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ORIGINAL ARTICLE

The Role of First Trimester Ultrasonography in Antenatal Care: A Study from a Single Perinatal Institute in India

Mythreyi Kunapareddy[1] · **Suseela Vavilala**[1]

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Abstract The aim of this study was to assess the role of ultrasound in first the trimester of pregnancy for confirmation of pregnancy, number of fetuses, chorionicity, amnionicity if multiples, viability, assessment of gestational age, identification of structural anomalies and assessment of risk for chromosomal abnormalities. This was a prospective observational study. All pregnant women registered within 13^{+6} weeks were offered a routine scan between 11^{+0} and 13^{+6} weeks. All scans were done by obstetricians, fetal medicine specialists or radiologists are accredited by the Fetal Medicine Foundation. All pregnant women undergoing 11^{+0} and 13^{+6} weeks scan were included. Women beyond 14 weeks of pregnancy and referrals from the other centres not delivered at our institute were excluded from the study. A total of 5923 scans were done between January 2016 and June 2017. Complete follow up was available for 2927 women (49.4%), 1925 (32.5%) are ongoing pregnancies and 1071 (18.08%) pregnant women were lost to follow up. The median maternal age in our study was 28 years and 349 (5.89%) mothers had advanced (> 35 years) maternal age. Increased nuchal translucency (NT) (> 95th percentile) was found in 272 cases (4.59%). Intra-uterine fetal death, miscarriages, termination of pregnancy and cardiac abnormalities were higher among women with an NT > 95th percentile. Statistical analysis included calculation of *p* values and odd's ratio. Skull and brain abnormalities were found in 28 cases, cystic hygroma in 20 cases, abdominal wall and spine abnormalities in 16 cases each, bladder abnormalities in 12 cases and cardiac abnormalities in 9 cases. Among 2927 women, 85 (1.43%) were screen positive. After counselling, only 20 women underwent invasive testing. The 11^{+0} and 13^{+6} weeks scan helps in determination of fetal viability, gestational age, number of fetuses and chorionicity and screening fetuses at risk for trisomy by including screening for structural abnormalities and plan pregnancy/terminate accordingly.

Keywords Nuchal translucency · Structural abnormalities · Trisomy · Karyotype

Introduction

Most pregnancies have good maternal and fetal outcomes. Fetal abnormalities, premature birth and impaired placentation account for more than 90% of perinatal deaths [1]. Obstetric ultrasound is a non-invasive test that provides highly useful information about the fetus and helps in the management of pregnancy. Fetal abnormalities are known to affect 3–5% of all pregnancies [2]. 'First trimester' refers to a stage of pregnancy starting from the time at which viability can be confirmed (i.e. presence of a gestational sac in the uterine cavity with an embryo demonstrating cardiac activity) and up to 13^{+6} weeks of gestation. The main goal of a fetal ultrasound scan is to provide accurate information that will facilitate the delivery of optimized antenatal care with the best possible outcomes for mother and fetus. An ideal time for first trimester scan is 11^{+0} and 13^{+6} weeks.

✉ Suseela Vavilala
drsuseela@fernandezhospital.foundation

Mythreyi Kunapareddy
mythreyi@gmail.com

[1] Department of Fetal Medicine, Fernandez Hospital Pvt. Ltd, Hyderguda, Hyderabad, Telangana 500029, India

Rationale for 11^{+0} and 13^{+6} Weeks Scans

Most aneuploidies can be identified at 11–13 weeks of gestation by a combination of maternal characteristics, ultrasound findings and biochemical testing of maternal blood. An integrated first hospital visit at 11–13 weeks combining data from maternal characteristics and history with findings of biophysical and biochemical tests can define the patient into low risk or high risk for a wide spectrum of pregnancy complications, including miscarriage and fetal death, preterm delivery, preeclampsia, gestational diabetes, fetal growth restriction and macrosomia.

Objective and Design

The objective was to assess the need for routine ultrasound in first trimester of pregnancy for detection of viability, number of fetuses, gestational age assessment, chorionicity and fetal structural abnormalities; Study the clinical utility of 11^{+0} and 13^{+6} weeks scan for screening the chromosomal abnormalities and to assess the potential value of the same ultrasound in early diagnosis of fetal structural anomalies.

Methods

This was a prospective observational study of all pregnant women registered for antenatal care at a tertiary care perinatal institute with 8000 deliveries per annum during January 2016 and June 2017. Every pregnant woman undergoes a series of investigations in accordance with hospital protocol. Each pregnant woman is subjected to three ultrasound examinations (one in each trimester) as a part of routine antenatal care. The study is approved by Institutional Review Board and written informed consent is obtained from all the participating women.

- *Inclusion criteria*
  - All expectant mothers who registered within 13^{+6} weeks of pregnancy.
  - Intrauterine gestation.
  - Underwent 11^{+0} and 13^{+6} weeks scan.
  - Those women delivered at our hospital.
- *Exclusion criteria*
  - Expectant mothers beyond 14 weeks of pregnancy.
  - First trimester bleeding.
  - Referrals.
  - Expectant mothers who missed 11^{+0} and 13^{+6} weeks scan.

The first trimester examination included gestational age estimation by crown-rump length (CRL) measurement. The detailed fetal anatomical survey included identification of skull contour, cerebral midline falx, orbits, four chamber view of the heart, anterior abdominal wall (intactness and cord insertion) and visualization of stomach, upper and lower limbs, including hands and feet. Chromosomal markers include Nuchal translucency, Fetal heart rate, additional markers like Nasal bone, Ductus Venosus Doppler, Tricuspid Regurgitation. After the assessment of background risk and chromosomal markers, women are categorised into low risk/high risk. Women carrying a fetus with increased risk for (> 1 in 250) trisomy 21 or (> 1 in 100) trisomy 18 or trisomy 13 were offered counselling and invasive procedures. Ultrasound examinations were performed with a GE Voluson E8/E6/S8 expert with curved array transabdominal transducer 3.5–5.0 MHz. The majority of scans are transabdominal. Transvaginal scans (6.0–7.5 MHz) are done if satisfactory views were not obtained with trans-abdominal scans. All ultrasound images are stored in ASTRAIA database software which is available for review of images for retrospective assessment. All ultrasound examinations were performed by Fetal Medicine Consultants/Trained Obstetricians/Radiologists who are accredited by Fetal Medicine Foundation (FMF), the UK for first trimester scan.

Outcomes

Primary outcome measures included detection of viability, number of fetuses, gestational age assessment, chorionicity if multiple pregnancy and structural abnormalities. Secondary outcome measures included incidence, type of major fetal abnormalities and fetal outcomes of pregnancies with increased nuchal translucency (95th percentile) and screen positive fetus.

Women who underwent the first trimester scan were followed up into the postpartum period, if they delivered at our hospital. Being a tertiary care institute, there is a significant number of referrals from other institutes and practitioners. Details regarding outcome of pregnancy was obtained through electronic medical records (EMR) and telephonic interviews if birthing did not happen at our hospital.

Statistical Analysis

Qualitative data was expressed in numbers and percentages. Quantitative data were expressed in means and standard deviations. We used R-script (version 3.4.1) for statistical analysis. The frequency distribution of nominal variables and mean, standard deviation and median of continuous variables are presented as appropriate. The

outcomes of interest include confirmation of viability, gestational age determination, determine the number of fetuses and chorionicity and evaluation of fetal structural abnormalities and estimating the risk for aneuploidy i.e., trisomy 21, trisomy 18/13 and uptake of interventions in screen-positive group, the incidence and type of major fetal abnormalities and fetal outcome in pregnancies with increased nuchal translucency (95th percentile). We estimated odds ratios (OR) and the 95% confidence intervals (CI) and p values to analyse outcomes of pregnancy with increased nuchal translucency thickness and structural abnormalities.

Results

We performed 5923 first trimester scans during the period from January 2016 to June 2017. Complete information including follow-up was available in 2927 (49.41%) women. Antenatal follow-ups were on-going for 1925 (32.5%) women and 1071 (18.08%) women were lost to follow up.

A total of 5923 women were evaluated, consisting of 5768 (97.38%) singleton and 155 (2.61%) multiple gestations (Table 1). Majority of the mothers are primigravida (one mother was G16 with two live children and recurrent pregnancy loss). Parity ranged from 0 to 6 for these 5923 women. High BMI (> 30 kg/m^2) is seen in 720 (12.1%) women. For 753 (12.7%) women, TVS also had to be done to complete the scan.

The results of our study are as follows:

(i) Confirmation of viability: We found 5890 fetuses with cardiac activity, 33/5923 (0.55%) cases among which 10 cases had triplet pregnancy with one sac empty/missed miscarriage and were continued as twin pregnancies. Among twin pregnancy, 20 cases had one sac empty/missed miscarriage/vanishing twin and continued as singleton pregnancies. Among singletons, 3 were diagnosed as missed miscarriage at the time of first trimester scan.

(ii) Gestational age determination: Gestational age corresponded to menstrual age in 4465 (75.38%) women and gestational age was ascertained as per CRL in 1458 (24.61%) women due to disparity in dates. The latter included 178 (3%) women who could not recall their last menstrual dates, 759 (12.8%) women who had irregular menstrual cycles and 521 (8.7%) women who had disparity in dates of more than 1 week probably due to delayed ovulation.

(iii) Confirmation of the number of fetuses and chorionicity as shown in Fig. 1.

(iv) Evaluation of fetal structural malformations: Among 5923 mothers, 94/5923 (1.58%) had structural malformations (Fig. 2). Intra-uterine fetal deaths (6%, p value < 0.001), miscarriage (1%, p value < 0.001) and termination of pregnancy (65%, p value < 0.001) were common among women with fetal structural malformations. Among twins, there were six cases with structural anomalies—two cases of MCDA twins with TRAP sequence, four cases of DCDA twins (discordant for anomalies)—one case with omphalocele and cystic hygroma, one case with cystic hygroma, one case with megacystis, one case with Pentalogy of Cantrell's with bilateral Talipes (Limb body wall complex).

(v) Assessment of chromosomal markers:

(a) Increased Nuchal translucency: Increased nuchal translucency thickness (NT) (> 95th percentile) was found in 272 (4.59%) scans. NT was higher among women < 35 years of age when compared to advanced maternal age [mean (SD) 2.67 and 0.92 respectively]. NT was measured in 5917/5923 of antenatal mothers. The NT of 6 mothers could not be assessed because of gross anomalies like anencephaly. NT > 95th percentile was seen in 100% of cases with cystic hygroma, 17% of neural tube defects, 7% of anterior abdominal wall defects and 5% of urinary abnormalities. IUFD (2.14%, p value < 0.001), miscarriage (1.42%, p value < 0.2), termination of pregnancy (17.14%, p value < 0.001) and cardiac anomalies (37.5%, p value < 0.0001) were common among women with NT > 95th percentile.

Table 1 Baseline characteristics

Maternal (n = 5923)	Mean ± SD/n(%)	Median
Age (years)	27.88 ± 4.2	28 (16–49)
AMA($\geq$ 35 years)	349 (5.8%)	
Singleton	5768 (97.38%)	
Multiples	155 (2.61%)	
BMI (kg/m^2)	24.86 ± 4.570	24.50 (13–58)
Fetal	**Mean (SD)/n(%)**	**Median**
CRL (mm)	62.81 ± 8.04	62.3
GA (weeks)	12.17 ± 0.59	13
NT > 95th percentile	272 (4.59%)	

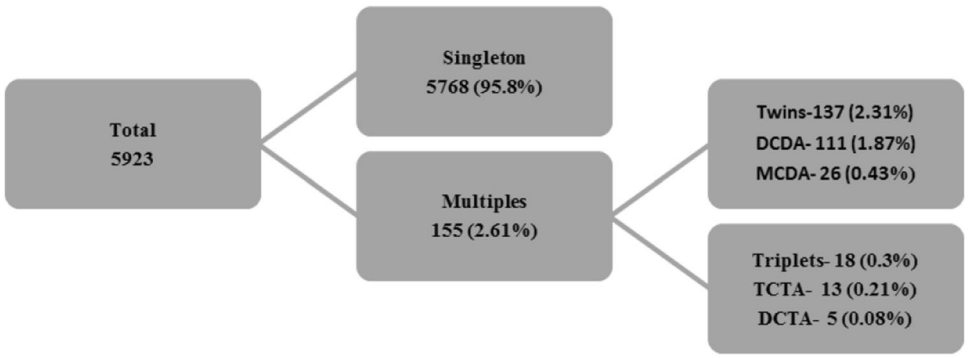

Fig. 1 Number of fetuses and chorionicity if multiple pregnancies

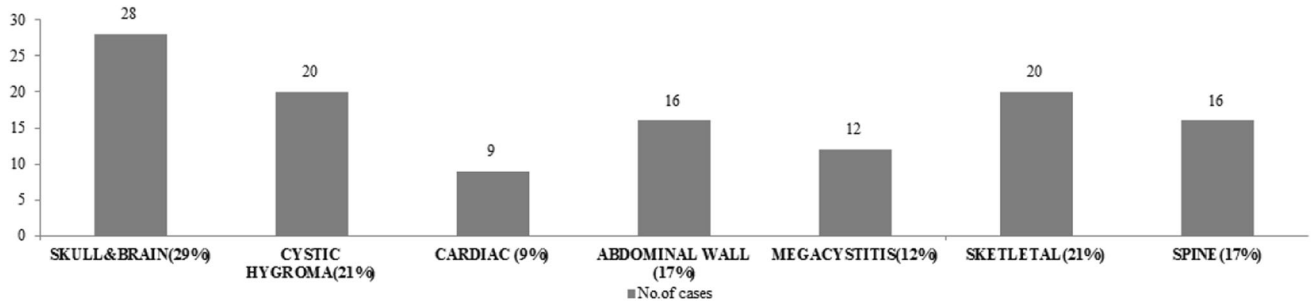

Fig. 2 Spectrum of structural abnormalities among $n = 94/5923$

Among twins, we had 3 cases concordant for increased NT (2-DCDA, 1 MCDA) and 8 cases discordant for increased NT (7-DCDA, 1-MCDA).

(b) Un-ossified nasal bone: Among 5923 women, there were 35 women who had fetuses with un-ossified nasal bone. Increased NT > 95th percentile along with un-ossified nasal bone was seen among 15 women and isolated un-ossified nasal bone was seen in 20 women.

(c) Additional markers: Ductus venosus (DV) reversal and Tricuspid regurgitation (TR): Ductus venosus and tricuspid flow Doppler was selectively done in cases of suspected chromosomal abnormalities by expert operators only. We found 6 cases of reversal of DV, of which 4 cases were associated with increased NT (1 case-IUFD, 1 case-Left ventricular outflow obstruction underwent termination, 2 cases with normal NT; one had a live birth and one underwent termination in view of deformed spine) and 8 cases of TR (4 cases were associated with increased NT and multisystem abnormalities underwent termination; 4 cases associated with normal NT-1 was MCDA twins with TRAP sequence which had IUFD, 1 case with intra-cardiac echogenic focus in left ventricle who had IUFD, 2 cases were lost to follow up). One case had fetal tachycardia. Based on these findings along with background risk of maternal age, using FMF/ASTRAIA database software risk calculation was made. Out of 5923 women, 85 (1.43%) women were found to be screen positive. After counselling, they were offered prenatal diagnostic procedures—amniocentesis or chorion villous sampling, 20 screen-positive women accepted and the rest declined to undergo the procedure. Eight women underwent amniocentesis and 12 women underwent chorionic villous sampling. Fifteen out of these 20 cases showed normal karyotype, confirmed trisomy 21 in two, trisomy 13 in one, Turner's syndrome (45X0) in one and translocation between chromosome 8 and 14 in one.

Distribution of screen positive women according to maternal age and gestational age has been shown in Table 2. The results of the study have been shown in Fig. 3.

Discussion

The mean maternal age and advanced maternal age, mean gestational age and CRL were similar to the study by Karadeniz et al. [3]. Previous studies have reported that

Table 2 Distribution of screen positive women as per gestational age and maternal age

Age/GA (yrs)	11 wks	12 wks	13 wks	NT > 95th percentile	Unossified NB	DV reversal	TR	Screen+	Invasive
< 20 s	9	58	21	1	1	0	0	2	0
20–29	387	2400	1065	159	24	4	5	48	9
30–39	227	1180	545	109	10	2	3	33	11
> 40	6	18	7	3	1	0	0	2	0
Total	629	3656	1638	272	36	6	8	85	20

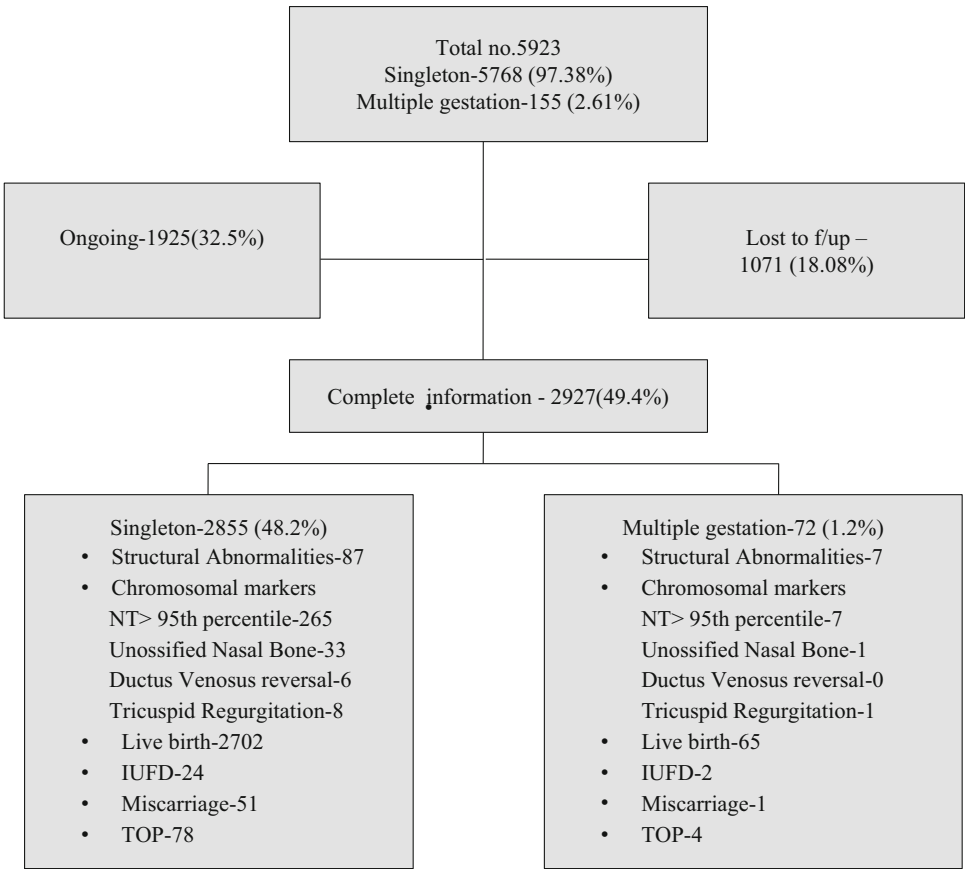

Fig. 3 Flowchart showing results of the study

visualization of fetal anatomy improves with gestational age. A complete anatomical survey is reportedly possible in 75% at 11 gestational weeks to 96% at 12 weeks and up to 98% at 13–14 weeks [4]. We found similar results in this study achieving a complete anatomic survey in the first trimester in more than 96.09% of the scans performed.

CRL is used to determine EDD which helps to avoid post-term births and unnecessary induction of labour. Cardiac activity is often evident when the embryo measures 2 mm or more but is not evident in around 5–10% of viable embryos measuring between 2 and 4 mm [5]. The cut-off for missed miscarriage in our study was 7 mm.

According to Syngelaki et al. [6], the incidence of fetal structural anomaly was 0.5–2%. Their study showed 22% central nervous system anomalies, 22% gastrointestinal system and abdominal wall anomalies, 22% major urinary anomalies, 21% major skeletal anomalies. The incidence of a fetal structural anomaly in our study was 1.58% and the majority were CNS anomalies (29%) with anencephaly being the most common. Cystic hygroma and skeletal anomalies contributed to 21% of total anomalies. Majority of them were lethal and ended up with termination.

We found the incidence of structural abnormalities was higher among women with age < 35 years when compared to > 35 years (AMA) (OR 0.69, 95% CI 0.25–1.91, p value 0.48, z statistic 0.69). Increased NT (> 95th percentile) is seen more commonly among women < 35 years (257 women; 94.4%) rather than women > 35 years (15 women; 5.5%). This reiterates necessity for a universal screening programme for assessment of chromosomal markers at

11^{+0} and 13^{+6} weeks for all women irrespective of their age.

Majority of the studies have excluded aneuploidies. NT > 95th percentile is seen among 272 (4.59%) women which is almost similar to the study by Iliescu et al. [7] (5.26%). IUFD (2.14%, p value < 0.001), miscarriage (1.42%, p value < 0.2), termination of pregnancy (17.14%, p value < 0.001) and cardiac anomalies (37.5%, p value < 0.0001) were common among women with NT > 95th percentile.

There was a small but definite number of cases with reversal of Ductus Venosus and Tricuspid regurgitation among aneuploid fetuses. This justifies the inclusion of Doppler as additional markers. However, larger studies are required to prove this.

The risk of miscarriage and termination of pregnancy was significantly higher for women whose fetuses were identified with structural abnormalities. Prenatal diagnosis by karyotype can confirm chromosomal abnormalities and provide useful information to counsel the pregnant mother on the course of pregnancy. In spite of extensive counselling, incidence of termination of pregnancy based on increased nuchal translucency alone was very high (0.45 vs 18.1% in normal versus increased NT, p value < 0.001). Also, the uptake of prenatal invasive test in our population is low. There are several reasons for the high termination rate and low uptake of prenatal diagnostic tests in this population. Perhaps due to cultural, social factors associated with prenatal diagnosis and probably the cost of the tests.

The lost to follow-up rate was high and it is possible that the outcomes of pregnancy from those who dropped out may alter the results. However, the odd's ratios for miscarriages and termination were so high that we didn't expect a significant alteration of results, even if we obtained information from those who dropped out. The dropout rate is reasonable considering that the institute is a tertiary care centre that receives referrals from all parts of the state.

Strengths

First Trimester scan helps to determine:

- Fetal viability
- Determination of Gestational age
- No. of fetuses and chorionicity
- Screening for structural anomalies

Limitations

- This study did not include combined screening.
- First trimester anomaly screening cannot replace examinations at a later gestational age because of evolving structural anomalies.
- Follow up of screen positive cases is difficult due to various social and cultural factors.
- Standard reference for determining the accuracy for first trimester anomaly screening was detection of fetal structures at birth or later. However, post-mortem examination is often not possible following first trimester termination of pregnancy.
- This is a single centre study. Therefore in terms of validity, it is limited when compared to multi-centre studies.

Conclusions

First trimester (11^{+0} and 13^{+6} weeks) ultrasound scan has the potential to identify fetuses affected with structural anomalies especially for the diagnosis of lethal anomalies like anencephaly. It should be tailored to the type of anomaly amenable to detection at that particular gestational age. This scan should be made universal to all pregnant women as a routine standard of antenatal care in India. The study emphasizes the need for use of high-end ultrasound machines, proper training and adoption of standardized protocols and an on-going audit for quality control.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards." The Fernandez Hospital ethical committee reviewed and approved the protocol (Protocol Ref. No. 08_2016, at Fernandez Hospital, Hyderabad, India).

Informed Consent Informed consent was obtained from all individual participants included in the study.

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