What Does 3/4D Ultrasound Add to 2D Examination in The Assessment of Fetal Neural Anomalies: Tertiary Center Experience

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ABSTRACT
Background: Central nervous system (CNS) malformations are the most common congenital abnormalities.
The detection of fetal anomalies was one of the earliest uses and remains a pivotal application of prenatal ultrasound.
Objective: This prospective study aims to clear out the value of 3/4D examination with advanced techniques (TUI, MIP & surface mode) over 2D in the evolution of fetal neural anomalies.
Patients and methods: 120 pregnant women with suspected CNS fetal anomalies by 2D US were examined over a period starting from January 2015 until October 2017. Fetal gestation ranged from 8-39 weeks with a 24-week mean age. In all patients, 2D and 3/4D ultrasound as well as fetal Doppler were performed.
Results: 3/4D ultrasound shows higher sensitivity in the detection of neural anomalies such as anencephaly, Chiari malformation, Hydranencephaly, holoprosencephaly, encephalocele, meningocele (spina bifida with no brain changes), Iniencephaly and Dandy-Walker variants, 3/4D ultrasound of 100% deletion rate over 85% for the 2D ultrasound. 3/4d & 2D ultrasound had the same detection rate of anomalies like hydrocephalus (communicating & non-communicating), microcephaly, and Dandy-Walker malformation.
Conclusion: 3/4D ultrasound had a higher sensitivity in the detection of fetal neural anomalies over 2D which allows early interference or decision-making to save fetal or material life.
Keywords: Prenatal ultrasound, 3D/4D ultrasound, Congenital brain anomalies, Fetal CNS.

INTRODUCTION

The most frequent developmental abnormalities identified at birth and in conceptuses that spontaneously abort are those affecting the central nervous system (CNS) [1]. There are 1 to 65 cases for every 1,000 births [2]. Embryos from spontaneous abortions have a rate of neural tube abnormalities that is around ten times greater than that of newborns. CNS abnormalities are typically found in early-death chromosomal syndromes in aborted embryos and less frequently in aborted babies with fewer chromosomal abnormalities [2,3].

Ultrasound has a major role in the evaluation of fetal anomalies, one of them being central nervous system anomalies, 2D ultrasound alone is helpful to evaluate several conditions but it lakes advanced capabilities to evaluate some structures as mid-line structures such as lakes of the general overview of the head and spine unlike volumetric assessment [3].

The rising of advanced ultrasound machines and their technologies to create volumetric examination of the fetus parallels the wider availability of 3/4D machines, and the assessment of the fetal body and CNS anomalies becomes easier, more efficient, and lesser time consumer [4].

3/4D ultrasound allows examination of the fetus in three orthogonal planes by taking one volume saving time and effort. It is considered also a quick way to image the mid-line structures in the brain, especially the corpus callosum & vermis. The surface mode helps to obtain a fully detailed image of any associated facial defect [2,4].

Following 2D ultrasonography, 3D/4D ultrasound has been employed as an imaging modality. Thus, the current paradigm involves using 3D/4D ultrasonography to do a target scan after 2D ultrasonography has formed an initial diagnostic impression [5,6].

So, this study aimed to clear out the value of 3/4D examination with advanced techniques (TUI, MIP & surface mode) over 2D in the evolution of fetal neural anomalies.

SUBJECTS AND METHODS

A prospective study was conducted at Minya University and OBST/GYN tertiary center, 120 pregnant women with suspected CNS fetal anomalies by 2D US were examined over a period starting from Jan 2015 until Oct 2017. Fetal gestation ranged from 8-39 weeks with a 24-week mean age. In all patients, 2D and 3D/4D ultrasound as well as fetal Doppler were performed.

Inclusion criteria:
1. Previous history of congenital anomalies.
2. Family history of congenital or chromosomal abnormalities.
3. Diabetic patients with polyhydramnios.
4. The patient who referred with a sonographic report showing or suspecting fetal anomalies.
5. Patient with +ve TORCH screen.
6. Ultrasound was done and revealed Polyhydramnios

Verbal consent was taken from all of them after an explanation of the techniques used and the aim of the current study.

Exclusion criteria: There is a known cause other than congenital anomalies for the polyhydramnios eg: Rh. incompatibility or placental anomalies.

Ultrasound machines:
1- Mindray M7:
   a. **2D convex probe:** C5-2s Convex probe, 50mm, Bandwidth: 2-5 MHz.
   b. **4D probe:** 4CD4s 3D/4D Convex probe, 40mm, Bandwidth: 2-6 MHz.

2- GE Voluson 730 pro V:
   a. **2D convex probe**: AC2-5 H46701U, Multi-frequency convex transducer for the technically difficult patient. Footprint:48x13mm, Bandwidth:2–5MHz FOV:60º.
   b. **4D probe:** RAB4-8L H48621Z, Micro 4D convex is a Real-Time 4D transducer with excellent resolution that is beneficial for an OB practice, Footprint:55x43 mm, Bandwidth:2 –8 MHz, FOV70º, Volume 85º x 70º.

Follow-up was done after delivery according to each case by MRI, CT, or photography using Philips Intellispace portal workstation ISP 9.

Ethical consent:
The Ethical Institutional Review Board at Minya University approved the study. After explaining our research objectives, written informed consent was obtained from all study participants. This study was conducted in compliance with the code of ethics of the world medical association (Declaration of Helsinki) for human subjects.

Statistical analysis
Statistical Package for Social Sciences (SPSS) version 18 for Windows was used to code, process, and analyze the obtained data (IBM SPSS Inc, Chicago, IL, USA). Using the Shapiro Walk test, the distribution of the data was examined for normality. Frequencies and relative percentages were used to depict qualitative data. Two independent groups of normally distributed variables were compared using the independent samples t-test (parametric data). Sensitivity or true positive rate: the percentage of patients who are accurately diagnosed as having the illness by the test. Specificity, also known

as the true negative rate, is the percentage of healthy people who the test accurately identifies as such.

RESULTS
120 pregnant women suspected to have fetal brain anomalies at 8-39weeks of gestation (with a 24-week mean) age prospectively examined. The maternal age ranged from 18-46 years (mean age 32 years).
113 cases (94.2%) were singletons while 7 cases were twins (5.8%), five were dichorionic- diamniotic pregnancies and the other two were mono-chorionic mono-amniotic pregnancies.
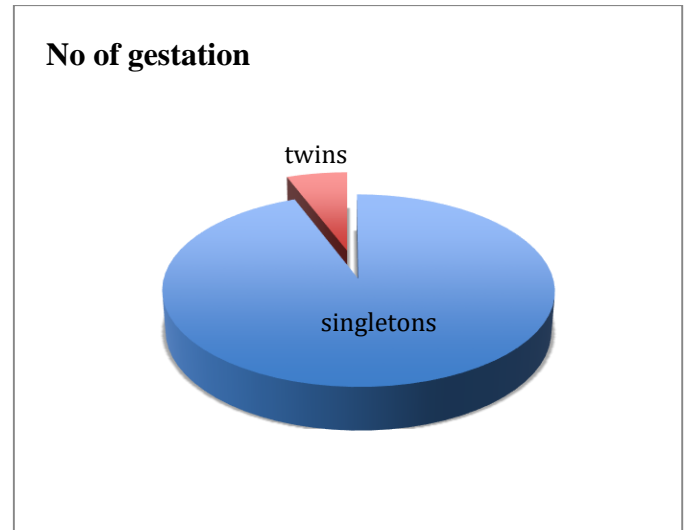

Fig. (1): Most cases have single viable intrauterine pregnancy.

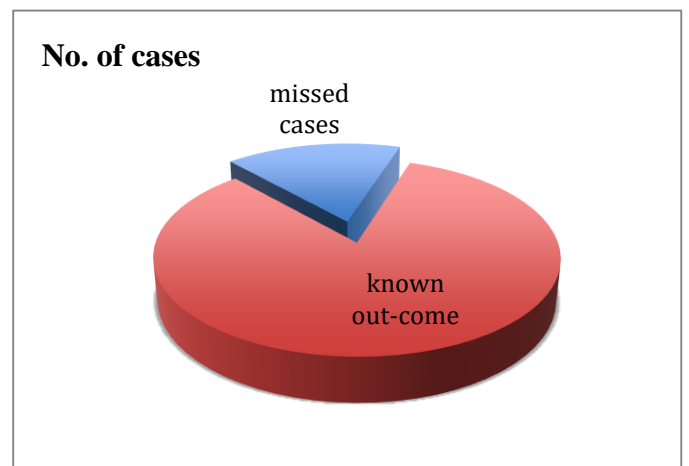20 cases of them were missed in follow-up with no known outcome.

Fig. (2): 20 cases were missed during the study.

Table (1): Types of CNS anomalies where variable deference is if detection rate between 2D and 3/4D:

CNS anomalies with known outcome	No. of cases detected by 2D	No. of cases detected by 3/4D	2D sensitivity	3/4D sensitivity
Anencephaly	18	20	90%	100%
Encephalocele	14	17	82.3%	100%
Arnold Chiari type II	12	14	85.7%	100%
Holoprosencephaly	5	6	83.3%	100%
Meningocele	2	5	40%	100%
Arnold Chiari type III	1	2	50%	100%
Hydranencephaly	3	4	75%	100%
Arnold Chiari type I	1	2	50%	100%
Iniencephaly	0	1	0%	100%

Table (2): Types of CNS anomalies where an equal detection rate between 2D and 3/4D is

CNS anomalies with known outcome	No. of cases detected by 2D	No. of cases detected by 4D	Outcome No. of Cases
Hydrocephalus "Non-communicating type"	18	18	18
Dandy walker malformation	4	4	4
Dandy walker Variant	3	3	3
Hydrocephalus "Communicating type"	2	2	2
Microcephaly	2	2	2
Total	**29**	**29**	**29**

The sensitivity of 2D and 3/4D in these anomalies is 100%

Table (3): The overall detection rate of CNS anomalies in 2D versus 3/4D examination

Type of Examination	No of cases detected	Out-come No of cases
2D	85	100
3/4D	100	100

The overall Sensitivity of 2D is 85%

The overall Sensitivity of 3/4D is 100%

Lethal anomalies that are incompatible with life were early detected in 32 cases in the form of 20 cases of acrania &17 cases of encephaloceles & 4 cases of hydranencephaly as well as one case of iniencephaly.

Most cases of encephalocele were occipital in location as noted in 14 cases, two cases were parietal, and one case was frontal encephalocele.

There were other 15 cases missed by the 2DUS and diagnosed by 3/4DUS. Positive family history of unexplained abortion or congenital anomalies was found in 23 cases. Positive history of previous fetal CNS anomalies was also noted in 12 cases.

Most cases were isolated anomalies; 7 cases (7%) had associated anomalies: (1) Two cases were Meckel Gruber syndrome with hypo-plastic lung. (2) One case was Meckel Gruber variant. (3) One case was associated with skeletal anomalies. (4) One case was mid-facial abnormalities showed proboscis. (5) One case was mid-facial abnormalities showed cleft lip and palate. (6) One case was hypo-plastic lung association with alobar holoprosencephaly.

Oligohydramnios or anhydraminos was detected in 3 cases all of them showed sluggish fetal movement on 4D ultrasound whereas Polyhydramnios were found in 75 cases.

Figure (1): Anencephaly. A & B, B-mode scans show a "frog eye" or "mickey mouse" appearance due to absent cranial bone/brain and bulging orbits. Arrows, C& D sagittal 3/4D images show no parenchymal tissue seen above the orbits, and calvarium is absent (arrowhead) and parts of the occipital bone and midbrain may be present (curved arrow).
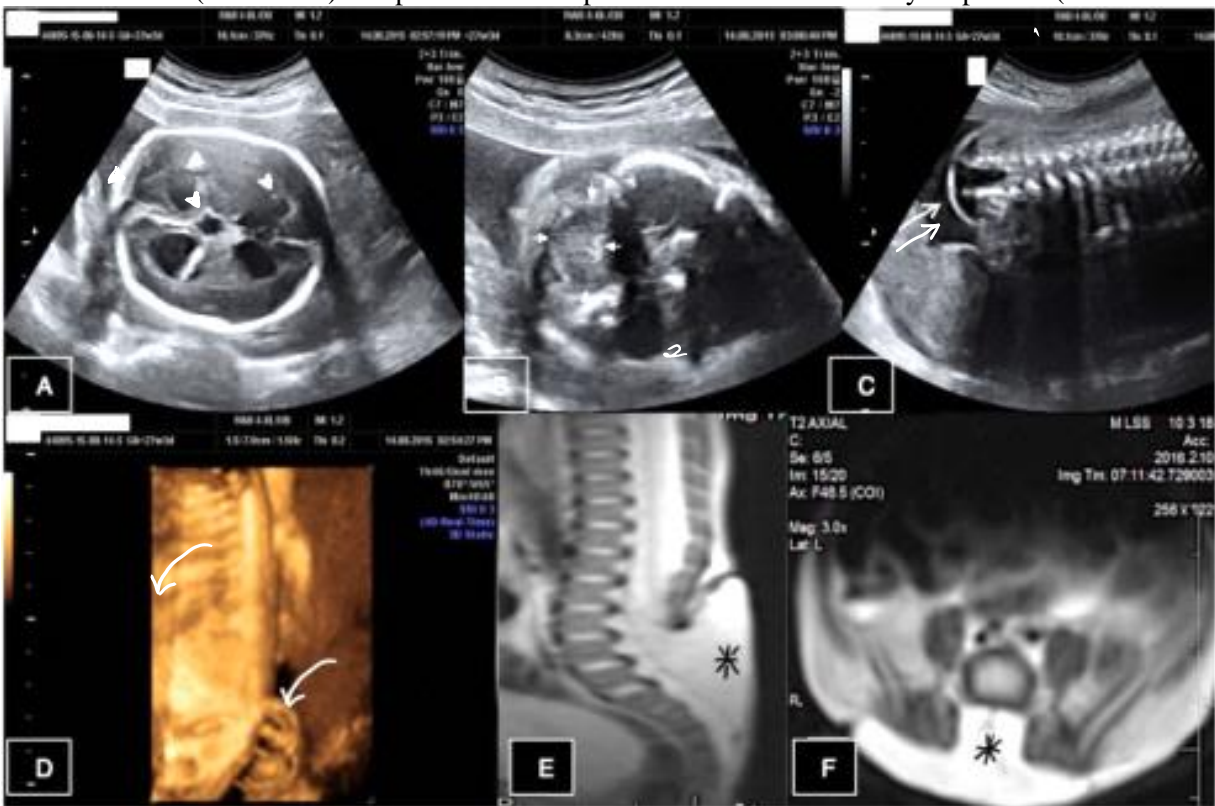

Figure (2): Chiari II malformation. A & B: B-mode scan axial cuts at the ventricular level and posterior fossa show mild to moderate hydrocephalic changes (arrowheads) with crowed small posterior fossa (arrows). C: B-mode shows lumber spine defect (arrow). D: the 4D image of the surface rendering shows a spinal defect with herniated theca (curved arrow). E& F: sagittal and axial MRI cuts show myelomeningocele through large distal lumber and sacral defect this is associated with tethered cord (black asterisk)

Figure (3): Encephalocele, also known as meningoencephalocele. A: axial B-mode image with chroma shows occipital herniation of the meninges and brain matter through skull defect (arrows). B & C: Mode 4D surface rendering images of the skull and spine show occipital defect with herniation (curved arrows) yet intact spine. D: post-natal photography shows occipital encephalocele (arrowhead) with an intact spine (asterisk)

Figure (4): Holoprosencephaly. A: 2D/US: Shows a coronal view of the brain that shows: Both lateral ventricles are seen fused (curved arrows) as well as fused both thalami. Absent falx cerebri…… Holoprosencephaly. The cortex appears thick slice (pancake appearance). B: surface mode of the face shows the nose is abnormally located above both eyes that are seen fused at midline…..cyclops with the proboscis (asterisk). C: coronal CT & D: axial CT images: show fused both lateral ventricles (arrowheads).
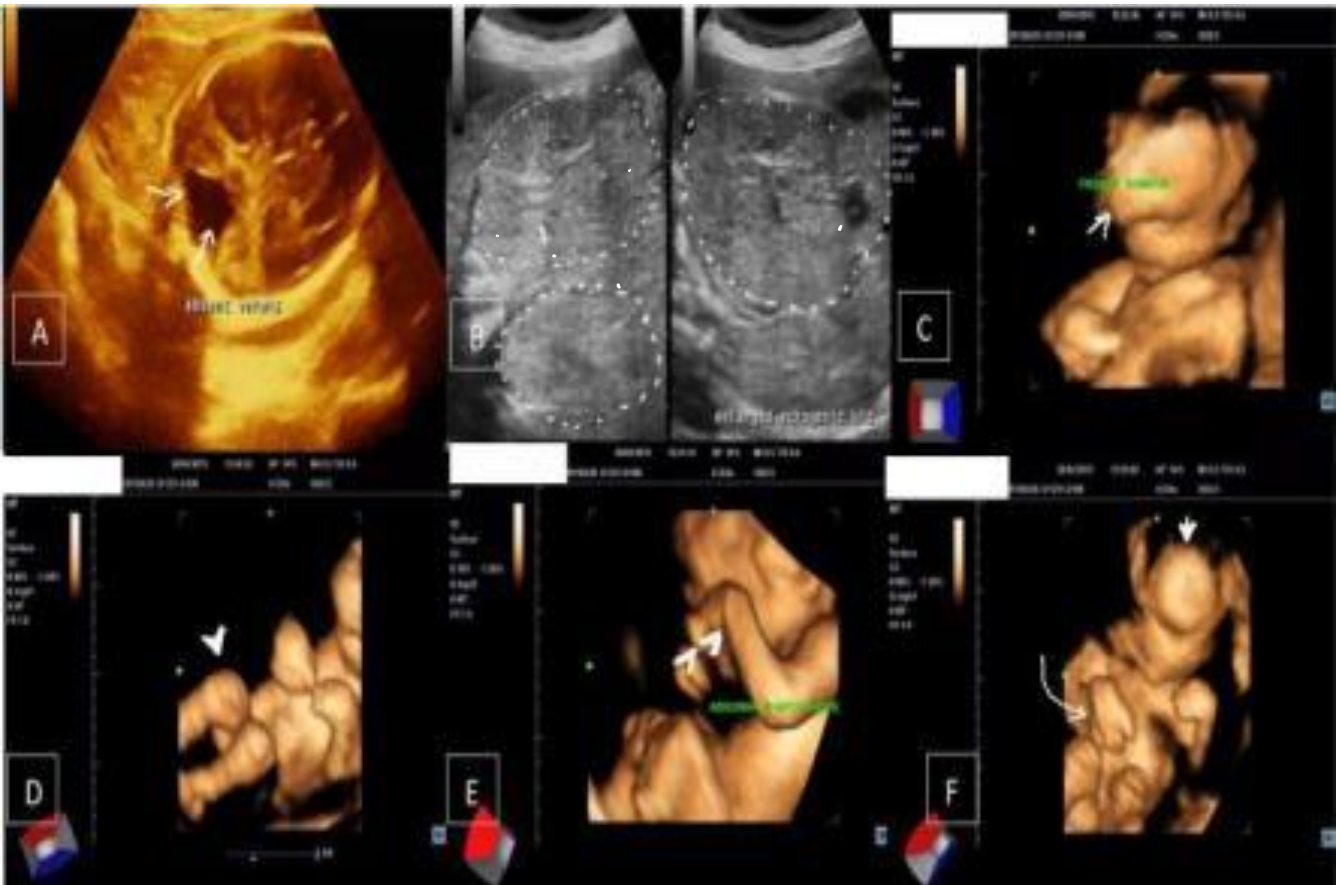
Figure (5): Meckel Gruber syndrome with skeletal anomalies. A: 2D/US axial view skull shows absent vermis (arrows). B: 2D/US axial view of the abdomen of the fetus that shows both kidneys are seen enlarged with lost corticomedullary differentiation…… potter disease type I.(dotted lines). C, D, D & F: 4DUS that shows abnormal facies with a prominent forehead and abnormal both eyes and nose (arrows), Both upper as well as lower limbs are seen flexed with dropped hands (arrowheads), and polydactyly (curved arrow).
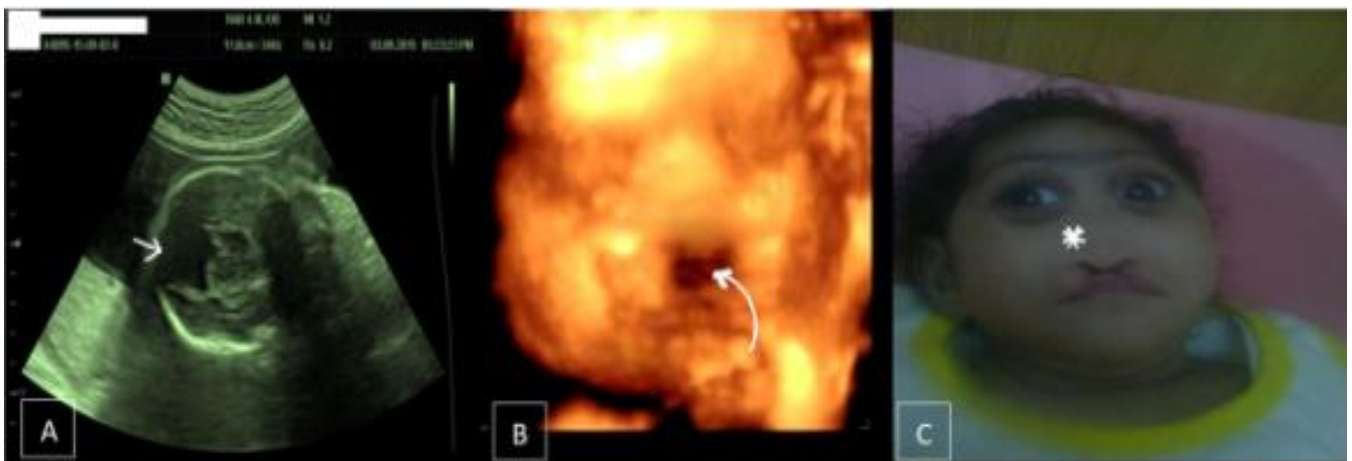

Figure (6): Cleft lip & palate. A: 2D/US: coronal view of the brain that shows cystic area replacing brain parenchyma with absent falx & fused both lateral ventricles……. Holoprosencephaly (arrow). B: 4D image shows a wide defect of the upper lip as well as the palate (curved arrow). C: post-natal photography shows cleft lip and palate (asterisk).
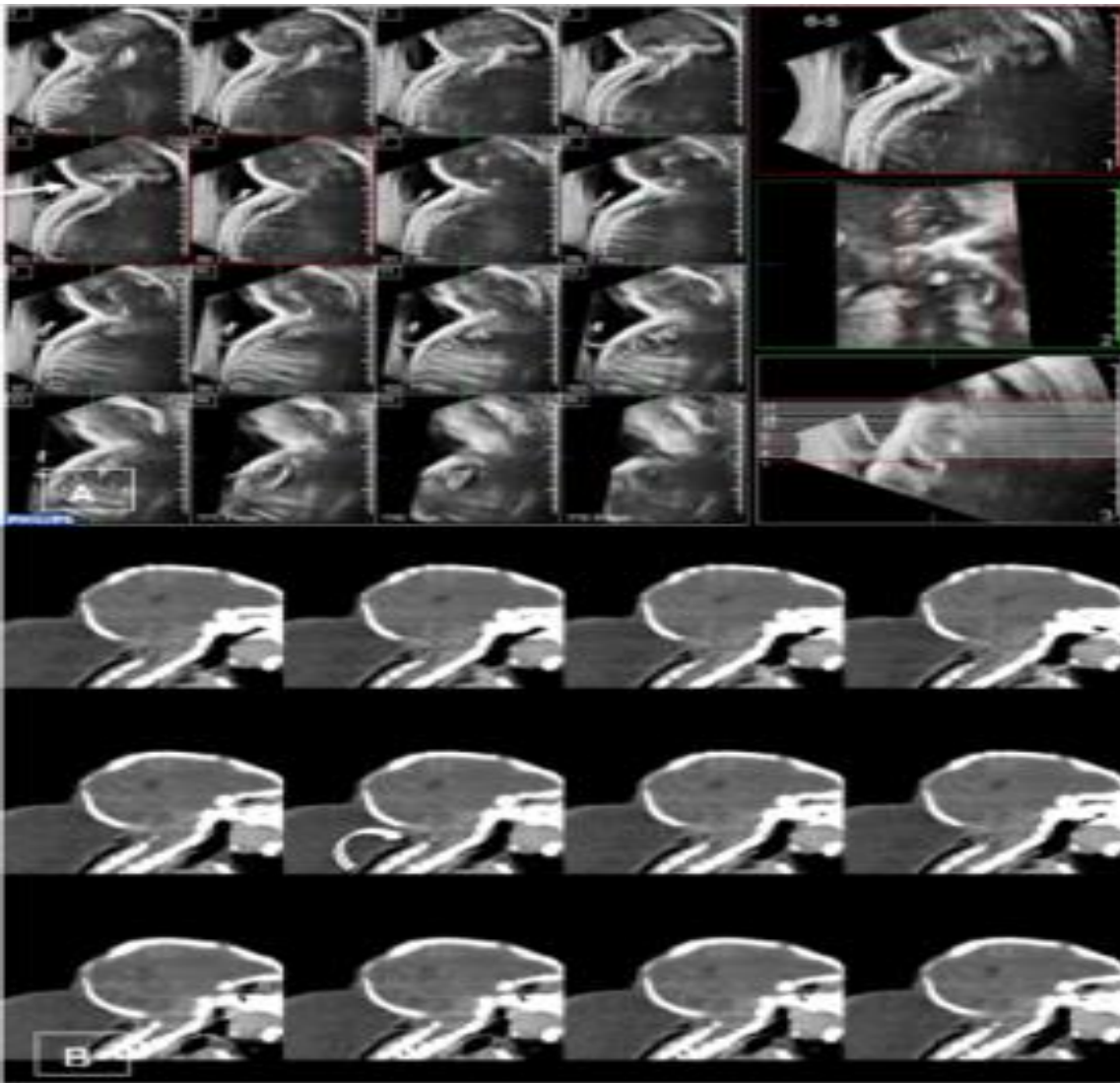
Figure (7): Occipital myelomeningocele. A: 4D/US: TUI of the carnio-cervical junction shows an occipital defect with a large meningocele. (arrow). B: CT of the head and neck with sagittal reformatted images that matches TUI images (curved arrow). The occipital bony defect is clearly seen in CT images while the myelo component is clearly seen at TUI.

DISCUSSION

The most frequent congenital anomalies are CNS defects. The most common CNS anomalies are neural tube defects, which affect 1-2 instances out of every 1000 infants, according to **Onkar *et al.*** [6], 0.31% of ultrasounds showed central nervous system abnormalities. Prenatal medicine has always sought to identify fetal anomalies as early as possible [7, 8]. It has been almost four decades since the first ultrasonic devices were developed for fetal imaging. Conventional B mode or 2-dimensional ultrasound (2DUS) had been used routinely for evaluation of the fetal growth and well-being for more than two decades. One of the first applications of prenatal ultrasonography was and still is the identification of fetal abnormalities. Prenatal detection of birth abnormalities is typically viewed as favorable and desired since caring for the disabled and handicapped places a significant load on local healthcare systems [7].

Fetal imaging and abnormality assessment have dramatically improved with the advent of 3D and 4D ultrasound equipment. Examiners may now visualize anatomical features in true 3D and 4D rather than only mentally reconstructing them in 3D from 2-dimensional (2D) photographs thanks to this technology [8]. Sonographers may now interact with volume data sets to evaluate important anatomical features in planes of section different than the ones used for initial acquisition, which frees them from the limits of static 2D pictures for making diagnoses [8,9].

Three-dimensional ultrasound also has a variety of rendering methods that allow the visualization of different features of the same volume set after the patient has left the examination room [10]. For example, a volume data set of the fetal back can reveal the external aspect of the meningocele when the surface is rendered and can reveal the underlying bony changes when rendered using the maximum intensity mode [11].

However, the 3D and 4D ultrasound modalities are just an important adjunct to the routine obstetric 2D ultrasound study. They are used for fetal evaluation after the initial diagnostic impression is made from the 2D images [12].

This early examination has traditionally included fetal anatomy assessment, and substantial advancements in ultrasound technology have been made recently [11,12]. Most anencephalies may be found during an ultrasound screening during the first trimester [13]. In our study, the first trimester was when all anencephalies and iniencephalies were discovered. **Cyr et al.** [13] description of the fetal rhombencephalon's sonographic appearance in 25 fetuses between 8 and 10 gestational weeks old. From 7 to 12 weeks, **Blaas et al.** [2, 14, 15] researches were able to show how the embryonic brain develops. The prevalence of CNS abnormalities has varied during these studies.

It was suggested that the most common of these anomalies is acrania, accounting for 20 - 28% [16,17, 18]. This matches with our study where the most common anomaly was anencephaly, accounting for 20% of cases. But, **Keersmaecker et al.** [19] **and Payam Saadai** [20] mismatched with our study, suggested that ventriculomegaly was the most frequent anomaly, accounting for 30%.

The second common anomaly in our study was the non-communicating type of hydrocephalic changes accounting for 18. In our study, it is seen isolated or associated with other anomalies being syndromal associated with syndromes like holoprosencephaly, dandy walker malformation, or associated with TORCH or brain hemorrhage. This matches with the study done by **Saleem** [21] that describe ventriculomegaly as isolated or associated with other anomalies. Our study stated that the most powerful observation for fetal brain abnormalities is the measurement of the atrial diameter of both lateral ventricles. The presence of dilated lateral ventricles directed us to search for other anomalies and the possible cause of hydrocephalus, e.g. meningocele, Arnold Chiari type II or III, Dandy Walker Malformation Encephalocele, accounting for 17%. In our study as well as the study done by **Liao et al.** [22] **and Sorak et al.** [23] revealed that the most common type was occipital encephalocele. The ability to detect the site and size of the cranial defect as well as the herniated contents is crucial to the patient's management.

3D ultrasound helped in the accurate diagnosis of the site and size of the defect. One case of encephalocele was seen associated with renal abnormality as part of Meckel Gruber syndrome. In our study as well as many other studies, the higher sensitivity of 3D and 4D ultrasound over the routine 2D ultrasound in the detection of CNS anomalies were noted as stated by **Pooh and Kurjak** [24] and **Kalache et al.** [25] using multi-planar modalities, volume rotation and volume contrast imaging which are all ultrasound tools that have greatly enhanced the detection of CNS anomalies.

We were able in our study to diagnose only 85 cases using 2D ultrasound. But with the addition of 3D and 4D ultrasound modes, we detected the whole 120 cases.

One case of Arnold Chiari type III was misdiagnosed as occipital encephalocele on the 2D scan, but with the use of a 4D scan, for the neck, the encephalocele was confirmed to be in the cervical region. This comes in agreement with **Kalache et al.** [25]. Similarly, another case of a small lumbar meningocele was missed by the 2D scan because the fetal position gave a persistent coronal view of its back. This diagnosis was only possible after volumetric acquisition of the fetal back in a 4D scan [26].

The diagnosis of Arnold Chiari's malformation is based upon the visualization of the myelomeningocele where open spinal dysraphism is noted associated with the diagnosis of a small posterior cranial fossa. The measurements of the posterior cranial fossa are considered a clue for diagnosis which can be done in 2D ultrasound scans if performed in 3 planes, which is time-consuming and liable to difficulties related to the fetal position. 3D ultrasound, on the other hand, allows rapid and easy evaluation of the posterior fossa and its structures, the vermis and the cisterna magna matched those of a study by **Júnior** [26] **and Goldstein and Poarasky** [27]. The latter stated that a 3-dimensional multi-slice view can deliver informative images of the region of interest, regardless of the fetal position, which is very helpful in the evaluation of complex CNS anomalies.

However, this disagrees with studies done by **Luís et al.** [28], who detected CNS anomalies equally by 2D and 3D methods.

Detailed scanogram, as well as surface mode modality of 3D/4DUS, plays an important role in the assessment of associated anomalies as stated in our study as well as other studies like **Balcy et al.** [29]. Dandy-Walker malformation may be associated with renal anomalies, e.g. autosomal recessive polycystic kidneys disease (ARPCK), a syndrome known as Meckel Gruber variant syndrome as mentioned as seen in one case in our study, we had also two cases of Meckel Gruber syndrome with encephalocele and ARPCK represented 2% of cases.

Holoprosencephaly is another important CNS anomaly as fetuses with this anomaly have a uniform poor outcome, **Lai et al.** [30] stated that it is essential to identify this anomaly antenatally and differentiate it reliably from hydrocephalic changes. In our study, we had 1 case (1%) with alobar holoprosencephaly, with a single midline ventricle, total loss of cortical mantle, absent midline structures, i.e. falx and corpus callosum, as well as fused thalami. **Dubourg et al.** [31] **and McGahan et al.** [32] described the high frequency of extra CNS anomalies in association with alobar holoprosencephaly, mainly midline facial anomalies. This agreed with our study, where we were able by 3D surface mode and 4D mode to demonstrate the

associated facial anomalies in our patient. These included a midline cleft lip and palate, clenched hand, hypotelorism and persistently flexed lower limbs.

Drawbacks

Our study had some drawbacks. The most important drawback is that it is a two centers study. The incidence of different anomalies is variable among different studies Although we agreed with some authors that anencephaly was the most common CNS anomaly, we disagreed with others. 3D and 4D ultrasound modes require experience. The sensitivity of these techniques greatly relies on the experience of the operator as in all ultrasound studies. The authors were experienced with these modalities in detecting fetal anomalies and this was important for the accuracy of the results. Results, however, may vary with less experienced sonographers.

CONCLUSION

Our study rolled out the importance of 3/4D ultrasound in the diagnosis of CNS anomalies and how they overcome the traditional limitations of 2D ultrasound, especially when it comes to the fetal position. The ability to simultaneously view and review a brain volume in all three scanning planes, and the ability to record the volume of interest for teaching purposes. The presence or absence of fetal congenital brain anomalies is very important in deciding on the termination or continuation of the pregnancy, hence it should be discovered as early as possible.

Conflict of interest: Nil.

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