Ultrasonographic Assessment Predicts Adverse Perinatal Outcomes

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Abstract
Background:
Objective: The aim of this work was to evaluate accuracy of the ultrasonographic assessment at the first or the second trimester of gestation as a predictor of adverse outcome in high risk pregnancies.
Patients and methods:A cross sectional study was conducted on 85 consecutive high risk pregnancies attending the Antenatal Clinic and Medical Genetics Center of Ain Shams University. Nuchal translucency thickness was obtained for all cases recruited during 1st trimester. Nuchal fold thickness was obtained for all cases recruited during 2nd trimester.We prospectively evaluated the outcome of each pregnancy.
Results: The mean age of participants, mean marriage duration, and gestational age were 32.5 ± 6 years, 7.1±3.3 years and 14.5±2.1weeks respectively.Increased NT thickness and NF thickness were present in5%, and 8.89% respectively.Down syndrome was found in 1.2% of current pregnancy outcome, while, cystic hygroma was found in 1.2%, cystic hygroma with hydrops was found in 1.2%, skeletal dysplasia and renal agenesis was found in1.2% missed abortion was found in 3.53%.There is a highly significant difference between normal outcome pregnancy and abnormal outcome pregnancy regarding mean NF thickness while no significant differences regarding NT thickness.
Conclusion: The findings of our prospective study demonstrate the feasibility of using NF thickness to screen for aneuploidies, adverse perinatal outcome in high risk   pregnancies.
Keywords: Nuchal fold thickness, Nuchal translucency, perinatal outcome, high risk pregnancy.

Introduction:
For decades, early pregnancy ultrasound was used only for the assessment of gestational age, detection of fetal viability, diagnosis of twins and the determination of their chorionicity. [1]

Recently, ultrasound screening in first trimester of pregnancy provides the most effective way of chromosomal abnormalities screening. The ultrasound assessment of nuchal translucency (NT) is used as non-invasive method for fetal abnormalities. [2]

The appearance of a thickened NT during 11-14 weeks of gestation is strongly associated with fetal structural defects, genetic syndromes, and poor perinatal outcomes. [3]

Increased NT can be caused by different mechanisms, such as disturbance in lymphatic development, altered extracellular matrix, and cardiac failure. [3]

A thickened nuchal fold is considered to be one of the most sensitive and specific of the minor markers for fetal Down syndrome. [4]

The 15-20 weeks of pregnancy is the optimum gestational age for nuchal fold measurement when the normal skin thickness tends to be relatively constant. [5]

Thickened nuchal fold ≥6 mm was found in 40% of fetuses with Down syndrome with a positive predictive value of 69% in the high-risk pregnancies. A thickened nuchal fold is associated with other euploid syndromes, such as Noonan syndrome, and heart defects. [5]

Subjects and Methods
- A cross sectional study was conducted on 85 consecutive high risk pregnancies attending the Antenatal Clinic and Medical Genetics Center of Ain Shams University.

• The high risk pregnancy included those with advanced maternal age (maternal age above 35 years).those with previous child with chromosomal abnormality, history of parental chromosomal abnormality or history of previous recurrent miscarriages.

• *Nuchal translucency thickness* was obtained for all cases recruited during 1st trimester. It was measured in the sagittal plane as the maximum thickness of the sonolucent zone between the fetal skin and the soft tissue overlying the cervical spine or the occipital bone. [6] Nuchal translucency thickness > 2.5 mm was considered abnormal. [7,8]

• *Nuchal fold thickness* was obtained for all cases recruited during 2nd trimester. It was measured from a transverse view of the fetal head that including the cerebellum, occipital bone and cavum septi pellucidi, slightly below the biparietal diameter. The calipers were placed from the outer edge of the occipital bone to the outer edge of the skin. [9] Nuchal fold thickness ≥6 mm was considered abnormal. [5]

The outcome of these pregnancies was assessed. The adverse pregnancy outcomes included termination of pregnancy for fetal malformations or intrauterine death, miscarriage and intrauterine growth restriction.

Ethical considerations

Informed consent was taken from every pregnant participating in this study. The study methodology was reviewed and approved by the Research Review Board of the Obstetric and Gynecology Department, Faculty of Medicine, Ain Shams University.

Statistical methods:

Statistical analysis was done on a personal computer using IBM© SPSS© Statistics version 21 (IBM© Corp., Armonk, NY, USA) and MedCalc© version 12.5 (MedCalc© Software bvba, Ostend, Belgium).

Numerical variables were presented as median and interquartile range and between-group differences were compared using the Mann-Whitney U test. Qualitative variables were presented as number and percentage and intergroup differences were compared using Fisher's exact test.

Receiver-operating characteristic (ROC) curve analysis was used to examine the value of continuous variables for prediction of binary outcomes. For categorical predictors, simple binary logistic regression was first applied to estimate the predicted probabilities of the binary outcomes of interest which were then used to plot the ROC curves. $P < 0.05$ is considered statistically significant.

Results:

The mean age of participant was 32.5 ± 6 years with mean gestational age of 14.5 ± 2.1 weeks (table 1). Only 2.4% of the participants were smokers. 5 patients (5.9%) of the participants were diabetics, 2 patients (2.4 %) were hypertensive, and 1 patient (1.2%) was hypothyroid.

Studying the history of previous miscarriages showed that single miscarriage occurred in 8 patients (9.4%) and 27 of the participants (31.7%) had repeated miscarriages.

The outcome of previous pregnancies was shown in table 2.

Exploring other risk factors for congenital anomalies revealed that consanguinity was present in 17.6% of the participants. Family history of Down syndrome was present in 9.4% of cases, Family history of other congenital anomalies was present in 5.9% of cases, and Parents chromosomal aberrations was relevant in 3.5% of the participants (table 3).

Forty (47.05%) participants were recruited in the 1st trimester and 45(52.95%) participants were recruited in the 2nd trimester.

Increased NT was found in 5% of participants recruited in the 1st trimester and increased NF was found in 8.9% of participants recruited in the 2nd trimester (table 4).

Increased NT thickness was observed in only 2 cases in the current study only one had poor outcome (50%).

Increased NF thickness was found in 4 cases with adverse outcome (80%). yet, none of the cases with normal outcome had increased NF thickness (p<0.001).

The outcome of the current pregnancy in the studied sample was 78 (91.8%) pregnancies ended with healthy alive newborn, 3 (3.5%) had missed abortion, 3 (3.5%) showed congenital anomalies, 1(1.2%) had Down syndrome (table 5).

The median NT in cases with poor outcome was 2.3 mm compared to 1.5 mm in normal fetuses

(p=0.09). Moreover, the median NF thickness was 3.9 mm in cases with normal outcome compared to 6.6 mm in cases with adverse perinatal outcome (table 6).

Figure 1 showed that: the increased NT thickness had an area under the curve of 0.86 (95% CI; 0.708 to 0.946, p = 0.005), is 100% sensitive, 71.4% specific for predicting abnormal pregnancy outcome.

Figure 2 showed that: the increased NF thickness had an area under the curve of 0.98 (95% CI; 0.886 to 1.000, p < 0.0001), is 100% sensitive, 90% specific for predicting abnormal pregnancy outcome.

Table (1): Baseline characteristics of the participants:

Variable	N	Min	Max	Median	IQR	Mean	SD
Age (yr)	85	22	42	33	30 - 36.3	32.5	6.0
Gestational age (wk)	85	12	19	15	13 – 16	14.5	2.1

Table (2): Outcome of previous pregnancies

Order of previous pregnancy	Outcome	Number	Percent
1st pregnancy	Living & well	43	51.8
	Down syndrome & living	10	12.0
	Down syndrome & died	24	28.9
	Congenital malformation & died	2	2.4
	Chromosomal aberration & died	1	1.2
	Stillbirth	1	1.2
	Infant death	2	2.4
2nd pregnancy	Living & well	29	50.9
	Down syndrome & living	10	17.5
	Down syndrome & died	9	15.8
	Congenital malformation & died	6	10.5
	Chromosomal aberration & died	1	1.8
	Stillbirth	1	1.8
	Infant death	1	1.8
3rd pregnancy	Living & well	9	31.0
	Down's syndrome & living	5	17.2
	Down's syndrome & died	6	20.7
	Congenital malformation & died	1	3.4
	Stillbirth	5	17.2
	Infant death	3	10.3
4th pregnancy	Living & well	2	15.4
	Down's syndrome & living	2	15.4
	Down's syndrome & died	2	15.4
	Congenital malformation & died	3	23.1
	Stillbirth	2	15.4
	Infant death	2	15.4
5th pregnancy	Down's syndrome & died	4	100.0

Table 2 showing the outcome of previous pregnancies of the participants

Table (3): Risk factors for adverse pregnancy outcome:

Risk factor		Number	Percent
Consanguinity	Irrelevant	70	82.4
	Relevant	15	17.6
Teratogens	Irrelevant	85	100.0
	Relevant	0	0.0
Parents' chromosomal aberrations	Irrelevant	82	96.5
	Relevant	3	3.5
Family history of Down syndrome	Irrelevant	77	90.6
	Relevant	8	9.4
Family history of fetal malformation	Irrelevant	80	94.1
	Relevant	5	5.9

Table 3: showing the prevalence of each risk factor for Down syndrome and congenital anomalies among participants. The highest was consanguinity which accounted for 17.6% of the participants.

Table (4): Qualitative assessment of sonographic indices

|		Number	Percent
NT thickness	Normal	38	95.0
	Abnormal	2	5.0
NF thickness	Normal	41	91.1
	Abnormal	4	8.9

Table (5): Outcome of current pregnancy

		Number	Percent
Outcome of current pregnancy	Normal	78	91.8
	Missed abortion	3	3.5
	Congenital anomalies	3	3.5
	Down syndrome	1	1.2

Table (6): Comparison of sonographic indices in patients with normal or abnormal outcome of current pregnancy

Variable	Normal outcome			Abnormal outcome			p-value
	N	Median	IQR	N	Median	IQR	
NT thickness (mm)	38	1.5	1.20 - 1.80	2	2.3	1.80 - 2.80	0.092
NF thickness (mm)	40	3.9	3.35 - 4.40	5	6.6	5.80 - 8.50	<0.001

FIGURE 1.ROC curve for prediction of abnormal outcomes using NT thickness.

The increased NT thickness had an area under the curve of 0.86 (95% CI: 0.708 to 0.946, p = 0.005) for predicting abnormal pregnancy outcome.
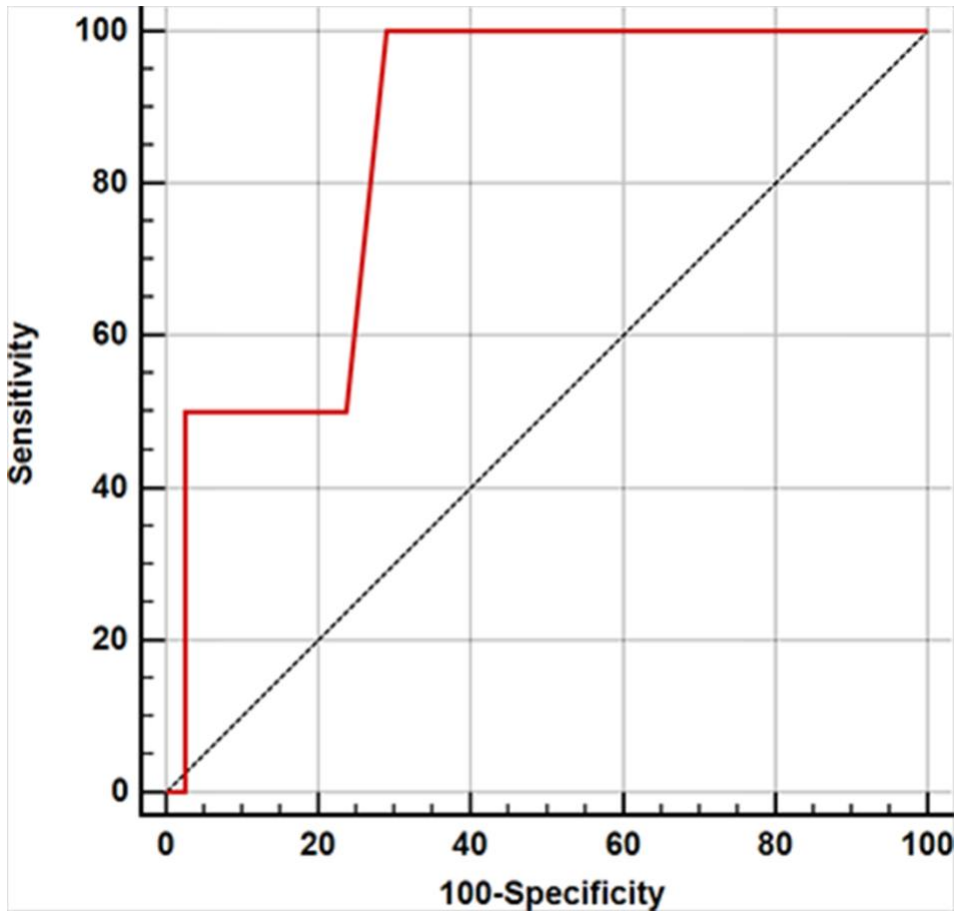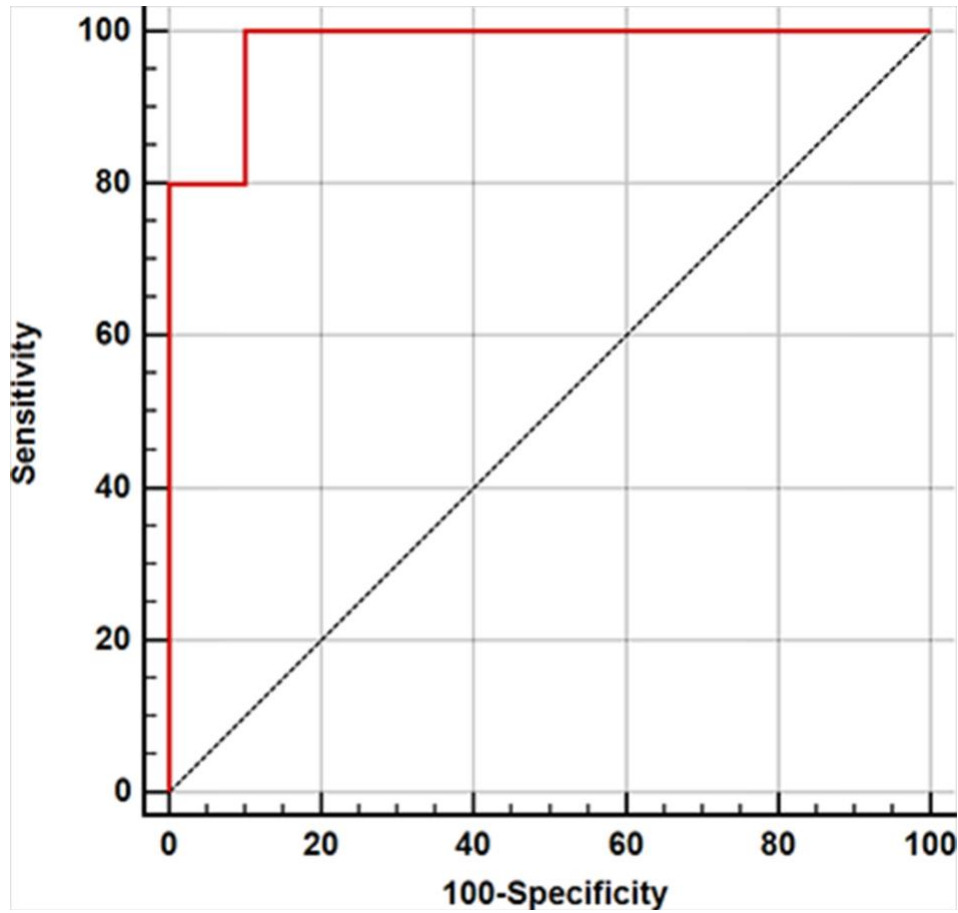
FIGURE 2.ROC curve for prediction of abnormal outcomes using NF thickness.

The increased NF thickness had an area under the curve of 0.98 (95% CI: 0.886 to 1.000, p <0.0001) for predicting abnormal pregnancy outcome.

Discussion

A wide range of screening tests for fetal aneuploidy, in particular trisomy 21, is now available in both the first and second trimesters. [10]

The aim of this work was to evaluate accuracy of the ultrasonographic assessment at the first or the second trimester of gestation as a predictor of adverse outcome in high risk pregnancies.

We recruited 85 consecutive high risk participants attending the Antenatal Clinic and Medical Genetics Center of Ain Shams University.

The mean age of participant was 32.5± 6 years with mean gestational age of 14.5± 2.1 weeks. Forty (47.05%) participants were recruited in the 1st trimester and 45(52.95%) participants were recruited in the 2nd trimester.

The outcome of the current pregnancy in the studied sample was 78 (91.8%) pregnancies ended with healthy alive newborn, 3 (3.5%) had missed abortion, 3 (3.5%) showed congenital anomalies, 1(1.2%) had Down syndrome.

In a study performed by Munoz and colleagues2 cases (1.4%) of chromosomal abnormality was detected among 144 pregnancies. [11]

In one large cross sectional study 1,183 cases were selected for analysis. From this number 1,170 fetuses were normal (98.9%) and 13 fetuses presented with adverse outcome at birth (1.1%), including fetal death, (trisomy 21 and 22) in two cases; genetic syndrome (Noonan) in one case; two cases of poly-malformed fetuses; cardiomyopathy in three cases; and other structural defects in five cases. [12]

In the present study, the NF thickness of the only detected fetus with Down syndrome was 6.6 mm.

The mean nuchal translucency was 1.6±0.4 mm among participants recruited in 1st trimester. The nuchal fold thickness was 4.2±1.4 mm among participants recruited in 2nd trimester.

There is little information, if any, regarding NT thickness in Egyptian healthy fetuses. The median NT thickness in the normal fetuses in the current study was 1.5 mm (range 1.80 - 2.8 mm).

In a study of a total of 2,577 Korean fetuses with a known normal outcome the mean NT thickness was 1.62±0.50 mm (range 0.5-5.0 mm). [13]

Increased NT thickness was observed in only 2 cases in the current study only one had poor outcome (50%).

This non significant relationship was observed due to small sample size with only two cases had NT thickness above 3mm.

The increased NT thickness had an area under the curve of 0.86 (95% CI; 0.708 to 0.946, p = 0.005), is 100% sensitive, 71.4% specific for predicting abnormal pregnancy outcome.

Indeed, different studies using different definitions of increased NT thickness reported that adverse perinatal outcome was associated with increased NT thickness.

In a study of 6650 pregnancies, among the chromosomally normal fetuses with increased NT and no obvious fetal defects, the prevalence of miscarriage or fetal death increased from 1.3% when NT was between the 95th and 99th percentiles up to20% for NT over 6.5 mm. [14]

Moreover, the prevalence of fetal abnormalities increased with increased NT: at NT of 3 mm the anomalies occurred in 2.4%; at NT of 4 mm the anomalies occurred in 7.1%; at NT of 5 mm the anomalies occurred in 12.3%; at NT of 6 mm the anomalies occurred in16.7%; and at NT of 7 mm the anomalies occurred in 35.6%. [14]

Increased NF thickness was found in 4 cases with adverse outcomes (80%). yet, none of the cases with normal outcome had increased NF thickness (p<0.001). The median NF thickness was 3.9 mm in cases with normal outcome compared to 6.6 mm in cases with adverse perinatal outcome.

The increased NF thickness had an area under the curve of 0.98 (95% CI; 0.886 to 1.000, p <

0.0001), is 100% sensitive, 90% specific for predicting abnormal pregnancy outcome.

Using NF alone with a commonly used threshold of 5 or 6 mm, reported detection rates for trisomy 21 vary widely, from 4% to 35%. [9]

In the current study, the sensitivity and specificity of different sonographic markers for predicting Down syndrome couldn't be assessed as only one case of Down syndrome was detected.

In conclusion, the findings of our prospective study demonstrate the feasibility of using NF thickness assessment in 2nd trimester to screen for aneuploidies, adverse perinatal outcome in high risk pregnancies.

Our study has some limitations. Importantly, this was a small single site observational study. Further studies with larger sample size are needed.

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