



## Original Article

## Sonographic Prenatal Screening in Diagnosis of Neural Tube Defects During 1st and 2nd Trimesters of Pregnancy

Aima Gilani<sup>1\*</sup>, Muhammad Nawaz Anjum<sup>2</sup>, Asif Hanif<sup>3</sup>, Zarnab Amin<sup>4</sup> and Seemal Masood<sup>2</sup>

<sup>1</sup>Salford Royal NHS, Foundation Trust, Salford, Manchester, United Kingdom.

<sup>2</sup>Radiology department, Faculty of Allied Health Science, University of Lahore, Lahore, Pakistan.

<sup>3</sup>University Institute of Public Health, University of Lahore, Lahore, Pakistan.

<sup>4</sup>Radiology department, Combined Military Hospital, Lahore, Pakistan.

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**\*Corresponding Author:**

Aima Gilani  
Salford Royal NHS, Foundation Trust, Salford, Manchester, United Kingdom  
[aimagilani1995@gmail.com](mailto:aimagilani1995@gmail.com)

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## ABSTRACT

Sonographic assessment offers several advantages in the diagnosis of Neural Tube Defects (NTDs). It is a safe and non-invasive procedure that poses minimal risks to both the mother and the fetus. During the 1st trimester, sonographic assessment includes measurement of nuchal translucency (NT), which, when increased, indicates a higher risk of NTDs and chromosomal abnormalities. In the 2nd trimester, a detailed anatomical scan evaluates the neural tube, brain, spine, and associated structures. **Objective:** To screen sonographically for the prenatal diagnosis of Neural Tube defects during 1<sup>st</sup> and 2<sup>nd</sup> trimesters of pregnancy. **Methods:** A prospective cohort study done in 9 months at Gilani Ultrasound Centre, Lahore, Pakistan by consecutive sampling. Total 7552 samples were estimated. We included all pregnant females visiting for regular antenatal checkup age between 18-45 years and Gestational age from week 6<sup>th</sup> till 26<sup>th</sup> weeks with any parity and excluded females needing emergency intervention. **Results:** Out of 7552 patients 319(4.24%) of fetuses were seen with minor abnormalities (Sonological Markers) in 319(4.28%) of patients examined of which 89(28.07%). Mild microcephaly was seen in 24(7.57%), of which 3 were seen in the 2<sup>nd</sup> trimester and 21 were seen in the 3<sup>rd</sup> trimester. Many other disorders were also observed in very low number of patients. **Conclusion:** Sonographic assessment is an essential tool in the prenatal screening and diagnosis of NTDs during the 1st and 2nd trimesters of pregnancy. Its widespread use and continuous improvement in technology have significantly contributed to the improved diagnosis and care of NTDs in prenatal settings.

## INTRODUCTION

Central nervous system (CNS) malformations are the second most frequent category of congenital anomalies, after congenital heart disease. Ultrasound examination is an effective modality for the prenatal diagnosis of these anomalies. An accurate fetal diagnosis depends upon a precise description of the sonographic appearance of the CNS and careful evaluation for associated malformations, which are often present [1]. Neural tube defect (NTD) is a simple term for a congenital malformation of the central

nervous system (CNS) existing secondary to lack of closure of the neural tube [2]. They occur in the first month of pregnancy. A baby's neural tube normally develops into the brain and spinal cord. It starts out as a tiny, flat ribbon that turns into a tube by the end of the first month of pregnancy. NTDs happen if the tube does not close completely. NTDs can cause serious problems for babies, including death [3, 4]. Folic acid deficiency is thought to be the cause of Neural tube defects by some authors. If women of childbearing

age take 400 micrograms of folic acid every day before and during early pregnancy, it can help reduce their baby's risk for NTDS. Folic acid is a vitamin-B that every cell in the body needs for normal growth and development. Neural tube formation is divided into primary (closure) and secondary (canalization) phases. Primary closure is initiated at several discrete points along the rostro caudal axis. First, at the boundary between future hindbrain and cervical spine (termed Closure 1), then around 12 hours later at the boundary between future forebrain and midbrain (Closure 2) and soon afterwards at the rostral extremity of the future forebrain (Closure 3) [5, 6]. NTDS are one of those types of abnormalities which can occur in the early development of a baby. The pathophysiology of the neural tube defects is still not known [7, 8]. There are many types of NTDS such as spina bifida which affects the spine and babies with spina bifida may have paralysis of the legs, lack of bladder and bowel control and curvature of the spine. It affects about 1,500 babies a year. Neural tube defects (NTD) range from the lethal (anencephaly) to the potentially asymptomatic (some closed spina bifida) [9, 10]. The overall incidence of major congenital abnormalities at birth in the general population ranges from 2-3% and these abnormalities are responsible for 20-25% of perinatal deaths and a higher percentage of perinatal morbidity [11]. Prenatal detection of an anomaly increases the options for informed pregnancy management and in some cases, the disorder may be amenable to intrauterine treatment. In low-risk populations, the sensitivity of detecting a congenital abnormality range from 14% to 85% and specificity ranges from 93% to 99%. Both in USA and Europe, the detection rates of congenital anomalies are about 3 times in Hospital Ultrasound departments and Laboratories (60-80%) than as compared to the Ultrasound examinations performed in individual doctors' offices and clinics (25-30%) [12]. The benefits of routine 2nd -trimester ultrasound screening include: More Accurate Gestational Age, Detection of major and minor malformations before birth, early detection of multiple pregnancies, fewer low birth weight single babies, reduction in the incidence of induction for preterm pregnancies, early detection of Placenta previa and reassurance of a normal Pregnancy. Maternal Age > 35yrs of age, genetic History, US at 11 - 14 weeks, nuchal translucency, presence of nasal bone, nasofrontal and naso-oral angles, history of Trisomy or Parental Translocation carrier and other sonographic markers [13, 15]. Ultrasound at-18-22 weeks-Anatomy/Anomaly Screening scan. Maternal Serum Biochemistry in the 1st trimester (11-14 weeks), Maternal Serum biochemistry in the 2nd Trimester 15-20 weeks), isolation and study of fetal cells in maternal circulation. To screen Sono graphically for the prenatal diagnosis of Neural Tube Defects during 1<sup>st</sup> and

2<sup>nd</sup> trimesters of pregnancy.

## METHODS

It was Prospective cohort study done at Gilani Ultrasound Centre Gaju Matta, Ferozpur Road, Lahore, Pakistan. Duration of Study was 9 months. Consecutive sampling was used to collect data. A sample of 7552 was estimated using the prevalence of NTD during as 9.1 per 10,000 births, at a 95% confidence level and 0.0008 margins of error. We included all pregnant females visiting for regular antenatal checkup age between 18-45 years and Gestational age from week 6<sup>th</sup> till 26<sup>th</sup> weeks with any parity and excluded females needing emergency intervention. The Toshiba, Aplio-400, machine was used for scanning with convex transducer frequency range 3.5-6 Mhz. After approval of the synopsis from the ethics committee of the university of Lahore, females were enrolled in the study and their written consent of all participants was taken. Sociodemographic and socioeconomic data were collected of all participants. The 1<sup>st</sup> examination is done at 6-7 weeks for detecting the fetal heart and measuring the Crown rump length (CRL), gestational sac (GS) and yolk sac dimensions. The 2<sup>nd</sup> examination at 11-14wks for measuring the Nuchal translucency and Nuchal skin fold thickness apart from measuring the CRL, biparietal diameter (BPD), femur length (FL) and locating the placental position and placental cord insertion and measuring the cervical length and width, Intra-Orbit width and funneling of Cervix. The 3<sup>rd</sup> examination is scheduled at 20-22wks for a detailed fetal anatomy scan to detect any congenital fetal anomalies – this examination includes a thorough examination of fetal brain structures and measuring the atrial width and cerebellar size, presence of cavum septum pellucidum and orbital width and inter orbital distance and Doppler examinations of middle cerebral arterial (MCA) to take the pulsatility index (PI) and resistive index (RI) readings as the baseline value. Placental position is reconfirmed, and amniotic fluid volume is measured as a single vertical pocket unless otherwise, the 4-quadrant average (Index) becomes mandatory. Amniotic fluid volume and Placental maturity and for detecting any signs of Intrauterine growth restriction (IUGR) or large for dates fetuses, especially in diabetic mothers. Antenatal Laboratory investigations were done as follows as routine check-ups but are not added in the analysis of this study as per objectives.

## RESULTS

A total of 7552 pregnant patients were examined for 9 months. Of 7552 patients, 4217 came for a single examination mostly either in the 2nd or in the late 3rd trimester of pregnancy and the remaining 3335 patients underwent multiple examinations as per our hospital's protocol of 3 examinations per patient per pregnancy as

mentioned before, 1st one in the early 1st trimester as the viability scan at 6<sup>th</sup> to 7<sup>th</sup> weeks of pregnancy, the 2nd examination between 11<sup>th</sup> to 14<sup>th</sup> weeks for the assessment of nuchal translucency and the fetal nasal bone measurements, the 3<sup>rd</sup> examination between 20<sup>th</sup> to 22<sup>nd</sup> weeks as a detailed anatomy scan. The number of diabetic pregnant patients in our group was 108(1.43%) of which 12 patients had diabetes before pregnancy (4 of them were of Insulin dependent diabetes mellitus (IDMM)) and 96 patients had Gestational diabetes mellitus (GDM) and most of them were controlled with dietary restrictions and the number of hypothyroid pregnant patients taking Eltroxin treatment were 6(0.08%). A total of 6 patients were seen with PIH and 7 were seen with pregnancy-induced mild edema. The total number of large for dates fetuses in our group were about 81(1.07%) and the overall incidence of post-mature deliveries in our group of patients was about 30(0.40%). 319(4.24%) of fetuses were seen with minor abnormalities (Sonological Markers) in 319(4.28%) of patients examined of which 89(28.07%) were seen with small for dates fetuses (IUGR) of which 13 had constitutional IUGR of which 11 were seen in the 2<sup>nd</sup> trimester and all had associated major anomalies with a single umbilical artery. Mild microcephaly was seen in 24(7.57%), of which 3 were seen in the 2<sup>nd</sup> trimester and 21 were seen in the 3<sup>rd</sup> trimester and only 1 fetus was seen with Mild macrocephaly in spite of many patients diagnosed with ventriculomegaly in the 2nd and 3rd trimester. A total of 18(5.67%) fetuses were seen with mild ventriculomegaly 14(4.41%) with the atrial measurements between 10 and 14 mms and 4(1.26%) were with borderline ventriculomegaly where in the atrial measurement was 10mms and mildly dilated cisterna magna (width 10mms or more) was seen in 8(2.52%). A total of 5 in the 2nd trimester and 3 in the 3rd trimester fetuses but all fetuses had normal appearance, pulse, grimace, activity, and respiration (APGAR) score of 10/10 at birth and uneventful neonatal period. A total of 12(3.78%) fetuses were seen with choroid plexus cysts; 4 had bilateral and 8 had unilateral and 1 was associated with mild ventriculomegaly. A total of 11 of these were seen in the 2<sup>nd</sup> trimester of pregnancy and all resolved uneventfully by 28 to 30<sup>th</sup> weeks of pregnancy and only 1 fetus was detected with a choroid plexus cyst in the 29<sup>th</sup> weeks of pregnancy but had an uneventful postnatal period. 19(6%) of fetuses were seen with mild dolichocephaly with a Cephalic index between 6.7 and 7.4 of which 1 was seen in the 2<sup>nd</sup> trimester and 18 were seen in the 3<sup>rd</sup> trimester and none of the fetuses had any sort of other associated major or minor abnormality during the antenatal period or postnatally and only 1 fetus was seen with brachycephaly in the 3<sup>rd</sup> trimester. 5 fetuses were seen with increased nuchal translucency of more than 3.5mms. A total of 2 were seen

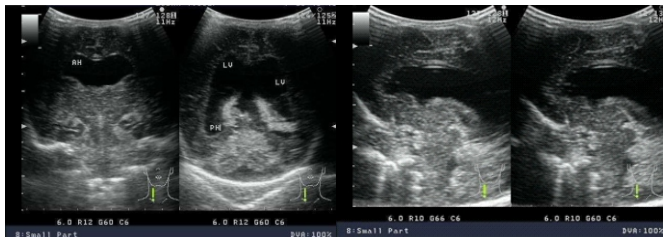
at 11<sup>th</sup> week of pregnancy and 3 were seen in the 13<sup>th</sup> week of pregnancy and 2 fetuses were seen with increased nuchal skin fold thickness of more than 6mms in the 2<sup>nd</sup> trimester but none of these patients had any cardiovascular or any other abnormality. Of the 29(9.14%) minor cardiovascular abnormalities 13 fetuses had echogenic foci in the heart. A total of 8 were in the Right ventricle and 5 were in the Left ventricle of which 7 were detected in the 2<sup>nd</sup> trimester and 6 were seen in the 3<sup>rd</sup> trimester and 16 fetuses were seen with transient dysrhythmias like transient bradycardias, Occasional ectopic beats, extrasystoles and on and off missed beats of which 11 were seen in the 2<sup>nd</sup> trimester and 5 were detected in the 3<sup>rd</sup> trimester-but none had any persistent abnormality after birth to best of our knowledge. In gastrointestinal tract (GIT) 9(2.84%) fetuses were seen with echogenic bowel loops. A total of 1 had grossly echogenic bowel loops and 8 had mild to moderate forms of which 4 were detected in the 2nd trimester and 5 in the 3rd trimester and 3 fetuses were seen with a physiological umbilical hernia. A total of 2 at 11<sup>th</sup> week of pregnancy and 1<sup>st</sup> at 14<sup>th</sup> weeks but all resolved at the time of detailed anatomy scans at 20<sup>th</sup> to 22<sup>nd</sup> weeks and 1 fetus was seen with macroglossia with tongue protruding through the lips in the 3<sup>rd</sup> trimester of pregnancy. Of the 21 (6.62%) minor urological cases, 13 were with mild hydronephrosis- 5 bilateral, 5 R sided and 3 L sided of which 6 were seen in the 2<sup>nd</sup> trimester and 7 in the 3<sup>rd</sup> trimester and 8 fetuses were seen with mild pelviectasis only. A total of 5 were bilateral, 1 was R-sided and 2 were L sided of which 4 were detected in the 2<sup>nd</sup> trimester and 4 in the 3<sup>rd</sup> trimester. 30(9.46%) fetuses showed hydrocoele of which 20 were bilateral and 5 R-sided and 5 L-sided respectively of which 27 were mild forms and 3 fetuses showed moderate-sized hydrocoele. The size of hydrocoele were more prominent in fetuses with polyhydramnios and all cases were detected in the 3rd trimester of pregnancies but no postnatal complaints came to light. Among the 17 minor skeletal abnormalities, 16(5.04%) showed short femoral lengths > 2 systolic/diastolic (S/D) shorter than the BPD, fetal head circumference (HC) and Fetal abdominal circumference (AC); of which 2 were seen in the 2nd trimester and 14 were seen in the 3rd trimester and 1 fetus showed sandal gap defect in the toes in the 3rd trimester. A total of 31(9.78%) patients were seen with polyhydramnios of which 21 were mild forms with amniotic fluid index (AFI) between 32 to 38cm, 6 were of moderate severity with AFI between 38 to 48cm and 4 were of the severe type with AFI of 48cm and above. Most of the mild polyhydramnios were isolated except 1 fetus which also showed mild ventriculomegaly, but the majority of the moderate and severe forms were associated with major fetal malformations like thanatophoric and campomelic skeletal dysplasia,



Esophageal atresia and tracheoesophageal fistulas, Duodenal atresia, large lower abdominal cyst and IUGR, spinal meningocele, Downs syndrome, Neu-Laxova syndrome and cleft lip and palate deformities. 1 patient had a large placental chorioangioma and gross polyhydramnios (AFI 56 cm).

**CASE 1: Had Rectocele and Cystocele**

Ultrasound image shows thin hyperechoic striations radiating from the edges of the lateral ventricles towards the brain substance. Complete agenesis of corpus callosum with moderate hydrocephalus and small 2.4 x 2.0cms posterior mid line meningocele near the posterior fontanelle. Corpus callosum was totally absent. A large fluid filled cavity was seen in the center of the skull below the cerebral cortices. All other structures of the brain -viz- Thalami, Basal ganglia, Mid brain, Pons, 4<sup>th</sup> ventricle, Cerebellum and Medulla oblongata were found to be normal. Vacuum extraction failed and patient was taken up for emergency caesarean section by the same doctor. Pediatrician notes after C/S showed that Babys APGAR score was 9/10, wt.= 3.5kgs, Ht =54cms, HC =37cm. Baby had a 2x2cms swelling in the midline occipital region covered with intact skin and no leak was noted (Suspected Meningocele?) and no neurological deficit was noted except for Occasional twitching of arms and legs, more on the R side. All reflexes of baby were normal and baby was moving all the limbs freely.



**Figure 1:** Had Rectocele and Cystocele

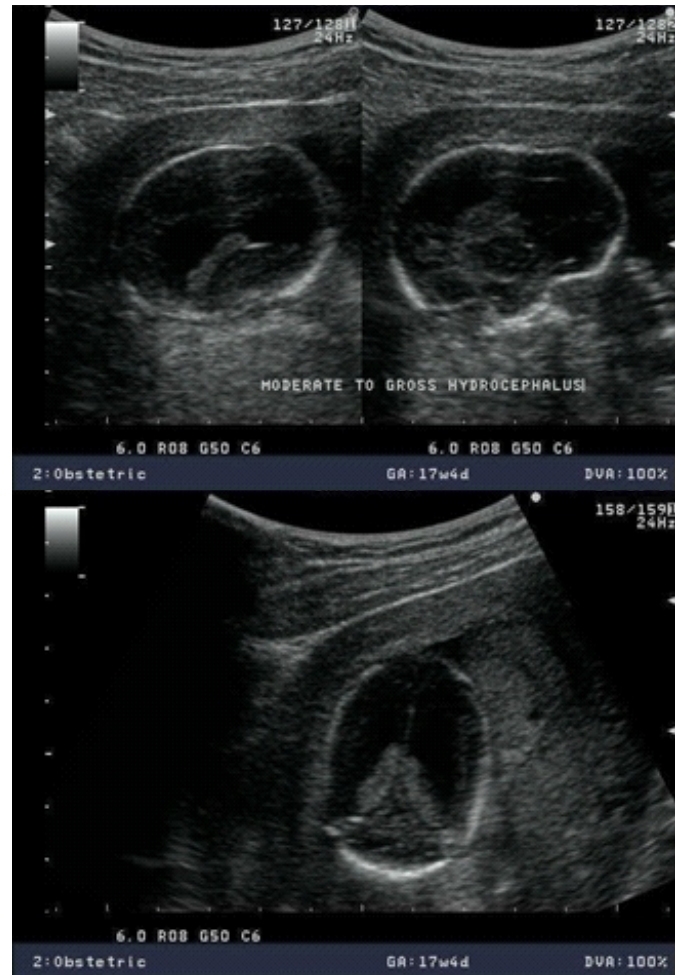
Ultrasound image shows moderately dilated both atria with free floating choroids plexuses. Dilated both lateral ventricles-Both anterior and posterior horns lying parallel to each and widely separated with absent cavum septum pellucidum.



**Figure 2:** The 3<sup>rd</sup> ventricle appeared mildly dilated and elevated

**CASE 2: H/O taking Hormonal treatment for induction of ovulation and conception.**

Ultrasound image shows the Clover leaf appearance of skull and moderately dilated Atrium 18mms).

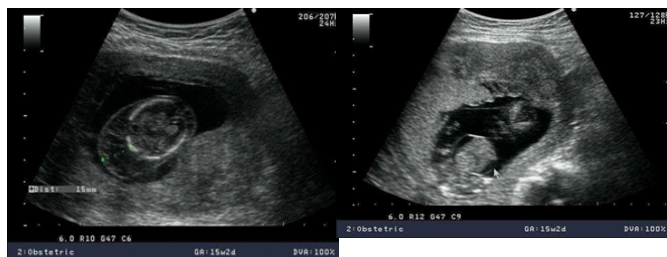


**Figure 3:** Clover leaf appearance of skull and moderately dilated Atrium

Excessive molding and Flexion of fetus and Oligohydramnios. Aquaeductal stenosis with gross hydrocephalus and mild IUGR and Oligohydramnios. (Suspected Renal Agenesis).

**CASE 3: G7P5A1-1<sup>st</sup> pregnancy -Abortion and Dand C and 1 child died 7hrs after birth. No H/O DM, HTN, Heart Disease, DVT. Patient was tasking Anti-Depressants and anti-Psychotic medicine and stopped at the beginning of Pregnancy.**

Ultrasound image shows the bony skull defect in the fronto-parietal region of the skull with a large cystic mass with internal echogenic areas (Encephalocele) Moderate S/C Edema of trunk large encephalocele and moderately severe hydrops fetalis.



**Figure 4:** Bony skull defect in the fronto-parietal region of the skull

## DISCUSSION

Neural tube defect (NTD) is a simple term for a congenital malformation of the central nervous system (CNS) existing secondary to lack of closure of the neural tube [2]. They occur in the first month of pregnancy. A baby's neural tube normally develops into the brain and spinal cord. It starts out as a tiny, flat ribbon that turns into a tube by the end of the first month of pregnancy. NTDs happen if the tube does not close completely. NTDs can cause serious problems for babies, including death [15]. The current study was conducted to evaluate prenatal diagnosis of Neural Tube defects during 1st and 2nd trimesters of pregnancy through ultrasound. In our study, out of total 7552 participants, 319(4.24%) of fetuses were seen with minor abnormalities (Sonological Markers) in 319(4.28%) of patients examined of which 89(28.07%) were seen with small for dates fetuses (IUGR) of which 13 had constitutional IUGR of which 11 were seen in the 2nd trimester and all had associated major anomalies with a single umbilical artery. Mild microcephaly was seen in 24(7.57%), of which 3 were seen in the 2nd trimester and 21 were seen in the 3rd trimester and only 1 fetus was seen with Mild macrocephaly in spite of many patients diagnosed with ventriculomegaly in the 2nd and 3rd trimester. A total of 18(5.67%) fetuses were seen with mild ventriculomegaly 14(4.41%) with the atrial measurements between 10 and 14 mms and 4(1.26%) were with borderline ventriculomegaly where in the atrial measurement was 10mms and mildly dilated cisterna magna (width 10mms or more) was seen in 8(2.52%). A same kind of study was conducted in Pakistan by Chen et al., 2019 that exhibited out of 30 patients 10 were diagnosed as Anencephaly (33.3%), 8 as hydrocephalus (26.6%), 4 as spina bifida (13.3%), 3 as meningoceles (10%), 2 as lumbar meningoceles (6.6%), 1 as hydranencephaly (3.3%), 1 as holoprosencephaly (3.3%) and 1 as encephalocele (3.3%) [16]. According to this, we found anencephaly is more common than any type of other neural tube defects. Wilcox et al., and others have demonstrated a 20% to 31% rate of early pregnancy loss after implantation in normal healthy people. Published data shows that 15% of fertilized ova fail to divide, 15% are lost before implantation, 30% are lost during implantation and 13 to 16% are lost after

implantation and the rate of unrecognized or pre-clinical pregnancy loss is about 22% [17]. Vettrai IM et al., demonstrated a high frequency of morphological abnormalities in aborted embryos and the pregnancy loss rates increased with increased maternal age, the use of tobacco and alcohol and the more severe the anomaly more the likely hood of early fetal demise. They demonstrated that the pregnancy loss rates were 8.5% when a normal yolk sac is seen, and 7.2 % in an embryo of CRL <5mms, 3.3% with a CRL of 6-10mms, 0.5% with a CRL of >10mms and about 2% from 14 to 20 weeks of GA with an overall pregnancy loss rate of 11.5% [18]. In this study, there was an overall pregnancy loss rate in the 1st trimester of about 101 (13.93%) almost comparable with established published data. The incidence of major congenital abnormalities at birth in the general population is estimated at 2% to 3%. There have been 5 studies published to date that have addressed the issue of screening in the general population of large numbers of women (>500) in a true low-risk unselected population. The frequency of major anomalies detected in these 5 major studies from Europe was as; Pedra et al., and Hungary 1997 found 43 major anomalies in 3991 patients giving an incidence of 1.22%- about 40.8% of those anomalies were diagnosed in the 1st trimester and 38% were diagnosed in the 2nd trimester and 20% were diagnosed in the immediate postnatal period [19]. Another study done by Tworetzky et al., from Italy in 2000 found 64 major abnormalities in 3592 pregnant patients screened in the low-risk population with a major abnormality rate of 1.78% and the majority of their abnormalities were detected in the 1st trimester with a frequency of about 33/64 (51.56%) and only 21/64 (32.80%) were detected in the 2nd trimester and 10/64 (15.62%) were detected in the immediate postnatal period [20]. Valsangiacomo et al., studied 3514 fetuses in 3490 unselected pregnancies in Italy by transvaginal ultrasound at 13 to 14 weeks and by T/A ultrasound at 20 to 22 weeks and found 52/3490 (1.49%) major structural anomalies out of which 33% of the defects were diagnosed at an early scan and further 48% were diagnosed at 20 to 22 weeks of pregnancy [21]. In 3 out of the 4 above-mentioned studies the commonest abnormality detected was in central nervous system (CNS) and the 2nd commonest was found in the neck as cystic hygromas except in the study done by Tworetzky et al., were cystic hygroma and neck abnormalities superseded the CNS malformations which were 2nd in number. In our study, we examined 7552 unselected low-risk pregnant women and found 118/7552 (1.58%) of major structural defects in 7511 live fetuses (1.57%). This study found the commonest major malformations in the CNS 39(33.05%) but the incidence of cystic Hygroma was quite rare (1/7552) as against the published incidence of 1/700 cases in

western countries where this study detected it in only 1 fetus of Russian women and our 2nd commonest major malformations were detected in the Urinary tract 24/7552(20.16%). According to a study published in the Journal of Pakistan Medical Association in 2015, the incidence of neural tube defects in Pakistan was reported to be around 5.6 per 1,000 live births [22] But in this study, the incidence found to be higher (approx. 18.18% in 3 trimesters). Overall, the incidence was lower in trimesters individually and this may be because of folate supplementation in the last few years as a part of the healthcare system in Pakistan. But there is a need to study this further at multi-center and especially in areas of malnutrition in the country. Since there were no neural tube defects, we were unable to associate it with folate, drug, and supplementary products, though other societies and populations did report the association before.

## CONCLUSIONS

Sonographic assessment is an essential tool in the prenatal screening and diagnosis of NTDs during the 1st and 2nd trimesters of pregnancy. It provides a safe, non-invasive, and real-time method for assessing the developing fetus and detecting abnormalities in the neural tube. Early detection of NTDs allows for appropriate counseling, intervention, and management strategies to be implemented, optimizing the outcomes for affected pregnancies. While sonographic assessment has certain limitations, its widespread use and continuous improvement in technology and expertise have significantly contributed to the improved diagnosis and care of NTDs in prenatal settings.

## Authors Contribution

Conceptualization: AG, MNA

Methodology: SM, ZA

Formal analysis: AH

Writing, review and editing: AG, MNA, SM, ZA, AH

All authors have read and agreed to the published version of the manuscript.

## Conflicts of Interest

The authors declare no conflict of interest.

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