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ORIGINAL ARTICLE

The 11-13^{+6} Weeks Scan: Where do We Stand? A 5-year Review at Fernandez Hospital

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ABSTRACT

Objective: To examine the clinical utility of 11-13^{+6} weeks scan for screening for chromosomal abnormalities and to assess the potential value of the same ultrasound examination in the early diagnosis of fetal structural anomalies.

Design: A prospective interventional study at Fetal Medicine Unit, Fernandez Hospital Pvt Ltd, a tertiary care perinatal center, Hyderabad, India, between September 2005 and March 2010.

Methods: All pregnant women < 13^{+6} weeks at booking are offered a routine obstetric scan between 11 and 13^{+6} weeks. All scans are done by obstetricians who are accredited by Fetal Medicine Foundation. All expectant mothers undergoing 11-13^{+6} weeks scan were included; all expectant mothers with antenatal booking after 14 weeks were excluded from the study.

Results: Between September 2005 and March 2010, a total of 11,012 scans were done between 11 and 13^{+6} weeks. Complete follow-up was available for 7,916 cases; 1,460 are ongoing pregnancies and 1,636 expectant mothers were lost to follow-up. The median maternal age in our population is 27 years and 340 (4.30%) mothers had advanced (> 35 years) maternal age. The median NT in our population is 1.58 mm. Increased nuchal translucency (NT > 95th percentile) was found in 362 (4.59%) scans. Miscarriages/abortions and termination of pregnancy were significantly higher in women whose fetus had an increased nuchal translucency thickness. Nuchal translucency thickness was significantly higher in women with advanced maternal age (ANOVA F = 0.002, Fishers exact test p-value for equality of medians = 0.04). Absent fetal nasal bones were present in 20 (5.57%) of women with increased NT compared to five (0.07%) women with normal NT. Among 7,916 women, 367 (4.64%) women were screen positive for chromosomal abnormalities. After counseling, only 40 screen-positive women accepted prenatal diagnostic procedures. Skull/brain abnormalities were found in 25 fetal images, abdominal abnormalities in 17, spinal abnormalities in eight, bladder abnormalities in five and cardiac abnormalities in five fetal images.

Conclusion: The 11-13^{+6} weeks ultrasound scan is an important diagnostic tool that should be offered to all pregnant women as a routine standard of antenatal care in the first trimester of pregnancy in India. However, as a screening tool, it mandates addition of cost-effective biochemical tests. To make the combined screening cost-effective, this study calls for making a national policy for Down's syndrome screening for India.

Keywords: Nuchal translucency, Trisomy, Aneuploidy, Karyotype, Structural malformations.

INTRODUCTION

Fetal abnormalities, premature birth and impaired placentation account for more than 90% of perinatal deaths.[1] Obstetric ultrasound is a non-invasive test which provides highly useful information about the fetus and helps in the management of pregnancy. The role of ultrasonography in obstetrics has emerged from confirmation of pregnancy, identification of number of fetuses, determination of their viability, through estimation of accurate gestational age and calculation of the expected date of delivery, and has even further evolved into early identification of chromosomal abnormalities and structural malformations.[2-6]

Conventionally, a targeted imaging for fetal anomaly (TIFFA) scan is performed in the second trimester (around 19-23 weeks) of pregnancy. Due to the advances in technology with the advent of high resolution equipment, it is now becoming possible for early identification of structural abnormalities. Also, measurement of fetal nuchal translucency thickness at the 11-13^{+6} weeks has been found to be an effective method of screening for chromosomal abnormalities.[5,6] Earlier identification of potentially fatal fetal structural abnormalities in the first trimester scan has several advantages. It helps to better inform the woman about the need for additional prenatal diagnostic tests, including molecular diagnosis, the progress and consequences of pregnancy, including early termination.

OBJECTIVE AND DESIGN

The study was designed to examine the clinical utility of 11-13^{+6} weeks scan for screening for chromosomal abnormalities and to assess the potential value of the same ultrasound examination in the early diagnosis of fetal structural anomalies in an unselected Indian population.

It is a prospective interventional study, done during September 2005 to March 2010, at the Fetal Medicine Unit,

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Fernandez Hospital Pvt Ltd (a tertiary perinatal care center, with around 4,500 deliveries a year) in Hyderabad, India.

METHODS

The study population comprised of pregnant women who were booked for antenatal care at Fernandez Hospital, India, from September 2005 to March 2010. All women booked for antenatal care receive standard obstetric care that includes history recording and a detailed clinical examination. Every pregnant woman undergoes a series of investigations in accordance with the hospital protocol. Each pregnant woman is scheduled for three ultrasound examinations (one in each trimester) as part of antenatal care at Fernandez Hospital.

All women booked into the clinic were offered 11-13^{+6} weeks scan. Details of the ultrasound examination were explained to each woman and a written informed consent was obtained prior to the ultrasound examination. All expectant mothers with antenatal booking after 14 weeks were excluded from the study. The study protocol was approved by the institutional review board of Fernandez Hospital, Hyderabad, India.

The first-trimester examination included gestational age estimation by crown-rump length (CRL) measurement. The detailed fetal anatomic survey includes 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, urinary bladder, upper and lower limbs, including hands and feet.[7]

Screening for trisomy 21 and other chromosomal abnormalities is done by the measurement of nuchal translucency thickness and assessment of the nasal bone. Subsequently, ductus venosus flow, tricuspid flow and facial angle are added as additional markers (guidelines adapted from FMF, London).[8] Risk calculation was carried out using the FMF software. In each case, the maternal age-related background risk was assessed and, depending upon the markers, an adjusted risk was calculated. Women at increased risk of (≥ 1 in 300) carrying a fetus with trisomy 21 or 18 or 13, were offered counseling and an invasive diagnostic procedure.

Ultrasound examinations are performed with Voluson 730 Expert with curved array transabdominal transducer AB 2-7 MHz with multihertz and harmonic capability (GE Medical system, Kretz ultrasound). All ultrasound images are stored in digital imaging media (DICOM, SONOCARE) and are available for retrospective assessment and re-measurement of all fetal parameters as required. The majority of scans are transabdominal. Transvaginal scans are offered after appropriate counseling, if satisfactory views are not obtained with transabdominal scans. All ultrasound examinations are performed by trained obstetricians who are accredited and licensed by the Fetal Medicine Foundation (FMF), London.

Outcome measures: The primary outcome measures include the detection rate for trisomy 21/18 or 13 and all other chromosomal abnormalities, false-positive rate and uptake of interventions in screen-positive group. The secondary outcome measures include incidence, type of major fetal abnormalities and fetal outcome in pregnancies with increased nuchal translucency (95th percentile).

Women who underwent the first-trimester scan were followed up into the postpartum period, if the delivery occurred at Fernandez Hospital. As Fernandez Hospital is a tertiary care institute, a significant number of scans are referrals from other institutes and practitioners. For this study, we excluded women who were booked or referred for care beyond the first trimester of pregnancy and for whom a first trimester scan was not performed at our unit. Details pertaining to outcomes of pregnancy were ascertained through telephonic interviews, (where possible) if the delivery was not at Fernandez Hospital. Data of women for whom follow-up information on delivery and status of the baby was not available, was excluded from further analysis.

STATISTICAL ANALYSIS

We used STATA version 9.0 (College station, Tx, USA) 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 the detection rate for trisomy 21, trisomy 18/13 and all chromosomal abnormalities, false-positive rate 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) around the point estimates to determine associations of advanced maternal age and outcomes of pregnancy with increased nuchal translucency thickness. A receiver operator characteristic (ROC) curve and the area under the curve were estimated to compare different screening methodologies in this population.

RESULTS

We performed 11,012 scans during the period from September 2005 to March 2010. Antenatal follow-ups are ongoing for 1,460 (13.2%) women and are excluded from further analysis. An additional 1,636 (14.9%) of women were excluded because we could not ascertain information on the outcomes of pregnancy. We report the results of the 7,916 women for whom we had complete information after follow-up.

The mean age (SD) of women in the study was 27.1 (4.5) years (median 27 years, range 14 to 47 years). Around 340 (4.30%) mothers were of advanced maternal age (> 35 years). 7,903 (99.8%) women were of an Asian Indian subcontinent origin; three women were of Afro-American descent, seven women were of Caucasian origin and three women were from other Asian regions. 414 (5.2%) of these 7,916 women had multiple pregnancies. Gravidity ranged from 1 to 10 (median 1) and parity ranged from 0 to 6 (median 0) for these 7,916 women.

A transabdominal scan was completed in 7,605 (97.1%) women. 212 (2.95%) women underwent a transvaginal scan in

addition to a transabdominal scan. Increased (> 95th percentile) nuchal translucency (NT) thickness was found in 362 (4.59%) scans. Table 1 shows the distribution of crown-rump length (CRL), nuchal translucency (NT) thickness and biparietal diameter (BPD) in this population.

We assessed the risk of chromosomal abnormalities by measuring the nuchal translucency thickness and presence or absence of nasal bone. Out of 7,916 women, 367 women were screen positive. We compared the results of screening with three different strategies to detect cases at risk for trisomy 21, the use of increased NT alone, the use of increased NT and nasal bone abnormalities and the use of increased NT and/or nasal bone abnormalities (Table 2). Receiver operator characteristic (ROC) curves confirmed a lack of difference in the use of increased NT or a combination of increased NT and/or nasal bone abnormalities as a screening strategy to identify fetuses at risk for trisomy 21 (Table 3). However, evidence shows that as the number of markers increases, the chance of chromosomal abnormalities increases. Perhaps our sample size is too small to prove this.

In our series, the incidence of structural abnormalities is not high among women with advanced age, i.e. age > 35 years (OR: 1.75, 95% CI: 0.63, 4.89, p = 0.28) when compared with women aged 35 years or younger. Miscarriage/abortion, termination of pregnancy and neonatal death were more common among women with an abnormal first trimester scan (Table 4) compared to women with a normal first trimester scan.

Table 1: Distribution of CRL, NT and BPD based on 11-13+6 weeks scan of 7,916 women

	Mean (SD)	*Median*	*5th percentile*	*95th percentile*	*99th percentile*
CRL	63.7 (9.0)	63.6	49.3	78.9	82.8
NT	1.6 (0.5)	1.6	1.1	2.1	2.7
BPD	21.4 (3.5)	21.2	16.8	26.2	28.3

CRL: Crown-rump length, NT: Nuchal thickness, BPD: Biparietal diameter

Table 2: Comparing three different screening strategies for the detection of fetuses at risk for trisomy 21

Characteristics	*Increased NT alone (n = 362)*	*Increased NT and nasal bone abnormality (n = 25)*	*Increased NT and/or nasal bone abnormality (n = 367)*
Sensitivity	81.8%	54.5%	81.8%
Specificity	95.5%	99.8%	95.5%
Positive likelihood ratio	18.3	227	18.1
Negative likelihood ratio	0.2	0.5	0.2
Positive predictive value	2.5%	24%	2.5%
Negative predictive value	100%	99.9%	100%
False-positive rate	4%	0.2%	5%
False-negative rate	18%	45%	18%

Table 3: Area under the receiver-operator characteristic curves for identifying fetuses at risk for trisomy 21

Area under the curve					
				Asymptotic 95% CI	
Test result variable(s)	*Area*	*Std. error[a]*	*Asymptotic significance[b]*	*Lower bound*	*Upper bound*
Advanced age	0.570	0.095	0.425	0.383	0.756
Increased NT	0.887	0.068	0.000	0.753	1.020
Increased NT and nasal bone abnormalities	0.772	0.095	0.002	0.585	0.958
Increased NT and/or nasal bone abnormalities	0.886	0.068	0.000	0.753	1.020

[a]Under the nonparametric assumption; [b]Null hypothesis: True area = 0.5

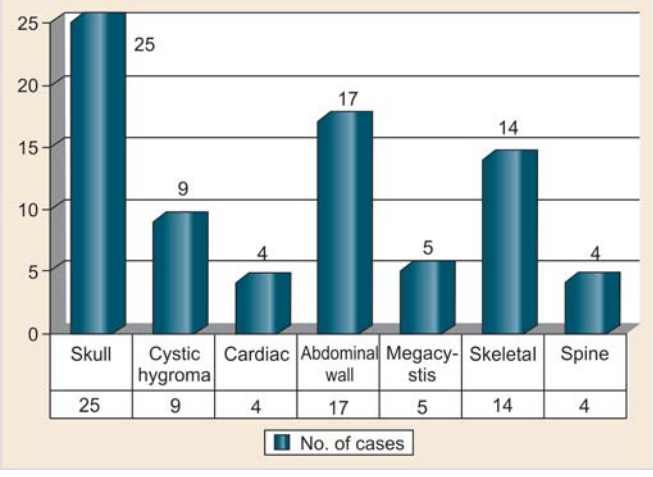
Table 4: Comparing outcomes of pregnancy among those with and without structural abnormalities in first trimester scan

Outcomes	*Normal 11-13+6 weeks scan (n = 7,861) N(%)*	*Abnormal 11-13+6 weeks scan (n = 55) N(%)*	*Odds ratio (95% CI)*	*p-value*
Live birth	7,526 (95.7)	2 (3.6)	1.00	—
Miscarriage/abortions	148 (1.9)	4 (7.3)	101.7 (18.5, 559.5)	< 0.001
Intrauterine death	76 (1.0)	0 (0.0)	—	—
Neonatal death	58 (0.7)	3 (5.5)	194.6 (31.9,1186.7)	< 0.001
Termination	53 (0.7)	46 (83.6)	3266 (773.0,13780)	< 0.001

Nuchal thickness was significantly higher in women with advanced maternal age compared to women aged 35 years or less (mean (SD) 1.7 (0.9) and 1.6 (0.5) respectively, ANOVA F = 9.5, p = 0.002, Fishers exact test p-value for equality of medians = 0.04). Table 5 shows the outcomes of pregnancy in women with an increased nuchal translucency thickness. Miscarriages/abortions and termination of pregnancy were significantly higher in women whose fetus had an increased nuchal translucency thickness, compared with women whose fetus had a normal (< 95th percentile) nuchal translucency.

Among the total of 7,916 women, 367 (4.64%) women were screen-positive for chromosomal abnormalities. After counseling, they were offered prenatal diagnostic procedure amniocentesis or chorion villous sampling, 40 screen-positive women accepted and the rest declined to undergo the procedure. 23 of these 40 cases showed normal karyotype, confirmed trisomy 21 in nine, trisomy 18 in two, Turners syndrome in two, unbalanced translocation in two, trisomy 13 in one fetus and 46 22 ps + in one fetus (a satellite body in the short arm of chromosome 22). The overall prevalence of trisomy 21 in this population based on clinical and prenatal diagnosis was 0.14% (n = 11, 95% CI: 0.07%, 0.25%). Nine (81.8%) of the 11 fetuses with trisomy 21 had an increased NT (> 95th percentile). The NT of the two trisomy 21 without increased NT was 1.97 and 1.98 respectively (cut-off criteria based on the 95th percentile = 2.1).

Structural abnormalities were detected in the fetuses of 55 (0.69%, 95% CI: 0.51, 0.88) pregnant women on the first trimester scan. Graph 1 shows the spectrum of the malformations detected in the first trimester scan. In our series, central nervous system anomalies are the commonest malformations followed by anterior abdominal wall defects. We could not pick-up structural abnormalities in nine fetuses (abnormalities that could have been picked up by ultrasound). These included four fetuses with polydactyly, one fetus spina bifida, three fetuses with lethal cardiac conditions and one fetus with phocomelia. The detection rate of structural abnormalities in this study is thus 85.94% (95% CI: 77.18%, 94.69%).



Graph 1: Spectrum of malformations (n = 55/7,916)

DISCUSSION

Previous studies have reported that visualization of fetal anatomy improves with increasing gestational age.[9-11] A complete anatomical survey is reportedly possible in 75% at 11 gestational weeks to 96% at 12 weeks and up to 98% at 13 to 14 weeks.[9] We found similar results in this study achieving a complete anatomic survey in the first trimester in more than 97.5% of the scans performed. It is possible that the rate of fetuses with structural abnormalities is an underestimate as we could not ascertain the cause of death or termination for all pregnancies (especially if the neonatal death or termination occurred elsewhere). Previous studies have reported detection rates using the first trimester scan ranging from 61 to 86% that are comparable with our detection rate.[12-18] The risk for miscarriages/abortions, termination of pregnancy and neonatal death 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 counseling, incidence of termination of pregnancy based on increased nuchal translucency alone was very high (0.8% *vs* 10.2% 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. The major reason is the cost of tests. Combined ultrasound and biochemistry (INR 4,500) and invasive testing (INR 15,000) are significantly more expensive than ultrasound examination (INR 700). An additional limitation is that facilities for prenatal diagnosis are limited to a few institutions in a few cities.

The loss to follow-up rate is high and it is possible that information on outcomes of pregnancy from those who dropped out may alter the results. However, the odds ratios for miscarriages, neonatal deaths and termination are so high that

Table 5: Outcomes of pregnancy and nuchal thickness

Outcomes	*Normal NT (n = 7554) N (%)*	*NT > 95th percentile (n = 362) N (%)*	*Odds ratio (95% CI)*	*p-value*
Live birth	7,223 (95.6)	305 (84.2)	1.00	
Miscarriage/abortions	138 (1.8)	14 (3.9)	2.4 (1.4, 4.2)	0.002
Intrauterine death	73 (1.0)	3 (0.8)	1.0 (0.3, 3.1)	0.96
Neonatal death	58 (0.8)	3 (0.8)	1.2 (0.4, 3.9)	0.73
Termination	62 (0.8)	37 (10.2%)	14.1 (9.3, 21.6)	< 0.001

we do not expect a significant alteration of the results, even if we obtained information from those who dropped out. The drop out rate is reasonable considering that the institute is a tertiary level care institute that receives referrals from all parts of the state. A significant population is referred only for ultrasound examinations and sent back to the primary obstetrician or are referred for delivery. We have included only the scans done at our institute, as the scans are performed by trained obstetricians licensed annually by the Fetal Medicine Foundation, UK.

Our results suggest that a first trimester scan for fetal abnormalities by trained personnel, adhering to a standardized protocol, is useful and can provide additional information to the mother on the progress, consequences and need for further prenatal testing. A complete fetal anatomical survey in the first trimester can help to identify fetuses with structural abnormalities earlier in the course of pregnancy and can help to offer choices pertaining to counseling, prenatal tests for karyotype and possible termination of pregnancy at an earlier stage, in case of need. This is important for a country like India, where karyotype and biochemical tests are costly and not easily available. Further research is needed to determine the detection rates in this population, using sequential first and second trimester scans and biochemical tests and karyotype in various combinations.

LIMITATIONS

The 11-13^{+6} weeks scan alone was used as a screening method for Down's syndrome. Universal combined screening (scan and biochemistry) could not be offered due to lack of facilities and cost factor (INR 4,500 *vs* INR 700). Majority of the patients declined the invasive tests because of financial constraints (cost of procedure INR 10,000). Ours is a single center study. Hence in terms of validity, it is limited when compared with a multi-center study.

CONCLUSION

To conclude, 11-13^{+6} weeks ultrasound scan constitutes an important diagnostic tool in the first trimester of pregnancy. It should be offered to all pregnant women as a routine standard of antenatal care in India, expanding its scope from dating of gestation, fetal viability and screening of fetuses at risk for trisomy to include screening for structural abnormalities. This will need the use of higher end ultrasound machines, proper training and the adoption of standardized protocols and an ongoing audit for quality control. However, as a screening tool, it mandates addition of cost-effective biochemical tests. To make the combined screening cost-effective, this study calls for making a national policy for Down's syndrome screening for India.

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