IJMA

International Journal of Medical Arts

Volume 3, Issue 4 [Autumn (October-December) 2021]

http://ijma.journals.ekb.eg/

Print ISSN: 2636-4174

Online ISSN: 2682-3780

About IJMA [last updated October, 1st, 2021]

- ✓ International Journal of Medical Arts is the Official Journal of the Damietta Faculty of Medicine, Al-Azhar University, Egypt
- ✓ It is an International, Open Access, Double-blind, Peer-reviewed Journal
- ✓ Published four times a year
- ✓ The First Issue was published in July 2019
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International Journal of Medical Arts 2021; 3 [4] October-December: 1803-1817

Available online at Journal Website
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Main subject [Radiology] *

Original Article

Ultrasonographic Evaluation of Fetal Brain Midline Structures in The Second Trimester: The role of 2D versus 4D, with post-natal correlation

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Submission date: August 20, 2021; Acceptance date: September 30, 2021

DOI: 10.21608/ijma.2021.200543

ABSTRACT

Background: Midline cerebral structures are essential for the normal morphogenesis and function of the fetal brain. However, the diagnosis of congenital anomalies of midline cerebral structures.

The Aim of The Work: This study aimed to evaluate the role of 2D versus 4D ultrasound in the diagnosis of midline structures of the fetal brain at the second trimester of pregnancy.

Patients and Methods: 200 pregnant women at the second trimester [18-22 weeks] were selected. They were clinically evaluated to check the female and fetal wellbeing. Then a screening of fetal brain midline strictures had been performed by two- and four-dimensional ultrasound, aiming to discover any anomalies of the fetal brain midline structure. Both scans were compared with the postnatal transcranial ultrasound.

Results: The 2D ultrasound detected no abnormality in 194 out of 200 fetuses [97.0%], and 4 cases [2.0%] had mega-cisterna magna, and 2 cases [1.0%] had encephalomylocele, which were detected by the 4 D and confirmed by postnatal transcranial ultrasound. The 4 D US discovered 2 cases [1.0%] of Dandywalker malformation, which was confirmed by postnatal transcranial US. There was a complete agreement between prenatal 4D ultrasound and postnatal transcranial ultrasound. The prenatal 2D ultrasound had a sensitivity of 75.0%, specificity of 100.0%, PPV of 100.0%, NPV of 98.7% and overall accuracy of 99.0%. Otherwise, the prenatal 4D ultrasound was 100.0% sensitive and specific.

Conclusion: 4D ultrasound showed superiority in the diagnosis and confirmation of the fetal brain midline structure's abnormalities. Also, the prenatal 4D ultrasound was 100.0% sensitive as postnatal transcranial US.

Keywords: Two-Dimensional; Four-Dimensional; Fetal Brain Midline Structures; Postnatal; Transcranial Ultrasound.

Citation: Abd El Salam AB, Mustafa FA, **Sayed ZS, Abuelmatti HM**. Ultrasonographic Evaluation of Fetal Brain Midline Structures in The Second Trimester: The role of 2D versus 4D, with post-natal correlation. IJMA 2021; 3 [4] October-December: 1811-1817. [DOI: 10.21608/ijma.2021.200543].

* Main subject and any subcategories have been classified according to the research topic

INTRODUCTION

Fetal malformations are associated with increased risk of newborn disability. If fetal malformations diagnosed early in pregnancy, it helps the decision of whether or not to terminate the pregnancy. Thus, regular prenatal screening is the key to decrease the rate of newborns' disability [1]. The reduction of malformed fetus improves the quality of the newborns and promote societal and family development. Thus, antenatal screening is of great value [2].

The organogenesis of the central nervous system from the neural tube begins early in the intrauterine life, and passes through a series of processes of differentiation until after birth [3]. The nervous elements that present in the midline cerebral structures are indispensable for the normal morphogenesis and function of the brain thus median echo should be assessed at the end of the first trimester [4].

The diagnosis of congenital brain anomalies including the median structures is difficult during fetal life as the routinely used standard axial sonographic do not show some cerebral structures as the cerebellar vermis and corpus collosum [5]. However, in high-risk pregnancies during the first to early second trimester, the midline anomalies could be visualized [6]. The classification of midline anomalies first reported by De Meyer and later revised by Fitz *et al*. includes two principal classes: closure defects and diverticulation disorders [7, 8]. The ontogenesis of cerebral midline occurs after the seventh week of amenorrhea recognized as ventral initiation related strictly to the development of the midface [9].

Routine ultrasound screening is an established tool of antenatal care as it represents a simple non-invasive method of great importance in routine prenatal assessment, starting point in neuroscientific studies [10, 11] as well as increased fetal brain malformations detection rate [12].

The use of a detailed morphologic ultrasound protocol permitted an increased first trimester detection rate of 69.5% major CNS malformations [13]. Visentin *et al*. reported their experience on the use of the transfrontal view as a novel two-dimensional [2D] method for imagining of the fetal midline cerebral structures and the facial profile [14].

4D ultrasound has been presented to the medical practice and played a complementary role to 2D and 3D ultrasound provision of real time images. 4D ultrasound allows visualization of embryonic movements two weeks earlier than 2D ultrasound [15] and have given the opportunity to explicit detail fetal anatomy and fetal activity [16]. However, 4D mainly used to assess fetal behaviour, but **Öcal *et al.*** [17] used it to evaluate different fetal malformations and concluded that, it may be used as a complementary instrument for fetal congenital malformation assessment, especially congenital anomalies of the face, spine, extremity, and abdominal wall. In high-risk fetuses to CNS malformations or in suspicious cases on basic examination, the fetal neurosonogram is warranted, that should be done by an expert investigator [6]. For the assessment of a satisfactory visualization of median structures, classic examination should be used in combination with modern techniques [18].

THE AIM OF THE WORK

This study was conducted to investigate the efficiency and the accuracy of the two-dimensional ultrasound versus four-dimensional ultrasound in diagnosing of the midline structures of the fetal brain at the second trimester of pregnancy [18-22 weeks] confirmed by post-natal trans-cranial ultrasound.

PATIENTS AND METHODS

After ethical approval from ethical committee of Obstetrics and Gynecology Department, Damietta Faculty of Medicine, and Assiut Faculty of Medicine, Al-Azhar University, an informed written approval was signed by each participant. The current work completed by 200 pregnant females during the second trimester [18-22 weeks of gestation]. The study was completed between January 2019 and June 2021. All pregnant females within the second trimester, normal and high-risk pregnancies [diabetes, hypertension, heart diseases, smoking cigarettes, drinking alcohol and using illegal drugs] and subjects having children with congenital brain anomalies were enrolled in this study. Any women refused to participate, at the first and third trimesters of pregnancy, who had twins or multiple pregnancies as well as intra-uterine fetal death, were excluded from the study.

All females were evaluated by clinical history taking and examination. Ultrasound evaluation of fetal midline structures was completed by a VoLuSON p5 device. A Curved Linear Array 2.0–5.0 MHz probe was used for 2D imaging, and a broadband volume curved ultrasound transducer of 2–6 MHz was used for 4D imaging. In each case, an attempt was made to obtain a median plane of the fetal brain with two-dimensional [2D] followed by four-dimensional [4D] ultrasonography at the same session. The transducer was aligned with the anterior fontanelle and the midline sutures by either a transvaginal approach [according to The International Society of Ultrasound in Obstetrics and Gynecology guidelines] or by a transabdominal scan when the transvaginal scan was technically difficult, or to obtain good images. All the fetal parts were assessed, beginning

by the fetal cranium, and the findings were recorded. Visualization of the relevant anatomic details of the median plane, the corpus callosum and cerebellar vermis in particular, was noted for both 2D and 4D images. An attempt was made to visualize the main landmarks of the cerebellar vermis, namely the fastigium of the fourth ventricle and the two main fissures. The 2D images were obtained first by the broad band volume curved probe. Then, 4D volume images were obtained after creating a field box fitted to the area of interest. Both images of 2 and 4Ds were put side by side on the screen and a 4D image was obtained on the full screen. The volume data were acquired with the 4D real time option, provided that, the acquisition times were < 20 s per cine volume, and scan angles ranging from 30^{o} to 60^{o}. Of the imaging modalities of 4D-USG, only surface rendering mode [SRM] was used. The mean duration of each examination was 25 min [20–30 min]. However, no time limit was set before the anomaly scan. Cephalocele was defined as a neural tube defect characterized by protrusions of intracranial structures [the brain tissue] through a defect in the skull. In axial view, it was recognized as a cystic cranial lesion in continuity with the brain [Figure 1]. On the other side, Mega cisterna magna characterized by a true enlarged retro and infracerebellar CSF space [the space between the inferior margin of the vermis and the posterior rim of the foramen magnum] [Figure 2].

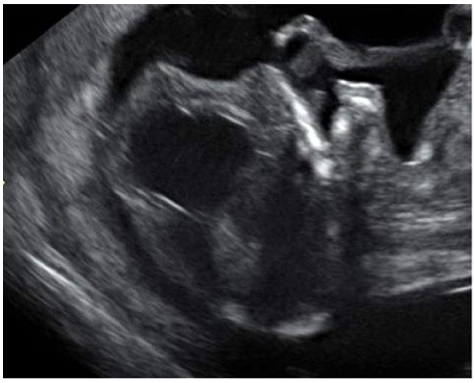

Figure [1]: Axial view of the fetal brain showed a cystic cranial lesion in continuity with the brain can [most probably encephalocele]

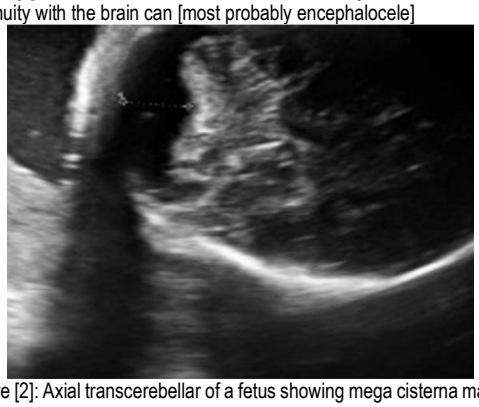

Figure [2]: Axial transcerebellar of a fetus showing mega cisterna magna.

Post-natal transcranial ultrasound was done for all newborns and used as the reference tool to ensure the efficiency of 2D and 4D ultrasound diagnosis.

Statistical analysis:

The data was anonymized and fed to Microsoft Excel, version 2016 [Microsoft Inc., USA]. Percentages were calculated for categorical data and diagnostic indicators of each modality were calculated manually from the following equations.

- Sensitivity = true positive [TP]/[true positive + false negative [FN]].
- Specificity = true negative [TN]/[true negative + false positive [FP]].
- Positive predictive value [PPV] = TP/[TP+FP].
- Negative Predictive value [NPV] = TN/[TN+FN];
- Overall Accuracy=TP+TN/TP+TN+FP+FN

RESULTS

The age of the study group ranged from 18-41 and was distributed as 20% of women less than 20 years old, 64% of women ranged from 20-30 years old and only 16% were more than 30 years old. The gestational age ranged from 18-22 weeks with a mean of 20 week.

In the current work, the 2D ultrasound detected no abnormality in 194 out of 200 fetuses [97.0%], and 4 cases [2.0%] had mega-cisterna magna, which were detected by the 4 D and confirmed by postnatal transcranial ultrasound. in addition, 2 D ultrasound detected 2 cases [1.0%] who had encephalomylocele, that discovered and confirmed by 4D and postnatal transcranial US. On the other side, 2D ultrasound did not discover any case of Dandywalker malformation, but 4 D US discovered 2 cases [1.0%] that was confirmed by postnatal transcranial US. There was a complete agreement between prenatal 4D ultrasound and postnatal transcranial ultrasound [Table 1].

Using postnatal transcranial ultrasound as a reference standard, the prenatal 2D ultrasound had a sensitivity of 75.0%, specificity of 100.0%, PPV of 100.0%, NPV of 98.7% and overall accuracy of 99.0%. Otherwise, the prenatal 4D ultrasound was 100.0% sensitive and specific [Table 2].

Table [1]: Diagnosis of detected anomalies among studied populations by different diagnostic modalities

Detected anomaly	2D [n=200]	4D [n=200]	Postnatal transcranial ultrasound [n=200]
NAD	**194 [97.0%]**	**192 [96.0%]**	**192 [96.0%]**
Mega-cisterna Magna	**4 [2.0%]**	**4 [2.0%]**	**4 [2.0%]**
Encephalomylocele	**2 [1.0%]**	**2 [1.0%]**	**2 [1.0%]**
Dandywalker malformation	**-**	**2[1.0%]**	**2[1.0%]**

Table [2]: Sensitivity and specificity of 2D and 4D for detection of fetal brain midline abnormalities using the postnatal transcranial ultrasound as a reference standard

	Two-dimensional ultrasound	Four-dimensional ultrasound
True positive [TP]	6	8
False positive [FP]	0	0
True negative [TN]	192	192
False negative [FN]	2	0
Sensitivity	75.0%	100.0%
Specificity	100.0%	100.0%
Positive predictive value [PPV]	100.0%	100.0%
Negative predictive value [NPV]	98.7%	100.0%
Overall accuracy	99.0%	100.0%

Sensitivity = TP/TP+FN; Specificity = TN/TN+FP; PPV: = TP/[TP+FP]; NPV: = TN/[TN+FN]; Accuracy=TP+TN/TP+TN+FP+FN

DISCUSSION

Fetal malformations are usually due to genetic aberrations. It could be stimulated by in-utero exposure to medications [e.g., tetracyclines and streptomycin], radiations, smoking and alcohol intake [19]. Currently, the two-dimensional ultrasound is routine prenatal screening method. However, it had certain limitations [e.g., artifacts and low image resolution] which reduce its diagnostic accuracy [20]. With technological advances, three- and four-dimensional ultrasound were introduced and played a supplementary role to 2D ultrasound, and could stand alone as an effective diagnostic tool [21].

In the current study, 2D revealed no abnormality among 97.0% of studied populations compared to 96% discovered by 4D ultrasound. The detected midline abnormalities were 3.0% and 4.0% by two and four-dimensional ultrasound, respectively. The detected anomalies by four-dimensional ultrasound were identical to the post-natal diagnosis by transcranial ultrasound. The reported incidence rate of midline cerebral abnormalities of fetal brain lies within the reported incidence in previous literature. For example, Milani *et al*. [6] reported that, fetal central nervous system [CNS] abnormalities are fairly common. The incidence rate ranges between 0.1 to 0.2% in live births and increased to 3-6% in stillbirths. In terms of frequency, the fetal CNS abnormalities comes after the cardiac abnormalities.

The prenatal ultrasound is a non-invasive, simple, readily available and cost-effective tool for prenatal screening. Thus, it could be an effective imaging modality for screening of fetal brain abnormalities, as reported by Onkar *et al*. [22] and Tutus *et al*. [23]. Gonçalves *et al*. [24] compared prenatal US with magnetic resonance imaging [MRI] and reported that, US was ablet to discover prenatal CNS abnormalities among 72.2% and had a specificity of 100.0%. They concluded that, US is relatively accurate, safe and relatively cheap tool for prenatal screening of CNS malformation. However, they used the 2D and 3D ultrasound modalities.

Here, we go one step forward and included 4D ultrasound, and instead of prenatal MRI, we used postnatal transcranial ultrasound to minimize the fetal and maternal risk of radiation exposure. In addition, we performed our examination at the second trimester of pregnancy [18- 22 weeks of gestations] as recommended by obstetric guidelines of antenatal care to check fetal anatomy. At this time, the major and midline intracranial structures have formed and can be traced by sonographic visualization [6].

Wang *et al*. [25] used 2D and 4D to estimate the diagnostic value in fetal craniocerebral malformations. They reported that, the accuracy of 4D alone was significantly higher than 2D and combined approaches [2D plus 4D] accuracy was better than each modality alone. Both methods were identical to the actual diagnosis for 96.05% of all anomalies, while 4 D was sensitive for 82.89% and 2 D sensitivity was 69.74%. Of note, all patients included in their study were known to have an abnormality before screening and their evaluation was a retrospective in manner.

4D ultrasound can give real time multi-layered images as it scans the organ from multiple angles. Thus, the fetus's subtle structures, can be examined directly in a clear way. By 4D ultrasound, accurate differentiated diagnosis of different brain lesions could be achieved by the observation

of the focal location, size and structure, the spatial relationship with surrounding parenchyma, as well as the stability of images with fetus movements [26].

In the current work, the 2D ultrasound failed to detect Dandywalker malformation. However, 4D could detect it and the diagnosis was confirmed to be correct by postnatal transcranial ultrasound. Correa *et al*. [27] described it as the commonest congenital cerebellar malformation, with cerebellar vermis hypoplasia or agenesis with posterior fossa enlargement, ventriculomegaly and dilation of fourth ventricle. These abnormalities could be detected by prenatal ultrasound. however, other abnormalities include cranial displacement of tentorium, torcula and lateral venous sinuses which could be seen by prenatal MRI. Bosemani *et al*. [28] reported that the prenatal US of the posterior fossa is a challenging task from the technical point of view. The agenesis of vermis with cerebellar vermian remnant cephalad rotation is best seen in the sagittal plane. In the axial plane, an artifactual vermian cleft could be created by excessive steep angulation, leading to a false positive diagnosis. Additionally, there are other anomalies that can mimic cisterna magna dilatation [e.g., mega cisterna magna and posterior fossa arachnoid cyst].

Dandy-Walker malformation may be isolated or associated with other genetic aberrations and its prognosis depends largely on the degree of ventriculomegaly, that necessitates close follow up with prenatal US and postnatal MRI to predict the severity of neurodevelopmental delay [29]. In line with the current work, Glenn *et al*. [30] reported that, fetus with Dandy-Walker malformation could have a normal intellectual function, especially with normal lobulation of the vermis and no additional fetal brain abnormalities.

Early diagnosis of Dandy-Walker syndrome is useful for prediction of prognosis and for planning for delivery [29].

In the present study, the diagnosis of mega cisterna magna and encephalomylocele was done using 2D and 4D US. Hamisa *et al*. [31] found that giant cisterna magna was diagnosed in three cases using 2D and 4D US during the prenatal period and this was confirmed by postnatal MRI. As for encephalocele, prenatal 2D US detects approximately 80% of encephaloceles [32]. In another study, 4D US and MRI confirmed the diagnosis of encephalocele more than 2D [33].

This study showed that, the sensitivity of 4D versus 2D was 100% versus 75.0%, the specificity and positive predictive value was 100% in 2D and 4D while the negative predictive value was 100% in 4D and 98.7% in 2D US. The accuracy of 4D was 100% in comparison with 99% for 2D US. In the study of Gonçalves *et al*. [34], fetuses were diagnosed by 2D ultrasonography showed an agreement with 3D/4D in 90.4% of the findings. When compared to diagnoses performed after delivery, the sensitivity and specificity of 3D/4D ultrasonography was 92.2% and 76.4% respectively and 2D ultrasonography was 96.1% and 72.7% but there were no significantly different [22].

On the other side, Mittermayer *et al*. [35] reported that, although 2D and 4D US are able to detect many kinds of fetal brain malformation, some studies have shown that 2D and 4D ultrasound detection rates of fetal brain anomalies are only about 40–50%.

The current work is unique in its prospective design, screening for malformations in whole cohort of pregnant females. However, one limiting step is the small number of included females in screening which yielded a low number of malformations. In addition, there are many challenges facing application of prenatal screening by ultrasound. These include maternal obesity, fetal position, reverberation antifiction and oligohydramnios which could limit the ability of US and reduce resolution of its images. The early ossification of fetal skull represents another challenge [36, 37]. Therefore, magnetic resonance imaging [MRI] has come into practice, with its advantages of better soft tissue contrast resolution, larger field of view and opportunity to obtain multiplane images make fetal MRI an important diagnostic tool [38].

On the other side, the quality of MRI images may be negatively affected by the movement of the fetus during the scan, which may limit MRI diagnostic accuracy in some cases. Hence, ultrafast MRI have been introduced to reduce the unfavourable effect of fetal motion [39, 40]. Hence, the use of 4D ultrasound which consider fetal movement as the ultrafast MRI and was free from high cost and radiation risk exposure, which adds to the value of the current study.

We could conclude that, the 2D ultrasound still have its role in the diagnosis of fetal brain midline abnormalities. The 4D ultrasound showed superiority in diagnosis and confirmation of the midline structure abnormalities, and it was in complete correlation with the diagnosis of postnatal transcranial US. However, further evaluation of the accuracy and efficiency of 4D in diagnosis of midline structure anomalies should be investigated in large population studies.

Financial and non-financial relationships and Activities of Interest

None

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International Journal of Medical Arts

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Print ISSN: 2636-4174
Online ISSN: 2682-3780