On first trimester Down syndrome screening

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Weekly Nuchal translucency measurement in normal fetuses

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We determined the longitudinal course of nuchal translucency thickness by weekly measurements between 10 and 15 weeks’ gestation in normal fetuses. The nuchal translucency was measured weekly from 10 to 15 weeks’ gestation in 64 fetuses with normal pregnancy outcome. The median and the fifth, 25th, 75th, and 95th percentile was calculated. Nuchal translucency measurement varied considerably with gestational age; this variation followed a fetus-specific pattern. In 94% of cases, we observed an increase followed by a steady decrease in nuchal translucency measurement. A visible nuchal translucency was found after 76 and 86 days’ gestation in 97% (95% confidence interval (CI): 89-100) and 100% (95% CI: 94-100) of the fetuses, respectively. The median nuchal translucency increased from 0.7 mm at 70 days’ gestation to 1.7 mm at 91 days’ gestation, after which it declined to 1.0 mm at 105 days’ gestation.

We concluded that a progressive increase and subsequent decrease in nuchal translucency thickness occurs with advancing gestation in most fetuses, but the timing of the peak thickening appears to be fetus-specific. In this study, each fetus developed a visible nuchal translucency. If the nuchal translucency measurement is 0 mm before 12 weeks, it may be advisable to repeat the measurement at 12 weeks’ gestation. In contrast, a nuchal translucency that cannot be measured from 12 weeks’ gestation onward suggest that this temporary entity is already in its waning phase.

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Chapter 5

Introduction

The appearance and disappearance of a translucent area between the skin outline and the soft tissue overlying the cervical spine (nuchal translucency) continuous to be a poorly understood feature in fetuses during the late-first and early-second trimester. This ultrasound finding can be imaged routinely in normal fetuses in between 10-14 weeks of gestation (Hertzberg et al., 1989). Despite lack of knowledge of the physiologic background and mechanism leading to this feature, it is accepted widely that an enlarged nuchal translucency is a marker for fetal aneuploidy (Nicolaides et al., 1992). In a previous study (Pajkrt et al., 1995), we reported the physiologic variation in nuchal translucency thickness in relation to gestational age in chromosomally and phenotypically normal fetuses between 9 and 14 weeks’ gestation. It appears plausible that this variation also is present and therefore can be observed in individual fetuses. However, the natural course of the nuchal translucency in individual fetuses has not yet been described. It is not known if each fetus develops a measurable nuchal translucency at a certain stage between 10 and 15 weeks’ gestation or if in some fetuses this finding remains not measurable during the whole period. The aim of the present study was to examine the course of the nuchal translucency thickness longitudinally from 10 to 15 weeks’ gestation by serial measurements in normal fetuses.

Materials and Methods

Sixty-five women with singleton pregnancies at 10 weeks’ gestation, as calculated from the first day of their last menstrual period were included in the study. They consented to undergo weekly ultrasound scans for 5 consecutive weeks. The women were recruited between January 1995 and July 1996, by means of a written form handed to them in the waiting room of the prenatal diagnosis or antenatal clinic of our hospital, before a routine initial scan. All women consented to participate in the study before the first ultrasound scan. The study was approved by the hospital’s ethics board. The gestational age was assessed by crown-rump length measurement (Robinson et al., 1975) of the fetuses at this first visit. In 33 women (51%), invasive prenatal diagnosis was performed for fetal karyotyping because of maternal age indication. Four women (one of whom was older than 36 years of age), had maternal serum screening at 15 weeks’ gestation. The remaining 28 women had no biochemical testing for aneuploidies or fetal karyotyping. All neonates were examined clinically after birth by a pediatrician. Fetuses with chromosomal or structural anomalies were excluded from the study.
Weekly NT measurement

The nuchal translucency was measured three times in a sagittal section of the fetus obtained by transabdominal ultrasound examination (curvilinear 3.5-MHz transducer; Hitachi EUB 525, Tokyo, Japan, and Toshiba SSA 250A, Tokyo, Japan). Two sonographers (EP, IG) performed the examinations, both in their own patients. The operators were blinded to the three actual measurements of the maximum thickness of the nuchal translucency by covering the numeric display on the ultrasound equipment. Moreover, all weekly measurements from the same patient were recorded on videotape and reviewed by the performing operator after the last visit. In this way, the operators were not influenced by their previous measurements. In cases in which the translucent nuchal area could not be measured because it was so thin that it was impossible to part the calipers from each other, the measurement was considered to be 0 mm.

The analysis was based on the mean of each set of three measurements. Exact confidence intervals (CIs) were computed (Gardner and Altman, 1989). As the nuchal translucency measurement were not performed on exactly the same gestational days in all fetuses, the measurements were corrected for differences in gestational age. For each fetus, the five mean nuchal translucency values were plotted against gestational age in days. Subsequently, for each individual fetus, the best polynomial function was estimated for the nuchal translucency measurements in time. On the basis of these 64 functions, the nuchal translucency measurements were calculated for 70, 77, 84, 91, 98, and 105 days’ gestation. In cases in which the correction of the nuchal translucency measurement resulted in a negative value, the value was truncated to 0 mm. Median and fifth, 25th, 75th, and 95th percentiles for 70, 77, 84, 91, 98, and 105 days’ gestation were calculated.

Results

The median (range) maternal age was 36.3 (18-41) years. The results from one fetus were excluded from the study because the neonate had pulmonary valve stenosis detected at birth. At the age of 6 months, the infant was diagnosed as having Noonan syndrome. The remaining 64 fetuses were delivered uneventfully and were chromosomally and anatomically normal at birth. The median (range) gestational age at delivery was 39.2 (33-42) weeks, and the median (range) birth weight was 3200 (1905-4990) g. We were successful in obtaining three measurements on each occasion in each patient. The intra-observer standard deviation was 0.25 mm, which means that in 95%, the measurements did not differ more than 0.5 mm.

A progressive increase followed by a steady decrease in nuchal translucency measurement was observed in 60 fetuses (94%). However, the gestational age at which
maximum thickness occurred was variable and clearly fetus-specific. In the remaining four fetuses (6%), the largest nuchal translucency measurement was obtained at the time of the first scan. Table 1 shows the gestational age at which the peak nuchal translucency thickness appeared in the 64 fetuses. In 31 fetuses (48%), this happened at 13 weeks’ gestation.

In 19 of the 64 fetuses (30%), the first measurement was made before 70 days’ gestation. The nuchal translucency was more than 0 mm in only seven (37%) of these 19 fetuses. In 51 (80%) of the 64 fetuses, the first nuchal translucency measurement was performed before 77 days’ gestation. Of these 51 fetuses, 35 (69%) had already developed a visible nuchal translucency. After 76 days’ gestation, a visible nuchal translucency was found in 62 (97%) of the 64 fetuses.

<table>
<thead>
<tr>
<th>GA (days)</th>
<th>weeks</th>
<th>N (%)</th>
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</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>9</td>
<td>1 (2)</td>
</tr>
<tr>
<td>70-76</td>
<td>10</td>
<td>2 (3)</td>
</tr>
<tr>
<td>77-83</td>
<td>11</td>
<td>4 (6)</td>
</tr>
<tr>
<td>84-90</td>
<td>12</td>
<td>16 (25)</td>
</tr>
<tr>
<td>91-97</td>
<td>13</td>
<td>31 (48)</td>
</tr>
<tr>
<td>98-105</td>
<td>14</td>
<td>10 (16)</td>
</tr>
</tbody>
</table>

GA = gestational age

In each fetus, a third-degree polynomial approximation with gestational age as the only independent variable was found to produce the best fitting curve for the nuchal translucency measurement. The median and the fifth, 25\textsuperscript{th}, 75\textsuperscript{th}, and 95\textsuperscript{th} percentiles of the nuchal translucency measurements as calculated for all fetuses at 70, 77, 84, 91, 98, and 105 days’ gestation are shown in figure 1. The median nuchal translucency measurement increased from 0.7 mm at 70 days’ gestation to 1.7 mm at 91 days’ gestation, after which it decreased to 1.0 mm at 105 days’ gestation.

**Discussion**

Our findings provide strong evidence that the development and disappearance of the nuchal translucency is a phenomenon common to all fetuses and that it follows an individual, fetus-specific pattern. Considerable variation in the nuchal translucency measurement with gestational age was observed in all fetuses.
Weekly NT measurement

![Graph showing nuchal translucency measurements as a function of gestational age.](image)

Figure 1. The fifth, 25\textsuperscript{th}, 50\textsuperscript{th}, 75\textsuperscript{th}, and 95\textsuperscript{th} percentiles (%ile) of nuchal translucency measurements in all fetuses, measured in millimeters as a function of gestational age.

This supports our previous findings in a cross-sectional study (Pajkrt \textit{et al.}, 1995) of 771 normal fetuses, in which the median nuchal translucency increased from 0.7 mm at 10 weeks’ gestation to 1.5 mm at 13 weeks’ gestation. The median obtained in this study is nearly identical. Additionally, the present study demonstrates that the most fetuses (48%) the nuchal translucency measurement reaches its maximum around 91 days’ gestation, after which a progressive decrease occurs. This decrease could be demonstrated because the measurements were continued to 14 completed weeks’ gestation, as opposed to stopping at 13 completed weeks, as we had done in our earlier study. Despite the general tendency for an initial increase followed by a decrease in the measurement, in 6% of the cases, the first measurement was higher than at the subsequent scans. However, these cases also shared decreasing measurements later in gestation. We hypothesize that we were too late to detect the waxing phase of the nuchal translucency in these fetuses. This further supports our finding that there is a distinct individual variation in nuchal translucency measurements.

In clinical practice, nuchal translucency measurements are used to estimate a woman’s risk for having a child with a chromosomal anomaly. However, there is disagreement about the gestational period at which the nuchal translucency should be measured. Some centers measure from 8 weeks’ gestation onward (Brambati \textit{et al.}, 1995; Bewley \textit{et al.}, 1995; Kornman \textit{et al.}, 1996), some from 9 weeks’ gestation (Comas \textit{et al.}, 1995; Szabo \textit{et al.}, 1995), and others do not start measuring until 10 weeks’ gestation (Nicolaides \textit{et
al., 1994; Pandya et al., 1995; Hafner et al., 1995). The accuracy of these studies varies enormously, with a reported sensitivity for the detection of Down syndrome ranging from 30% (Brambati et al., 1995; Bewley et al., 1995; Kornman et al., 1996) and 50% (Comas et al., 1995; Hafner et al., 1995) up to a sensitivity of 80% or more (Szabo et al., 1995; Nicolaides et al., 1994; Pandya et al., 1995). Differences in gestational age at time of measurement may explain the reported variation in performance. In a screening program for fetal trisomies, physiologic variation in nuchal translucency measurement must be taken into account, and a gestational age dependent cutoff point for normal should be adopted. Alternatively, if a single cutoff point is used, it is important to standardize the gestational age at which screening is performed.

Roberts et al. (1995) proposed 11 weeks as the optimal gestational age at which to measure the nuchal translucency because in their study, the failure rate in obtaining a measurement was lowest at this gestational age. Comas et al. (1995) proposed 12 weeks' gestation as the optimum time to screen because visualization of fetal anatomy is clearer. We were able to obtain good visualization of the nuchal translucency in all cases and at any observation. In the course of our study, all fetuses developed nuchal translucencies that were ultrasonographically visible. The study population was large enough to certify that 94% or more of the fetuses would develop a nuchal translucency thickness larger than 0 mm. At 77 days' (11 weeks) gestation, 97% of the fetuses had visible nuchal translucencies, which suggest that it may be appropriate to make the measurement from 11 weeks' gestation onward. Furthermore, an not measurable nuchal translucency at 70 days' (10 weeks) gestation could, theoretically, still increase above a chosen cutoff level for normal at a later gestational age. Because all fetuses in this study developed a measurable nuchal translucency by 86 days' gestation (12 weeks) gestation, it appears advisable to repeat the measurement at 12 weeks if the initial measurement is 0 mm. In contrast, a nuchal translucency that cannot be measured from 12 weeks' gestation onward may suggest that the waning phase of this temporary anatomic entity has already begun. It is possible that in the near future, with ongoing improvement in resolution and magnification of ultrasound equipment and the development of three-dimensional techniques, there no longer will be cases in which it is impossible to obtain a measurement even of the smallest nuchal translucency.

The developmental, functional, and biochemical natures of the anatomic entity defined as nuchal translucency are still unknown. Enlarged nuchal translucency measurements are encountered in both chromosomally normal and abnormal fetuses, but the pathophysiologic processes that induce the development of enlarged nuchal translucencies in both groups remains unclear. Longitudinal data on the natural course of nuchal translucency measurements in normal as well as aneuploid fetuses may help
Weekly NT measurement

in understanding the pathophysiological background of this entity and may possibly be of diagnostic value.

References


