report. *Prenat Diagn* 1999; 19: 159–62
- Greco P, Resta M, Vimercati A, Dicunzio F, Loverro G, Vicino M, Selvaggi L. Antenatal diagnosis of isolated lissencephaly by ultrasound and magnetic resonance imaging. *Ultrasound Obstet Gynecol* 1998; 12: 276–9
- Saltzman DH, Krauss CM, Goldman JM, Benacerraf B. Prenatal diagnosis of lissencephaly. *Prenat Diagn* 1991; 11: 139–43
- Lituanian M, Passamonti U, Cordone MS, Magnano GM, Toma P. Schizencephaly: prenatal diagnosis by computed sonography and magnetic resonance imaging. *Prenat Diagn* 1989; 9: 649–55
- Klingensmith WC 3d, Cioffi-Ragan DT. Schizencephaly: diagnosis and progression in utero. *Radiology* 1986; 159: 617–8
- Onyeije CI, Sherer DM, Jarosz CJ, Divon MY. Prenatal sonographic findings associated with sporadic subcortical nodular heterotopia. *Obstet Gynecol* 1998; 91: 799–801
- Mitchell LA, Simon EM, Filly RA, Barkovich AJ. Antenatal diagnosis of subependymal heterotopia. *Am J Neuroradiol* 2000; 21: 296–300
- Bennett GL, Bromley B, Benacerraf BR. Agenesis of the corpus callosum: prenatal detection usually is not possible before 22 weeks of gestation. *Radiology* 1996; 199: 447–50
- Sherer DM, Onyeije CI. Prenatal ultrasonographic diagnosis of intracranial tumors: a review. *Am J Perinatol* 1998; 15: 319–28
- Yagel S, Weissman A, Rotstein Z, Manor M, Hegesh J, Anteby E, Lipitz S, Achiron R. Congenital heart defects: natural course and in utero development. *Circulation* 1997; 96: 550–5