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Effect of study design on the association between nuchal translucency measurement and Down syndrome

Ben W. J. Mol, MD, PhD, Jeroen G. Lijmer, MD, Jan van der Meulen, MD, PhD, Eva Pajkrt, MD, PhD, Caterina M. Bilardo, MD, PhD, and Patrick M. M. Bossuyt, PhD

Objective: To evaluate the effect of verification bias on the accuracy of first-trimester nuchal translucency measurement for Down syndrome detection.

Methods: We used MEDLINE and EMBASE to identify all papers relating the results of nuchal translucency measurement to fetal karyotype. The detected studies were scored for verification bias. Fifteen studies without and ten with verification bias were included.

Results: Sensitivity and specificity were calculated for each study. For studies with verification bias, adjusted estimates of the sensitivity were calculated assuming a fetal loss rate for Down syndrome pregnancies of 48%. The sample size weighted sensitivity was 55% in studies without and 77% in those with verification bias, for specificities of 96% and 97%, respectively. After adjustment for verification bias, the sample size weighted sensitivity changed from 77% to 63%.

Conclusion: Studies with verification bias reported higher sensitivities, but also slightly higher specificities of nuchal translucency measurement than studies without verification bias. The difference in sensitivity is greater than could be explained by verification bias. We postulate that the experience of the sonographist might be an explanation for the differences. (Obstet Gynecol 1999;94:864–9. © 1999 by The American College of Obstetricians and Gynecologists.)

Since the early 1990s, first-trimester nuchal translucency thickness has been recognized as a marker for Down syndrome. The probability of a Down syndrome pregnancy strongly increases with the nuchal translucency thickness. Detection rates of first-trimester nuchal translucency measurement vary between 29% and 100%, for a false-positive rate of approximately 5%, when a cutoff of about 3 mm is used.

The use of nuchal translucency measurement in the first trimester of pregnancy is still a controversial issue. Whereas in some centers nuchal translucency measurement has been implemented, others claim that no scientific arguments justify its implementation or that the emotional and financial implications of this screening need further investigation. In this debate, there seems to be little controversy about the diagnostic performance of nuchal translucency measurement itself.

Criticism has been raised about the design of studies that evaluate nuchal translucency measurement. Most studies performed in low-risk populations suffer from this verification bias because fetal karyotyping is restricted to women with an increased nuchal translucency thickness.

A second concern about most of the study designs is the association between an increased nuchal translucency thickness and an increased fetal loss rate. This association is reported in normal as well as Down syndrome pregnancies. If true, this association would reduce the value of nuchal translucency measurement because the Down syndrome pregnancies with an abnormal nuchal translucency measurement would be
less likely to result in live birth than Down syndrome pregnancies with a normal nuchal translucency.

To assess the impact of study design on the performance of nuchal translucency measurement, we compared published studies with and without verification bias.

Materials and Methods

A computerized search was performed with the keyword “nuchal” using MEDLINE and EMBASE (Excerpta Medica Medical Communications BV, Reed Elsevier plc, Amsterdam, The Netherlands) between January 1990 and February 1998 to identify articles reporting on the performance of nuchal translucency measurement for the detection of Down syndrome. In addition, references in the selected articles were checked for other studies on the subject. All articles comparing the result of nuchal translucency measurement and fetal karyotype were included in the analysis. To be included in the analysis, nuchal translucency measurements in each study had to be performed before 15 weeks’ gestation. Verification bias was suspected when fetal karyotyping was performed in fetuses with an increased nuchal translucency measurement, whereas pregnancy outcome was awaited in fetuses that showed a normal measurement. The gestational age at which nuchal translucency measurement was measured was also registered.

For each study, we calculated the sensitivity and specificity of nuchal translucency measurement in the detection of Down syndrome. Since the principal aim of nuchal translucency measurement is the prevention of live birth of Down syndrome-affected fetuses, pregnancies with other aneuploidies were considered normal in this calculation.

For studies with verification bias, we recalculated sensitivity and specificity after correction for verification bias, assuming an extremely high fetal loss rate of 48% (Hackshaw et al. Lancet 1996;348:1740).6 Assuming the observed number of false-negatives in studies with verification bias to be only 52% (100% – fetal loss rate), the true number of false-negatives should have been equal to the observed number of false-negatives, multiplied by 0.52⁻¹ [1/(1 – fetal loss rate)].

The results of the studies before and after adjustment for verification bias were plotted, and sample size weighted means of sensitivity and specificity were calculated. Logistic regression was used to compare the performance of nuchal translucency measurement in studies with and without verification bias. For this purpose, we pooled the results of the studies on the basis of the numbers of the pregnancies in each cell of the reconstructed 2 × 2 tables, considering the pregnancies as the units of study. Performance of nuchal translucency measurement was expressed as a diagnostic odds ratio (OR); the higher the diagnostic OR, the better the performance of nuchal translucency measurement.

To assess the association between the performance of nuchal translucency measurement and study size, we plotted for each study both sensitivity and specificity against the number of women incorporated in that particular study. The correlation between sensitivity and specificity on one hand and study size on the other hand was expressed by a Pearson correlation coefficient.

Results

Twenty-nine studies were found. Four studies had to be excluded, three because they reported on the overall detection rate for all aneuploidies, but not specifically Down syndrome,9–11 and one because it compared Down syndrome cases and normal controls in a non-consecutive way (Szabó J, Gellén J. Nuchal fluid accumulation in trisomy 21 detected by vaginosonography in first trimester [letter]. Lancet 1990;II:1133). Of the remaining 25 studies, ten suffered from verification bias,3,12–20 whereas 15 did not (Table 1) (Haddow JE, Palomaki GE. Down syndrome screening [letter]. Lancet 1996;347:1625).2,21–33 Figure 1A shows the sensitivity and specificity reported by the included 25 studies. The studies affected by verification bias tended to report a higher sensitivity and specificity than the ones without verification bias. This was confirmed by logistic regression analysis, which showed that the performance reported in studies affected by verification bias was four times better than that reported in studies not affected by verification bias (relative diagnostic OR 4.2, 95% confidence intervals [CI] 2.7, 6.6). The sample size weighted mean sensitivity calculated from studies affected by verification bias was 77% for a specificity of 97%. In studies without verification bias, a sample size weighted mean sensitivity of 55% could be calculated for a specificity of 96%.

Figure 1B shows the adjusted sensitivity and specificity of nuchal translucency measurement for studies with verification bias, assuming a fetal loss rate of 48% between the moment of nuchal translucency measurement and birth. The sample size weighted adjusted sensitivity was 63%, which was still 8% higher than the sensitivity reported in studies without verification bias. Logistic regression analysis showed that even with adjusted sensitivities, estimates of studies with verification bias reported significantly better performance of nuchal translucency measurement than studies without verification bias (relative diagnostic OR 2.1, 95% CI 1.4, 3.5).

The reported gestational age at which nuchal tran-
lucency thickness was measured varied between 8 and 14 weeks. Studies in which nuchal translucency thickness measurements began at 8 weeks performed slightly better than studies in which these measurements began at 10 weeks, but this difference was not statistically significant (relative diagnostic OR 1.6, 95% CI 0.93, 2.7). Incorporation of the presence of verification bias and the gestational age at which nuchal translucency was measured in one logistic model did not alter the effect of verification bias.

Figure 2 shows the sensitivity and specificity of nuchal translucency measurement in relation to study size. There seemed to be no relation between sensitivity and sample size (r = 0.09; P = 0.56), whereas the specificity clearly improved with study size (r = 0.58; P = 0.02).

Discussion
This study suggests that the sensitivity of nuchal translucency measurement is considerably overestimated in studies in which the decision to perform fetal karyotyping depends on the result of nuchal translucency measurement. The overestimation of the sensitivity can be understood if one realizes that in studies in which the results of the nuchal translucency measurement were used in the decision for karyotyping, a significant

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Table 1. Studies Reporting on the Performance of Nuchal Translucency Measurement in the Diagnosis of Chromosomal Abnormalities

<table>
<thead>
<tr>
<th>Study (y)</th>
<th>No. of patients</th>
<th>Cutoff value (mm)</th>
<th>Gestational age (wk)</th>
<th>Trisomy 21 TP</th>
<th>No trisomy 21 FN</th>
<th>Prevalence of Down syndrome (%)</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
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<tbody>
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<td>Studies with verification bias</td>
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<td></td>
<td></td>
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<tr>
<td>Hafner et al23 (1995)</td>
<td>1972</td>
<td>2.5</td>
<td>10–14</td>
<td>2</td>
<td>24</td>
<td>1944</td>
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<td>3</td>
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<td>28</td>
<td>68</td>
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<td>*</td>
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<td>978,317</td>
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<td>5</td>
<td>34</td>
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<td>3</td>
<td>27</td>
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<td>*</td>
<td>&gt;10</td>
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<td>38</td>
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<td>0.91</td>
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<td>*</td>
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<td>168</td>
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<td>Pakk et al20 (1998)</td>
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<td>3</td>
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<td>6</td>
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<td>32</td>
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<td>Studies without verification bias</td>
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<td>13</td>
<td>8</td>
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<tr>
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<td>10–13</td>
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<td>2</td>
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<td>3</td>
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<td>3</td>
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<td>7</td>
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<td>445</td>
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<td>10</td>
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<td>139</td>
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<td>1.3</td>
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<td>3212</td>
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<td>212</td>
<td>2,968</td>
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<td>Martinez et al26 (1997)</td>
<td>553</td>
<td>3.5</td>
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<td>4</td>
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<td>26</td>
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<td>487</td>
<td>3</td>
<td>10–13</td>
<td>8</td>
<td>10</td>
<td>35</td>
<td>434</td>
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<tr>
<td>Orlandi et al26 (1997)</td>
<td>744</td>
<td>3</td>
<td>9–15</td>
<td>4</td>
<td>3</td>
<td>46</td>
<td>691</td>
<td>0.9</td>
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<td>Hafner et al26 (1996)</td>
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<td>3</td>
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<td>71</td>
<td>4,155</td>
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<td></td>
<td></td>
<td>1.1</td>
<td>0.55</td>
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</table>

TP = true positive; FN = false negative; FP = false positive; TN = true negative; Sens = sensitivity; Spec = specificity.
* Cutoff was at the 95th percentile limit, but its value was unspecified.
† Cutoff was at the 99th percentile limit, but its value was unspecified.

Figure 1. Receiver operating characteristic plot of studies comparing nuchal translucency measurement in the discrimination between normal and abnormal karyotype before (A) and after (B) correction for verification bias. The closed symbols represent studies with verification bias, whereas the open circles represent studies with verification bias.
number of Down syndrome fetuses were not identified, especially in the group with a normal nuchal translucency. This issue should be taken into account in the interpretation of studies with such a design. The difference in sensitivity reported by studies with and without verification bias could be explained only partly by a fetal loss rate of about 50% between the moment of nuchal translucency measurement and birth.

Even after adjustment for verification bias, the sensitivity reported in studies with verification bias remained higher than the sensitivity reported in studies without verification bias. The use of lower cutoff levels for test-positivity is an unlikely explanation, since only one study affected by verification bias used cutoff levels of 2.5 mm. However, the majority of studies used cutoff levels of 3 mm, and two studies used even higher cutoff levels. Furthermore, the expected decrease in specificity with increasing sensitivity as a consequence of lower cutoff levels was not observed in our analysis.

A second possible explanation for the differences in test performance may be the result of acquired technical experience, because studies were not done by uniformly trained operators. The better specificity observed in studies affected by verification bias could be the result of skill and experience, since these studies were usually larger. Schuchter et al showed that the specificity of nuchal translucency measurement improved if the measurements were repeated, up to six times. Unfortunately, the studies included in the present meta-analysis do not allow for assessment of exact methodology for nuchal translucency measurement or for the level of training of the sonographers in the technique of nuchal translucency measurement. This might explain the great variance among the reported detection rates, even within the subgroups of studies with and without verification bias.

Selection bias may be a third explanation for the observed differences in sensitivity. Selection bias occurs if pregnancies with an increased nuchal translucency thickness are more likely to be included in the study than pregnancies with a normal nuchal translucency thickness. The difference with verification bias is that when selection bias is present, fetuses with a normal nuchal translucency are less likely to be included in the study, whereas when verification bias is present, women with a normal nuchal translucency are always included, but their pregnancy is less likely to be karyotyped. Therefore, selection bias results in an overestimation of the sensitivity and underestimation of the specificity, whereas in this case, verification bias only affects the sensitivity. The presence of selection bias could be ascertained only in three small studies unaffected by verification bias. Both the sensitivity and the specificity were better in studies with verification bias, which speaks against selection bias.

It has been suggested that the risk of fetal loss in pregnancies with increased nuchal translucency is twice as high as in pregnancies with a normal nuchal translucency. This association between fetal loss and nuchal translucency would reduce the increasing effect of verification bias on sensitivity, because fetal loss is more likely to occur in Down syndrome pregnancies with an increased nuchal translucency (since these would be terminated) and less likely to occur in Down syndrome pregnancies with normal nuchal translucency (since these might be identified at birth as pregnancies with false-negative translucency). In other words, if an increased nuchal translucency is indeed linked to a higher fetal loss rate, verification bias increases the sensitivity to a lesser extent than we have adjusted for in our review. This implies that the differences in sensitivities between studies with and without verification might be even larger than the 8% difference we presented after adjustment for verification bias. On the other hand, a higher fetal loss rate in Down syndrome pregnancies with increased nuchal translucency might considerably reduce the clinical value of nuchal translucency measurement, because nuchal translucency would detect Down syndrome pregnancies that would not result in the birth of viable infants.

A last explanation could be that in studies with verification bias, in which pregnancy outcome is awaited after a normal pregnancy, some Down syndrome pregnancies that resulted in a live birth were not recognized as such immediately after birth. It is therefore of importance to compare the number of Down syndrome fetuses with a normal nuchal translucency thickness.
syndrome fetuses observed in a study with the expected number of Down syndrome fetuses, based on the distribution of maternal age in that study. Such data were recently provided by Snijders et al in a study that reported on over 100,000 women, thereby being the largest cohort thus far.\textsuperscript{35} This study, not included in the present analysis since it was published after February 1998, is an extension of the study published by Pandya et al.\textsuperscript{14} It is a study with verification bias, and the sensitivity of nuchal translucency measurement is 71% for a specificity of 4.6%, a result concordant with the present meta-analysis. Among the 100,000 pregnancies, Snijders et al expected 266 infants born with Down syndrome, in the absence of screening. Haddow showed that this number corresponded with 443 Down syndrome fetuses at the moment of nuchal translucency measurement, and that the detection rate of nuchal translucency measurement in combination with maternal age was only 60%, rather than the 82% reported by the author.\textsuperscript{36} Apart from this correction of the detection rate, comparison of the expected and observed number of Down syndrome cases raises the suspicion that not all live born Down syndrome newborns are recognized as such. From the 443 expected Down syndrome pregnancies at 12 weeks, 268 were detected. From the remaining 175 Down syndrome pregnancies, one would expect about 90 fetuses to result in live birth. However, in the study of Snijders et al, there were only 58 Down syndrome pregnancies not detected by nuchal translucency measurement. This discrepancy shows that some Down syndrome pregnancies with a nuchal translucency measurement less than 3 mm were not detected as such. The same mechanism might also explain the high sensitivity in some studies with verification bias.

References

25. Hewitt BG, De Crespiiny L, Sampson AJ, Ngu ACC, Shekleton P,
Tocolytics for preterm labor: A systematic review

Kristen Gyetvai, Mary E. Hannah, MDCM, Ellen D. Hoñnett, PhD, and Arne Ohlsson, MD

Objective: To examine the effectiveness of any tocolytic compared with a placebo or no tocolytic for preterm labor.

Data Sources: We checked MEDLINE (1966–1998) and the Cochrane Controlled Trials Register for articles, using the search terms “randomized controlled trial” (RCT), “preterm labor,” “tocolysis,” “betamimetics,” “ritodrine,” “terbutaline,” “hexaprenaline,” “isoxuprine,” “prostaglandin synthetase inhibitors,” “indomethacin,” “sulindac,” “calcium channel blockers,” “nifedipine,” “oxytocin receptor blockers,” “atosiban,” “nitroglycerine,” and “magnesium sulfate.”

Methods of Study Selection: We included all RCTs that compared effect of a tocolytic with a placebo or no tocolytic in women in preterm labor, and reported perinatal, neonatal, or maternal outcomes. Studies were excluded if loss to follow-up exceeded 20% of those originally enrolled, or if data were not reported on a per-patient-treated basis. Eighteen of 76 articles retrieved met the inclusion criteria.

Tabulation, Integration, and Results: Two authors independently reviewed the articles and abstracted the data. Discrepancies were resolved by consensus. Meta-analyses (odds ratio [OR] and 95% confidence interval [CI]) were done for each outcome for all trials and for specific types of tocolytic therapy when possible. Tocolytics decreased the risk of delivery within 7 days (OR 0.60, 95% CI 0.38, 0.95). Betamimetics, indomethacin, atosiban, and ethanol, but not magnesium sulfate, were associated with significant prolongations in pregnancy. Tocolytics were not associated with improved perinatal outcomes. Maternal side effects significantly associated with tocolytic use were palpitations, nausea, tremor, chorioamnionitis, hyperglycemia, hypokalemia, and need to discontinue treatment.

Conclusion: Although tocolytics prolong pregnancy, they have not been shown to improve perinatal or neonatal outcomes and have adverse effects on women in preterm labor. (Obstet Gynecol 1999;94:869–77. © 1999 by The American College of Obstetricians and Gynecologists.)