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ROLE OF NUCHAL TRANSLUCENCY (NT) AT 11-14 WEEKS OF GESTATION AS A SCREENING TOOL TO IDENTIFY FETAL ABNORMALITIES

Medical Science

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ABSTRACT

The present study was conducted to establish the role of Nuchal translucency as a screening tool for identifying patients at risk for chromosomal and congenital abnormalities and to ascertain its value in planning further management in cases of abnormal Nuchal Translucency. 200 pregnant women, between 11-14 weeks of gestation as per the inclusion and exclusion criteria were included in this study. A detailed history and clinical examination was followed by counselling and ultrasonography by trained sonologists. If NT > 95th centile for that gestational age, the women were considered to be at high risk (screen positive) of having aneuploidy/cardiac defects/other structural defects and hence these women were offered karyotyping.If karyotyping was normal, then follow up was done with an anomaly scan at 20-22 weeks of gestation.If lethal anomaly detected at anomaly scan, pregnancy was terminated. If no congenital anomalies picked up, fetal echocardiography done to detect any congenital cardiac defect.If no lethal cardiac defect detected, pregnancy was continued and followed by term scan. After delivery, the baby was evaluated by the pediatrician for anomalies. Ultrasound findings along with nuchal translusency and the pregnancy outcome were noted.

RESULTS In this study, majority of the women were between 21-25 years of age, equal distribution between primigravida and multigravida, majority of the women were screened between 12-14 weeks of gestation. (37% between 12.1-13 weeks, 33% between 13.1–13.6 weeks), 22% of pregnant women had significant risk factors in the past obstetric history (e.g.; previous history of fetal anomalies, previous history of Down's syndrome, previous history of unexplained fetal loss).96.5% of pregnant women had normal nuchal translucency (i.e., NT<95th centile), 7 patients(3.5%) with increased nuchal translucency (NT>95th centile) had true positive results. However, 4 patients were found to have false negative results. Overall, our study showed 100% specificity with 10% fetus showing true positive results and 60% sensitivity with 4 fetus having false negative results. Positive predictive value was 100% and false positive rate was 0%.

Conclusion : fetal abnormalities are significantly related to increased NT.

KEYWORDS

Nuchal Translusency, Aneuploidies

INTRODUCTION

Chromosomal abnormalities are important causes of perinatal death and childhood handicap.[1] The incidence of significant chromosomal abnormalities and birth defects is 3% out of which 66% constitutes Down's syndrome (Trisomy 21).[2]

Down's syndrome is the cause of 25% of severe mental retardation in children and throughout the world the frequency is about 0.13% of births. In India, the incidence is 1 in 600-700. It is important to screen for Down syndrome because the fetus usually survives with mental and physical disabilities causing mental trauma to the family and society. Hence, prenatal screening becomes important in order to reduce the live birth of Down's babies.[3]

Prenatal screening for Down syndrome and other aneuploidies has extended substantially over the past 20 years. Initially, only women of advanced maternal age (≥35 years old) or those with a previously affected pregnancy were offered the option of invasive prenatal diagnosis using amniocentesis/Chorion Villus Sampling (CVS)/ cordocentesis. Subsequently, prenatal diagnosis of aneuploidy became possible for those in the general obstetric population identified at increased risk for Down syndrome by second trimester multiple marker serum screening or abnormal second-trimester sonographic markers, or soft markers, for Down Syndrome.[4] This combination approach yields sensitivities for Down syndrome of 67% to 76% for a false positive rate of 5%.[5]

This common method of screening has several limitations. The earliest it can reliably be performed is 15 weeks of gestation limiting the choice of definitive diagnosis of aneuploidy to amniocentesis and pushing prenatal diagnosis into the latter second trimester.

Furthermore, over 25% of Down syndrome cases are not detected with this screening approach and the 5% false positive rate ensures that as many as 60 amniocentesis procedures need to be performed for every single case of Down syndrome detected. Given the pregnancy loss rate of 1 in 200 associated with amniocentesis, about 1 normal fetus is lost for every 3 fetus with Down syndrome detected.[6]

Clearly, the current approach of second trimester screening is not ideal and the search is on for earlier markers. A great deal of interest has been directed towards shifting prenatal screening for Down Syndrome and other aneuploidies to the first trimester between 11-14 weeks of gestation using the sonographic measurement of the fetal Nuchal Translucency (NT) alone and or in combination with other sonographic and serum markers (PAPP-A + β-HCG).[7] Chromosomal abnormalities may be present in 45% - 70% of cases between 11-14 weeks of gestation. It has been known that 50% of first trimester miscarriages are due to chromosomal abnormalities.[8]

Sonographic screening of aneuploidy became a reality in 1985 when Beryl Benacerraf demonstrated thickened nuchal fold in a Down's syndrome fetus.[9]

It was Dr. Langdon Down (it is after his name that Down's syndrome has been named) 100 years back, had reported that skin of affected fetus at the back of the neck was too large and swollen. This excess skin thickness can be easily studied by ultrasound as Nuchal Translucency (at 11-14 weeks of gestation).[10]

Fetal Nuchal Translucency (NT) thickness at 11-14 weeks scan has been combined with maternal age to provide an effective method of screening for Trisomy 21; for an invasive testing rate of 5%, about 75% of trisomy pregnancies can be identified.

In addition, increased nuchal translucency, identifies a high proportion of other chromosomal defects, major cardiac defects, skeletal defects and a wide range of genetic syndromes.[11]

METHODOLOGY

AIM

To study the role of fetal Nuchal translucency (NT) in an unselected population of pregnant women with viable singleton pregnancies between 11-14 weeks of gestation.

OBJECTIVES

- To establish the role of Nuchal translucency as a screening tool for identifying patients at risk for chromosomal and congenital abnormalities.
- To ascertain its value in planning for further management in cases of abnormal Nuchal Translucency.

Design
This study was conducted at Mahatma Gandhi missions Institute of health sciences and Research Centre, which is a teaching institution.

This prospective study has been conducted on 200 pregnant women, between 11-14 weeks of gestation with singleton pregnancies with reliable date of birth and reliable LMP details attending antenatal clinic at Mahatma Gandhi Missions Hospital, during a period of two and half years from 2013-2015.

METHOD
The patient's detailed history was taken and any risk factors of having fetal abnormality noted. A thorough clinical examination was made at booking, blood pressure, pulse rate, presence of pallor/edema/Icterus noted. A detailed systemic examination and obstetric examination was made. All preliminary investigations as outlined in the proforma carried out.

All 200 pregnant women between 11-14 weeks of gestation were offered counselling before the screening. In the counselling the patients were made aware of the uses of ultrasound at 11-14 weeks of gestation (such as to date the pregnancy accurately, to diagnose multiple pregnancy, to diagnose the viability of the fetus, to assess the chance of Down's syndrome and other chromosomal abnormalities/ fetal abnormalities by measuring fetal nuchal translucencyThe women were counselled about the interpretation of the results of the screening procedure and the possibility of an invasive procedure for fetal tissue sampling for karyotyping such as Chorion Villus sampling or amniocentesis if the patient turns out to be at high risk for Downs syndrome or other fetal abnormalities.

The women were counselled about the risks of pregnancy loss associated with the invasive procedures.

After counselling, pregnant women were offered ultrasonography. The scans were carried out by the trained sonologists who have been certified from fetal medicine foundation for measuring fetal nuchal translucency.

During the 11-14 weeks scan, the fetal CRL, Nuchal translucency, any structural abnormalities in the fetus, uterine anomaly, adnexa, cervix and the internal os were noted.

After the scan, the estimated chance for having Down's syndrome or other fetal abnormalities was discussed with the pregnant woman and her family. If the woman was at high risk, she was offered an invasive test to determine the karyotype of the fetus by either Chorion Villus Sampling /Amniocentesis/Cordocentesis.

Our institution is registered under PNDT Act and will follow the rules and regulations according to the act.

INCLUSION CRITERIA
- Study of 200 pregnant women with reliable LMP details.
- Singleton viable intrauterine pregnancy.

EXCLUSION CRITERIA
- Pregnant women with unreliable LMP details.
- Multiple pregnancies.

Results are documented as follows:
If NT > 95th centile for that gestational age, the women were considered to be at high risk (screen positive) of having Down's syndrome/other chromosomal abnormalities/cardiac defects/other structural defects

Interpretation and action
These women were subjected to invasive procedures such as CVS/amniocentesis/cordocentesis in order to determine the karyotype of the fetus.

If karyotyping normal, then follow up was done with an anomaly scan at 20-22 weeks of gestation.

If lethal anomaly detected at anomaly scan, pregnancy was terminated. If no congenital anomalies picked up, fetal echocardiography done to detect any congenital cardiac defect.

If no lethal cardiac defect detected, pregnancy was continued followed by term scan. After delivery, the baby was evaluated by the pediatrician for anomalies.

Endpoints to assess outcome of pregnancy:
- Pregnancy loss - Spontaneous abortions
- Fetal aneuploidy (Trisomy 21, 13, 18 Turner's syndrome)
- Cardiac Defects/Pulmonary defects/Abdominal wall defects/ Skeletal defects/Genetic Syndrome
- Perinatal morbidity
- Perinatal mortality

Interpretation and action
Increased NT - Karyotyping (by CVS/Amniocentesis/Cordocentesis)

• Karyotyping Abnormal	- Termination of pregnancy
• Karyotyping Normal	- Continue pregnancy do anomaly scan
• Lethal anomalies detected	- Termination of pregnancy
• No lethal anomalies	- Fetal 2D Echo
• Fetal 2D Echo (N)	- Continue pregnancy
• Lethal Cardiac anomaly	- Termination of pregnancy
• Following delivery	- Evaluation by Paediatrician

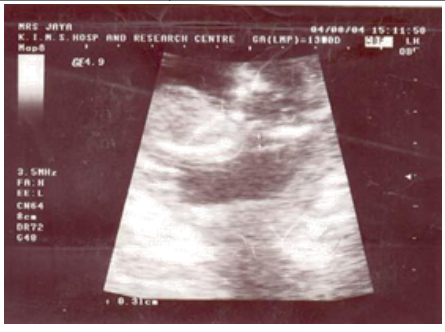


Fig 13: Normal NT (NT < 95th centile) - 1.2 mm at 12+6 Weeks of gestation

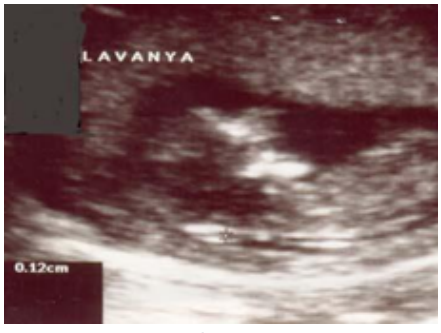


Fig. 14: Abnormal NT (NT > 95th centile) – 3.1 mm at 11+3 weeks of gestation

Statistical Methods: Fisher exact test have been used to test the significance of fetal abnormalities in relation to the NT and Diagnostic statistics were used to find the diagnostic value of NT in relation to fetal abnormalities

Fisher Exact Test

Class 1	Class 2		Total
Sample1	a	B	a+b
Sample2	c	D	c+d
Total	a+c	b+d	n
Fisher Exact Test statistic= $\sum p$ =	$\frac{(a+b)!(c+d)!(a+c)!(b+d)!}{}$		1
$n!$			$\sum a!b!c!d!$

Diagnostic Statistics

Test	Criteria		
	+	-	Total
+	A	B	A+B
-	C	D	C+D
Total	A+C	B+D	N

Sensitivity= A/(A+C)
Specificity= D/(B+D)
PPV =A/(A+B)

Statistical software: The Statistical software namely SPSS 11.0 and Systat 8.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

OBSERVATION AND RESULTS

A Prospective clinical study consisting of 200 pregnant women is undertaken to study the fetal nuchal translucency at 11 to 14 weeks of gestation as a screening tool to identify fetal abnormalities.

TABLE 1 Age distribution

Age in years	Number	Percent
≤ 20	40	20.0
21-25	84	42.0
26-30	64	32.0
31-35	8	4.0
>35	4	2.0
Total	200	100.0

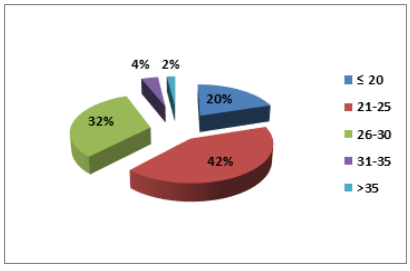


Fig. 15 .Age distribution

Majority of the pregnant women were between 21-25 years (42%), 32% were between 26-30 years, 20% were ≤ 20 years, 4% between 31-35 years and 2% more than 35 years.

TABLE 2 Gravida distribution

Gravida	Number	Percent
Primi gravida	100	50
Multi gravida	100	50

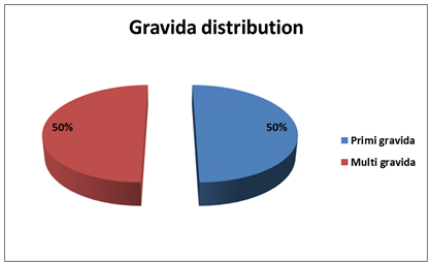


Fig. 16. Gravida distribution

There was equal distribution between primigravida and multigravida (50%).

Table 3 Gestational age

Gestational age	Number	Percent
11.0-12.0	60	30.0
12.1-13.0	74	37.0
13.1-13.6	66	33.0

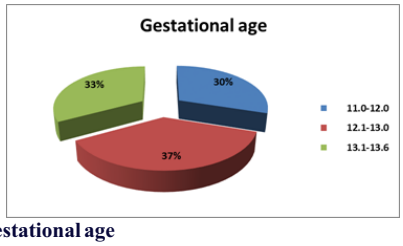


Fig. 17. Gestational age

Maximum number of scans were done between gestational age of 12.1-13.0 weeks (37%), 33% between 13.1-13.6 weeks and 30% at 11.0-12.0 weeks.

TABLE 4 Previous obstetric history

Previous obstetric history	Number	Percent
Nil	156	78.0
Previous history of unexplained first trimester pregnancy loss	20	10.0
Previous history of unexplained term intra uterine death	5	2.5
Previous history of Down's syndrome	1	0.5
Previous history of baby having anomalies	3	1.5
Previous history of still birth	1	0.5
Previous history of baby having epilepsy	1	0.5
Previous history of molar pregnancy	1	0.5
Previous history of neonatal death	2	1.0
Previous history of preterm delivery	10	5.0

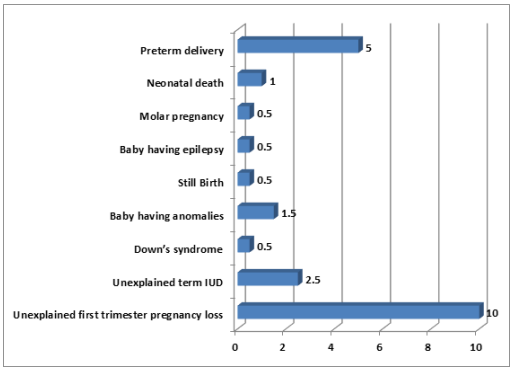


Fig. 18. Previous Obstetric History

78% of patients had no significant past obstetric history, 10% had history of unexplained loss of pregnancy at first trimester, and 2.5% patients had unexplained term intra uterine demise.

One patient (0.5%) had history of previous baby having Down's syndrome, 1.5% had previous babies having anomalies, 5% patients had history of preterm delivery, 1% had history of neonatal death, 0.5% had history of baby having epilepsy and 0.5% had history of molar pregnancy.

Table 5 Maternal Risk factors in the present pregnancy identified at the time of NT scan

Risk factors in the present pregnancy	Number	Percent
Nil	173	86.5
Overt diabetic	2	1.0
Previous LSCS	20	10.0
Elderly primi	5	2.5
	200	100.0

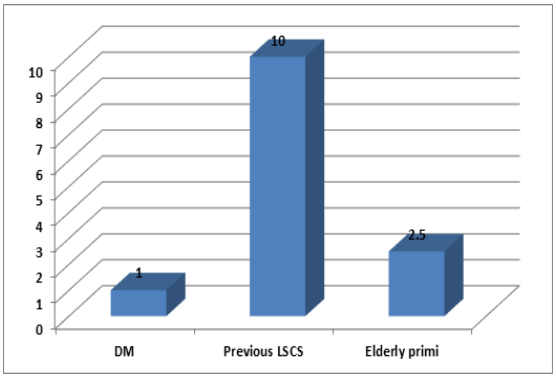


Fig. 19. Maternal risk factors in present pregnancy

10% patients had history of previous LSCS, 2.5% patients were elderly primigravida and 1% patient had diabetes mellitus.

Table 6 Risk factors in the present pregnancy developed after 20 weeks

Risk factors developed after 20 weeks	Number	Percent
Nil	126	63.0
GDM	2	1.0
Gestational HTN	20	10.0
Postdated pregnancy	20	10.0
Oligo hydroamnios	14	7.0
Breech presentation	4	2.0
PROM	12	6.0
PPROM	2	1.0
	200	100.0

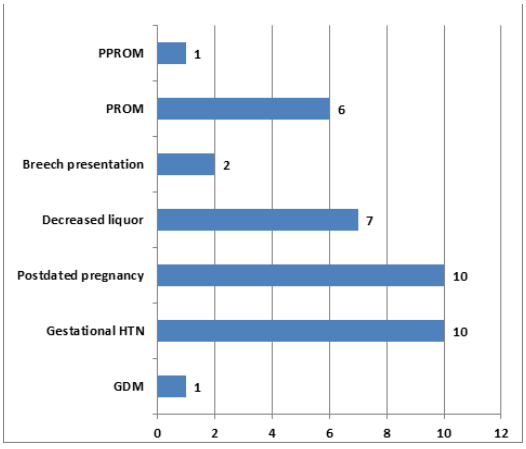


Fig. 20. Risk factors developed in present pregnancy after 20 weeks

After 20 weeks of gestation, 10% developed Gestational hypertension, and 1% had Gestational diabetes mellitus.

10% had postdated pregnancy,7% had oligo hydroamnios, and 2% had breech presentation.

6% patients had PROM and 1% had PPROM.

Table 7 Nuchal translucency (NT)

Nuchal translucency	Number	Percent
<95th centile	193	96.5
>95th centile	7	3.5

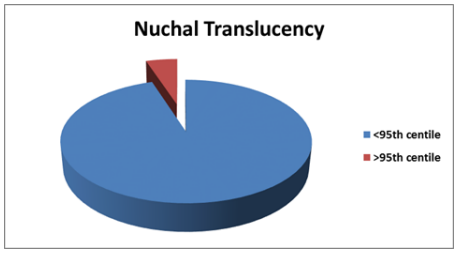


Fig. 21. Nuchal translucency

7 patients (3.5%) had nuchal translucency >95thcentile.

Table 8 Nuchal translucency (NT) outcome

NT (centile)	Spontaneous abortion	MTP	Delivery		Total
			Vaginal	C-section	
<95th centile	03	03	118	69	193
>95th centile	0	03	01	03	07

Out of 193 patients with NT <95th centile, 3 had spontaneous abortion. Three of them were found to have congenital abnormalities in the anomaly scan at 20 weeks. 118 patients had vaginal delivery and 69 patients underwent C-section.

One of the patients had failed to follow up after her initial 1st trimester scan, delivered a baby with ambiguous genitalia.

Hence, out of 193 patients with NT <95th centile, 4 had false negatives, that is, were found to have fetal abnormalities.

7 patients had NT >95th centile and 3 of them underwent MTP. Three delivered by C-section and one had vaginal delivery.

Table 9 Total Outcome

Nuchal translucency	Number	Delivery		Abortion (spontaneous)	MTP
		Vaginal	C-section		
True negative	189	117	69	03	0
False negative	04	01	0	0	03
True positive	07	01	03	0	03
False positive	0	0	0	0	0
Total	200	119	72	03	06

189 patients had true negative result out of which 3 had spontaneous abortion. 117 delivered vaginally and 69 by C-section.

4 patients were found to have false negative result out of which 3 underwent MTP after finding anomalies (dandy walker malformation, anencephaly and meningocoele) in the 2nd trimester anomaly scan. However, one of the patients had failed to follow up after the first trimester scan, delivered a baby with ambiguous genitalia.

7 patients had true positive result. 3 out of these underwent MTP (Turner's syndrome, Sirenomylia and Achondroplasia). Three fetus with cardiac defects and one with polydactyly were delivered.
There were no false positive results.

Table 9 Association of increased NT (> 95th centile) with fetal abnormalities

Fetal abnormalities	Increased NT (n=7)
Trisomy 21	-
Trisomy 18	-
Trisomy 13	-
Cardiac defects	3(1.5%)
Pulmonary defects	-
Abdominal wall defects	-
Skeletal defects	2(1.0%)
Genetic syndrome	1(0.5%)
Polydactyly	1(0.5%)

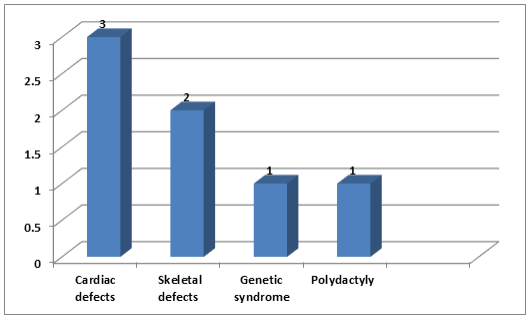


Fig. 23 Fetal abnormalities

One fetus was found to have Turner's syndrome on karyotyping.

6 fetus were found to have normal karyotyping. On further investigations of anomaly scan and fetal cardiography, 3 fetus were found to have cardiac defects (all 3 had VSDs), 2 fetus had skeletal defects (one had Sirenomyelia and the other had Achondroplasia), one patient was found to have polydactyly.

Table 10 Association of Normal NT (<95th centile) wiyh fetal abnormalities

Fetal abnormality	NT <95th centile with abnormality (False Negative) n=4
Trisomy 21	-
Trisomy 18	-
Trisomy 13	-

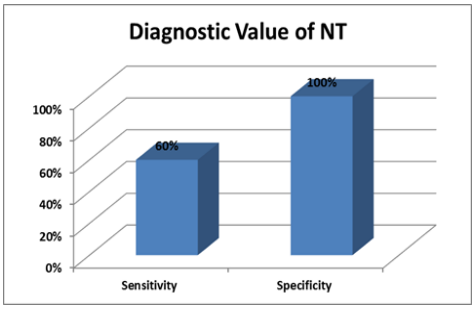
Cardiac defects	-
Pulmonary defects	-
Abdominal defect	-
Skeletal defect	03 (1.5%)
Genetic defect	01
Polydactyly	-

Out of 4, three fetus were found to have skeletal defects, that is, Dandy –walker malformation, meningocoele and anencephaly.

One was found to have genetic defect. (Ambiguous Genitalia)

Table 11 Diagnostic value of increased NT in relation to fetal abnormalities

Diagnostic value of NT	Number
True positive	07
False positive	0
True negative	189
False negative	4
Sensitivity	60%
Specificity	100%
PPV	100%
p value	<0.001



Overall, our study showed 100% specificity with 10% fetus showing true positive results and 60% sensitivity with 4 fetus having false negative results. Positive predictive value was 100% and false positive rate was 0%.

Fetal abnormalities are hence, significantly related to increased NT with p<0.001.

DISCUSSION

One of the major goals of antenatal screening of fetal nuchal translucency at 11-14 weeks of gestation is early identification of the anomalous fetus.

There are various methods of identifying the anomalous fetus such as by maternal serum markers, second trimester anomaly scan, invasive tests such as CVS/ amniocentesis / cordocentesis (for fetal karyotyping) but the ideal one is that which is a non-invasive, less expensive, gives reliable information at the earliest, so that the affected women can be offered an early termination option. All the above parameters of an ideal screening test is fulfilled by nuchal translucency.[12,13]

In this study, majority of the women were between 21-25 years of age, equal distribution between primigravida and multigravida, majority of the women were screened between 12-14 weeks of gestation. (37% between 12.1-13 weeks, 33% between 13.1–13.6 weeks), 22% of pregnant women had significant risk factors in the past obstetric history (e.g.; previous history of fetal anomalies, previous history of Down's syndrome, previous history of unexplained fetal loss).

96.5% of pregnant women had normal nuchal translucency (i.e., NT<95th centile), 3.5% of pregnant women had increased nuchal translucency (NT>95th centile).

All the 7 of pregnant women underwent invasive testing for fetal karyotyping to confirm chromosomal abnormalities. The karyotyping of 6 fetus were normal, pregnancy was continued and further evaluated by 2nd trimester anomaly scan and fetal 2D echocardiography.
One fetus karyotyping result was found to be 46+XO chromosomes (Turner's syndrome). MTP was done for this patient.

Among 7, one baby had polydactyly, two were found to have skeletal defects (one had sirenomelia, one had Achondroplasia), three fetus were found to have cardiac defects (all 3 had VSDs).

Pregnancies with skeletal defects were also terminated.

However, there were 3 patients with NT <95th percentile and yet their anomaly scans showed abnormalities in the fetus. On their 2nd trimester anomaly scan one fetus had Dandy- walker malformation, one had Anencephaly and another one had occipital meningocoele.

One patient who had failed to follow up after her first trimester, delivered a baby with ambiguous genitalia at term. She too had NT<95th percentileIncreased nuchal translucency thickness identifies a group at risk not just of chromosomal abnormalities but of all major cardiac defects, structural defects.

Our study shows that 42% of major abnormalities of the heart and great arteries are associated with increased nuchal translucency thickness at 11-14 weeks of gestation. This method of screening compared favorably with the reported sensitivity of 26% using the four-chamber view of the heart at 16-22 weeks of gestation. The clinical implication of our findings is that increased nuchal translucency thickness constitutes an indication for specialist fetal echocardiography.

Pregnancies identified by nuchal translucency scanning as being at high risk of cardiac defects need not wait until 20 weeks for specialist echocardiography.[22] Improvements in the resolution of ultrasound

Studies showing implementation of fetal nuchal translucency screening

	Year	No. of Patient	Gestation Age	NT Cut off	Sensitivity	FPR	Specificity	PPV
Kypros H Nichlaides et al[14]	1994	1273	10-13 weeks	≥ 3 mm	85%	5%	95.9%	35.5%
Taipele et al[15]	1997	10010	10-14 weeks	≥ 3 mm	62.3%	0.6%	99.4%	24%
Pandya et Al[16]	1995	1763	10-13 weeks	≥ 2.5 mm	75%	8%	92%	-
Hafner et al[17]	1998	4233	10-14 weeks	> 2.5 mm	65%	1.5%	98.5%	14.8%
Bewley et al[18]	1995	1127	8-13 weeks	≥ 3 mm	40%	6.1%	94%	
Schwarzler et al[19]	1999	4523	10-14 weeks	>2.5 mm	76%	4.7%	95.3%	8.2%
Economides et al[20]	1998	2281	11-14 weeks	≥ 99th Centile	81%	0.4%	99.6%	
Snijders et al[21]	1998	96127	10-14 Weeks	≥ 95th Centile	77%	4.4%	91%	8.3%
Present Study	2015	200	11-14 Weeks	≥ 95th Centile	60%	0%	100%	100%

machines have made it possible to undertake detailed cardiac scanning in the first trimester of pregnancy.

In our study, we found that most of the cardiac defects, skeletal defects, and genetic syndromes can be detected using NT scan by combining it with other detection tests and helps early management of the pregnancy.

Also, the 2nd trimester anomaly scan is a must for detecting fetal abnormalities as the sensitivity of the study was found to be only 60%.

Other uses of first trimester ultrasound examination include confirmation of fetal viability, accurate dating of pregnancy, early diagnosis of multiple pregnancies and the detection of major anomalies and the condition of the uterus, adnexa and the cervical length.

Measurement of fetal nuchal translucency at 11-14 weeks of gestation – traditionally used to identify fetuses at high risk of aneuploidy – also identifies the majority of pregnancies with major cardiac defects, structural defects. Thus, fetal NT is an early screening tool to identify fetal abnormalities

CONCLUSION

Measurement of Nuchal translucency is a noninvasive, reliable, early screening tool to determine the fetuses at risk for fetal aneuploidies/ structural defects/ genetic syndromes.

Nuchal translucency ultrasound has pushed prenatal screening for Down syndrome into the first trimester.

About 75% of Trisomy 21 can be detected, when maternal serum free βHCG and PAPP-A at 11-14 weeks of gestation were also taken into account. The detection rate of chromosomal defects increases up to 85-90%, when absent nasal bone is also included with the first trimester nuchal translucency.

Other benefits of 11-14 weeks scan include confirmation of fetal viability, accurate dating of pregnancy, early diagnosis of major fetal abnormalities, detection of multiple pregnancies, and the condition of uterus, adnexa and the cervical length.

Measurement of normal fetal nuchal translucency in the first trimester between 11-14 weeks of gestation reassures the woman that her fetus is not at risk of chromosomal abnormalities and thereby reduces the number of invasive procedures like CVS/ amniocentesis/ cordocentesis.

Measurement of increased fetal nuchal translucency provides women with affected fetuses an early termination option.

Ultrasound examination of the fetus is a subjective process that is highly dependent on operator skills and the quality of the sono¬graphic equipment which can be one of the reasons for false negative results. These limitations militate against the deploy¬ment of ultrasound as a screening tool in the manner in which maternal serum biochemistry has been used. For repro¬ducible and accurate measurements of NT, strict adherence to quality guidelines of the technique, training and supervision of the sonologist is of utmost importance.

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