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Research Article

Proportion of Central Nervous System Fetal Malformations in patients attending Fetomaternal Unit Minia University as an observation study

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Abstract
Background: Central nervous system (CNS) anomalies are the most serious congenital abnormalities. Ultrasound examination is an effective and non-invasive modality for prenatal diagnosis of these anomalies. The objectives of this study were to detect the proportion of C.N.S malformations in patients attending the feto-maternal unit at Minia University and analyze the related factors at 22nd to 28th weeks of gestation and detect the diagnostic accuracy of Ultrasound in the diagnosis of CNS malformations. **Methods:** This is a prospective study that was conducted on 100 women who were referred to Fetomaternal Unit at Minia University for any C.N.S anomalies, in the period between September 2019 and September 2020. **Results:** 35% of cases had a family history of congenital fetal malformations and 8% of cases had a family history of C.N.S fetal malformations. 42% of cases had a history of aneuploidy and 46% of cases had a history of congenital infections. **Conclusion:** Dimensional ultrasonography is useful in detecting and diagnosing some fetal central nervous system abnormalities. However, owing to the location of the fetus, some defects may be difficult to identify with two-dimensional ultrasonography. For example, while acquiring the median plane with 2D transabdominal ultrasonography is difficult and requires specific competence in transvaginal transfontanelle scanning, it is often regarded as a good preliminary diagnosis tool for screening for fetal defects.

Keywords: Central nervous system, Ultrasound examination, feto-maternal

Introduction
Congenital anomalies can be defined as structural or functional anomalies (for example, metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth, or sometimes may only be detected later in infancy, such as hearing defects .In simple terms, congenital refers to the existence at or before birth. Congenital central nervous system (CNS) malformations constitute a common group of anomalies in fetuses second only to cardiac malformations. The incidence of congenital central nervous system malformations ranges from 1 to 2 cases per 1000 births[(1)] and its epidemiology is influenced by environmental and genetic factors as evidenced by geographical variations in its incidence[(2)].

Such malformations have clinical importance because they are associated with high rates of morbidity and mortality influencing the neurocognitive and motor development of the survivors who may have lifelong sequelae. Therefore it's extremely important to assess the fetal CNS during the prenatal period. In order to identify any changes in its development and give appropriate advice to parents regarding pregnancy follow up. Options for fetal therapy and the timing/type of delivery as well as the postnatal treatment and prognosis. Many authors investigated the congenital fetal CNS anomalies during the gestation follow-up [(3-7)].

The evaluation and diagnosis of CNS malformation during the prenatal period can be performed by the US at any gestational age. The ultrasonography evaluation includes the study of the brain and spinal cord. It is important to determine whether the CNS structures present complex embryology and anatomy because the CNS undergoes most of its changes during gestation. CNS changes are associated with

changes in the US aspects of the CNS during gestation.

Therefore, every professional involved in the fetal evaluation should be aware of the embryology and anatomy of CNS as well as of its ultrasound characteristics of different gestational ages to avoid diagnostic errors. In addition, it is of fundamental importance to understand the congenital malformations that can affect the CNS regarding the following aspects.

Ultrasonography evaluation of the fetal CNS in the first trimester is usually performed in the axial, sagittal, and coronal planes using abdominal and vaginal approaches. Most efforts to diagnose CNS malformations occur during the second trimester in the examination of fetal morphology conducted at 20 to 24 weeks of gestations[(8)]. Brain development features are susceptible to changes throughout gestation mainly secondary to the effect of external agents such as infection, trauma, and hemorrhage. So, it is important to emphasize that abnormal CNS assessment in the second-trimester morphology scan does not exclude the emergence of fetal alterations during pregnancy, hence it's necessary to re-evaluate the fetal brain morphology throughout pregnancy[(9)]. Conventionally, the ultrasound evaluation of brain development during pregnancy is performed in the axial planes of the fetal skull; however, that type of evaluation has some limitations.

For instance, the attenuation of the sound beam by the skull can impair the evaluation of the cerebral hemisphere proximal to the transducer, and because the brain is a three-dimensional organ with a complex anatomy, the midline structures such as the corpus callosum, the brain stem, the cerebellar vermis and the cerebral cortex are not probably evaluated if the scan of the fetal skull is performed only in the axial planes[(9)]. In 1996 Timor -Tritsch et al., [(10)] described a fetal neurosonography technique that involves multiplaner analysis of the fetal brain structures incorporating sagittal and coronal views of the fetal skull. The international society of ultrasound in obstetrics and gynecology (ISUOG) has issued guidelines for the ultrasonographic study of the brain and spine in fetuses; they are divided into two categories: basic CNS assessment and neurosonographic evaluation[(8)].

There is a substantial gap in our knowledge of how CNS anomalies arise[(11)]. Therefore, the aim of the current research was to detect the proportion of C.N.S malformations in patients attending the fetomaternal unit at Minia university and analyze the related factors at the second trimester "22-28 weeks ", and to detect the diagnostic accuracy of Ultrasound in the diagnosis of CNS malformations.

Patients and methods

This prospective study was conducted on 100 women who were referred to Fetomaternal Unit at Minia University for any C.N.S anomalies, in the period between September 2019 and September 2020. Inclusion criteria were; previous or family history of Congenital Fetal Malformations or CNS Fetal malformations or congenital infections, diabetic mothers, patients received medications as those on Anti-epileptic drugs, history of aneuploidy, patients exposed to X-ray in early pregnancy, patients with polyhydramnios, patients referred to fetal-maternal unit (due to suspected C.N.S anomalies by the routine US), gestational age: 22 to 28 weeks, multiple pregnancies, positive history of first-degree consanguinity, and Malpresentation. Exclusion criteria were; women with Intrauterine Fetal Death (IUFD) or other medical causes.

Complete history was taken from patients including personal history and menstrual history; including age of menarche, menstrual disturbance, dysmenorrhea or related symptoms, obstetric history including parity and mode of delivery, present history of chronic diseases and medication, past history of HTN, DM, family history of similar condition or diabetes, history of allergy to any medication, and finally surgical history of operation, laparoscopic interference or treatment of hirsutism by Laser.

General examination was carried out to all cases for evaluation of vital signs and measurement of weight and height (BMI). Abdominal and clinical examination were performed, to assess fundal level and gestational age, scar of previous operation, mass, tenderness or rigidity, and any abdominal or pelvic clinically

detectable pathology. Bimanual pelvic examination of both adenexa, and uterus was done for the detection of any abnormalities of female genitalia. Laboratory investigations according to the hospital policy were applied. Routine Ultrasound was carried out for estimated fetal weight (EFW), and umbilical and middle cerebral resistance index Doppler studies. Selective ultrasound examination was indicated for screening of congenital malformation of the high-risk women. All patients were examined at second trimester of pregnancy by D ultrasonography as confirmed by the Feto-maternal Unit Protocol of examination using 2D US (VOLUSON S8 MODEL5451540). C.N.S anomalies were analyzed and categorized into subtypes as: Ventriculomegaly, Hydrocephalus, Anencephaly, Spina bifida, Holoprosencephaly, Cephalocele, Corpus callosum agenesis, posterior fossa anomalies or any other CFMF with C.N.S malformations.

Statistical analysis

Data was collected, coded then entered as a spread sheet using Microsoft Excel 2016 for Windows, of the Microsoft Office bundle; 2016 of Microsoft Corporation, United States. Data was analyzed using IBM Statistical Package for Social Sciences software (SPSS), (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution. Continuous data was expressed as mean ± standard deviation, median & IQR while categorical data as numbers and percentage. A statistical value <0.05 was considered as significant.

Results

The present observational study was conducted on 100 women who referred to Fetomaternal Unit at Minia University for any C.N.S anomalies. Table (1) showed that the mean maternal age in our studied cases was 28.15± 4.31 years, and ranged from 20 to 42 years. The BMI ranged from 18.3 to 36.0 Kg/m2 with mean was 28.37± 3.88 Kg/m^2. Regarding residency, 62% of cases lived in rural areas and 38% of cases lived in urban areas. According to Table (2), the mean gestational age in our studied cases was 24.99± 1.87 weeks, and ranged from 22 to 28 weeks. Regarding gravidity, 43% cases were gravida 3, 29% of cases were gravida 4, 19% cases were gravida 5 and 9% of cases were gravida 6. Regarding the parity, 86% of cases were para 2, 7% of cases were para 1 and para 3.

As demonstrated by Fig. (1), 25% of cases had a previous history of congenital fetal malformations and 6% cases had previous history of C.N.S fetal malformations. 35% of cases had a family history of congenital fetal malformations and 8 % cases had family history of C.N.S fetal malformations. 42% of cases had a history of aneuploidy and 46% of cases had a history of congenital infections. Ultrasound detected CNS anomalies in 79 fetuses.

According to Fig. (2), the most common anomaly detected was Ventriculomegaly that found in 22% of cases followed by Spina Pifida that found in 17% of cases. 9% of cases had corpus callosum agenesis, 8% of cases had posterior fossa anomalies, 7% of cases had Anencephaly and Holoprosencephaly, 6% of cases had Cephalocele and 3% had Hydrocephalus.

Out of 79 fetuses with CNS anomalies, 60% of cases were treated by conservative management while 19% of cases were treated by therapeutic termination of pregnancy, as shown in Fig. (3). After delivery, 64% of cases confirmed the diagnosis of anomalies after delivery,. Based on confirmation after delivery as a reference standard, ultrasound can detect CNS fetal malformation in 62 patients (true positives) and did not detect the CNS fetal malformation in 19 patients (true negatives), as demonstrated in Table (3). We found that the US had overall sensitivity, specificity, and diagnostic accuracy of 96.88%, 52.78% and 81%, respectively in detecting C.N.S fetal malformation in our patients. Positive predictive value was 78.48% while the negative predictive value was 90.48%.

Table (1): Demographic characteristics among the studied cases

		Studied cases (No. = 100)	
		No.	%
Mothers' age (years)	Mean± SD	28.15± 4.31	
	Median	28.0	
	Range	20.0- 42.0	
BMI (Kg/m^2)	Mean± SD	28.37± 3.88	
	Median	28.75	
	Range	18.3 – 36.0	
Residency	Rural	62	62.0%
	Urban	38	38.0%

No.= number, %= percentage

Table (2): Distribution of the studied cases as per gravidity, parity and gestational age.

		Studied cases (No. = 100)	
		No.	%
Gestational age (weeks)	Mean± SD	24.99± 1.87	
	Median	25.0	
	Range	22.0- 28.0	
Gravidity	G3	43	43.0%
	G4	29	29.0%
	G5	19	19.0%
	G6	9	9.0%
Parity	P1	7	7.0%
	P2	86	86.0%
	P3	7	7.0%

No.= number, %= percentage

Table (3): Accuracy measures of US in diagnosis of C.N.S fetal malformation in relation to confirmation after delivery:

US	Confirmation after delivery					Sensitivity	Specificity	PPV	NPV	Accuracy
	Positive (n=64)		Negative (n=36)		Total					
	No.	%	No.	%						
Positive	62	62%	17	17%	79	96.88 %	52.78 %	78.48 %	90.48 %	81%
Negative	2	2%	19	19%	21					
Total	64	64%	36	36%	100 (100%)					

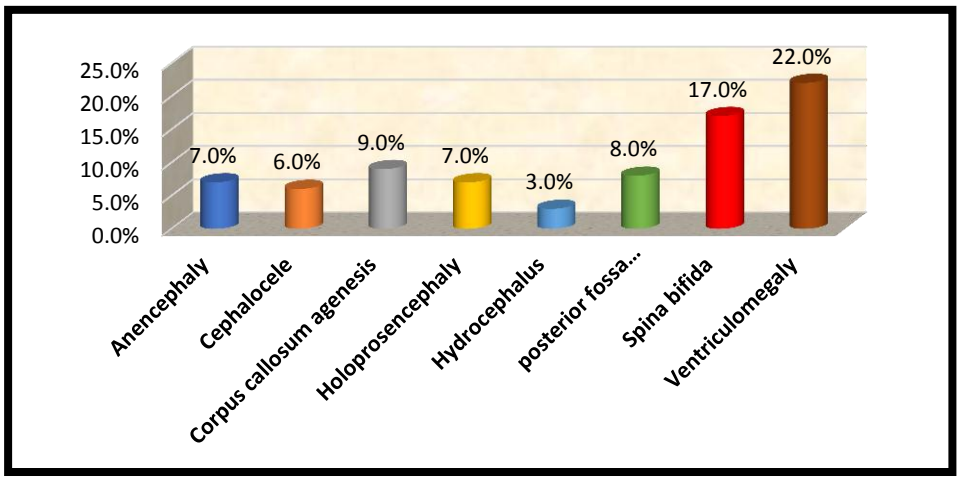

Figure (1): Distribution of studied cases regarding history.

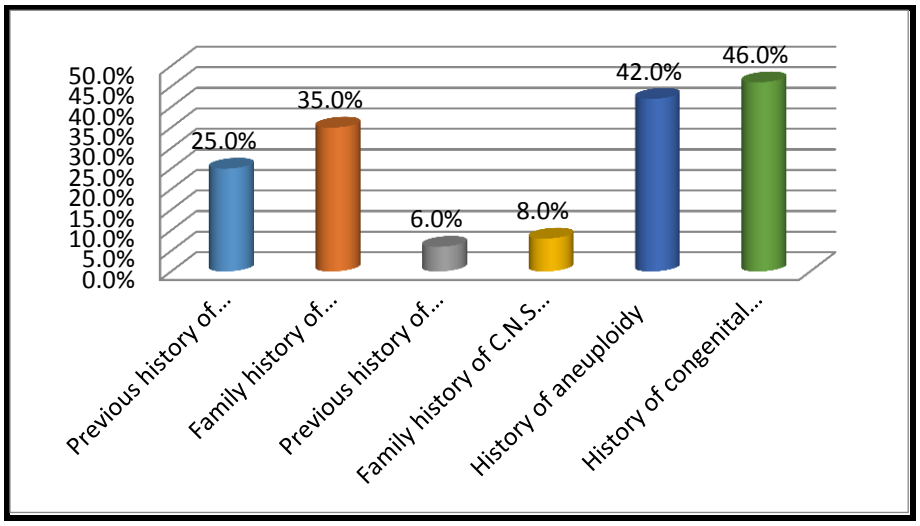

Figure (2): Distribution of studied cases regarding anomalies detected by U.S.

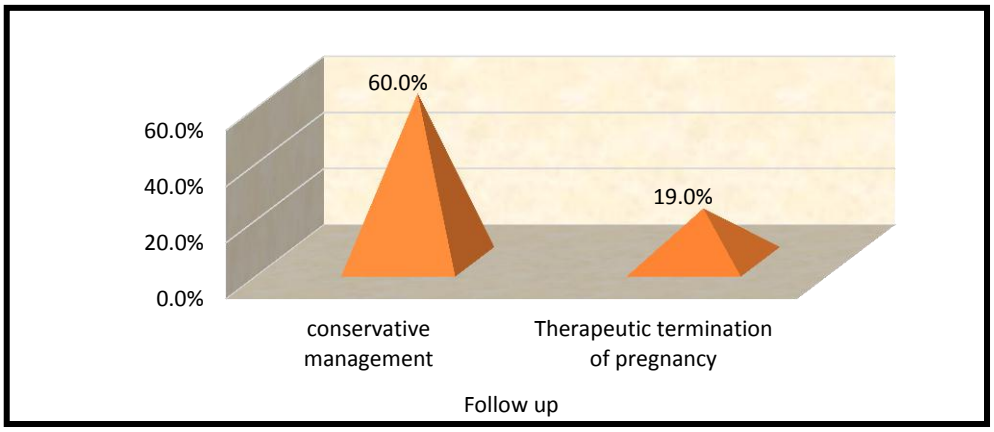

Figure (3): Distribution of studied cases regarding follow up

Discussion

Central nervous system malformations are the second most frequent class of congenital anomalies, following congenital diseases of the heart[12]. About 21% of congenital malformations of the CNS, including one of the most common congenital disorders, and may occur either isolated or associated with other anomalies of the neural system itself or other systems [13]. Fetal congenital anomalies risk is reported to be about 2% to 3% regardless of their prior history, family history, maternal age, or lifestyle. This risk increases in some patients (high-risk pregnancy). The neural system malformation is one of the common congenital anomalies encountered in pregnancy. They represent about 0.3-1 % of all live births. During prenatal anomaly scan, detection of CNS malformation is important, especially since these anomalies have a poor prognosis and are also associated with genetic syndromes or chromosomal anomalies [14].

Ultrasonography can detect many CNS anomalies in the first and early second trimester. Some of them develop or become obvious at end of pregnancy. The earlier in detection, the more time available for the parents and clinician to plan the outcome of pregnancy. Extensive and severe life threatening disorders give a reason for early termination of pregnancy, and detection of minor disorders helps everybody to be prepared and reassured for post-delivery management [15]. Two-dimensional (2D) ultrasonography, antenatal detection of many types of central nervous system anomalies have been detected. 2D sonography can diagnose many fetal abnormalities.

The sonographic examination is the chosen modality and an effective method for the diagnosis of congenital anomalies. It has been used for more than three decades as the main modality to help diagnose fetal CNS anomalies [13]. Several studies have shown an accuracy of 92% to 99.7% for ultrasonographic detection of CNS anatomic anomalies [16]. Routine anomaly scan during the antenatal period has become a part of obstetric care and the best time for fetal malformation scanning is approximately at 11-14, 18-20, and 28-30 weeks of gestation [17].

The study's strength point was the high incidence of CNS abnormalities as ventriculomegaly being the most prevalent foetal anomalies. The fundamental weakness in this line of research is the lack of studies that analyze the prevalence of congenital defects in Minia governorate, hence this study should be carried out as a first step toward filling that gap. The primary limitations of this study were, first and foremost, a lack of understanding about the benefits of the advanced Ultrasound anatomy scan, as well as a delay in attendance at the unit and return to follow up. Another impediment was the lack of a comparable study in this area of inquiry in our governorate.

In our study, regarding the distribution of the studied cases regarding history, the results showed that, that 25% of cases had a previous history of congenital fetal malformations, and 6% of cases had a previous history of C.N.S fetal malformations. The risk of aneuploidy increases with maternal age. Other factors also influence patients' risk in any given pregnancy, including the presence of birth defects or soft markers on ultrasound and past obstetric history, particularly if it is notable for a prior pregnancy affected by aneuploidy or another genetic disorder [18]. A past family history of aneuploidy increases the current pregnancy risk of aneuploidy, especially if a parent is a balanced Robertsonian translocation carrier, though most cases are sporadic and secondary to chromosomal nondisjunction. Patients report many different motivations for pursuing aneuploidy screening or prenatal diagnosis. Some may choose pregnancy termination if the defect is identified at an early enough gestational age. Others may choose to pursue screening or testing to allow them time to process the diagnosis and seek experienced clinicians who may be able to aid them in preparation for caring for an affected infant and to care for their child after delivery [19].

Some birth defects, such as some neural tube defects, may be eligible for prenatal treatment with subsequently improved neonatal outcomes [10]. All patients choosing to undergo screening or testing should receive counseling regarding risks, benefits, and limitations of their chosen testing plan from their health care provider or

genetic counselor. It is important to note that aneuploidy screening and testing decisions are heavily value-driven; a frank discussion of the benefits, risks, and limitations of tests is key in ensuring that care is appropriate for each patient's individual goal [(20)]. In 2007, the American Congress of Obstetricians and Gynecologists (ACOG) released "ACOG Practice Bulletin No. 77," which recommended making aneuploidy screening or invasive testing available for all women, ideally at their first prenatal visit [(21)]. This idea was revolutionary at the time, as previously only women who were considered to be at high risk had been offered these tests [(18)].

Also in our study, as regarding Ultrasound detected CNS anomalies in 79 fetuses. The most common anomaly detected was Ventriculomegaly that found in 22%. Ventriculomegaly should be interpreted with care as brain formation is still ongoing and mild ventriculomegaly may still be a variation of normal. Nevertheless, first-trimester enlargement of the lateral ventricle has been described in fetuses with aneuploidy; this explains the high percentage of Ventriculomegaly in our sample as 42% of cases had a history of aneuploidy. Ultrasound examination is operator dependent with entails trial and error needs careful and skillful examination. In a study done by Sefidbakht et al., [(22)], they evaluated fetal CNS Anomalies Detected by Magnetic Resonance Imaging.

Also, the current study agrees with the study by Fatma et al.,[(23)] who reported that 3D ultrasonography is effective in the assessment of fetal CNS anomalies with detection of CNS anomalies on ultrasound was 90%. In the study of Guardiola et al.,[(24)], they concluded that among 26,588 births registered in this period, 3.67% presented with malformations (IC=95%; 3.44–3.9), being 0.36% of the CNS (IC=95%, (0.29–0.43)). The most common CNS malformation was meningomielocele (10.4%). In our study, regarding out of 79 fetuses with CNS anomalies, 60% cases were treated by conservative management while 19% cases were treated by therapeutic termination of pregnancy, After delivery, 64% cases confirmed the diagnosis of anomalies after delivery.

So, based on confirmation after delivery as a reference standard, ultrasound can detect CNS fetal malformation in 62 patients (true positives) and did not detect CNS fetal malformation in 19 patients (true negatives). We found that the US had overall sensitivity, specificity, and diagnostic accuracy of 96.88%, 52.78%, and 81% respectively in detecting C.N.S fetal malformation in our patients. The positive predictive value was 78.48% while the negative predictive value was 90.48%. US examination is an effective modality for prenatal diagnosis of C.N.S anomalies. It is a non-invasive technique that is more acceptable by patients. Several studies have shown an accuracy of 92% to 99.7% for US detection of CNS anatomic anomalies[(25)]. As regarding efficacy, previous studies demonstrated that 3D ultrasonography is sensitive in the assessment of fetal CNS anomalies. In our present study, the detection of CNS anomalies on ultrasound was 96% which is more than was reported by Barros et al.,[(26)] as they reported 90% sensitivity.

Despite extensive epidemiological studies, the etiology of CNS malformations remains obscure in most cases. Women, who previously have had a child with a neural tube defect, have an increased risk of recurrence as reported in our study an early diagnosis of CNS malformations allows a precise prognosis to be made. The efficiency of ultrasound screening in the prenatal diagnosis of CNS anomalies has been demonstrated[(27)]. The important component of a better detection rate of CNS malformations is the improvement in ultrasound technology. The development of techniques for prenatal diagnosis of fetal malformations has raised considerable ethical and practical problems, because of elective terminations. 3D detailed Ultrasonography is used nowadays as a routine procedure for the detection of fetal malformations. It is used for pregnant women due to its efficiency, availability, low cost, and real-time capability.

Also, Fatma et al.,[(23)] concluded that in our study CNS malformations have been detected prenatally in 90 % of patients. Similar results, from the study of NTD, have been published, with a detection rate of 80%. Prenatal diagnosis

of brain malformations has improved with the advances of 3D ultrasonography imaging techniques. The information obtained has significant implications for parental counseling regarding both the type of malformation and neurological and developmental prognosis. Hydrocephalus can be effectively managed by ventriculoperitoneal shunt or other shunting operations. But, even in such cases, neuro-developmental disorders may persist after the successful operation as diffuse brain abnormalities may be present in addition to hydrocephalus.

Conclusion

From all the aforementioned data we can conclude that dimensional ultrasonography plays an important role in the detection and diagnosis of some fetal central nervous system anomalies. However, some anomalies may be difficult to be detected by two-dimensional ultrasonography due to the position of the fetus. For example, the acquisition of the median plane may be impossible with 2D transabdominal ultrasound and require special expertise in transvaginal transfontanelle scanning, but in many way, it's considered a good provisional diagnosing tool for screening for fetal anomalies. We recommend screening for all pregnant women by ultrasonography at various times of pregnancy.

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