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Reviews

EFFECT OF STUDY DESIGN ON THE ASSOCIATION BETWEEN NUCHAL TRANSLUCENCY MEASUREMENT AND DOWN SYNDROME

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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 sonographer might be an explanation for the differences. (Obstet Gynecol 1999;94:864–9. © 1999 by The American College of Obstetricians and Gynecologists.)

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Since the early 1990s, first-trimester nuchal translucency thickness has been recognized as a marker for Down syndrome.¹ 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.^{2,3}

The use of nuchal translucency measurement in the first trimester of pregnancy is still a controversial issue.⁴ 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 (Mol BWJ, Pajkrt E, Van Lith JMM, Bilardo CM. Screening for fetal trisomies by maternal age and fetal nuchal translucency thickness at 10 to 14 weeks of gestation [letter]. *Br J Obstet Gynaecol* 1996;103:1051–2; Hackshaw AK, Wald NJ, Haddow JE. Down syndrome screening with nuchal translucency [letter]. *Lancet* 1996;348:1740). Fetuses with an increased nuchal translucency thickness were more likely to undergo fetal karyotyping than fetuses with a normal nuchal translucency thickness in some studies. This implies that Down syndrome fetuses with an increased nuchal translucency thickness almost always were detected, whereas the false-negatives, ie, Down syndrome fetuses with a normal nuchal translucency thickness, had about a 50% chance of being missed due to fetal loss.⁵ This type of bias in the evaluation of diagnostic tests is known as verification (or ascertainment) bias and occurs when the selection for verification of the diagnosis depends on the results of the test under study.⁶ In the case of nuchal translucency measurement, verification bias is likely to cause an overestimation of the detection rate. Most studies performed in low-risk populations suffer from this verification bias because fetal karyotyping is restricted to women with an increased fetal 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.^{7,8} 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% ($100\% - \text{fetal loss rate}$), the true number of false-negatives should have been equal to the observed number of false-negatives, multiplied by $0.52^{-1} [1/(1 - \text{fetal loss rate})]$.

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 pregnan-

cies 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 trans-

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

Study (y)	No. of patients	Cutoff value (mm)	Gestational age (wk)	Trisomy 21		No trisomy 21		Prevalence of Down syndrome (%)	Sens (%)	Spec (%)
				TP	FN	FP	TN			
Studies with verification bias										
Hafner et al ¹³ (1995)	1972	2.5	10–14	2	2	24	1944	0.2	0.50	0.99
Szabo et al ³ (1995)	3380	3	9–15	28	3	68	3281	0.9	0.90	0.98
Pandya et al ¹⁴ (1995)	20,381	*	10–13	66	20	978	19,317	0.4	0.77	0.95
Kornman et al ¹² (1996)	923	3	<10	2	5	34	882	0.8	0.29	0.96
Kadir and Economides ¹⁶ (1997)	1302	†	10–13	5	1	17	1279	0.5	0.83	0.99
Taipale et al ¹⁵ (1997)	10,010	3	10–16	7	6	69	9928	0.1	0.54	0.99
D'Ottavio et al ¹⁷ (1997)	3509	4	13–15	7	3	27	3472	0.3	0.70	0.99
Spencer et al ¹⁸ (1997)	416	*	>10	20	2	38	356	0.3	0.91	0.91
Theodoroupolos et al ¹⁹ (1998)	3550	*	10–14	10	1	168	3371	0.3	0.91	0.95
Pajkrt et al ²⁰ (1998)	1473	3	10–14	6	3	32	1432	0.7	0.66	0.98
Pooled estimate	46,916							0.4	0.77	0.97
Studies without verification bias										
Savoldelli et al ²¹ (1993)	1400	3	10–14	15	13	8	1364	2.0	0.54	0.99
Nicolaides et al ²² (1994)	1273	3	10–13	21	4	64	1184	2.0	0.84	0.95
Bewley et al ²³ (1995)	1127	3	8–14	1	2	69	1055	0.3	0.33	0.94
Comas et al ²⁴ (1995)	481	3	9–13	4	3	47	427	1.5	0.57	0.90
Salvesen and Goble ² (1995)	96	3	11–14	3	0	7	86	0.3	1.0	0.92
Hewitt et al ²⁵ (1996)	1312	3	9–13	12	9	52	1239	1.6	0.57	0.96
Scott et al ²⁷ (1996)	445	2.5	10–13	3	7	27	408	2.3	0.30	0.94
Zimmerman et al ²⁸ (1996)	1151	3	10–13	2	2	29	1118	0.3	0.50	0.97
Haddow and Palomaki [‡] (1996)	2348	*	10–14	10	20	139	2179	1.3	0.33	0.94
Biagiotti et al ²⁹ (1997)	3212	3	10–13	17	15	212	2968	1.0	0.53	0.93
Martinez et al ³⁰ (1997)	553	3.5	9–13	4	5	26	518	1.6	0.44	0.95
Borrell et al ³¹ (1997)	487	3	10–13	8	10	35	434	0.4	0.44	0.93
Orlandi et al ³² (1997)	744	3	9–15	4	3	46	691	0.9	0.57	0.94
Hafner et al ³³ (1998)	4233	2.5	10–13	3	4	71	4155	0.2	0.43	0.98
Pajkrt et al ²⁶ (1998)	2212	3	10–14	25	11	91	2085	1.7	0.69	0.95
Pooled estimate	21,074							1.1	0.55	0.96

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.

‡ Haddow JE, Palomaki GE. Down syndrome screening [letter]. *Lancet* 1996;347:1625.

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 ($r = .09$; $P = .56$), whereas the specificity clearly improved with study size ($r = .58$; $P = .02$).

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

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.

Figure 2. Sensitivity and specificity of nuchal translucency measurement in relation to study size. Whereas there seems to be no relation between sensitivity and study size, the specificity is higher in larger studies.

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.¹³ However, the majority of studies used cutoff levels of 3 mm, and two studies used even higher cutoff levels.^{16,17} 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.³⁴ 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.^{25,28,32} 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.⁸ 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 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.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.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.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

1. Nicolaides KH, Azar G, Byrne D, Mansur C, Marks K. Fetal nuchal translucency: Ultrasound screening for chromosomal defects in first trimester of pregnancy. *BMJ* 1992;304:867-9.
2. Salvesen DR, Goble O. Early amniocentesis and fetal nuchal translucency measurement in women requesting fetal karyotype for advanced maternal age. *Prenat Diagn* 1995;15:971-4.
3. Szabó J, Gellén J, Szemere G. First-trimester ultrasound screening for fetal aneuploidies in women over 35 and under 35 years of age. *Ultrasound Obstet Gynecol* 1995;5:161-3.
4. Neilson JP. Assessment of fetal nuchal translucency for Down syndrome. *Lancet* 1997;350:754-5. Comment in *Lancet* 1997;350:1629-32.
5. Macintosh MCM, Wald NJ, Chard T, Hansen J, Mikkelsen M, Therkelsen AJ, et al. Selective miscarriage of Down syndrome fetuses in women aged 35 years and older. *Br J Obstet Gynaecol* 1995;102:798-801.
6. Begg CB, McNeil BJ. Assessment of radiologic tests: Control of bias and other design considerations. *Radiology* 1988;167:565-9.
7. Bilardo CM, Pajkrt E, De Graaf I, Mol BWJ, Bleker OP. Outcome of

fetuses with enlarged nuchal translucency and normal karyotype. *Ultrasound Obstet Gynecol* 1998;11:401-6.

8. Hyett JA, Sebire NJ, Snijders RJ, Nicolaides KH. Intrauterine lethality of trisomy 21 fetuses with increased nuchal translucency thickness. *Ultrasound Obstet Gynecol* 1996;7:101-3.
9. Brambati B, Cislighi C, Tului L, Alberti E, Amidani M, Colombo U, et al. First-trimester Down syndrome screening using nuchal translucency: A prospective study in patients undergoing chorionic villus sampling. *Ultrasound Obstet Gynecol* 1995;5:9-14.
10. Jauniaux E, Gravill P, Khun P, Kurdi W, Hyett J, Nicolaides KH. Fetal heart rate and umbilico-placental Doppler flow velocity waveforms in early pregnancies with a chromosomal abnormality and/or increased nuchal translucency thickness. *Hum Reprod* 1996;11:435-9.
11. Hernadi L, Torocsik M. Screening for fetal anomalies in the 12th week of pregnancy by transvaginal sonography in an unselected population. *Prenat Diagn* 1997;17:753-9.
12. Kornman LH, Morssink LP, Beekhuis JR, De Wolf BTHM, Peringa MP, Mantingh A. Nuchal translucency cannot be used as a screening for chromosomal abnormalities in the first trimester of pregnancy in a routine ultrasound practice. *Prenat Diagn* 1996;16:797-805.
13. Hafner E, Schuchter K, Philipp K. Screening for chromosomal abnormalities in an unselected population by fetal nuchal translucency. *Ultrasound Obstet Gynecol* 1995;6:330-3.
14. Pandya PP, Snijders RJM, Johnson SP, De Lourdes Brizot M, Nicolaides KH. Screening for fetal trisomies by maternal age and fetal nuchal translucency thickness at 10 to 14 weeks of gestation. *Br J Obstet Gynaecol* 1995;102:957-62.
15. Taipale P, Hjilesmaa V, Salonen R, Ylostalo P. Increased nuchal translucency as a marker for fetal chromosomal defects. *N Engl J Med* 1997;337:1654-8.
16. Kadir RA, Economides DL. The effect of nuchal translucency measurement on second-trimester biochemical screening for Down syndrome. *Ultrasound Obstet Gynecol* 1997;9:244-7.
17. D'Ottavio G, Meir YJ, Rustico MA, Pecile V, Fischer-Tamaro L, Conoscenti G, et al. Screening for fetal anomalies by ultrasound at 14 and 21 weeks. *Ultrasound Obstet Gynecol* 1997;10:375-80.
18. Spencer K, Noble P, Snijders RJM, Nicolaides KH. First trimester free beta hCG, beta core and total oestriol in pregnancies affected by Down syndrome: Implications for first-trimester screening with nuchal translucency and serum free beta hCG. *Prenat Diagn* 1997;17:525-38.
19. Theodoropoulos P, Lolis D, Papageorgiou S, Papaioannou S, Plachouras N, Makrydimas G. Evaluation of first-trimester screening by fetal nuchal translucency and maternal age. *Prenat Diagn* 1998;18:133-7.
20. Pajkrt E, Van Lith JJM, Mol BWJ, Bleker OP, Bilardo CM. Screening for Down syndrome by fetal nuchal translucency measurement in a general obstetric population. *Ultrasound Obstet Gynecol* 1998;12:163-9.
21. Savoldelli G, Binkert F, Achermann J, Schmid W. Ultrasound screening for chromosomal anomalies in the first trimester of pregnancy. *Prenat Diagn* 1993;13:513-8.
22. Nicolaides KH, Brizot ML, Snijders RJM. Fetal nuchal translucency: Ultrasound screening for fetal trisomy in the first trimester of pregnancy. *Br J Obstet Gynaecol* 1994;101:782-6.
23. Bewley S, Roberts LJ, Mackinson AM, Rodeck CH. First-trimester fetal nuchal translucency: Problems with screening the general population. *Br J Obstet Gynaecol* 1995;102:386-8.
24. Comas C, Martinez JM, Ojuel J, Puerto B, Borrell A, Fortuny A. First-trimester nuchal edema as a marker of aneuploidy. *Ultrasound Obstet Gynecol* 1995;5:26-9.
25. Hewitt BG, De Crespigny L, Sampson AJ, Ngu ACC, Shekleton P,

- Robinson HP. Correlation between nuchal thickness and abnormal karyotype in first trimester fetuses. *Med J Aust* 1996;165:365-8.
26. Pajkrt E, Mol BWJ, Van Lith JMM, Bleker OP, Bilardo CM. Screening for Down syndrome by fetal nuchal translucency measurement in a high-risk population. *Ultrasound Obstet Gynecol* 1998;12:156-62.
 27. Scott F, Boogert A, Sinosich M, Anderson J. Establishment and application of a normal range for nuchal translucency across the first trimester. *Prenat Diagn* 1996;16:629-34.
 28. Zimmerman R, Hucha A, Salvodelli G, Blinkert F, Achermann, Grudzinskas JG. Serum parameters and nuchal translucency in first trimester screening for fetal chromosomal abnormalities. *Br J Obstet Gynaecol* 1996;103:1009-14.
 29. Biagiotti R, Periti E, Brizzi L, Vanzi E, Cariatti E. Comparison between two methods for standardization for gestational age differences in fetal nuchal translucency measurement in first-trimester screening for trisomy 21. *Ultrasound Obstet Gynecol* 1997;9:248-52.
 30. Martinez JM, Borrell A, Antolin E, Puerto B, Casals E, Ojuel J, et al. Combining nuchal translucency with umbilical Doppler velocimetry for detecting fetal trisomies in the first trimester of pregnancy. *Br J Obstet Gynaecol* 1997;104:11-4.
 31. Borrell A, Costa D, Martinez JM, Delgado RD, Farguell T, Fortuny A. Criteria for fetal nuchal thickness cutoff: A re-evaluation. *Prenat Diagn* 1997;17:23-9.
 32. Orlandi F, Daminai G, Hallahan TW, Krantz DA, Macri JN. First-trimester screening for fetal aneuploidy: Biochemistry and nuchal translucency. *Ultrasound Obstet Gynecol* 1997;10:381-6.
 33. Hafner E, Schuchter K, Liebhart E, Philipp K. Results of routine fetal nuchal translucency measurement at weeks 10-13 in 4223 unselected pregnant women. *Prenat Diagn* 1998;18:29-34.
 34. Schuchter K, Wald NJ, Hacksaw AK, Hafner E, Liebhart E. The distribution of nuchal translucency in 10-13 weeks pregnancy. *Prenat Diagn* 1998;18:281-6.
 35. Snijders RJ, Noble P, Sebire NJ, Souka A, Nicolaides KH. UK multicentre project on the assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks gestation. *Lancet* 1998;351:343-6.
 36. Haddow JE. Antenatal screening for Down syndrome: Where are we and where next? [editorial]. *Lancet* 1998;352:366-7.

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TOCOLYTICS FOR PRETERM LABOR: A SYSTEMATIC REVIEW

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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," "nitroglyceride," and "magnesium sulfate."

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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.)