Nuchal translucency beyond Down syndrome screening

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Male gender as a favourable prognostic factor in pregnancies with enlarged nuchal translucency

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Chapter 2

ABSTRACT

Objective The aim of this study was to investigate the influence of fetal gender on pregnancy outcome in fetuses with enlarged nuchal translucency (NT).

Methods Pregnancy outcomes of all women who underwent an NT measurement at our institution between January 2000 and November 2007 were retrospectively reviewed. Separate analyses were performed for fetuses with normal and with enlarged (≥95th percentile) NT.

Results A normal NT was measured in 3637 males (51.4%) and 3435 females (48.6%). Of the fetuses with enlarged NT 365 were males (57.4%) and 271 females (42.6%) (P = 0.001). In this group a normal pregnancy outcome – of those pregnancies for which the outcome was known – was registered for 187/332 (56.3%) of the male fetuses and 98/249 (39.4%) of the female fetuses (P < 0.001; relative risk (RR) for adverse outcome for male gender, 0.72). Eighty percent of the chromosomally normal male fetuses with an enlarged NT had an uneventful pregnancy outcome; this increased to 90% when only the male fetuses with NT measurements ≥95th percentile and <99th percentile and normal karyotype were considered (RR for adverse outcome for male gender, 0.47).

Conclusion In a population of fetuses with enlarged NT there are significantly more males. Male fetuses with enlarged NT and normal chromosomes have an almost two-fold greater chance of a favourable outcome than females. We believe that a minimal degree of NT enlargement in male fetuses without genetic or structural anomalies may be interpreted as a feature of accelerated growth or, alternatively, as a maturational delay of the cardiovascular system more common in males, leading to moderately increased nuchal fluid accumulation.
INTRODUCTION

In the attempt to optimize first-trimester screening for chromosomal anomalies, the effect of covariables that may affect screening results has been studied extensively. One of these covariables is gender. It has been suggested that fetal sex influences the concentrations of first-trimester maternal serum markers. The risk of abnormal maternal serum screening results is in fact higher in the presence of a male fetus. The impact of fetal gender on nuchal translucency (NT) thickness has been less studied and is still controversial. Some authors have found a significant gender difference in NT thickness, but other studies have found no difference. However, all of these studies investigated gender differences in a general population or in a population of fetuses with normal NT thickness and normal outcome. The aim of this study was to investigate the influence of fetal sex on pregnancy outcome in fetuses with an enlarged NT.

METHODS

Our fetal medicine unit – the Academic Medical Centre in Amsterdam – acts as a tertiary referral centre for a large geographical area. Many cases diagnosed with enlarged NT in other centres are referred to our hospital for advanced first-trimester sonography, invasive testing and genetic counselling. First-trimester ultrasound screening is also offered routinely to all women booking at our hospital.

The prenatal database of the Academic Medical Centre was searched for all fetuses with enlarged NT measured between January 2000 and November 2007. Enlarged NT was defined as a measurement ≥95th percentile for the normal range, according to The Fetal Medicine Foundation. Cases with normal NT measured in the same period were also retrieved and analysed separately.

Karyotyping was offered to all patients with a risk for Down syndrome of more than 1 in 200 based on maternal age, NT and first-trimester maternal serum pregnancy associated plasma protein-A and free β-human chorionic gonadotropin. Before first-trimester serum screening was available, karyotyping was offered in cases of enlarged NT or maternal age above 36 years. In all cases of enlarged NT and normal karyotype a two-step ultrasound investigation at 13–16 and 20–24 weeks’ gestation was performed to exclude structural anomalies.

Demographic data that may influence first-trimester screening results, such as maternal age, parity, weight and smoking were recorded for both the normal and enlarged-NT group. Pregnancy outcome was obtained in all cases from forms filled in by patients or staff at maternity wards or midwife practices and by reviewing neonatal, pathology and clinical pediatric notes, when appropriate. When the infant was born without structural
defects or dysmorphic features the chromosomes were assumed to be normal. In all cases of enlarged NT or antenatal suspicion of abnormal development the infant was investigated by a neonatologist, pediatric cardiologist or geneticist, as indicated. Adverse pregnancy outcome was defined as chromosomal anomalies, structural anomalies, genetic disorders, intrauterine death (IUD) or neonatal death (NND) and termination of pregnancy (TOP) on parental request. Statistical analysis was performed with SPSS statistics 14.0 (SPSS Inc., Chicago, IL, USA). The chi-square test was used for inter-group comparisons to assess gender differences in outcomes between fetuses with normal and enlarged NT, and between groups of fetuses with different degrees of NT enlargement; \( P < 0.05 \) was considered statistically significant.

RESULTS

The study population consisted of 636 fetuses with enlarged NT and 7072 fetuses with normal NT. The demographic data of both groups (normal and enlarged NT), with respect to fetal sex, are reported in Table 1. Crown–rump length (CRL) was significantly larger in male fetuses in both groups.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Parameters measured at first-trimester screening and maternal demographic data of fetuses with enlarged (( \geq 95^{th} ) percentile) and normal ((&lt; 95^{th} ) percentile) nuchal translucency (NT) thickness, Data expressed as median (range) or %. *Significant difference between normal and enlarged-NT groups (( P &lt; 0.01 )). †Significant gender difference (( P &lt; 0.01 )). BMI, body mass index; CRL, crown–rump length.</th>
<th>Enlarged NT</th>
<th>Normal NT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal</td>
<td></td>
<td>All</td>
<td>Male</td>
</tr>
<tr>
<td>CRL (mm)</td>
<td>60 (40 – 90)†</td>
<td>62 (40-90)*</td>
<td>58 (40 - 90)†</td>
</tr>
<tr>
<td>NT (mm)</td>
<td>3.7 (2.2-24.0)†</td>
<td>3.4 (2.2-24)*</td>
<td>3.9 (2.2-20)*</td>
</tr>
<tr>
<td>Maternal</td>
<td></td>
<td>All</td>
<td>Male</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34 (18-45)†</td>
<td>34 (19-44)</td>
<td>34 (18-43)</td>
</tr>
<tr>
<td>Parity ≥1 (%)</td>
<td>64</td>
<td>69</td>
<td>58</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.9 (17-43)</td>
<td>22.1 (18-36)</td>
<td>22.3 (18-43)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>10.5</td>
<td>10.4</td>
<td>10.8</td>
</tr>
</tbody>
</table>

Normal nuchal translucency

Of the 7072 fetuses with normal NT measurement (\(< 95^{th} \) percentile) 3637 were males (51.4%) and 3435 females (48.6%). This gives a male : female ratio of 1.059 : 1, which is consistent with the normal Dutch sex birth ratio. Mean NT was 1.35 mm in the male population and 1.30 in the female fetuses (\( P < 0.001 \)). Outcome data of the pregnancies were available in all cases. 6739 children (95.3%) were born alive and well.
Enlarged nuchal translucency

Of the 636 fetuses with enlarged NT (≥95th percentile) 365 were males (57.4%) and 271 females (42.6%), a male : female ratio of 1.35 : 1 (P = 0.001). Pregnancy outcome was available in 581 (91.4%) cases. Of the remaining 55 fetuses with unknown pregnancy outcome 33 were males and 22 were females, all of whom had normal chromosomes.

The overall rate of adverse pregnancy outcome – in the 581 cases for which the outcome was known – was 50.9% (296 fetuses: 145 males and 151 females, P = 0.49). The most common causes of adverse outcome were chromosomal anomalies (65.5%) and structural defects (14.5%). The remaining were miscarriage/ IUD, genetic syndromes, very preterm birth leading to NND and TOP because of deteriorating fetal hydrops.

A normal pregnancy outcome was registered in 56.3% (187/332) of the males and in 39.4% (98/249) of the females (relative risk (RR) for adverse outcome in males 0.72 (95% CI, 0.61–0.84); P < 0.001). Overall a normal pregnancy outcome was recorded in 285 infants (49.1%), and of these 65.5% were males (P < 0.001).

Table 2 reports the gender distribution according to degree of NT enlargement. Male gender was predominant, especially in the group of fetuses with mildly enlarged NT (≥95th percentile and <99th percentile). In this group there were 178 males (65.7%) and 93 females (34.3%) (P < 0.001). Female gender was more common in fetuses with an NT ≥5.5 mm. In Table 3 and Figure 1 the distribution of chromosomal anomalies, other causes of adverse outcome and uneventful outcome are reported according to fetal gender and the degree of NT enlargement.

Chromosomal anomalies were diagnosed in 194 of the fetuses (98 male and 96 female) with enlarged NT (30.5%). There were no differences in the type of chromosomal anomalies in male or female fetuses (except for sex chromosome anomalies), and after exclusion of sex chromosome anomalies there were no gender differences in the group of fetuses with NT above 4.5 mm (83 male and 91 female fetuses, P = 0.54).

<table>
<thead>
<tr>
<th>NT</th>
<th>Males (% of male fetuses)</th>
<th>Females (% of female fetuses)</th>
<th>Male: female ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>P95 to 2.9 mm</td>
<td>88 (24.1)</td>
<td>56 (20.7)</td>
<td>1.6 : 1</td>
</tr>
<tr>
<td>3.0 to 3.4 mm</td>
<td>90 (24.7)</td>
<td>37 (13.7)</td>
<td>2.4 : 1</td>
</tr>
<tr>
<td>3.5 to 4.4 mm</td>
<td>96 (26.3)</td>
<td>62 (22.9)</td>
<td>1.6 : 1</td>
</tr>
<tr>
<td>4.5 to 5.4 mm</td>
<td>38 (10.4)</td>
<td>30 (11.1)</td>
<td>1.3 : 1</td>
</tr>
<tr>
<td>5.5 to 6.4 mm</td>
<td>17 (4.7)</td>
<td>23 (8.5)</td>
<td>0.7 : 1</td>
</tr>
<tr>
<td>≥ 6.5 mm</td>
<td>36 (9.9)</td>
<td>63 (23.2)</td>
<td>0.6 : 1</td>
</tr>
<tr>
<td>ALL (≥P95)</td>
<td>365 (100)</td>
<td>271 (100)</td>
<td>1.3 : 1</td>
</tr>
</tbody>
</table>
Table 3 Distribution of adverse and uneventful outcomes in the total group of fetuses with enlarged (≥95th percentile) nuchal translucency (NT) according to fetal gender and to degree of NT enlargement. Data are expressed as n (%), with % calculated using the total with known outcomes. *Significant at P < 0.05. †Significant at P < 0.001. ‡Includes miscarriage, termination of pregnancy, intrauterine demise and neonatal death.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total</th>
<th>NT 95th to 99th percentile</th>
<th>NT ≥ 99th percentile to 4.4 mm</th>
<th>NT ≥ 4.5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Chromosomal anomaly</td>
<td>98 (30)</td>
<td>96 (39) *</td>
<td>27 (17)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Structural anomaly</td>
<td>18 (5.4)</td>
<td>25 (10) *</td>
<td>6 (3.7)</td>
<td>7 (8.5)</td>
</tr>
<tr>
<td>Genetic disorder</td>
<td>12 (3.6)</td>
<td>8 (3.2)</td>
<td>4 (2.5)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Loss ‡</td>
<td>17 (5.1)</td>
<td>22 (8.8)</td>
<td>3 (1.9)</td>
<td>4 (4.9)</td>
</tr>
<tr>
<td>Uneventful outcome</td>
<td>187 (56)</td>
<td>98 (39) †</td>
<td>122 (75)</td>
<td>58 (71)</td>
</tr>
<tr>
<td>Total (known outcome) *</td>
<td>332</td>
<td>249</td>
<td>162</td>
<td>82</td>
</tr>
<tr>
<td>Unknown outcome</td>
<td>33</td>
<td>22</td>
<td>16</td>
<td>11</td>
</tr>
</tbody>
</table>

581 fetuses

Male n = 332
- Normal karyotype n = 234
  - NT 95th to 99th percentile n = 135
    - Uneventful outcome n = 122
    - Males overall Uneventful outcome n = 187/332 (56%)
- Chromosomal anomalies n = 98
  - NT > 99th percentile n = 99
    - Uneventful outcome n = 65

Female n = 249
- Normal karyotype n = 153
  - NT 95th to 99th percentile n = 73
    - Uneventful outcome n = 58 (79%)
- Chromosomal anomalies n = 96
  - NT > 99th percentile n = 80
    - Uneventful outcome n = 40 (50%)

Females overall Uneventful outcome n = 98/249 (39%)

Figure 1 Pregnancy outcome according to fetal gender and degree of nuchal translucency (NT) enlargement in fetuses with enlarged NT (≥95th percentile).
In Table 4 the RRs and corresponding 95% CIs for adverse outcome dependent on fetal gender are reported for all fetuses with enlarged NT, and for those with enlarged NT and normal karyotype according to degree of NT enlargement. Overall, male fetuses with normal karyotype had almost twice as high a chance of uneventful outcome than females (RR for adverse outcome 0.56 (95% CI, 0.40–0.78); \( P < 0.01 \)). The chance of normal outcome was the highest in chromosomally normal males with mildly enlarged NT (≥95th percentile and <99th percentile), where the RR for an adverse outcome was 0.47 (95% CI, 0.24–0.93); \( P < 0.01 \).

Table 4 Relative risk (RR) for adverse outcome in male compared with female fetuses with enlarged (≥95th percentile) nuchal translucency (NT), with sub-analyses of those with normal karyotype according to NT percentile P95; 95th percentile

<table>
<thead>
<tr>
<th>Uneventful outcome</th>
<th>RR for adverse outcome (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (n(%))</td>
<td>Females (n(%))</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>187/332 (56)</td>
<td>98/249 (39)</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>187/234 (80)</td>
<td>98/153 (64)</td>
</tr>
<tr>
<td>NT P95 to P99 &amp; normal karyotype</td>
<td>122/135 (90)</td>
<td>58/73 (80)</td>
</tr>
<tr>
<td>NT ≥ P99 &amp; normal karyotype</td>
<td>65/99 (66)</td>
<td>40/80 (50)</td>
</tr>
</tbody>
</table>

DISCUSSION

In our population of fetuses with enlarged NT male gender was predominant, but males were more likely to have a favourable outcome. Overall, 80% of the chromosomally normal males had an uneventful pregnancy outcome. This increased to 90% when the degree of NT enlargement was marginal (≥95th percentile and <99th percentile). Fetal gender differences in the first trimester have been extensively investigated. It has been suggested that fetal sex influences first-trimester maternal serum marker concentrations, with male fetuses associated with a higher chance of abnormal serum marker concentrations. However, gender differences in miscarriages do not show any clear trends. The issue of the impact of gender on the degree of nuchal fluid accumulation has also been studied, with slightly controversial results. Yaron et al. and Prefumo et al. did not find NT to be significantly related to gender, whereas Lam et al. reported NT to be significantly larger in male fetuses (with a gender difference of 0.06–0.1 mm) and Larsen et al. also found NT to be slightly, but significantly, smaller in female fetuses. Similarly, Spencer et al. found NT to be 3–4% smaller in both chromosomally normal and Down syndrome female fetuses.
In our large population of fetuses with normal NT, mean NT was slightly, but significantly, larger (by 0.05 mm) in male than in female fetuses. In spite of the statistical significance, the clinical implications of this NT difference between sexes are probably limited. Intra-observer variation and limitations in ultrasound resolution may have an even larger impact on the measurement than 0.05 mm, suggesting no need for gender correction of NT in first-trimester risk assessment. Moreover, this correction may not always be readily applicable at the time of NT screening, as determination of fetal gender by ultrasound examination can only be performed with reasonable accuracy after 12 weeks’ gestation. However, considering that the goal of a good screening program is to minimize the false-positive rate, information on fetal gender, when available, should be included as additional information with the potential for further refining the accuracy of the algorithm used for first-trimester risk assessment. Potentially, this may reduce the false-positive rate in male fetuses.

Thus far there is no hint as to a possible unequivocal explanation for the gender difference observed in nuchal fluid accumulation. The underlying mechanism of NT enlargement itself is still poorly understood. Possible explanations for this transient finding have been sought in hemodynamic disturbances causing temporary cardiac dysfunction, alterations in the extracellular matrix and/or perturbed lymphangiogenesis accompanied by endothelial dysfunction. There is therefore an interesting question regarding which of these hypotheses best explains the observed gender difference.

One may speculate that delayed maturation is more common in male fetuses. Prefumo et al. suggested a delay in myocardial maturation in male fetuses as an explanation for the higher ductus venosus pulsatility index and enlarged NT observed in male fetuses. However, their study lacked the power to confirm a relationship between NT thickness and fetal gender.

From animal studies it is known that myocardium is stiffer during fetal life and that functional changes take place during intrauterine development, from as early as 10 weeks’ gestation, as suggested by changes in diastolic Doppler flow patterns across the atrioventricular valves from monophasic (A-wave) to biphasic (E and A-waves). As hypothesized by Prefumo et al., it is possible that if normal myocardial development and maturation are delayed, persistence of a less compliant myocardium beyond 10 weeks may lead to impaired diastolic filling, with raised atrial pressures and, ultimately, more pronounced fluid accumulation in the fetal neck. A possible delay in myocardial maturation in male fetuses may therefore explain the mechanism of more pronounced fetal fluid accumulation in fetuses of this gender.

Alternatively, the Y chromosome itself may be responsible for different growth and maturation patterns in male fetuses, as suggested by the fact that 46,XY fetuses with androgen insensitivity syndrome show female growth patterns. This may indeed provide a simple explanation for the fact that a faster growth pattern in males, as also supported by their statistically significantly greater CRL, may result in a physiologically but significantly
larger nuchal fluid accumulation. Other examples of physiologically larger anatomical structures may be provided by renal pelvis and posterior horn measurements of the lateral ventricles, both of which are larger in males than in females.

It is not known whether growth and maturation progress synchronously. In the hypothesis that fetal growth is more accelerated than cardiac maturation, this could provide the second alternative explanation for relatively larger NT in males. Investigations of early cardiac function have been performed in fetuses with normal and with increased NT, but this has not yet been studied separately in male and female fetuses. Further investigations on early cardiac function in male and female fetuses are necessary in order to test the hypothesis that gender-related differences may play a role in determining differences in maturation and nuchal fluid accumulation.

It is generally accepted that male sex is considered an independent risk factor for adverse pregnancy outcome. However, based on our data, this does not seem to hold true in cases of enlarged NT, as in our population of fetuses with enlarged NT the chance of adverse outcome was significantly lower in male fetuses. In agreement with previous studies we did not find, in fetuses with enlarged NT, any gender differences in the number of chromosomal anomalies. However, after the detection of enlarged NT a significantly greater proportion of chromosomally normal male fetuses had a favourable pregnancy outcome than did chromosomally normal female fetuses. Enlarged NT is known to be associated with a wide range of rare genetic syndromes that may not be recognizable at birth. However, very large series are needed in order to determine whether developmental delays in infants born alive and well after detection of enlarged NT are more common in either of the sexes.

Based on our data we can conclude that in a population of fetuses with enlarged NT and normal karyotype the chance of a normal outcome is 1.8-fold higher in males than in females (adverse outcome 35.9% for female and 20.1% for male fetuses). These data may play a role in parental counselling, although increased NT with normal karyotype and no structural defects generally has a good prognosis. Further investigation is required to determine whether different algorithms for risk assessment and management protocols should be developed for male and female fetuses.
REFERENCES


