Neuroimaging parameters in early open spina bifida detection. Further benefit in first trimester screening?

D. ILIESCU1), A. COMĂNESCU1), P. ANTSAKLIS2), ŞTEFANIA TUDORACHE1), MIRELA GHILUŞI3), VIALETA COMĂNESCU3), DANIELA PAULESCU9), IULIANA CEAUŞU5), A. ANTSAKLIS2), LILIANA NOVAC1), N. CERNEA1)

1)Department of Obstetrics and Gynecology, Prenatal Diagnostic Unit, University of Medicine and Pharmacy Craiova, Romania
2)1st Department of Obstetrics and Gynecology, University of Athens, Greece
3)Department of Pathology, Emergency County Hospital, Craiova
4)Department of Obstetrics and Gynecology, Prenatal Diagnostic Unit, Gaia Hospital, Athens, Greece
5)University Department of Obstetrics and Gynecology II, "Dr. Ioan Cantacuzino" Clinical Hospital, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Abstract

Objective: Morphological investigation of the central nervous system (CNS) in fetuses with positive markers for open spina bifida (OSB) detection, visualized by ultrasound during the first trimester of pregnancy. Materials and Methods: Data from fetuses that underwent routine first trimester ultrasound scan in our center during September 2007–March 2011 and presented abnormal aspects of the fourth ventricle, also referred as intracranial translucency (IT), provided the morphological support to evaluate CNS features. A neuro-histological study of posterior cerebral fossa illustrated anatomical features of the structures involved in the sonographic first trimester detection of neural tube defects. Results: Abnormal IT aspects were found in OSB cases examined in the first trimester, but also in other severe cerebral abnormalities. Brain stem antero-posterior diameter (BS) and brain stem to occipital bone (BSOB) ratio may be more specific for OSB detection. Correlations between histological aspects of posterior brain fossa and ultrasound standard assessment have been made; highlighting the anatomical features involved by the new techniques developed for OSB early detection. Conclusions: Preliminary results show that modern sonographic protocols are capable to detect abnormalities in the morphometry of the posterior brain. First trimester fourth ventricle abnormalities should be followed by careful CNS evaluation because are likely to appear in OSB affected fetuses, but also in other CNS severe anomalies; in such cases, normal BS and BSOB ratio may serve as indirect argument for spine integrity, if specificity is confirmed in large series of fetuses. Keywords: neurosonogram, posterior brain, intracranial translucency, spina bifida, first trimester screening.

Introduction

Neural tube defects (NTDs) are considered the second most common fetal malformations, surpassed only by congenital heart defects. Congenital anomalies of the nervous system include neural tube defects such as spina bifida, meningocele, meningomyelocele, encephalocele and anencephaly; other congenital anomalies of the nervous system include the Arnold–Chiari malformation, the Dandy-Walker malformation, hydrocephalus, microencephaly, megencephaly, lissencephaly, polymicrogyria, holoprosencephaly, and agenesis of the corpus callosum. The worldwide incidence of (NTDs) ranges from 1.0 to 10.0 per 1000 births with almost equal frequencies between two major categories: anencephaly and OSB [1]. Is been suggested that fetal spinal abnormalities diagnosed during the first trimester are severe, and frequently part of syndromes in association with other major anomalies. Conversely, the diagnosis of small and/or isolated defects is difficult, and usually are detected only using second-trimester morphological markers [2, 3]; because this is the prevalent form of OSB, the diagnosis is usually missed at the first trimester morphologic evaluation [2, 4, 5].

The direct visualization of the spine at the respective gestational age is often difficult even with the help of high-resolution ultrasound machines; local conditions related to the thickness of the maternal abdomen, the anterior position of placenta, the small size of the fetus, unfriendly position or the poor echogenity of the spine and suprajacent teguments provide the reasons for non-visualization of the entire cervico-sacral aspects of spine. Consequently, the introduction of an early morphological marker for OSB is important because of the possibility to diagnose this condition during first trimester, along the majority of all major fetal
abnormalities [6]. Abnormal posterior brain, retraction of frontal bones and ventriculomegaly provide indirect signs for SB with large prevalence during second trimester and subsequently were developed first trimester indirect sonographic markers to identify the caudal displacement of the brain, similarly to second trimester. The morphological abnormalities proposed for the first trimester evaluation consisted in: retraction of frontal bones and parallel aspect of cerebral peduncles [7], and measurable parameters in the posterior brain: the fourth ventricle – intracranial translucency (IT) [8], brain stem/brain stem-occipital bone distance ratio (BS/BSOB) [14]. Because of its rapid assessment in the same standard sectional plane as used for the main morphogenetic markers [9–13], with no investment in additional scanning time, IT measurement became a routine in our center, and BS/BSOB measurement was reserved for the cases with abnormal IT. Due to small prevalence of affected first trimester fetuses in centers with experienced sonographers, results based on large series are still expected regarding the efficiency and specificity of these markers.

The main objective of our study was to investigate the CNS features and abnormalities in fetuses found with abnormal aspect of IT having in mind that the OSB affected fetuses scanned during first trimester were detected during examination. A morpho-histological study of posterior brain complex was considered useful to clarify anatomical aspects related to the sonographic features.

Materials and Methods

Retrospectively we studied stored acquisitions from the fetuses presenting abnormal IT during first trimester (11–13 weeks of gestation) genetic and morphologic screening programme, scanned between September 2007 and March 2010. At the first trimester morphological scan, we consider the following standard planes important for early central nervous system (CNS) evaluation: sagittal view of the face, transverse planes of cranium at the level of choroid plexus and cerebral peduncles, sagittal plane of spine on the section used for the measurement of crown-rump length (CRL). The planes are imagined in Figure 1, showing normal aspects of structures in early neurosonogram. The acquisition of images below was realized transabdominally and transvaginally using probes from GE Voluson 730 Pro and Expert, GE medical Systems, Kretztechnik, ZIPF, Austria. Approval for the study was obtained from the hospital Ethics Committee. However, the visualization of some structures figured below is age-dependent: cerebellum is best visualized transabdominally after 13+0 weeks of gestation, and the regular echogenicity of spine – after 12 weeks; therefore, the complete evaluation may require transvaginal examination in fetuses of 11–12 weeks gestational age and as well in cases of poor visualization due to local conditions (abdominal scar, large BMI, unfriendly tissue, fetal persistent uncomfortable position). The planes mentioned above offer a good visualization of the markers proposed for OSB early detection: shape of the cranium, choroid plexus, cerebral peduncles, cerebellum, posterior brain and spine.

Using the sagittal plane of the fetal face, we selected the fetuses showing abnormal IT; consecutively, the planes showing CNS morphology were studied in order to investigate the presence of associated anomalies. Two fetuses with OSB were scanned during the first trimester in the mentioned period in our center, and both were diagnosed as shown before.

The measured parameters when visible were (Figure 2) the vertical thickness of the brain stem (BS), the vertical distance between the brain stem and the occipital bone (BSOB), measured as suggested by Lachmann R et al. [14], and the fourth ventricle as intracranial translucency (IT), measured as described by Chaoui R et al. [8]: before the BS measurement a line was imagined along the middle of the echogenic border between the brain stem anteriorly and the fourth ventricle posteriorly; then a perpendicular line was drawn anteriorly to the sphenoid bone, representing BS.
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diameter; consecutively, a perpendicular line was drawn posteriorly to the occipital bone, representing BSOB diameter; the fourth ventricle was visualized and measured in the widest diameter between the brain stem and the choroid plexus of the fourth ventricle.

Figure 2 – Normal IT measured in the sagittal plane of the fetal face used for the assessment of genetic markers (nuchal translucency, nasal bone, fronto-maxillary angle) in a chromosomal normal fetus (A, B) and a chromosomal abnormal fetus (C, D) with trisomy 21, presenting increased nuchal translucency, increased facial angle and absent nasal bone. Red lines are drawn along the posterior border of the sphenoid bone, along the middle of the echogenic border between the brain stem anteriorly and the fourth ventricle posteriorly and on the anterior border of the occipital bone, for appreciation of the posterior brain parameters; measurement of the fourth ventricle (IT) in the widest diameter. NB: Nasal bone, M: Maxilla (palate), D: Diencephalon, S: Sphenoid bone, MB: Midbrain, BS: Brain stem, IT: Intracranial translucency (fourth ventricle), p: Choroid plexus of the forth ventricle, OB: Occipital bone, MO: Medulla oblongata, NT: Nuchal translucency.

In all cases, second trimester anomaly scan was recommended as follow-up for CNS anatomy. Cranium sagittal planes of the fetus were obtained and posterior brain complex was evaluated by histological approach in order to identify anatomical aspects related to the sono graphical features. The pathological material on which this study is based consists of five autopsied cases. The material was paraffin embedded, routine sagittal sections performed, Hematoxylin and Eosin (HE) stained and microscopic features were evaluated.

Results

Retrospective evaluation of fetuses with abnormal IT

A total of 2017 cases entered the study and were examined during the first trimester. A number of 193 cases were lost (9.56%), as only 1824 cases were followed-up.

The stored images were examined by sonographers with extensive experience in first-trimester scanning who had obtained the Fetal Medicine Foundation Certificate of Competence in the 11 to 13 weeks scan.

We had seven cases of abnormal IT, representing 0.34% of the first trimester studied fetuses and 0.38% of the fully studied group; we divided the group into two subgroups: associated with OSB – two cases, associated with other type of neural tube defect (NTD) – two cases (acrania and encephalocele), and without NTD – three cases (aqueductal stenosis, holoprosencephaly, Dandy-Walker syndrome). During the first trimester, we did not found fetuses with severe CNS anomalies and normal IT. However, in the second trimester we identified two important abnormalities in fetuses presenting normal IT during the first trimester (one porencephaly and one Dandy–Walker malformation), along six other minor abnormalities. The overall rate of CNS abnormalities was 0.82%.

The two cases associated with OSB are presented in Figure 3. One case associated with OSB was a singular affected gemelar from a bichorial gemelar pregnancy. The acquisition of images was particular difficult because of the maternal BMI, fetal position and lack of first trimester reexamination, as recommended. We found abnormal posterior brain complex with not measurable intracranial translucency, normal aspects of cranium shape, choroid plexus and cerebral peduncles; the spine defect and persistent exomphalos were associated; the other gemelar showed normal genetic and sono graphical features. During the second and third trimester in the affected fetus was visualized the open defect of the spine and the CNS anomaly was confirmed at birth (Figure 3G). The other case showed not measurable fourth ventricle on the sagittal view of fetal face, normal aspect of choroid plexus with rather acorn contour of cranium, also parallel peduncles were suspected. A reassessment was recommended for fetal spine, suspicion of heart anomaly, but we did not perform an extensive exam, because the pregnancy was terminated at request for familial reasons. However, medical abortion was suggested and performed; the pathologic exam confirmed open neural tube defect of sacral spine.

Two cases with abnormal IT resulted in fetuses unaffected by OSB, but presenting other forms of NTD: one encephalocele (Figure 4) and one acrania with exencephaly (Figure 5).
Figure 3 – Ultrasound cranium sections in fetuses with associated SB. A (Case I): Non identifiable/measurable IT on sagittal view of fetal face. B (Case I): Spine defect. C (Case II): Sagittal view of the face with measurement of nuchal translucency and facial angle and present nasal bone (arrow), non measurable intracranial translucency. D–F (Case I): CNS indirect (cranial) and direct (spinal) typical findings in lumbar spinal defect visualized by 2D and 3D ultrasound in second trimester: obliteration of cistern magna (arrow) with distortion of the cerebellum to form the banana sign (red curved line) (D); dilatation of the lateral ventricles (arrows) (E); spinal defect and myelomeningocele (open star) visualized by 3D ultrasound in sagittal, coronal and axial planes with reconstruction of lumbo-sacral spine (F); G (Case I): Confirmation of the defect at birth.

Figure 4 – Fetus with encephalocele. A: Abnormal structure of the brain with protrusion in occipital region (arrows); B: 3D rendering of occipital region of fetal cranium showing occipital mass (arrow); C: Abnormal contour of posterior calvaria, with discontinuity (arrows) and protrusion of brain.

Figure 5 – Fetus with acrania/exencephaly. A: Absence of calvaria in axial plane and brain disorganization; B and C: Sagittal planes with evident disorganization of neural structures including the posterior brain.

Three cases with abnormal IT resulted in fetuses unaffected by NTD, but in all fetuses we found CNS abnormalities. The cases are presented in the following. Abnormal IT was found in one fetus with morphological features suggesting aqueductal stenosis (Figure 6) presenting marked disproportion between the head and the rest of normal biometry – correlated to the menstrual age in a normal menstruate woman, ventriculomegaly with floating aspect of the small plexus within the cerebrospinal fluid; however, the new parameters for
posterior brain complex evaluation (BS, BS/BSOB ratio) appeared negative for open SB, suggesting a better specificity than IT for SB.

A holoprosencephalic fetus is presented in Figure 7, showing abnormal posterior brain complex with intracranial translucency not measurable and abnormal aspects of cranium shape and choroids plexus; also, we found early growth restriction and multiple abnormalities involving face, abdominal wall, oligoamnios and early severe growth restriction. The pregnancy was later interrupted and cytogenetic evaluation confirmed trisomy 13.

A fetus confirmed in second trimester of gestation with Dandy–Walker syndrome (cerebellar cleft and cisterna magna measuring 17 mm) presented abnormal IT at the first trimester evaluation, with a cystic aspect of a structure situated posterior to the midbrain (Figure 8).

Figure 6 – Fetuses presenting abnormal IT unaffected by OSB, but neurologically abnormal. Aqueductal stenosis suspected in 11–12 weeks’ fetus. A: Severe disproportion of fetal head related to CRL and other fetal segments. B: Sagittal plane of the fetal head with visualization abnormal IT but normal BS and BS/BSOB ratio. C: Small plexus with floating aspect in cerebrospinal fluid.

Figure 7 – Fetus presenting abnormal IT unaffected by OSB, but neurologically abnormal. Holoprosencephalic fetus showing A: Abnormal cranium shape, choroid plexus and median septum, B: Abnormal posterior brain complex and facial profile, C: Microftalmia, D: Pathologic correlation. E: Earlier sagittal global aspect of fetus with severe abnormalities of cranium and face (arrows to nose and mouth).
Histological approach for sono-histological structural correlation

Cranium sagittal planes of the fetus were obtained and posterior brain complex was evaluated by histological approach in order to evidentiate anatomical aspects related to the sonographic features. We considered important to perform such sonographic-histological associations, because in our knowledge, there are no data published in literature regarding the correlations of these morphological features.

Morphologically normal considered fetuses at the first trimester ultrasound exam and aborted between 11–13+6 weeks of gestation for medical reasons or at request were subsequently studied in the Pathology Department, with examination of sagittal planes of the fetal head HE stained, using magnifier and 4× objective.

When compared to ultrasound images showing mid-sagittal planes of the fetal head, the morphological assessment showed a good correlation of the landmarks and the neural structures presented a similar morphological pattern in the sonographic and histological approach. The parameters considered important in OSB early detection are highlighted with microscopic resolution in Figures 9 and 10.
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Discussion

Neural tube defects (NTD) are some of the most frequent fetal malformations; anencephaly and spina bifida are the most common NTD’s manifestation with a nearly equal prevalence of 1–5‰. Consequently, widespread and expensive educational programs and prevention protocols were imagined and implemented, as the anomaly represents an important epidemiologic issue. For the NTD prevention, planned folic acid fortification was postponed with periconceptional use as a public health strategy, and a 50% decline in NTD-affected pregnancies was confirmed in large studies [20].

Also, early detection by second trimester maternal serum screening techniques for NTD detection were stated [15, 16] using AFP (alpha fetoprotein) with expected detection rates for OSB of 65–90% for false-positive rates between 1% and 5% [17]. However, appropriate recommendations for follow-up of screen positive results include amniocentesis and measurements of AFP and acetylcholinesterase (AChE) in amniotic fluid, in combination with ultrasound, for fetal diagnostic of OSB [16]. The morphological ultrasound exam is mandatory, and studies confirmed decades ago that sensitivity in identifying OSB exceeds 99% in mid-second and third trimester of pregnancy [18].

All these considerable efforts justify the need of effective early screening, because OSB remains one of the few severe anomalies with poor detection rates during first trimester assessment; therefore diagnosing spina bifida in morphologic assessment by ultrasound before 14 weeks of gestation, in order to offer the couple an early diagnostic and the choice of first trimester evacuation of pathologic pregnancy, remains difficult [3], because the incidence of these sonographic markers is gestational age-dependent. Thus, the cranial signs were reported in 98% and 72% of spina-bifida fetuses examined between 16 to 24 weeks and in 13% and 81% of cases, respectively, in the third trimester [19].

Effective screening for open spina bifida is provided nowadays mainly by the classical cranial indirect markers in the second trimester and perhaps surprisingly, direct assessment of spine even in advanced stages of ossification after 20 weeks of gestation is less helpful [19]. Such conclusions should encourage the researchers to look also for cranial signs in first trimester evaluation. The case presented in Figure 3 (D–F) shows the evident ventricular enlargement and posterior fossa aspect of Arnold–Chiari malformation with obliteration of cisterna magna and cerebellum aspect of “banana sign”; The cranial signs are explained by the downward displacement of the brain secondary to cerebrospinal fluid leakage into the amniotic cavity and hypotension in the subarachnoid spaces, leading to caudal displacement of the brain with obstructive hydrocephalus [19].

In the same figure spinal defect is visualized, but the morphological features appear discrete in comparison to the cranial signs; they consist in the separation of lateral vertebral processes and the exposure of neural canal posteriorly; the presence of a satellite myelomeningocele that is seen in our case presented in Figure 4 and certainly aids the diagnosis, whereas his absence can make detection difficult.

We may conclude that the accuracy of ultrasound morphologic exam in OSB detection in mid-second and...
third trimester performed in referral centers is near to certitude. In contrast to second and third trimester, visualization of the spine (for OSB detection using direct signs) cerebellum (for OSB detection using indirect signs – Arnold–Chiari malformation) is not easy in transversal planes before 14 weeks [7], although our histologic assessment of sagittal sections of fetal cranium identified the CNS structures of posterior fossa and showed anatomical rapports as seen in second trimester ultrasound scan. Prenatal diagnosis of spina bifida in the first trimester remains a major challenge in obstetric ultrasound, as extensive studies have reported that in addition to aneuploidies, the 11–13-week scan can identify the majority of all major fetal abnormalities [20], but low detection rates for OSB [2–4] are communicated. In 1997, Sebire NJ et al. [4] reviewed database of 61 972 pregnancies, which had undergone first trimester genetic screening and the study group noted 29 cases of spina bifida, from which none had been diagnosed in the first trimester. In the presented context, recent preliminary results suggest that indirect markers related to abnormal posterior brain measurements may offer the possibility of first trimester diagnosis of open spina bifida [8, 14]. Following the same morpho-physiologic pattern as in Arnold–Chiari malformation, the new researches propose the sagittal visualization of the caudal displacement of the brain stem and compression of the fourth ventricle–cisterna magna complex within the confined space between the sphenoid and occipital bone and loss of the normal intracranial translucency. It was not in our intention to propose sensitivity or specificity rates for these parameters, because of the small number of affected fetuses investigated during the study period. In fact, this is a limitation of most studies, because of the small number of anomalous fetuses properly examined in the first trimester, partially due to the small prevalence of OSB in general population, and on the other hand because of the insufficient addressability to experienced centers. Thus, our intention was to perform a careful morphological assessment of CNS in OSB affected fetuses and in fetuses with abnormal aspect of the fourth ventricle – IT. All first trimester fetuses with abnormal fourth ventricle fetuses were having neuro-morphologic abnormalities as NTD (anencephaly, spina bifida, encephalocoele), holoprosencephaly, aqueductal stenosis with the appearance of early hydrocephaly and Dandy–Walker syndrome. It is not in our intention to propose intracranial translucency as a marker for anencephaly or encephalocele detection, because there are easy detectable with pathognomonic features as acrania or calvaria defects with the brain appearing usually at varying degrees of distortion and disruption; however, Johnson SP et al. [21] reported in large multicenter studies (34 830 fetuses) of first trimester screening for aneuploidies that the diagnosis of anencephaly was made in 74% of the affected fetuses. Thus, such a detection marker present in the standard plane used in first trimester genetic assessment may be useful in less experienced hands, when the sonographers are not specifically instructed to look for acrania/calvaria defect or they are not informed of the different diagnostic features of anencephaly in the first compared to the second trimester.

We also found that all OSB diagnosed cases screened in the first trimester in our center presented abnormal markers of posterior brain, thus morphometric assessment of posterior brain appears to become a useful tool in OSB early detection. However, in our small series of fetuses with abnormal IT, when measurable, BS antero-posterior diameter and BS to BSOb ratio were more specific for neural tube defects as they were found normal in fetuses with early ventriculomegaly/hydrocephaly and Dandy–Walker.

We consider that the main message from our case presentations is that abnormal aspect of IT should be followed by extensive and careful examination of CNS morphology, because other anomalies seems to associate this finding; we suggest the sections used in our center’s routine: cranial axial planes at the level of choroid plexus and cerebral peduncles, axial-oblique plane at the level of cerebellum hemispheres, sagittal view used for genetic screening and sagittal plane for spine evaluation.

Consequently, the assessment of posterior brain is likely to improve the performance of first-trimester morphological screening, and because the sonographic evaluations are made using an obligatory plane for the genetic screening, also used for accurate assessment of nuchal translucency, nasal bone and facial angle, little time for supplementary examination of the fetus is involved.

Our histological mid-sagittal sections of the fetal head were correlated with the visible structures related by ultrasound assessment and considered important in OSB early detection. In a previous research, we showed that measurement of the IT is reproducible, at least in normal neurological fetuses and increases proportionally with fetal CRL [22]. Other studies confirmed the intraobserver and interobserver reproducibility [14] of BS antero-posterior diameter and BS to BSOb ratio. These findings confirm the possibility to use posterior brain parameters in first trimester morphologic screening for OSB and other CNS anomalies.

Conclusions

Abnormal aspect of the fourth ventricle may become a marker easily evaluable with little investment of additional time in ultrasound morphologic assessment in first trimester fetuses; abnormal aspects may be associated to severe CNS abnormalities, therefore further neuro-morphological assessment by experienced examiners is recommended.

However, accurate assessment of the IT, BS, BSOb necessitates extensive experience in scanning and it is therefore unlikely that all measurements will be incorporated into routine first-trimester sonographic screening in all cases; an alternative approach is to routinely assess the IT and to reserve further evaluation for the subgroup of pregnancies with an increased risk for neural tube defects, which constitutes about 5‰ of the total population.
Neurologically normal considered fetuses at the first trimester ultrasound exam showed a good morphological histo-sonographic correlation of the anatomical neural structures involved in early OB detection.

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Corresponding author

Alexandru Comănescu, Teaching Assistant, MD, PhD, Department of Obstetrics and Gynecology, Prenatal Diagnostic Unit, University of Medicine and Pharmacy of Craiova, 2–4 Petru Rareș Street, 200349 Craiova, Romania; Phone +40723–888 773, Fax +40251–502 179, e-mail: alexcom8000@yahoo.com

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