

## Gestational Diabetes Mellitus Prediction by the Use of Nuchal Translucency Screening in High Risk Pregnancy

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**Abstract: Objective:** To evaluate whether increased nuchal translucency can predict gestational diabetes mellitus. **Design:** Prospective screening study. **Setting:** feto-maternal unit, university hospital. **Patients:** 580 high risk pregnant women at 11 – 14 weeks of pregnancy who came to our feto-maternal unit for a first trimester screening test, 244 pregnant women whose nuchal translucency above 95th centile were selected as the study group and 236 age-matched pregnant women whose nuchal translucency were within the normal range were enrolled as a control group. **Interventions:** Subjects underwent a 50 g glucose screening test; if it was positive then a 100 g oral glucose tolerance test was performed. **Main outcome measures:** Prevalence of gestational diabetes mellitus and impaired glucose tolerance and the number of macrosomic infants. **Results:** Impaired glucose tolerance was more common in pregnant women whose nuchal translucency was above the 95th centile (P. 0.048). In addition, macrosomic infants were also more common in pregnant women with a fetal nuchal translucency above the 95th centile (P 0.045). Macrosomia was more common in the study group with gestational diabetes mellitus (P 0.046). **Conclusion:** In conclusion, increased nuchal translucency seems to be predictive for impaired glucose tolerance and macrosomia, which are associated with gestational diabetes mellitus.

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**Key words:** nuchal translucency, impaired glucose tolerance, gestational diabetes, macrosomia

### 1. Introduction

Gestational diabetes mellitus (GDM) is associated with increased risk of maternal and perinatal short-term and long-term complications (Casey *et al.*, 1997; Crowther *et al.*, 2005; Clausen *et al.*, 2008; Feig *et al.*, 2008; Metzger *et al.*, 2008; Bellamy *et al.*, 2009). The frequency of adverse pregnancy outcomes can be reduced by the appropriate treatment of GDM (Crowther *et al.*, 2005; Horvath *et al.*, 2010). However, there is no internationally accepted method of screening. In the UK, it is recommended that an oral glucose tolerance test (OGTT), which is the diagnostic test for GDM, should be offered to women with any one of the following risk factors: body mass index (BMI) > 30 kg/m<sup>2</sup>, previous history of GDM or macrosomic baby (>4.5 kg), family history of diabetes or racial origin with a high prevalence of diabetes such as South Asian, African-Caribbean and Middle Eastern (NICE, 2008). The performance of such screening is poor with a detection rate of about 60% at a false-positive rate of 30 to 40% (Scott *et al.*, 2002; Waugh *et al.*, 2007).

Sonographic assessment of nuchal translucency (NT) thickness has been accepted as an effective means of screening for trisomy 21 and other chromosomal abnormalities at 11 – 14 weeks' gestation. Up to 80% of aneuploid fetuses have increased NT, but this feature is also found in 5% of karyotypically normal fetuses at this stage of the pregnancy (Snijder *et al.* 1998).

As well as being associated with chromosomal abnormalities, increased NT is known to be associated with a variety of other fetal structural and metabolic defects and genetic syndromes. This may represent the mild end of a spectrum of hydropsfetalis, which is also seen in fetuses with cardiovascular defects, skeletal dysplasias, and congenital infection, metabolic and hematological disorders (Snijder *et al.* 1998).

The possible mechanisms for increased NT included temporary cardiac failure, venous congestion, increased vascular permeability, altered composition of the extra cellular matrix and abnormal or delayed development of the lymphatic system (Nicolaidis *et al.* 2002; Haak and Van Vugt 2003).

Despite the numerous publications on increased NT, the exact etiology remains unknown especially in chromosomally normal fetuses. Diabetes mellitus could potentially alter NT measurements in two ways. First, hyperglycemia itself may increase microvascular permeability in both types of diabetes (Antonetti *et al.* 1998; Brausewetter *et al.* 2001). Second, congenital cardiac malformations are directly related to hyperglycemia.

Previously it was considered that NT could be used as a marker for gestational diabetes mellitus. Based on this hypothesis, we designed this prospective study to evaluate whether the increased NT in the first trimester of pregnancy could predict gestational diabetes mellitus.

## 2. Materials and methods

This prospective observational study was conducted in our prenatal unit, which is part of the Fetal Medicine unit in el-mineya maternity university hospital, between April 2006 and February 2008. Each of the pregnant women signed an informed consent.

A total of 580 single pregnant women were selected for the study at 11 – 14 weeks of pregnancy for a routine first trimester screening program. Crown-rump-length, biparietal diameter, fetal heart rate, and nuchal translucency measurements were assessed by the trans-abdominal approach.

Inclusion criteria were single pregnancy at 11 – 14 weeks and no previous known risk factors for gestational diabetes mellitus. Risk factors included a strong family history of diabetes, abnormal glucose tolerance tests (GTT) in previous pregnancy, persistent glucosuria, giving birth to large infants, previous congenital anomalies and unexplained fetal losses.

Among the pregnant women at 11 – 14 weeks of pregnancy who were transferred to our prenatal unit for the first trimester screening test, 244 pregnant women with an NT greater than or equal to the 95th centile were selected as the study group and 236 age-matched consecutive pregnant women whose NT were within the normal range (95th centile) were enrolled as the control group (Figure 1). A total of 6 invasive diagnostic procedures (done on the Egyptian national research center) were performed in pregnant women whose NT was above the 95th centile, after counselling the parents. As a result, two chromosomal abnormalities and one intrauterine death were excluded from the study. At 20 –23 weeks of pregnancy a detailed fetal anatomic survey was done in all pregnant women. Twelve pregnant women in the control group and 11 pregnant women in the study group were lost to follow-up.

At 24 – 28 weeks of pregnancy, the 50 g glucose screening test was performed in all patients. The test was positive (glucose >140 mg/dl 1 h after intake of glucose) in 7 pregnant women in the control group and 14 pregnant women with a fetal NT above the 95th centile. During the 3 days before the oral glucose tolerance test (OGTT), the patients were advised to eat a sufficient amount of carbohydrates and to have normal physical activity. The 100 g OGTT, during which we applied the criteria for diagnosis of gestational diabetes (National Diabetes Data Group) was performed in all pregnant women with a positive screening test. two gestational diabetics and five cases of impaired glucose tolerance (single level in one of four blood glucose above normal range) were diagnosed in pregnant women with fetal NT <95th centile. four gestational diabetics and 10 cases of

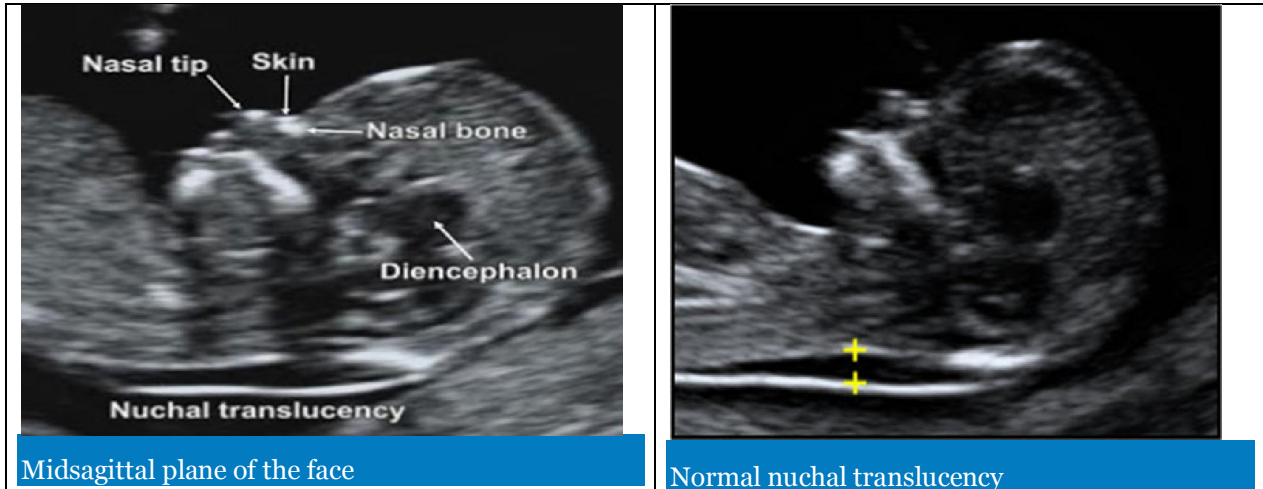
impaired glucose tolerance were diagnosed in pregnant women with a fetal NT >95th centile. Parents were requested to fill in and return a follow-up questionnaire a few weeks after delivery and telephone inquiries were made if reports were not returned. Macrosomic babies (54000 g) were confirmed by birth certificate. The main outcome measures were the prevalence of gestational diabetes mellitus, impaired glucose tolerance and the number of macrosomic infants.

Protocol for measurement of nuchal translucency

- The gestational period must be 11 to 13 weeks and six days.
- The fetal crown-rump length should be between 45 and 84mm.
- The magnification of the image should be such that the fetal head and thorax occupy the whole screen.
- A mid-sagittal view of the face should be obtained. This is defined by the presence of the echogenic tip of the nose and rectangular shape of the palate anteriorly, the translucent diencephalon in the centre and the nuchal membrane posteriorly. Minor deviations from the exact midline plane would cause non-visualization of the tip of the nose and visibility of the zygomatic process of the maxilla.
- The fetus should be in a neutral position, with the head in line with the spine. When the fetal neck is hyperextended the measurement can be falsely increased and when the neck is flexed, the measurement can be falsely decreased.
- Care must be taken to distinguish between fetal skin and amnion.
- The widest part of translucency must always be measured.
- Measurements should be taken with the inner border of the horizontal line of the callipers placed ON the line that defines the nuchal translucency thickness - the crossbar of the calliper should be such that it is hardly visible as it merges with the white line of the border, not in the nuchal fluid.
- In magnifying the image (pre or post freeze zoom) it is important to turn the gain down. This avoids the mistake of placing the calliper on the fuzzy edge of the line which causes an underestimate of the nuchal measurement.
- During the scan more than one measurement must be taken and the maximum one that meets all the above criteria should be recorded in the database.
- A new approach for the measurement of NT which improves the accuracy of measurements, is with the use of a semi-automated technique. The operator places a box in the nuchal area and the machine automatically selects the best

measurement, which uses an algorithm that draws a line through the centre of the nuchal membrane and another line at the edge of the soft tissue overlying the cervical spine. The measurement obtained by this method is similar to that obtained manually and it is therefore applicable to the software of the Fetal Medicine Foundation.

- The umbilical cord may be round the fetal neck in about 5% of cases and this finding may produce a falsely increased NT. In such cases, the measurements of NT above and below the cord are different and, in the calculation of risk, it is more appropriate to use the average of the two measurements.



### Methodology:

Statistical analyses were performed with SPSS 11.0 software for Windows (SPSS Inc., Chicago, Illinois, USA). In the analyses of continuous variables, groups were compared by a Student's t-test, for discrete data this was done by means of the w2 test and Fisher's exact test, where appropriate. Differences were considered statistically significant when  $p < 0.05$ .

### 3. Results

Two groups were similar in terms of maternal age, parity, gestational age and body mass index (Table I). The distribution of eight fetal chromosomal

abnormalities in pregnant women with fetal NT 595th centile were as follows: Two Down syndrome, one trisomy 18, one trisomy 13, one trisomy 16, one 45, X0, one XXY, one 45, X0 mosaicism.

There were no significant differences between the two groups in respect of the prevalence of abnormal 50 g glucose screening test results and gestational diabetes mellitus. Impaired glucose tolerance was more common in pregnant women whose NT was above the 95th centile than the control group ( $p = 0.048$ ). In addition, macrosomic infants were also more common in pregnant women with a fetal NT above the 95th centile ( $p = 0.045$ , Table II).

The distribution of macrosomic infants in both groups are summarized in Table III. As compared with the control group, macrosomia was more

common in the study group with gestational diabetes mellitus ( $p = 0.046$ ) and also in the study group with impaired glucose tolerance ( $p = 0.042$ ).

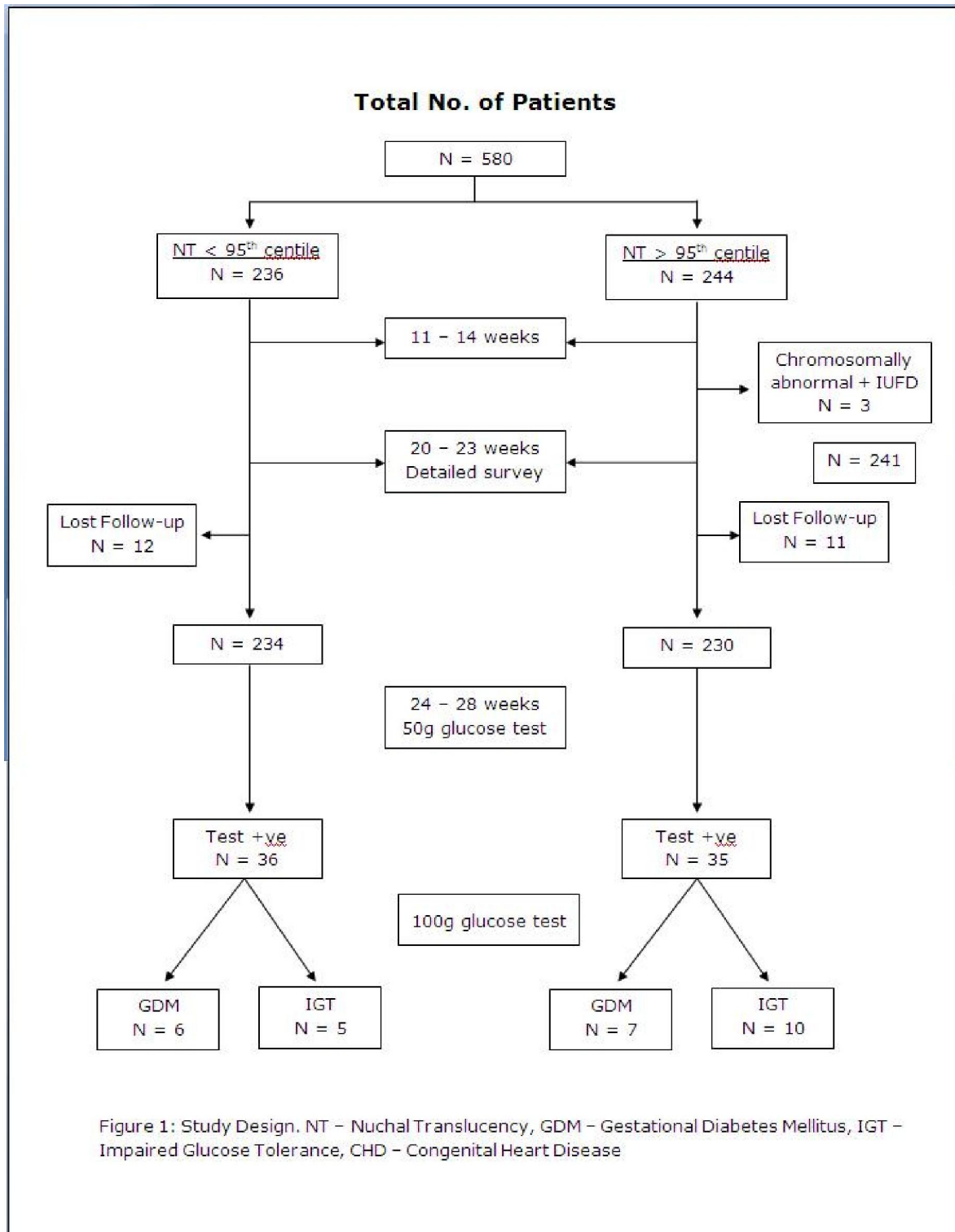


Figure 1: Study Design. NT - Nuchal Translucency, GDM - Gestational Diabetes Mellitus, IGT - Impaired Glucose Tolerance, CHD - Congenital Heart Disease

Table I. Demographic variability in both groups

	NT<95 <sup>th</sup> centile (n 234)	NT>95 <sup>th</sup> centile (n 230)	p value
Age (years)	23.8 + 4.2	24.6 + 5.9	0.580
Parity (n)	2.0 + 0.9	2.4 + 0.8	0.546
Gestational age (weeks)	1.4 + 0.7	1.2 + 0.6	0.402
Gravida (n)	12.6 + 0.9	12.9 + 1.0	0.806
BMI (kg/m)	24.3 + 2.6	24.8 + 3.2	0.820

Values are expressed as means + SD. NT, nuchal translucency; BMI, body mass index.

Table II. Main outcome measures in both groups

	NT<95 <sup>th</sup> centile (n 234)	NT>95 <sup>th</sup> centile (n 230)	p value
Abnormal 50 g glucose screening	36 (14.5)	35 (13.9)	0.626
Abnormal single level at100 g OGTT (IGT)	6 (2.1)	7 (3.6)	0.048
Gestational diabetes mellitus	5 (2.3)	5 (2.6)	0.795

Values are expressed as n (%). NT, nuchal translucency; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.

Table III. The distribution of macrosomic infants in both groups

	NT<95 <sup>th</sup> centile (n 234)	NT>95 <sup>th</sup> centile (n 230)	p value
Gestational diabetes mellitus	2	4	0.046
Abnormal single level at100 g OGTT (IGT)	1	2	0.042
Normal	1	7	0.058

Values are expressed as n (%). NT, nuchal translucency; OGTT, oral glucose tolerance test; IGT: impaired glucose tolerance.

#### 4. Discussion

This is the third study relating to the prediction of gestational diabetes mellitus using nuchal translucency thickness measurement. It was found that there was no significant difference in the prevalence of gestational diabetes mellitus in those with NT measurements above the 95th centile, whereas impaired glucose tolerance and macrosomic infants were more common in this group than those with an NT within normal range. Despite numerous publications on increased NT, the exact aetiology remains unknown, especially in fetuses with normal karyotype.

Diabetes mellitus is a well-known pathophysiological condition where the microcirculation is markedly impaired (Plante et al. 1996). Capillary permeability has been reported to be increased in both type 1 and type 2 diabetes mellitus compared with age- and sex-matched controls (Brausewetter et al. 2001). The possible causes of increased NT measurements such as chromosomal abnormalities were excluded from this study.

Bartha et al. (2003) reported that metabolic control in insulin dependent diabetes mellitus did not affect ultra-sound-determined fetal NT. However, the pathophysiology of increased nuchal translucency in diabetes may not be due to a single causative

mechanism. Diabetes seems not only to be able to alter capillary permeability but also to enhance lymph flow (Brausewetter et al. 2001).

Increased nuchal translucency with normal karyotyping is associated with poor perinatal outcome such as intrauterine growth abnormalities (Fukada et al. 1998). The increased macrosomia in our study may be due to the increased prevalence of impaired glucose tolerance. In addition, congenital cardiac anomaly which has adverse effects on fetal growth was excluded in our study. In selected cases, an increased nuchal translucency may be of predictive value in fetal macrosomia, which is the outcome of some importance, since those whose mothers had diabetes had excessive fat deposition on the shoulders and trunk, predisposing these fetuses to shoulder dystocia. However, at time of writing, only about 50% of the risk factors causing macrosomia are known. Thus, increased NT may be an additional factor for prediction of fetal macrosomia.

Thickened nuchal translucency has been associated with many fetal structural abnormalities and genetic syndromes that include a variety of cardiac defects, diaphragmatic hernia, exomphalos, body stalk anomaly, Smith LemliOpitz, and a number of lethal skeletal dysplasias that include achondrogenesis type II and thanatophoric dysplasia.



According to the largest population-based study in Sweden, impaired glucose tolerance has an increased risk of high birth weight (Aberg et al. 2001). Another study suggested that the increased rate of adverse maternal and fetal outcome, especially large size for gestational age, was associated with untreated mild gestational hyperglycemia in women compared with a control group (Vambergue et al. 2000). Our study was compatible with these studies.

Results of the current study show that increased nuchal translucency was associated with impaired glucose tolerance and macrosomia but not gestational diabetes mellitus. However, aforementioned studies revealed that macrosomia and impaired glucose tolerance were evidently related to gestational diabetes mellitus. Increased nuchal translucency may have been shown to be associated with gestational diabetes if our sample size had been larger.

**In conclusion**, even though this was a preliminary study, NT seems to be predictive for impaired glucose tolerance and macrosomia, which are associated with gestational diabetes mellitus. If proven by larger prospective randomized clinical trials, increased NT may be an additional factor in predicting both impaired glucose tolerance and fetal macrosomia.

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