First Trimester Anomaly Scan—The Last Redoubt Won: Open Spina Bifida

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ABSTRACT

Open spina bifida (OSB) is a non-lethal fetal anomaly, yet often leads to severe disability. Most cases of open spina bifida are detected at the second trimester fetal anomaly ultrasound scan. The 11 to 13 weeks of amenorrhea scan evolved over the last 20 years from essentially a dating scan, to a genetic scan, and recently to one which includes, in addition to the genetic markers, a basic checklist for examination of the whole fetal anatomy. The direct visualization of the spine at the first trimester (FT) scan remained difficult, despite the wider use of high-resolution ultrasound machines and the volumetric approach. Thus, indirect intracranial morphological markers for OSB were proposed to diagnose this neural tube defect.

The present review aims to describe the specific anatomical feature of the spine and the posterior brain, both on parasagittal and on axial planes, recently proposed for the early detection of OSB.

Specialists involved in the prenatal diagnosis will eventually elaborate in the future a screening protocol for OSB in the FT of pregnancy, using the most valuable and easy to obtain marker, in a single 2D plane.

The offer of an early diagnosis of possible severe anomalies, such as OSB, is a tool enhancing the autonomy of the pregnant woman.

Keywords: Open spina bifida, First trimester, Anomaly scan, Posterior brain.

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INTRODUCTION

The First Trimester Anomaly Scan

Maternal-fetal medicine is a nowadays' reality. It is the branch of obstetrics that focuses on the medical and surgical management of pathologic pregnancies. This science is promoting equality between the two patients: the mother and the fetus. Management includes monitoring and treatment: comprehensive ultrasound, chorionic villus sampling, genetic amniocentesis, and fetal surgery or treatment.

The prenatal diagnosis became an integral part of obstetric modern care and is standard care in most European countries. The ultrasound (US) examination is the single most important noninvasive technique used for the fetal study. In addition, we are witnessing a long-term safety record of pregnancy ultrasound imaging¹, thus an extensive use in modern obstetric care.

Since 2011, when the new, inverted pyramid of prenatal care was proposed,² the 12 weeks scan became the pillar of obstetric care. Examining the fetus at this gestational age (GA) rapidly became the most important scan throughout the whole pregnancy.

We already have proof that the 12 weeks of amenorrhea (WA) scan allow the most performant screen for chromosomal anomalies (nuchal translucency-NT being the most important marker), using the combined test.³ Moreover, at this GA, due to ever-growing resolution of the system used, we are able to detect the vast majority of major fetal congenital structural anomalies.⁴⁻¹⁷ Recent literature reports high detection rates for all fetal systems' major anomalies, including, more recently, isolated congenital heart diseases.

Nowadays, efforts are made to develop algorithms based on combinations of maternal characteristics, early ultrasound findings and biochemical testing of maternal blood. This approach proved efficient in predicting most major aneuploidies,² miscarriage and fetal death,^{18,19}

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preterm delivery,^{20,21} preeclampsia,²² gestational diabetes,²³⁻²⁵ fetal growth restriction²⁶ and macrosomia.²⁷ Recently, international leading societies, as ISUOG (International Society of Ultrasound in Obstetrics and Gynecology),²⁸ NICE (National Institute for Clinical Excellence)²⁹ and ACOG (American College of Obstetricians and Gynecologists)³⁰ have issued guidelines on routine prenatal care recommending that all pregnant women should be offered the first trimester (FT) ultrasound scan.

Early detection of fetal malformations offers the possibility of an earlier and safer termination of pregnancy (TOP) in cases with severe structural abnormalities detected, with less economic and emotional costs.³¹ This will probably have an impact in perinatal demographic figures, because major fetal abnormalities accounted until recent for 25% of neonatal deaths and usually lead to long-term disabilities and high socioeconomic costs.³²

Still, an extensive assessment of the fetal anatomy at the FT scan requires appropriate training of sonographers and high-resolution equipment. This type of examination may be dragged down by low availability of human resources and material endowments, local medical practice and legal considerations and insurance-related cost reimbursements.

Regarding the fetal morphologic assessment, the current policy of most healthcare systems is to offer routinely a transabdominal ultrasound examination performed at 18+0 – 23+6 WA,²⁸ because some structural anomalies may develop at later stages of pregnancy or may develop from pathophysiological process undetectable in the FT. Thus, the standard second trimester (ST) scan cannot be replaced, and still represents the gold standard test against which the FT assessment should be compared.³³⁻³⁷

Gradually, the 11-13 WA scan evolved over the last 20 years from essentially a dating and genetic scan to one which also includes a basic checklist for examination of the whole fetal anatomy. Diseases that are either lethal or are associated with possible survival and severe immediate or long-term morbidity^{4-17,38} are usually accessible at this GA. Common sense, supported by objective studies, tells us that parents want to know about any fetal problems as early in pregnancy as possible.³⁹

Using a complete morphology protocol is a prerequisite for high detection rates of major anomalies, which can reach around 80%.¹⁰⁻¹⁷ This figure is not far from the efficiency of ST anomaly scan.^{28,33,37,40} A systematic review on the ST anomaly scan effectiveness reported that about 45% of the major anomalies were detected routinely,⁴¹ with large differences between studies in

detection rates which ranged from 15 to 85%, and also large differences in overall detection rates according to the type of fetal anomaly. This variation depends on the type of studied malformations, the follow-up method and the extension of the scan protocols.

The First Trimester Central Nervous System Morphological Assessment

Central nervous system (CNS) malformations are some of the most common congenital abnormalities (10 per 1000 live births, compared to heart at 8 per 1000, kidneys at 4 per 1000, and limbs at 1 per 1000⁴⁴). The FT scan was reported recently with a higher degree of detection for major CNS anomalies - 53-69%.^{17,42}

On the other hand, there are important limitations in the prenatal diagnostic of CNS abnormalities ultrasound,^{16,43} as most of the congenital anomalies of the nervous system are undetectable during the FT evaluation. They may be associated only with subtle findings in early gestation as the brain continues to develop during pregnancy and into the neonatal period. Agenesis of corpus callosum, microcephaly and hydrocephaly usually cannot be detected in the FT, and sometimes these findings are apparent only in late stages of pregnancy. Also, some cerebral lesions are not due to defective embryological development but represent the consequence of acquired prenatal or perinatal damage.⁴⁴⁻⁴⁶

The most important congenital anomalies of the nervous system concerning prevalence and severity are usually detectable during the FT scan, including holoprosencephaly and some neural tube defects (NTDs). The visualization of the falx cerebri, calvaria and head shape are easily achieved in the FT transverse incidence, thus, holoprosencephaly and encephalocele are detectable.

The minimum requirements recommended by the ISUOG Practice Guidelines²⁸ for a basic fetal anatomical survey at the end of the FT of pregnancy are two axial planes: the transthalamic (the biparietal diameter - BPD measurement) plane, and the third-ventricle plane, with the demonstration of the symmetric, normal choroid plexuses. Also, about the spine, the mentioned guidelines state that an 'attempt should be made to show intact overlying skin. However, in the absence of obvious anomaly, failure to examine the spine at this time should not prompt further examination earlier than the mid-trimester scan'. In terms of parasagittal fetal face planes, the statement is as it follows: 'It has been proposed that the posterior fossa intracranial translucency can be evaluated between 11 and 13+6 weeks as a screening test for open neural tube defect, but this is not a standard'.

Open Spina Bifida—The Importance of the Disease

Open spina bifida is a nonlethal fetal anomaly. Significant progress has been made in the prevention, diagnosis and treatment of open spina bifida over the past 75 years.

There are two forms of spina bifida cystica (open spina bifida): meningocele (a rare type of spina bifida in which only the membranes protecting the spinal cord herniate through the vertebrae), and myelomeningocele. Myelomeningocele is the most serious form of spina bifida, it accounts for 75% of cases. Between 70 and 80% of children with OSB will also develop hydrocephalus.⁴⁷ The condition appears to be caused by a combination of genetic factors and environmental influences. The specific genes and environmental factors are not completely understood.⁴⁸ OSB occurs in approximately 6 per 10,000 births.⁴⁹ Liveborn infants with myelomeningocele have a death rate of approximately 10%.⁵⁰

Most cases of open spina bifida are detected at the 18+0WA – 20+6 WA fetal anomaly US scan.⁴⁸

Although efforts are made toward new approaches to the fetal treatment of OSB,^{51,52} the management of OSB is only finalized in many European countries (including ours) after birth, when the type and size of the lesion is assessed. The treatment depends upon the position and the severity of the lesion. Most cases of OSB require an operation to repair the neural tube after birth. It is common that some damage to the newborn's nervous system already took place and surgery is not often able to correct all problems. If the child develops hydrocephalus, this also needs to be treated with surgery as increased pressure induced by the excessive fluid can cause brain damage. Surgery involves draining the fluid into the abdomen (a ventriculo-peritoneal shunt). This often needs to be replaced as the child grows because of problems with blockage and infection.⁵³⁻⁵⁷

The prognosis for babies born with OSB depends on the location, size and extent of the defect and the presence of hydrocephalus, and the range of disability caused is variable. Still, it often leads to severe disability. Children with spina bifida frequently have problems controlling the bladder and bowels functions. In serious cases, the baby may have problems walking or be unable to walk. Hydrocephalus cause learning difficulties. Generally, abnormalities higher on the spine produce a greater risk of paralysis and other debilitating complications.⁵³⁻⁵⁷

Nowadays, all women are advised to take a supplement of 400 mg of folic acid for at least 3 months before pregnancy and up to the end of the 12th week of pregnancy.⁵⁸ Women who have a family history of NTDs are advised to take a higher dose of 5 mg of folic acid, as this has been shown to reduce their chances of having another baby with an NTD.⁵⁸

Depending on the US findings, additional information from a pediatric team with expertise in the care and management of children with OSB should be offered. If the FT diagnosis is performed, a TOP should be offered following appropriate counselling. Women should be offered the opportunity to discuss the possible implications of continuing or ending their pregnancy. In our country, TOP at maternal request at more than 13+6 WA for non-lethal diseases such as OSB is illegal, thus the FT anomaly scan is more important than in other European states.

Because early TOP seems to include less risks and less harm for the women (although, of course any TOP because of fetal anomalies is associated with distress and intense psychological morbidity for some), it is comprehensible that women prefer earlier TOP as compared with later.

Some women choose to continue the pregnancy, and these parents will need ongoing care and support. Women who wish to continue their pregnancy should be antenatally referred to the pediatric surgery team who will care for their baby. Ongoing antenatal care involves ultrasound scans to monitor the fetus.

OSB Diagnosis at the End of the FT of Pregnancy—The Limits of the Current Approaches

The direct visualization of the spine NTDs at the FT scan remained difficult, despite the wider use of high-resolution ultrasound machines. Thus, indirect intracranial morphological markers for open spina bifida were proposed to diagnose this NTD.

Since 1997, when the lemon sign was described at 10 to 14 weeks of amenorrhea,⁵⁹ the US of the fetal head holds promise for the early detection of spina bifida (OSB) at the end of the FT, instead of the fetal spine. At this GA, as said before, the direct diagnosis on the basis of the myelomeningocele remained extremely challenging, due probably to size restrictions.

Posterior brain anomalies, usually having subtle changes, can be yet identified in the parasagittal plane, used for the NT thickness measurement: compression of the fourth ventricle, leading to decrease or disappearance of the normal intracranial translucency (IT),⁶⁰⁻⁶² altered ranges of the brain stem,⁶³ nonvisualization of the cisterna magna^{64,65} (changes that give the subjective impression of the caudal displacement of the brainstem), decreased frontomaxillary facial (FMF) angle.⁶⁶

Also, in axial views, the third-ventricle plane offers the measurements of the lateral ventricle area, the diameter of the roof of the third ventricle and the transthalamic plane—the diameter of the aqueduct of Sylvius, significantly decreased, all demonstrating the alteration of intracranial collection of cerebrospinal fluid.⁶⁷ These

Table 1: 2D planes and 2D markers for fetal CNS morphologic evaluation at the first-trimester ultrasound scan

	Normal aspects	OSB findings
Skull and brain	<p>1. Axial planes of cranium: a. Transthalamic view*</p> <ul style="list-style-type: none"> • Skull (bone ossification) • BPD • HC • OFD • Thalamus • Third ventricle • Symmetry <ul style="list-style-type: none"> • The aqueduct of Sylvius position normal • The transverse diameter of the aqueduct of Sylvius—normal <ul style="list-style-type: none"> • Cerebral peduncles position normal	<ul style="list-style-type: none"> • The Crush sign • The transverse diameter of the aqueduct of Sylvius—decreased <ul style="list-style-type: none"> • Cerebral peduncles parallel
	<p>b. Lateral third-ventricle view*</p> <ul style="list-style-type: none"> • Skull (bone ossification) • Midline falx echo; • Choroid plexuses • Interhemispheric fissure • Posterior horns LV	<ul style="list-style-type: none"> • Dry brain phenomenon present: (subjective large choroid plexus)

Contd...

Contd...

	<ul style="list-style-type: none"> • Lateral walls of anterior horns LV • Thin brain mantle • The choroid plexus area measurement • The LV area measurement 	
	<p>C. Fourth-ventricle view</p> <ul style="list-style-type: none"> • Fourth-ventricle normal	<ul style="list-style-type: none"> • Fourth-ventricle decreased or absent
NT	<p>2. Parasagittal plane of the cranium* Sonographic measurement of nuchal translucency (NT) thickness</p> <p>Posterior brain morphometry</p> <ul style="list-style-type: none"> • IT normal • Brainstem diameter normal • CM normal <ul style="list-style-type: none"> • Brainstem to brainstem—occipital bone distance ratio normal	<p>Posterior brain morphometry</p> <ul style="list-style-type: none"> • Subjective caudal displacement of the brainstem • IT absent/decreased • BS enlarged? • CM absent/decreased <ul style="list-style-type: none"> • Brainstem to brainstem—occipital bone distance ratio normal

Contd...

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	<ul style="list-style-type: none"> • FMF angle measurement normal	<ul style="list-style-type: none"> • FMF angle measurement decreased
2D spine assessment	<p>Longitudinal section of the spine*</p> <ul style="list-style-type: none"> • Normal vertebral alignment and integrity • Intact overlying skin <p>Axial views of the spine*</p>	<ul style="list-style-type: none"> • Meningocele
Additional data	<p>1. The ratio BPD/TAD</p> <p>2. The ratio choroid plexus/LV area</p>

alterations were described as a subjective sign, the 'dried-up brain phenomenon'. In the transthalamic axial view, also the 'acorn-shaped head' was described, with the cerebral peduncles appearing parallel to each other,⁶⁸ and more recently, the posterior-caudal displacement of the mesencephalon and its flattening against the occipital bone ('crash sign').⁶⁹

Moreover, it have been demonstrated that fetuses with OSB have smaller heads,⁷⁰⁻⁷² thus have altered intrafetal ratios.⁷³

Easy to see, the screening in the FT using only the two axial planes recommended in recent guidelines, without searching for any other marker, will miss virtually all OSB cases, especially if performed by a less experienced observer.

Along with the fetal heart, in terms of FT OSB screening, no protocols are available yet.

In a series of 18 published screening studies^{4-17,34,74-76} reporting on the effectiveness of the first-trimester scan in the diagnosis of fetal major abnormalities, all using a standard screening protocol, we numbered 118110 cases and we collected 5 cases diagnosed, and 34 cases missed. This underlines the difficulties encountered in OSB diagnosis in the FT. On the contrary, it is likely that adding at least a marker for OSB, we will be ending up by diagnosing the majority of cases, since introducing just a simple and reproducible parameter as BPD resulted in detecting half of the cases.⁷⁰

OSB Diagnosis at the End of the FT of Pregnancy —the Future

In Table 1, we describe the planes that were proposed in searching for markers, and the anatomical features that proved efficiency in the early diagnosis of OSB. We also demonstrate with images the differences between normal cases and OSB cases.

Volumetric Ultrasound

Three-dimensional (3D) rendering images provide lately an entirely new visual experiences for some examiners and couples owing to the anatomically realistic depiction of normal and abnormal fetal surfaces. However,

Fig. 1: 3D static acquisition of the fetal head, surface rendering, normal case. The acquisition plane—the sagittal plane

Fig. 2: 3D static acquisition of the fetal spine, surface rendering, from posterior insonation, normal case. In terms of spine, the postprocessing allows probably a better discrimination of signals for skin lesions, as shown in Figure 3

although 3D US may be an adjunctive tool, there is scarce evidence that it alters anything in terms of the diagnosis, outcome, or subsequent counseling, regardless the GA.

Fig. 3: 3D static acquisition of the fetal spine, surface rendering, from posterior insonation, OSB case. Steps of the postprocessing seen. Correlation with pathologic aspect of the specimen. Studies involving large sample size populations are needed to confirm the true usefulness of 3D US

In terms of FT OSB, both 3D static volumes of the fetal head (transabdominally or transvaginally acquired) (Fig. 1) and 3D static volumes of the spine (Fig. 2) may be advocated.

The most important advantage of postprocessing the 3D datasets of the fetal head is finding the accurate plane to be interpreted.⁶⁷

DISCUSSION

There are many important questions that we must find the answer: first of all, should we perform, in general, screening tests in prenatal medicine? Do we need a FT screening protocol for OSB? Or we do not need to search for OSB at all in the FT? Or we do need a diagnosis test in the FT?

If the answer is yes, if we should search for OSB in the FT, should we look at the fetal spine, eventually by the transvaginal route,⁷⁷ or should we look at the intracranial indirect markers⁶¹?

If the fetal head remains the answer for the early detection of OSB, should we use axial or parasagittal planes for screening?^{60,61,63,65,68-70}

The first question, probably the most important one, is extremely difficult to answer, due to the conflict between ethical principles and available human and technical resources, especially in developing countries.

Routine obstetric ultrasound testing in general has been shown to be a positive and very much anticipated experience for most patients. On the contrary, women who were told their child might have an anomaly, based on ultrasound findings (either false-positive or true-positive cases) are usually intensely anxious the time interval between the screening ultrasound and the conclusive exam, and even beyond it.⁷⁸⁻⁸⁰ The experience itself of waiting for a detailed scan provokes increases in anxiety beyond what pregnant women typically experience. Referral for any highly specialized scan and all specialized prenatal testing are independently associated with increased parental anxiety.

On the other hand, if we decide against offering detailed scans to every pregnant woman, these examinations will be restricted to women that can afford the costs by themselves, and this approach is very near to violating of the principle of justice for all.

Debates have already taken place in regards to whether we need or we do not need a screening tool for OSB in the first trimester.^{61,77}

The WHO defines certain criteria for screening tests.⁸¹ The disease must be of sufficient prevalence and severity and should have a fixed spectrum of symptoms, the screening method should be simple and acceptable, screening should be accurate, confirmation and follow-up should be available, the disease should be treatable and

screening should show improved outcome and a positive cost/benefit ratio.

The prenatal diagnosis of OSB fulfills completely the criteria of a target lesion for a screening test. The strongest reason against elaborating a FT protocol⁷⁷ is the circumstance that the intrauterine repair of OSB, demonstrated to be efficient in ameliorating the CNS damage, is only technically feasible late in pregnancy, during the second half of the second trimester.^{82,83}

For the lifesaving effects of prenatal medicine, in most of the cases a diagnosis early in pregnancy is not mandatory, thus, for continuing pregnancies, it is no disadvantage if diagnosed in the second half of pregnancy.

In case of TOP, the situation is different: there are strong medical and ethical arguments against late TOP. Late TOP includes several risks and is evaluated as being worse than early TOP, because of at least two reasons: in general, maternal pregnancy-involved risks are related to the GA, and so women who continue their pregnancy and terminate it in later stages suffer a greater risk, and the mother–embryo/fetus-relationship will deepen as the pregnancy continues. This will lead to a stronger burden for the mother if she decides for late TOP in consequence of the late detection of a major anomaly.

Because early TOP seems to include less risks and less harm for the women it is comprehensible that women prefer earlier TOP as compared with later.

The offer of an early diagnosis of possible severe anomalies is a tool enhancing the autonomy of the pregnant woman (resources within the healthcare systems are constantly shortened). If autonomy is regarded as an important right in one's life, women should have the right to choose whether to take advantage of prenatal diagnosis or not. If women decide to claim for prenatal medicine, it seems to be part of their right to get all possible screening options offered by prenatal medicine they want to have access to.

There are arguments against the concept of offering a screening test/a detailed anomaly scan to all patients: besides the problem of limited resources in healthcare systems, is the question of detection rate of anomalies in fetuses with relative low-risk.

We have also to prevent the false positive results with the risk of termination of unaffected fetuses, which is an argument to perform detailed scans only in specialized centers in which skill, detection rate and accuracy of the prenatal diagnosis are continuously audited.

Concerning the most efficient approach, meaning to choose between looking at the fetal spine or the fetal brain, transabdominal or transvaginal, in 2D conventional US or in volumetric US, probably only large, prospective, collaborative studies or randomized trials will give us the answer.

On the other hand we already have proof that the more extended the protocol used, regardless the GA, the lower figures of false-negative and false-positive cases were reported. Thus, we will probably achieve the highest detection rates if using both axial and parasagittal views.

CONCLUSION

With the advance of both technology and research, early pregnancy screening is becoming ever more sophisticated and more complex. In the near future, the first trimester ultrasound will probably target, beside major chromosomal abnormalities, all isolated major structural anomalies, such as OSB.

The prenatal ultrasound examination is however a highly system-dependent and operator-dependent technique. Using high resolution machines on one hand, and on the other, the operator's knowledge about the normal and pathological fetal first trimester neuroanatomy, natural history of OSB function of the extension and location of the lesion, experience, appropriate technical skills and clinical judgment are of paramount importance for obtaining the correct diagnostic images and for interpretation of the diagnostic images. Therefore, for the time being, local conditions and expertise in individual centers may critically affect the accuracy of the US diagnostic modalities for early OSB diagnosis.

While there are clear benefits to most women receiving early reassurance that their baby is developing as expected, there is no evidence that an earlier prenatal diagnosis has less long-term emotional impact than at later gestations.

Because the first trimester scan information may change radically management of the pregnancy, professionals involved in screening need to recognize and acknowledge the adverse side-effects of such an US scan and should develop the skills necessary to help the parents to understand the concept of screening and the uncertainties inherent to this process.

However, when the technical and available expertise issues will be overcome, the offer of an early diagnosis of all possible severe anomalies, including OSB, will be a tool enhancing the autonomy of the pregnant woman.

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