THE VALUE OF ROUTINE NUCHAL TRANSLUCENCY IN DETECTION OF CHROMOSOMAL ANOMALIES IN A LOW RISK POPULATION

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ABSTRACT

BACKGROUND

Every pregnant woman desires a healthy child who is free of anomalies. In general population, the overall risk of having a child with a major malformation is 3% to 5%. The ability conferred by the increasing sophistication of ultrasonography and biochemical testing to screen for foetal abnormalities is of growing importance to obstetricians and their patients, as greater proportion of woman delay childbirth. The incidence of significant chromosomal abnormalities and birth defects is 3% out of which 66% constitutes Down's syndrome. 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 foetus 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.

Aim- 1) Detection rate by NT followed by CVS/amniocentesis in screen positive cases 2) The normograms of nuchal translucency in our study population. 3) Follow up with genetic sonogram after NT screening.

MATERIALS AND METHODS

Study Design- Prospective Study.

In this prospective clinical study, 575 pregnant women were recruited between 10-14 weeks of gestation with singleton pregnancy with known dates over a period of 1 year attending the antenatal clinic at the Department of Obstetrics and Gynaecology at St. Philomena's Hospital, Bangalore.

RESULTS

Screening by foetal nuchal translucency was performed for all the 575 pregnant women between 10^{+6}-13^{+6} weeks of gestation after categorizing into low risk and high-risk group. It also includes detailed survey for any anomalies. In this study, majority of women (49.2%) were between 21-25 years of age, 32.3% between 26-30 years, 13.2% between 31-35 years, 0.5% > 35 years, 4.7% ≤20 years. The sensitivity of nuchal translucency for foetal abnormalities on the whole is 66.6%, specificity is 100%, accuracy is 99.6%. The sensitivity of nuchal translucency for aneuploidy alone is 50%, specificity is 100%, accuracy 99.82%. Sensitivity of nuchal translucency in relation to genetic scan is for detecting foetal abnormalities is 20%, specificity is 100%. Sensitivity of foetal nuchal translucency more than 2.5 mm (95^{th} centile) for screening foetal aneuploidy/cardiac defects is 66.6%, specificity –100%. Positive predictive value – 99.8%. Sensitivity of foetal nuchal translucency more than 2.5 mm (95^{th} centile) for screening aneuploidy is 50%, specificity 96.9%, positive predictive value 99.2%. Foetal abnormalities are significantly related to increased NT with accuracy of 99.8% in high risk population.

CONCLUSION

Measurement of Nuchal translucency is a non-invasive, reliable, early screening tool to determine the foetus at risk for foetal aneuploidies/structural defects/genetic syndromes. For a false positive rate of 5% about 75% of Trisomy 21 can be detected, when maternal serum free β-HCG and PAPP-A at 10-14 weeks of gestation were also taken into account, the detection rate of chromosomal defects increases upto 85-90%, when absent nasal bone is also included with the first trimester nuchal translucency and serum biochemistry detection rate increases to more than 95%.

KEYWORDS

Nuchal Translucency, Down's Syndrome.

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BACKGROUND

Every pregnant woman desires a healthy child who is free of anamolies.[1,2] In general population, the overall risk of having a child with a major malformation is 3% to 5%. The ability conferred by the increasing sophistication of ultrasonography and biochemical testing to screen for foetal abnormalities is of growing importance to obstetricians and their patients as greater proportion of woman delay childbirth.[3,4,5] The shortened reproductive

window has increased the pressure on all for a successful outcome. Foetus with aneuploidy account for 6% to 11% of stillbirth and neonatal deaths whereas chromosomal defects that are compatible with life, but associated with significant morbidity, occur in 0.65% of newborn.[6,7,8]

Chromosomal abnormalities occur in 0.1% to 0.2% of live births. Chromosomal abnormalities are important causes of perinatal death and childhood handicap.[9,10,11] The incidence of significant chromosomal abnormalities and birth defects is 3% out of which 66% constitutes Down's syndrome (Trisomy 21).[12] 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.[13] It is important to screen for Down syndrome because the foetus usually survives with mental and physical disabilities causing mental trauma to the family and society[14]. Hence, prenatal screening becomes important in order to reduce the live birth of Down's babies.[15]

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.[16] This combination approach yields sensitivities for Down syndrome of 67% to 76% for a false positive rate of 5%.[17]

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. 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[30]. Given the pregnancy loss rate of 1 in 200 associated with amniocentesis, about 1 normal foetus is lost for every 3 foeti with Down syndrome detected.[18,19] 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 10-14 weeks of gestation using the sonographic measurement of the foetal Nuchal Translucency (NT) alone and or in combination with other sonographic and serum markers (PAPP-A + β-HCG).[20] Chromosomal abnormalities may be present in 45% - 70% of cases between 10-14 weeks of gestation. It has been known that 50% of first trimester miscarriages are due to chromosomal abnormalities. Sonographic screening of aneuploidy became a reality in 1985 when Beryl Benacerraf demonstrated thickened nuchal fold in a Down's syndrome foetus.[21] 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 foeti 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 10-14 weeks). Nuchal translucency along with maternal age was an effective method of screening for Trisomy 21; for an invasive testing rate of 5%, about 75% of trisomic 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.[22] About Down Syndrome, it is the most common serious autosomal chromosomal disorder which is usually caused by an extra copy of chromosome 21(Trisomy 21) causing mental retardation with an incidence of 1 in 700 live births. It is characterized clinically, by growth retardation, varying degree of mental retardation and a spectrum of somatic abnormalities including head and facial features. 95% of Trisomy 21 occurs due to non-disjunction during meiosis. Unbalanced Translocation contributes to 3-4% and Mosaicism 1-2%. Usually there won't be any family history of down syndrome. (95%).Aside from mental retardation, infants with Down syndrome are at high risk of having associated structural defects, including congenital heart disease, craniofacial abnormalities and gastrointestinal abnormalities.[23]

Screening is the process of surveying a population at risk, using a specific marker or markers to define screening cut-off levels, to identify the individuals in the population at higher risk for particular disorder. Screening for structural abnormality at midtrimester (Midtrimester Anomaly Scan) is an integral part of antenatal care world over and more than 90% detection has been achieved for all other aneuploidies other than Down syndrome. However Down syndrome escapes detection by MTAS because only 25-33% of foetuses have ultrasonographically recognisable structural abnormalities.[24]

Over the years ultrasound and biochemical markers have evolved and a higher detection rate has been achieved in the recent past by using sonographic markers in the first and second trimester scans combined with biochemical screening as proposed by Nicolaides K H et al which will help detect 90% of structural abnormalities and 90-98% detection of certain chromosomal abnormalities like Trisomy 18, followed by genetic sonogram in the midtrimester as an added tool to detect those foetuses which remain undetected during initial screening tests.[25]

The first trimester biochemical screening along with NT scan also achieves similar detection rate. Detection rate can be increased to 95% or false positive rates can be decreased to 2-3% versus 5% by combining first trimester biochemical markers like b-HCG, PAPPA, with nuchal translucency and other ultrasound markers. First trimester screening is followed by a genetic sonogram which is a part of MTAS done ideally between 18-20 weeks but can be stretched to 23 weeks. Even though we know that a

combination of NT with biochemical screening gives a very good detection rate and is the ideal way of screening; in practice ideal situations may not always exist. In a vast country like ours, accessibility to various types of tests may not be cost effective. Ultrasound which is versatile and is of extensive use in obstetrics and gynaecology as well as extensive multidisciplinary action it is more likely to be available in a country like ours. Hence, ultrasound as a primary modality for screening for Down syndrome is a definite option.

Aims and Objectives

I. Detection rate by NT followed by CVS/amniocentesis in screen positive cases.
II. The normograms of nuchal translucency in our study population.
III. Follow up with genetic sonogram after NT screening.

MATERIALS AND METHODS

Study Design

Prospective Study

In this prospective clinical study, 575 pregnant women were recruited between 10-14 weeks of gestation with singleton pregnancy with known dates over a period of 1 year attending the antenatal clinic at the Department of Obstetrics and Gynaecology at St. Philomena's Hospital, Bangalore.

Inclusion Criteria

Gestational age: For NT 10^{+6} weeks to 13^{+6} weeks. For Genetic Sonography from 18-20 weeks of gestation. In case of late bookers, the period can be extended upto 24 weeks. Known dates either by early scan or LMP.

Exclusion Criteria

The patients who do not attend the scan within the specified period of gestational weeks will be excluded from the study. Twin gestation was excluded from the study.

RESULTS

Study Design- An observational screening clinical study with 575 women presented in 1st trimester is undertaken to study the NT accuracy in screening for foetal aneuploidy and trisomy and cardiac abnormalities in low risk Indian population and to define the role of routine nuchal translucency screening followed by genetic sonogram in low-risk Indian population for detection of foetal abnormalities.

Age in Years	Number of Patients	%
18-20	27	4.7
21-25	283	49.2
26-30	186	32.3
31-35	76	13.2
36-40	2	0.3
>40	1	0.2
Total	**575**	**100.0**

Table 1. Distribution of Age in Years of Subject Studied

Mean ± SD: 25.63 ± 4.02

The majority of population were between 21-25 yrs. (49.2%), 26-30 yrs. (32.3%), 31-35 yrs. (13.2%), 18-20 yrs. (4.7%), 36-40 yrs. (0.3%) and >40 yrs. (0.2%).

Diagnostic value of Increased NT	
True Positive	2
False Positive	0
False Negative	1
True Negative	565
Sensitivity%	66.67
Specificity%	100.00
PPV %	100.00
NPV%	99.82
Accuracy%	99.83

Table 2. Diagnostic Value of Increased NT in Relation to Foetal Abnormalities (in both Low and High-Risk Population)

In this study, the sensitivity of increased NT in relation to foetal abnormalities is 66.67%, specificity is 100%, positive predictive value is 100%, negative predictive value is 99.82% and accuracy is 99.83% (irrespective of both high and low risk population).

Diagnostic value of Increased NT	
True Positive	1
False Positive	0
False Negative	1
True Negative	565
Sensitivity%	50.00
Specificity%	100.00
PPV %	100.00
NPV%	99.82
Accuracy%	99.82

Table 3. Diagnostic Value of Increased NT in Relation to foetal Aneuploidies (in both Low and High-Risk Population)

The sensitivity of increased NT in relation to foetal aneuploidy is 50%. Specificity is 100% and PPV, NPV is 100%.

Nuchal Translucency	Low Risk Patients	High Risk Patients	Total
Abnormal	-	2(1.9%)	2 (0.35%)
Normal	463 (100.0%)	102 (98.1%)	565 (99.6%)
Total	**463 (100.0%)**	**104 (100.0%)**	**567 (100.0%)**

Table 4. Nuchal Translucency in Low and High-Risk Patients

This study routine screening detected 8 failed intrauterine pregnancy. So Total number of patients in the above table is 567.

In this study, only the high-risk group had abnormal NT. Only 2 (0.35%) of total women had increased nuchal translucency. Rest 99.6% of women had normal nuchal translucency.

DISCUSSION

One of the major goals of antenatal screening of foetal nuchal translucency at 10-14 weeks of gestation is early identification of the anomalous foetus.

There are various methods for identifying the anomalous foetus such as maternal serum markers, second trimester anomaly scan which is followed by the invasive tests such as CVS/ amniocentesis / cordocentesis (for foetal karyotyping) for confirmation. The nuchal translucency is a non-invasive, less expensive, gives reliable information at the earliest, hence the affected women can be offered an early termination option. All the above parameters of an ideal screening test is fulfilled by nuchal translucency.

In this study, there was no interobserver variation as all NT screening was done by a radiologist.

In this study, the women were randomized into low risk and high risk depending on age>30 yrs., recurrent pregnancy loss >3, previous history of structurally, chromosomally abnormal babies, family history of abnormal babies.

In this study, majority of the women were between 21-25 years of age, distribution between primigravida and multigravida were 69.4% and 30.6%. The majority of the women were screened between 12-13 weeks of gestation (63%).7.3% of pregnant women had significant risk factors in the past obstetric history (e.g.; previous history of foetal anomalies, previous history of Down's syndrome, previous history of unexplained foetal loss). 7.8% of women had significant past history of (e.g.: epilepsy, diabetes, hypothyroid, hyperthyroid, TB, bronchial asthma). 0.5% of women had significant family history of (e.g.: Down syndrome, congenital deafness).

Out of 575 women screened, in 3, nuchal translucency was increased (>2.5 mm). Out of 3, all of them were under high risk group. One woman was reluctant for karyotyping and terminated due to social reasons. Rest 2 of them, underwent detailed survey for animalise and results were- 1st foetus was sonographically normal and the 2nd foetus had evidence of tricuspid regurgitation. On biochemical screening both the foetusus were found to have a high risk for aneuploidy. After getting the consent, proceeded for invasive testing for karyotyping to confirm chromosomal abnormalities. Out of the 2, 1st foetus karyotyping was abnormal revealed trisomy 21 hence termination was done. As the karyotyping of 2nd foetus was normal, the foetus had only mild tricuspid regurgitation pregnancy was continued, further evaluated by 2nd trimester anomaly scan and foetal 2D echocardiography. This scan revealed 1 soft marker- pyelectasis and tricuspid regurgitation and foetus had evidence of cardiac failure, hence followed at 22 weeks it had intrauterine foetal demise. In low risk patients, nuchal translucency was normal.

Increased nuchal translucency thickness identifies a group at risk not just of chromosomal abnormalities but of all major cardiac defects, structural defects in high risk patients. In this study, only one foetal aneuploidy was detected as the study population was 575 pregnant women and the incidence of Down's syndrome is 1 in 600-700. In this study, the normograms of NT - 95% centile is 1.9 mm and 0.5% centile is 0.74 mm. In this study, as CRL increases there were increase in nuchal translucency. This study routine screening detected 8 failed intrauterine pregnancy.

Other uses of first trimester ultrasound examination include confirmation of foetal 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. Thus, foetal NT is an early screening tool to identify foetal abnormalities in high risk patients.

Those foetuses which had normal nuchal translucency and were structurally normal foetus were followed with genetic ultrasound from 18-22 weeks. The outcome of the genetic scan was out of 567 women. 4 were detected to have abnormalities. All 4 of them were in low risk population. Out of 4, 2 foetuses were detected to have cardiac abnormalities-hypoplastic left heart syndrome, hence termination of pregnancy done. 2 foetuses detected to have 2 soft markers, hence karyotyping done that revealed Klinefelter syndrome and trisomy 21. Hence, termination of pregnancy done. These abnormalities were not detected by the nuchal translucency screening.

Hence, in a low resource setting like ours, routine nuchal translucency in a low risk population is of questionable value as both screened positive women were in a high-risk population. So, there is a concern to implement NT-based screening into general population i.e. those with no other identifiable risk factors for aneuploidy as it has low screen positive rate. To increase the detection rate and to decrease the false-positive rate it will be cost effective to do combined first trimester screening. Widespread implementation will be contingent on the availability of quality sonographic testing, which in a Indian setting is very poor. Performance of NT sonography at "expert centers" will not solve the problems of how to implement universal population screening. Similarly, the argument that NT may be used to reduce the need for invasive testing in high-risk population which will not be a relevant issue in general population screening. So, currently, estimating risk based on NT along with maternal age, i.e. in high risk women is early and reliable screening for aneuploidy.

But it is mandatory to do detailed genetic scanning for general population irrespective of risk as it has detected both cardiac abnormalities and aneuploidy which was not picked up by routine nuchal translucency. So, it is not cost effective to do routine nuchal translucency in a low risk population as a screening for aneuploidies. For low risk women if necessary combined screening with β-hCG, PAPP-A would be an effective option as it decreases the false-positive rate from 18% to 4.8% when NT is done alone. To formulate a definitive protocol, study should continue with larger number of patients.

Studies	Year	No. of Patients	Gestation Age	NT Cut-off	Sensitivity	FPR	Specificity	PPV
Kypros H. Nicolaides[26]	1994	1273	10-13 weeks	≥ 3 mm	85%	5%	95.9%	35.5%
Taipele et al[27]	1997	10010	10-14 weeks	≥ 3 mm	62.3%	0.6%	99.4%	24%
Pandya et al[28]	1995	1763	10-13 weeks	≥ 2.5 mm	75%	8%	92%	-
Hafner et al[29]	1998	4233	10-14 weeks	> 2.5 mm	65%	1.5%	98.5%	14.8%
Bewley et al[30]	1995	1127	8-13 weeks	>3 mm	40%	6.1%	94%	-
Schwarzler et al[31]	1999	4523	10-14 weeks	>2.5 mm	76%	4.7%	95.3%	8.2%
Economides et al[32]	1998	2281	11-14 weeks	≥ 99th centile	81%	0.4%	99.6%	-
Snijders et al[33]	1998	96127	10-14 weeks	>95th	77%	4.4%	91%	8.3%
Present Study	2010	575	10-14 weeks	>2.5 mm	50%	-	-	-
Studies Showing Implementation of Foetal Nuchal Translucency Screening								

CONCLUSION

- In this prospective clinical study, 575 pregnant women were recruited between 10-14 weeks of gestation with singleton pregnancy with known dates over a period of 1 year attending the antenatal clinic at the Department of Obstetrics and Gynaecology at St. Philomena's Hospital, Bangalore. Screening by foetal nuchal translucency was performed for all the 575 pregnant women between 10^{+6}-13^{+6} weeks of gestation after categorizing into low risk and high-risk group. It also includes detailed survey for any anomalies. Screen positive women i.e., NT >2.5 mm (95th centile) were offered invasive testing for the confirmation of foetal karyotyping by CVS after subjecting them for biochemical screening with b-HCG and PAPP-A. Those women with screen negative were followed with genetic scan. Screen positive i.e. >2 soft markers, any structural anomaly, any major marker were offered foetal karyotyping.
- The sensitivity of nuchal translucency for foetal abnormalities on the whole is 66.6%, specificity is 100%, accuracy is 99.6%.
- The sensitivity of nuchal translucency for aneuploidy alone is 50%, specificity is 100%, accuracy 99.82%.
- Those women who were screen negative were followed with genetic scan which detected 1 trisomy 21(0.18%),1 Klinefelter syndrome (0.18%), 2 cardiac defects namely hypoplastic heart syndrome (0.35%) in the low risk population which were not detected by NT scan. In high risk population, it detected 1 intrauterine death due to tricuspid regurgitation with failure (0.18%) whose NT was also increased.
- So sensitivity of nuchal translucency in relation to genetic scan is for detecting foetal abnormalities is 20%, specificity is 100%.
- Sensitivity of foetal nuchal translucency more than 2.5 mm (95th centile) for screening foetal aneuploidy/cardiac defects is 66.6%, specificity –100%. Positive predictive value – 99.8%.
- Sensitivity of foetal nuchal translucency more than 2.5 mm (95th centile) for screening aneuploidy is 50%, specificity 96.9%, positive predictive value 99.2%. Foetal abnormalities are significantly related to increased NT with accuracy of 99.8% in high risk population. Measurement of Nuchal translucency is a non-invasive, reliable, early screening tool to determine the foetus at risk for foetal aneuploidies/structural defects/genetic syndromes.
- Measurement of normal nuchal translucency reduces the number of invasive procedures like
- CVS/amniocentesis/cordocentesis.
- For first-trimester screening with nuchal translucency alone to be successful it must be implemented in a competent and coordinated manner.
- There is sufficient data to perform NT screening, but that screening should only be conducted where the centre has a staff with high level of ultrasound competence and experience required which has been certified by an external agency and subject to external quality control procedures. In India such a ideal condition doesn't exist.
- So routine nuchal translucency in a low risk population could be optional.
- For low risk population, issues raised in this critique should be discussed with all low risk women and they should each be given the option to have screening performed if they choose.
- Genetic sonogram between 18-22 weeks should be offered as a routine in both low and high-risk populations as detection rate for aneuploidies and structural anomalies is high.
- The majority of foetal structural and chromosomal abnormalities can be detected by sonographic screening at 11-14 weeks if done by a expert sonologist alone but the second trimester scan should not be abandoned.
- The numbers of pregnant women in this study were 575. To formulate definitive protocol, study should continue with larger number of patients.
- The cost-effective screening test for Down's syndrome in a low risk population is yet to be established.

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