Second-Trimester Ultrasound to Detect Fetuses With Down Syndrome

A Meta-analysis

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Context Second-trimester prenatal ultrasound is widely used in an attempt to detect Down syndrome in fetuses, but the accuracy of this method is unknown.

Objective To determine the accuracy of second-trimester ultrasound in detecting Down syndrome in fetuses.

Data Sources English-language articles published between 1980 and February 1999 identified through MEDLINE and manual searches.

Study Selection Studies were included if they recorded second-trimester findings of ultrasonographic markers, chromosomal abnormalities, and clinical outcomes for a well-described sample of women. A total of 56 articles describing 1930 fetuses with Down syndrome and 130365 unaffected fetuses were included.

Data Extraction Articles were independently reviewed, selected, and abstracted by 2 reviewers. Discrepancies in data abstraction were resolved by consensus with a third reviewer. Overall estimates of sensitivity, specificity, and positive and negative likelihood ratios were calculated for the following markers: choroid plexus cyst, thickened nuchal fold, echogenic intracardiac focus, echogenic bowel, renal pyelectasis, and humeral and femoral shortening. Results were stratified by whether markers were identified in isolation or in conjunction with fetal structural malformations.

Data Synthesis When ultrasonographic markers were observed without associated fetal structural malformations, sensitivity for each was low (range, 1%-16%), and most fetuses with such markers had normal outcomes. A thickened nuchal fold was the most accurate marker for discriminating between unaffected and affected fetuses and was associated with an approximately 17-fold increased risk of Down syndrome. If a thickened nuchal fold is used to screen for Down syndrome, 15893 average-risk women or 6818 high-risk women would need to be screened for each case of Down syndrome identified. For each of the other 6 markers, when observed without associated structural malformations, the marker had marginal impact on the risk of Down syndrome. Because the markers were detected in only a small number of affected fetuses, the likelihood of Down syndrome did not decrease substantially after normal examination findings (none of the negative likelihood ratios were significant).

Conclusions A thickened nuchal fold in the second trimester may be useful in distinguishing unaffected fetuses from those with Down syndrome, but the overall sensitivity of this finding is too low for it to be a practical screening test for Down syndrome. When observed without associated structural malformations, the remaining ultrasonographic markers could not discriminate well between unaffected fetuses and those with Down syndrome. Using these markers as a basis for deciding to offer amniocentesis will result in more fetal losses than cases of Down syndrome detected, and will lead to a decrease in the prenatal detection of fetuses with Down syndrome.

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CHROMOSOMAL ABNORMALITIES occur in 0.1% to 0.2% of live births,[1-4] and the most common clinically significant chromosomal abnormality among liveborn infants is Down syndrome (trisomy 21). Aside from mental retardation, infants with Down syndrome are at high risk of having associated structural defects, including congenital heart disease, craniofacial abnormalities, and gastrointestinal abnormalities.[5] Having a child with Down syndrome can be traumatizing and disruptive to families, and the financial burden, including health care expenditures, physical therapy, and special education, can be substantial.[6,7] There has been a growing interest in the prenatal detection of affected fetuses so that parents can be prepared for the birth of an affected child or consider pregnancy termination.

The incidence of Down syndrome increases with maternal age,[1,8] and until 1984, advanced maternal age was the only factor usually considered to identify those at sufficiently high enough risk to justify amniocentesis and fetal karyotyping. Subsequently, the levels of 4 maternal serum biochemical markers in the second trimester of pregnancy—alpha fe-

See also Patient Page.

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toprotein, human chorionic gonadotropin, estriol, and inhibin A—have been found to be associated with Down syndrome.[9-11] Second-trimester maternal biochemical serum screening for abnormal levels of some or all of these markers is now part of routine obstetrical care in the United States and allows the detection of approximately 60% of cases of Down syndrome, with a false-positive rate of 7%.[12-14] Since there is considerable overlap of maternal serum values for unaffected and chromosomally abnormal fetuses, a positive screening test result needs to be followed by a diagnostic test. Amniocentesis can reliably determine fetal karyotype, but there is a 0.5% to 1.0% fetal mortality rate associated with this procedure.[15-20]

Most pregnant women undergo prenatal ultrasound during the second trimester as a routine part of antenatal care, and the majority are not at elevated risk of having a fetus with Down syndrome based on age or serum testing results. A high percentage of chromosomally abnormal fetuses have structural abnormalities that might be recognized on prenatal ultrasound, although these have typically been difficult to detect.[21-40] Several sonographic "markers" have also been reported to be associated with chromosomal abnormalities, including choroid plexus cysts and nuchal fold thickening. While not pathologic themselves, these markers have been used to screen for or adjust the risk for Down syndrome.[41-47] Two previous quantitative summaries of second-trimester ultrasound for the detection of Down syndrome have been published[48,49]; however, both pooled the results of all studies despite profoundly inconsistent results, and neither study stratified the results by whether the markers were seen in conjunction with fetal structural abnormalities. Thus, the true accuracy of the markers is unknown.

While ultrasound has potential to improve the performance of a Down syndrome screening program, it can also cause harm by prompting unnecessary medical intervention, anxiety related to false-positive findings, and false reassurance to women with affected pregnancies who may be dissuaded from undergoing a diagnostic test because of a normal ultrasound result.[49,50] We reviewed the literature and used meta-analytic techniques to estimate the accuracy of prenatal ultrasound in screening for Down syndrome.

METHODS

Data Sources

We performed a MEDLINE search for articles published between January 1980 and February 1999 and manually searched bibliographies of relevant published articles. The MEDLINE search included the following second-trimester ultrasonographic markers that have been reported to be associated with chromosomal abnormalities: *choroid plexus cyst, nuchal fold thickening, echogenic intracardiac focus, echogenic bowel, renal pyelectasis, shortened humerus, shortened femur,* and *fetal structural malformations*. Additional MEDLINE search terms included *Down syndrome, trisomy 21, prenatal ultrasound, chromosomal abnormality, diagnostic tests, biochemical testing,* and *genetic ultrasound*. Review articles, letters, case reports, comments, and non–English-language articles were excluded.

Study Selection

Articles were independently selected and reviewed, and their data were extracted by 2 investigators. Studies were included that recorded second-trimester prenatal ultrasonographic markers and outcome information on a well-described sample of women, and from which estimates of sensitivity and specificity could be calculated (n = 220). Retrospective studies were included provided that the original ultrasound interpretation was used. Active ascertainment of all pregnancy outcomes by chromosomal analysis or visual inspection was required for study inclusion. Studies were excluded if they reported fewer than 5 fetuses with a chromosomal abnormality (n=15); obtained outcome data only on fetuses with a specific ultrasound finding (n=68); had incomplete follow-up (n=11); performed the ultrasound following genetic testing (n=7); or were primarily focused on a different topic (eg, only looked at major structural abnormalities or had no information on clinical outcomes) (n=45). Studies that were based on first-trimester ultrasound were not included (n=18). When relevant data could not be extracted from published articles, the corresponding author was contacted to obtain additional information (n=5, 1 of whom responded.) For studies that resulted in multiple publications, data from the most recent publication were used. A full list of excluded studies is available from the authors with reasons for their exclusion.

Data Abstraction

Data were abstracted for each of the following ultrasonographic markers: choroid plexus cyst, nuchal fold thickening, echogenic intracardiac focus, echogenic bowel, renal pyelectasis, shortened humerus, shortened femur, and fetal structural malformations. Data are not presented for the following: shortened ear length, shortened middle phalanx, sandal gap deformity, and increased iliac angle (other markers of Down syndrome), because fewer than 5 articles were found for each and most did not meet the inclusion criteria. The types of fetal structural abnormalities were recorded by organ system (central nervous system, neck, heart, lung, intestine, renal, face, other, and unspecified) and included a range of malformations.

For each article, 2 of the authors abstracted and recorded the number of true-positive, false-positive, true-negative, and false-negative results for each of the markers. Whenever possible, data were abstracted separately for the markers seen as an isolated abnormality or in combination with fetal structural malformations. The following definitions of the markers were used: choroid plexus cysts, cysts of any size or number in the cerebral ventricles (FIGURE 1A); nuchal fold thickening, thickness of 6 mm or greater (Figure 1B); echogenic intracardiac focus, punctate intracardiac echogenic focus within either ventricle (Figure 1C); renal pyelectasis, anterior-posterior diameter of the renal pelvis of 4 mm or greater (Figure

1D); and echogenic bowel, echogenicity (brightness) equal to or greater than bone (Figure 1E). Data were abstracted for more than 90% of the studies using these definitions. Femur and humerus shortening were less consistently defined (not shown). They were most often defined as an observed-to-expected length ratio of less than 0.90, and the expected length was based on the biparietal diameter using an equation generated from a normal population. Seven of the 11 humerus and 19 of the 29 femur studies used these definitions. In 8 of the femur studies, the definition of a shortened femur was a ratio of biparietal diameter to femur length of greater than 1.5 SDs from the mean for the normal population.

Because some of the abnormal ultrasound findings have been described in association with other chromosomal anomalies as well as Down syndrome, 3 fetal outcomes were considered: unaffected, Down syndrome, or all chromosomal abnormalities when data for Down syndrome alone were unavailable. All chromosomal abnormalities was the outcome used in 50% of the articles relating to the finding of choroid plexus cyst. For the other ultrasonographic markers, we were able to abstract data specifically for Down syndrome from the vast majority of articles.

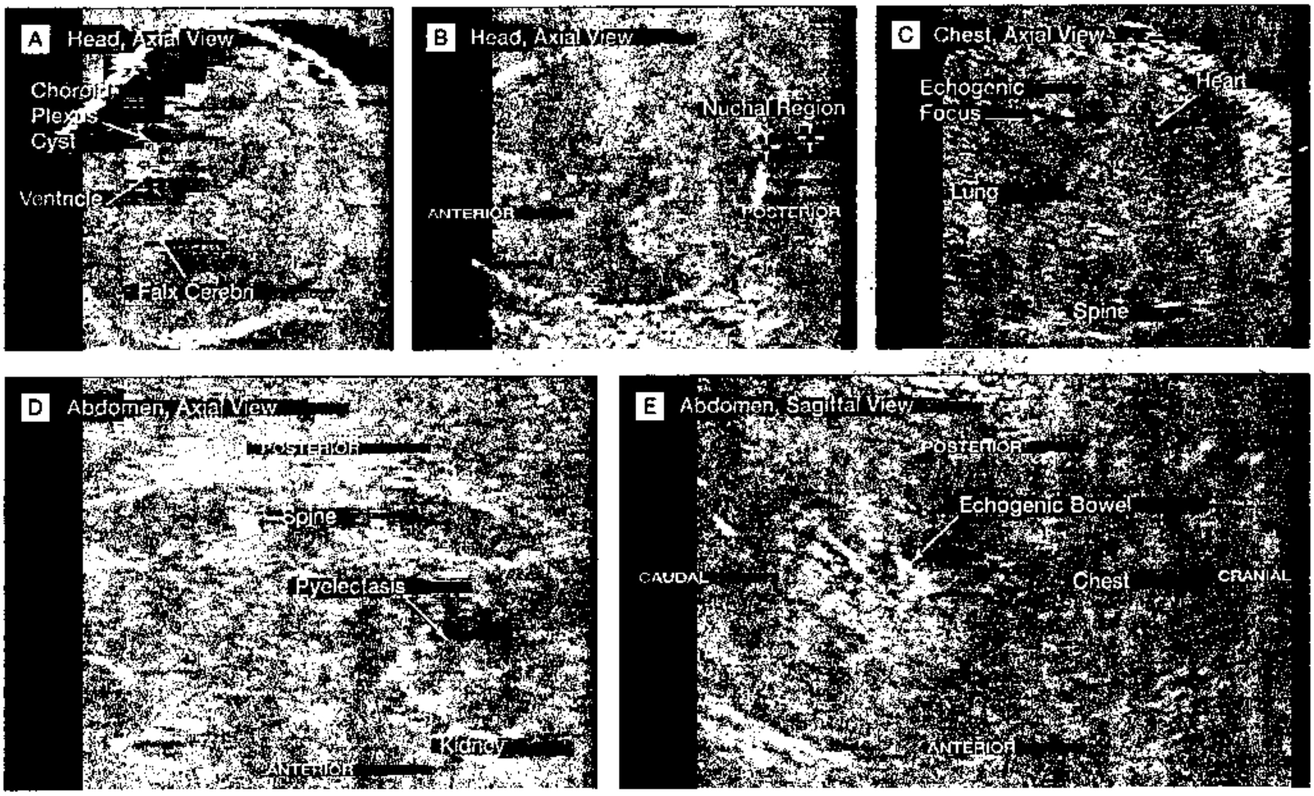
For each article, the study date, maternal risk of chromosomal abnormality, and the presence and type of structural abnormalities were recorded. Discrepancies in data abstraction between investigators were resolved by reaching a consensus with a third author.

Data Synthesis

For each study, the sensitivity, specificity, and exact 95% confidence intervals (CIs) were calculated for each of the ultrasound findings. Although we used narrow definitions for each of the markers, studies may have used varying implicit definitions for an abnormal result.[51] Before we combined the results across studies, we sought evidence of a trade-off between sensitivity and specificity introduced through varying thresholds by testing for a correlation between true-positive and false-positive rates.[52] Such a trade-off would argue against the appropriateness of summarizing the accuracy measures as single point estimates, favoring the use of more complex summary receiver operating characteristic curve analysis.

Pooled estimates of sensitivity and specificity were calculated for each ultrasound finding using a single-term logistic regression model, and the unit of analysis was the study. This method produces results similar to those ob-

Figure 1. Fetal Ultrasonographic Markers for Risk of Down Syndrome



A, Fetal brain with a choroid plexus cyst. B, Fetal neck demonstrating thickening of the nuchal region. C, Bright focus in the fetal heart (echogenic intracardiac focus). D, Dilation of the renal collecting systems (renal pyelectasis). E, Increased brightness in the fetal bowel (echogenic bowel). Humeral and femoral shortening are defined by comparing measurements to a normal distribution and are not illustrated.

tained from calculating a weighted average of the sensitivities and specificities, weighting by sample size. The consistency of the study results was assessed by considering the "goodness-of-fit" deviance statistic. The dispersion of the data was calculated by dividing the deviance statistic by its *df*: dispersions >1 correspond to variability greater than that expected by chance. Where the fit was poor, the model was adjusted to account for the overdispersion by multiplying the SE by the square root of the dispersion statistic.

The sensitivity and specificity estimates were calculated stratified by whether the finding was seen as an isolated abnormality or in conjunction with other structural abnormalities. When studies did not explicitly state either, they were labeled as unknown and analyzed separately. Results were also stratified by study design and size. To identify whether the results might be influenced by study design, sample size, or by whether the markers were reported in isolation, terms for these factors were introduced into the logistic regression model.

Positive and negative likelihood ratios (LRs) were calculated for each ultrasound finding, stratified by whether it was seen in isolation or in association with fetal structural malformations, and were pooled using a DerSimonian and Laird random effects method for pooling risk ratios.[53] All analyses were performed with STATA statistical software (release 6.0, STATA Corp, College Station, Tex).

Positive and negative predictive values were calculated at a disease prevalence of 1:700 (the population prevalence of Down syndrome) and 1:300 (equivalent to the mid second-trimester prevalence in a 35-year-old woman and generally considered high-risk for Down syndrome) by application of Bayes theorem to the estimated LRs. For each ultrasound finding, the number of women that would need to be screened to detect a case of Down syndrome was calculated as the inverse of the product of the prevalence of Down syndrome and the sensitivity of the ultrasound finding. The number of normal fetuses that would be lost for each case of Down syndrome identified was calculated assuming that all screen-positive ultrasound examinations were followed by invasive diagnostic testing, and that the rate of fetal loss per amniocentesis procedure is 0.8%.[16-20]

RESULTS

Fifty-six studies met inclusion criteria and described 130365 unaffected fetuses and 1930 cases of Down syndrome (TABLE 1).[22,26,27,38,40-46,54-98] The mean maternal age was 34 years, and 88% of the studies (n=49) included women at increased risk of chromosomal abnormality based on age (n=39), serum biochemical testing (n=36), or family history of chromosomal abnormality (n=16). The number of women who were at increased risk for each indication was generally not provided. The overall prevalence of Down syndrome was 1.5% (compared with 0.1% in the general population). Down syndrome was present in 6% of the women in case-control studies (n=24) compared with 1% in the prospective studies. Outcome ascertainment included fetal karyotyping in 53 studies (95%). The number of studies that evaluated each marker ranged from 5 to 29. For studies that included fetal structural malformations, the types of abnormalities specified varied widely, ranging from mild, such as cleft lip, to lethal, such as anencephaly.

Sensitivity and Specificity

The sensitivity and 1 − specificity (false-positive rate) reported by each study for the ability to detect cases of Down syndrome are presented for each ultrasonographic marker in FIGURE 2. The results were markedly heterogeneous for all findings. For example, the percentage of fetuses with Down syndrome correctly identified using a thickened nuchal fold varied from 7%[63] to 75%.[41,68] These reported differences in detection were not the result of a trade-off between the sensitivity and specificity (Spearman correlations between the sensitivity and the specificity were not significant, and there is no obvious trend in the false-positive rates in Figure 2 when ordered by the sensitivity rates).

We explored possible reasons for the inconsistency across studies, illustrated for nuchal fold in TABLE 2. There were no differences in the sensitivity based on study size (test for difference between groups, $P = .23$). However, we found significant differences in the reported accuracy based on study design (test for difference, $P = .008$) and whether the marker was seen as an isolated abnormality or in association with fetal structural abnormalities (test for difference, $P < .001$).

The sensitivity was significantly lower among studies that reported the results of the markers as isolated abnormalities, illustrated for thickened nuchal fold in FIGURE 3. For example, a thickened nuchal fold observed in isolation was seen in 4% of cases of Down syndrome, compared with 26% when observed in addition to other abnormalities. Additionally, the results were more consistent among the studies that reported on the isolated findings: most of the CIs for these studies overlap the summary estimate (Figure 3).[99]

For each of the ultrasonographic markers, the sensitivity for Down syndrome was low when the marker was seen without associated structural malformations or other markers, ranging from 1% for choroid plexus cyst (95% CI, 0%-3%) to 16% for shortened femur (95% CI, 5%-40%) (TABLE 3). The specificity for each of the markers was greater than 95% when the finding was seen as an isolated abnormality.

Positive and Negative LRs

If nuchal fold thickening is identified in the second trimester, the odds of Down syndrome increase by approximately 17-fold (positive LR, 17; 95% CI, 8-38) (TABLE 4). For the other 6 markers, the positive LRs were significantly lower, and for choroid plexus cyst and renal pyelectasis, the positive LRs were not significant. Because the markers were seen in only a minority of abnormal fetuses, a normal finding did not substantially decrease the risk of a fetus having Down syndrome. None of the negative LRs were significant.

Table 1. Description of Included Studies*

Study, y	Design	Down Syndrome Cases	Unaffected Fetuses	Composite Score Sens	Composite Score 1-Spec	Choroid Plexus Cyst Sens	Choroid Plexus Cyst 1-Spec
Bahado-Singh et al,[54] 1995	Prospective	7	647				
Bahdo-Singh et al,[55] 1996	Prospective	40	2188	19/40	275/2188		
Benacerraf et al,[56] 1985	Prospective	6	898				
Benacerraf et al,[57] 1987	Prospective	8	2111				
Benacerraf et al,[41] 1987	Case-control	28	192	21/28	4/192		
Benacerraf et al,[36] 1989	Case-control	20	3480†				
Benacerraf et al,[58] 1991	Case-control	24	400	18/24	25/400		
Benacerraf et al,[59] 1992	Case-control	32	588	26/32	26/588		
Benacerraf et al,[60] 1994	Case-control	45‡	106‡	33/45	4/106		
Biagotti et al,[61] 1994	Case-control	27	500				
Borrell et al,[62] 1997	Prospective	24	1365				
Boyd et al,[63] 1998	Prospective	70§	33 306§			5/52	62/15 081
Bromley et al,[42] 1995	Prospective	22	1312				
Bromley et al,[64] 1997	Case-control	53‖	177‖	44/53	31/177		
Brumfield et al,[65] 1989	Case-control	15	45				
Campbell et al,[66] 1994	Prospective	5	264				
Chan et al,[67] 1989	Prospective	9	504			0/9	13/504
Crane and Gray,[68] 1991	Prospective	16	3322				
Cuckle et al,[69] 1989	Case-control	83	1360				
Deren et al,[70] 1998	Prospective	44¶	3674				
DeVore and Alfi,[71] 1995	Prospective	32	2000	28/44	441/3674		
Dicke et al,[72] 1989	Case-control	33	177	24/32	60/2000	1/32	42/2000
Donnenfeld et al,[73] 1994	Prospective	13	1346				
D'Ottavio et al,[74] 1997	Prospective	10	3504				
Drugan et al,[75] 1996	Prospective	11	1133	6/11	56/1133		
Ginsberg et al,[76] 1990	Case-control	12#	212	9/12	14/212		
Grandjean and Sarramon,[77] 1995	Prospective	34	2763				
Grandjean and Sarramon,[78] 1995	Prospective	44	3205				
Gray et al,[79] 1996	Prospective	16	18 845			7/16	201/18 845
Gray and Crane,[80] 1994	Prospective	32	8106				
Grist et al,[81] 1990	Prospective	6	428				
Hill et al,[26] 1989	Case-control	22	286	10/22	22/286		
Johnson et al,[82] 1993	Prospective	14	331				
Johnson et al,[83] 1995	Case-control	36**	794**				
Lafollette et al,[84] 1989	Case-control	30	229				
Lockwood et al,[43] 1987	Case-control	35	349††				
Lockwood et al,[85] 1993	Prospective	42	4949	21/42	242/4949		
Lynch et al,[27] 1989	Case-control	9	9	[illegible]	[illegible]		
Manning et al,[86] 1998	Prospective	16	884				
Marquette et al,[87] 1990	Case-control	31	155				
Nadel et al,[46] 1995	Case-control	71	694	59/71	88/694		
Nicolaides et al,[88] 1992	Prospective	301	1785			33/301	87/1785
Nyberg et al,[44] 1990	Case-control	49	572				
Nyberg et al,[22] 1990	Prospective	25	3500				
Nyberg et al,[89] 1993	Case-control	45	942				
Nyberg et al,[90] 1995	Prospective	18	232	9/18	24/232		
Nyberg et al,[40] 1998	Case-control	142	930	97/142	116/930		
Rodis et al,[91] 1991	Case-control	11	1890				
Shah et al,[92] 1990	Case-control	17	17				
Verdin and Economides,[93] 1998	Case-control	11	449	9/11	44/449	0/11	27/449
Vergani et al,[94] 1999	Prospective	22	898	13/22	48/898	1/22	24/898
Vibhakar et al,[95] 1999	Prospective	84	2328				
Vintzileos et al,[96] 1996	Prospective	22	493				
Vintzileos et al,[45] 1997	Prospective	23	581	20/23	39/581		
Watson et al,[97] 1994	Prospective	14	1453				
Wickstrom et al,[98] 1996	Prospective	19	7457				
Total		**1930**	**130 365**		**18**	**7**	

*Composite score includes some or all of the ultrasonographic markers. Sens indicates sensitivity; 1-spec, 1-specificity; and EIF, echogenic intracardiac focus. See "Methods" section for more information.

†Includes 709 unaffected fetuses for femur length.

‡Includes 37 Down syndrome and 84 unaffected cases for humerus length.

§Includes 52 Down syndrome and 15 081 unaffected cases for choroid plexus cysts.

Echogenic Bowel		EIF		Femur Shortening		Humerus Shortening		Nuchal Fold Thickening		Renal Pyelectasis	
Sens	1–Spec	Sens	1–Spec	Sens	1–Spec	Sens	1–Spec	Sens	1–Spec	Sens	1–Spec
								3/7	9/647		
								2/6	1/898		
								2/8	3/2111		
								21/28	4/192		
				7/20	28/709			8/20	10/3480		
				10/24	40/400	12/24	25/400	12/24	0/400		
				23/32	63/588	17/32	34/588	22/32	2/588		
7/45	1/106			20/45	4/106	20/37	3/84	19/45	0/106	11/45	0/106
				13/27	60/500	15/27	73/500				
								10/24	2/1365		
1/26	30/10 592							5/70	105/33 306		
		4/22	62/1312								
13/53	4/177	16/53	8/177	25/53	14/177	19/46	5/149	27/53	1/177		
				6/15	1/45						
				2/5	20/264						
[illegible]	[illegible]			[illegible]	[illegible]			[illegible]	25/3322		
				20/83	84/1360						
								5/44	22/3674	1/44	22/3674
5/34	73/3674							4/32	13/2000	6/32	26/2000
6/32	31/2000			5/33	18/177						
								1/13	16/1346		
								1/10	8/3504	0/10	24/3504
				5/11	14/212			5/12	0/212		
				15/34	495/2763						
								17/44	273/3205		
								14/32	81/8106		
				3/6	25/428						
				4/22	6/286						
				10/14	31/331						
				15/36	127/794	8/33	24/486				
				4/30	27/229						
				18/35	24/349						
				6/42	163/4949	12/42	198/4949	21/42	242/4949		
				5/9	5/9			5/9	0/9		
		2/16	21/884								
				3/31	14/155						
								53/301	91/1785		
				7/49	35/572						
								4/25	10/3500		
				11/45	44/942	11/45	42/942				
1/18	5/232			5/18	14/232			3/18	1/232	3/18	5/232
28/142	8/930	24/142	33/930	7/142	33/930	4/142	2/930	33/142	4/930	18/142	27/930
				2/11	95/1890	7/11	95/1890				
				3/17	1/17						
2/11	5/449			6/11	5/449					5/11	10/449
0/22	7/898									4/22	18/898
		22/84	246/2328								
				5/22	50/493	10/22	49/493				
								7/14	27/1453		
										1/19	115/7457
9		5		29		11		26		9	

and 26 Down syndrome and 10 592 unaffected cases for echogenic bowe

ıncludes 46 Down syndrome and 149 unaffected cases for humerus length

¶Includes 34 Down syndrome cases for echogenic bowel.

#Includes 11 Down syndrome cases for femur length.

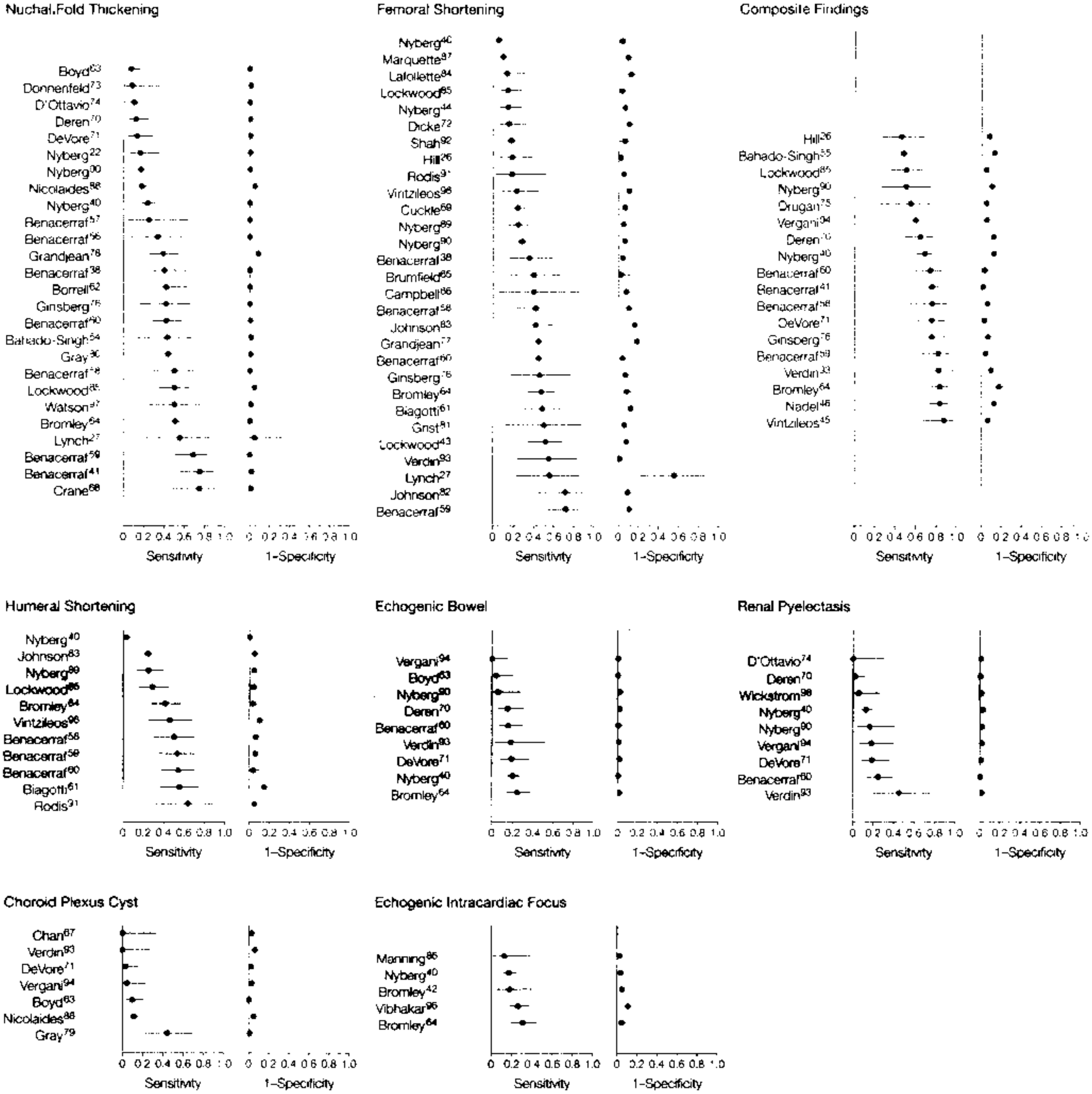
**Includes 33 Down syndrome and 486 unaffected cases for humerus length

††Data are from 1 of 2 centers.

Positive and Negative Predictive Values

Among women at average risk of having a fetus with Down syndrome, if a thickened nuchal fold is identified, the risk is 2% (Table 4), and among women at high risk, the risk is 5%. The positive predictive values were significantly lower for the 6 other markers (≤1% in low-risk women, and ≤2% in high-risk women for each of the markers). The negative predictive value for each of the markers was greater than 99%, reflecting the rarity of Down syndrome.

Figure 2. Sensitivity and False-Positive Rates (1 – Specificity)



Nuchal Fold Thickening

Femoral Shortening

Composite Findings

Humeral Shortening

Echogenic Bowel

Renal Pyelectasis

Choroid Plexus Cyst

Echogenic Intracardiac Focus

Data shown for all studies that examined the ultrasonographic markers as screening tests for Down syndrome. One summary estimate is included for each study. The category of "composite findings" was defined differently by each study, but in general included some or all of the markers, in addition to structural abnormalities. Error bars indicate 95% confidence intervals.

Number Needed to Screen

If ultrasound screening is used in women who are at average risk of having an affected fetus, the number needed to be screened to detect a case of Down syndrome is high (range, 4454-87 413) depending on the marker used (Table 4). For each case of Down syndrome correctly identified, there will be false-positive diagnoses, ranging from 79 (for nuchal fold) to 611 (for choroid plexus cysts). Because an abnormal finding is followed by amniocentesis to make a definitive diagnosis, there will be inevitable losses of unaffected fetuses as a complication of amniocentesis. For example, if the presence of an echogenic intracardiac focus is used as a basis to offer amniocentesis, 2 fetal losses in low-risk women and 1 fetal loss in high-risk women will occur as complications for each case of Down syndrome identified.

Sensitivity Analysis

One study contributed approximately 25% of the unaffected fetuses to our meta-analysis (n=33 000).[63] To determine the impact of this study on the overall summary measures, the sensitivity and specificity rates were recalculated excluding that study's data, and there was no change in the sensitivity rates for any of the markers. On the other hand, the false-positive rates doubled when this study was deleted (for choroid plexus cyst, the false-positive rate increased from 1% to 3%, for nuchal fold from 0.5% to 0.9%, and for echogenic bowel from 1% to 3%). Within the studies that considered isolated markers, there was typically no evidence of a trade-off between the true-positive and false-positive rates (eg, for nuchal fold the correlation between sensitivity and specificity was not significant [$P=.27$]), and thus summary statistics could be calculated and are valid.

COMMENT

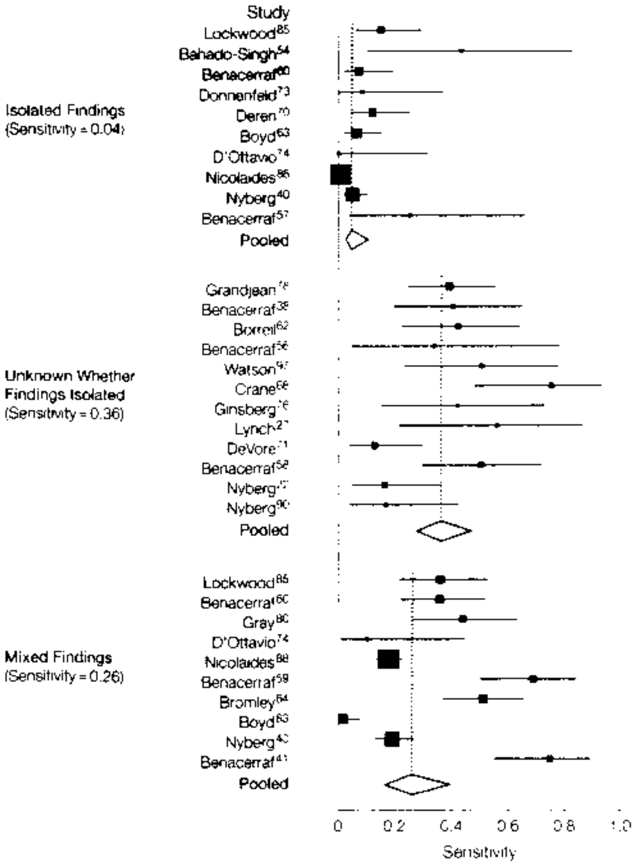
When seen as isolated findings, the second-trimester ultrasonographic markers of choroid plexus cyst, echogenic intracardiac focus, echogenic bowel, renal pyelectasis, shortened humerus, and shortened femur are not helpful in either confirming or excluding the presence of Down syndrome.[100] Only 1 marker, thickened nuchal fold, may be useful at distinguishing between unaffected and affected fetuses. If nuchal fold thickening is identified, the risk of

Table 2. Investigation of Reasons for Heterogeneity of Studies Examining Nuchal Fold Thickening as a Marker for Down Syndrome (n = 26)

Possible Reasons to Explain Heterogeneity	Subgroups	No. of Studies	Sensitivity (95% CI)	Specificity (95% CI)
Study design	Case-control studies	9	0.42	1.00
	Prospective studies	17	0.23	0.99
	Test for difference		$P = .008$	$P = .47$
Sample size	<25 Down syndrome cases	13	0.39	0.99
	≥25 Down syndrome cases	13	0.28	0.99
	Test for difference		$P = .23$	$P = .30$
Whether marker was seen in isolation*	Isolated finding	10	0.04	1.00
	Unclear whether isolated finding	12	0.36	0.98
	Finding plus structural abnormalities	10	0.26	0.99
	Test for difference		$P<.001$	$P = .05$

*Results are based on data from 31 data points presented in the 26 studies. For some studies, data could be extracted for both isolated findings and findings plus structural abnormalities; thus, there are more data points than studies.

Figure 3. Sensitivity for All Studies That Examined Nuchal Fold Thickening



Data shown for all studies using nuchal fold thickening as a screening test for Down syndrome. Studies are stratified by whether the nuchal fold was evaluated as an isolated abnormality, was seen in conjunction with other abnormalities, or the study did not report whether the nuchal fold was seen as an isolated abnormality (unknown). For studies in which data could be abstracted for both an isolated nuchal fold and for a nuchal fold seen in addition to other abnormalities, 2 data points are included. Size of data markers reflects study sample size; dotted line reflects the point estimates for pooled data.

Down syndrome increases by approximately 17-fold. However, this marker is present in only a minority of fetuses with Down syndrome, and many fetuses would need to be screened for nuchal fold thickening to make a single diagnosis of Down syndrome.

Moreover, because the sensitivity of the ultrasonographic markers is so low, and because Down syndrome is rare, the vast majority (>99%) of fetuses with an isolated marker will be unaffected. The use of the ultrasonographic markers as an indicator for invasive testing with amniocentesis will lead to an increase in the number of unaffected fetuses lost as a complication of the procedure. Although women may place different values on the balance between the identification of a fetus with Down syndrome and the loss of an unaffected fetus due to a complication of amniocentesis,[101] this highlights an important potential harm associated with a test often considered risk-free. If, for example, identification of an echogenic intracardiac focus is used as a ba-

Table 3. Summary Sensitivity and Specificity for Each Ultrasonographic Marker*

Marker	How Identified	No. of Studies	Sensitivity (95% CI)	Specificity (95% CI)
Thickened nuchal fold	Isolated finding	10	0.04 (0.02-0.10)	0.99 (0.99-1.00)‡
	Unknown	12	0.36 (0.27-0.47)	0.98 (0.96-0.99)‡
	With structural abnormalities	10†	0.26 (0.16-0.40)‡	0.99 (0.98-1.00)‡
Choroid plexus cyst	Isolated finding	3	0.01 (0-0.03)	0.99 (0.97-1.00)§
	Unknown	2	0.02 (0-0.15)	0.98 (0.97-0.98)
	With structural abnormalities	4	0.11 (0.06-0.20)	0.99 (0.98-1.00)§
Femur length	Isolated finding	4	0.16 (0.05-0.40)‡	0.96 (0.94-0.98)‡
	Unknown	22	0.31 (0.25-0.38)	0.91 (0.88-0.93)‡
	With structural abnormalities	4	0.51 (0.34-0.68)	0.94 (0.86-0.97)‡
Humerus length	Isolated finding	2	0.09 (0.01-0.64)‡	0.97 (0.91-0.99)§
	Unknown	7	0.39 (0.30-0.50)‡	0.94 (0.91-0.96)§
	With structural abnormalities	2	0.54 (0.42-0.65)	0.94 (0.93-0.96)
Echogenic bowel	Isolated finding	3	0.04 (0.01-0.18)	0.99 (0.97-1.00)§
	Unknown	2	0.14 (0.05-0.33)	0.98 (0.98-0.99)
	With structural abnormalities	6	0.16 (0.10-0.25)	1.00 (0.99-1.00)
Echogenic intracardiac focus	Isolated finding	3	0.11 (0.06-0.18)	0.96 (0.94-0.97)
	Unknown	0	. . .	. . .
	With structural abnormalities	3	0.20 (0.14-0.27)	0.95 (0.93-0.96)
Renal pyelectasis	Isolated finding	4	0.02 (0.01-0.06)	0.99 (0.98-0.99)‡
	Unknown	1	0.19 (0.07-0.36)	0.99 (0.98-0.99)
	With structural abnormalities	5	0.16 (0.10-0.25)	0.99 (0.97-0.99)
Multiple findings	Ultrasonographic markers plus structural abnormalities	18	0.69 (0.63-0.75)‡	0.92 (0.90-0.94)‡

*Stratified by whether the marker was seen as an isolated abnormality or in conjunction with fetal structural abnormalities. For some markers, data could be abstracted for both isolated findings and those with structural abnormalities; thus, the number of studies for each marker may total more than shown in Table 1 and Figure 2. CI indicates confidence interval; ellipses, not applicable.

†Correlation between true-positive and false-positive rates, $P = .07$.

‡Heterogeneity of study results compared to that expected by chance greater than 10-fold.

§Heterogeneity of study results compared to that expected by chance greater than 50-fold.

Table 4. Summary Accuracy Measures for Each Ultrasonographic Marker When Identified as an Isolated Abnormality*

					Women at Average Risk of a Fetus With Down Syndrome			Women at High Risk of a Fetus With Down Syndrome		
Marker	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	PPV	Fetal Losses per Case Diagnosed	No. Needed to Screen	PPV	Fetal Losses per Case Diagnosed	No. Needed to Screen
Thickened nuchal fold	0.04 (0.02-0.10)	0.99 (0.99-0.99)	17 (8-38)	0.97 (0.94-1.00)	0.024	0.6	15 893	0.053	0.2	6818
Choroid plexus cyst	0.01 (0-0.03)	0.99 (0.97-1.00)	1.00 (0.12-9.4)	1.00 (0.97-1.00)	0.002	4.3	87 413	0.003	1.8	37 500
Femur length	0.16 (0.05-0.40)	0.96 (0.94-0.98)	2.7 (1.2-6.0)	0.87 (0.75-1.00)	0.004	1.2	4454	0.009	0.5	1911
Humerus length	0.09 (0-0.60)	0.97 (0.91-0.99)	7.5 (4.7-12)	0.87 (0.67-1.1)	0.011	1.9	8038	0.024	0.8	3448
Echogenic bowel	0.04 (0.01-0.24)	0.99 (0.97-1.00)	6.1 (3.0-12.6)	1.00 (0.98-1.00)	0.009	1.0	19 425	0.020	0.4	8333
Echogenic intracardiac focus	0.11 (0.06-0.18)	0.96 (0.94-0.97)	2.8 (1.5-5.5)	0.95 (0.89-1.00)	0.004	2.0	6536	0.009	0.8	2804
Renal pyelectasis	0.02 (0.01-0.06)	0.99 (0.98-1.00)	1.9 (0.7-5.1)	1.00 (1.00-1.00)	0.003	2.6	30 404	0.006	1.1	13 043

*The positive predictive value (PPV), fetal losses per case of Down syndrome diagnosed, and the number of women who would need to be screened for each case of Down syndrome identified were calculated for 2 hypothetical cohorts: women at average risk of carrying a fetus with Down syndrome, defined as the population risk (1:700), and those at high risk of carrying a fetus with Down syndrome, defined as the mid-trimester risk in a 35-year-old woman (1:300). CI indicates confidence interval; and LR, likelihood ratio.

sis for offering amniocentesis to pregnant women at low risk of carrying an affected fetus, 2 unaffected fetuses will be lost as a complication of amniocentesis for each correctly identified Down syndrome case. Additionally, because the false-positive rate is 1% or greater for most of the markers, when all of these markers are used in aggregate, the false-positive rate may approach 10% or more, leading to much needless anxiety throughout pregnancy and beyond.[50,102-104]

Furthermore, if women who are at elevated risk of carrying a fetus with Down syndrome based on maternal age or serum testing results are dissuaded from amniocentesis due to the absence of ultrasonographic markers, this will reduce the prenatal detection of fetuses with Down syndrome as well as the effectiveness of biochemical screening.[49] Finally, there are significant costs associated with ultrasound screening for Down syndrome, particularly those that relate to the further evaluation of detected findings. Even for nuchal fold thickening, more than 15000 scans would need to be performed in average-risk women and more than 6000 scans in high-risk women to detect a single case of Down syndrome. Based on available data, the accuracy of a second-trimester ultrasound screening program would be far less, and the cost far greater, than that achieved by current biochemical screening.[105] There are no data on whether serum markers and these ultrasonographic markers are independent indicators of Down syndrome risk, and thus it is unclear whether the use of the ultrasonographic markers contributes any additional detection to that achievable with serum testing.

Although our results suggest poor accuracy for most of these ultrasonographic markers, it is common practice for clinicians to use them as evidence of an increased risk of Down syndrome.[40,106] For example, in a large health maintenance organization in California, all pregnant women are offered second-trimester ultrasound to screen for fetal anomalies. If a choroid plexus cyst is identified, the patient literature reports that the fetus has a 1:100 risk of chromosomal abnormality and the woman may undergo amniocentesis. This is 7-fold her a priori risk of chromosomal abnormality, and this increased risk is not supported by our results. Similarly, Boyd et al[63] found that while the presence of ultrasonographic markers increased the prenatal detection of malformed fetuses by only 4%, identification of the markers was responsible for a 12-fold increase in the false-positive rate.

Although our review cannot exclude the possibility that there is benefit to identifying these markers, their validity is not supported by our findings. Furthermore, although we focused on the most common ultrasonographic markers used to screen for chromosomal abnormalities, there are many others described in the literature and evaluated in even fewer patients.

Our meta-analysis focused on the ultrasonographic markers that may be seen in isolation. Many of the studies examined these markers in conjunction with other markers and with fetal structural abnormalities. Using such a combination may improve the accuracy of screening with ultrasound. However, these studies reported statistically inconsistent results, and thus a summary measure of the accuracy of a composite score could not be determined. Furthermore, the low sensitivity of the isolated markers suggests that these may not contribute to the information provided by the presence of fetal structural malformations. Our analysis suggests that the high sensitivity for Down syndrome reported by many studies using ultrasonographic markers may be due to the detection of the associated structural abnormalities. None of the negative LRs were significant; thus, the absence of an individual marker could not be used to rule out Down syndrome. Therefore, it seems improbable that the absence of a combination of ultrasonographic markers would substantially decrease the risk of Down syndrome.

It is important to distinguish between the ultrasonographic markers, which are themselves harmless, and fetal structural abnormalities for several reasons. First, the prenatal identification of fetal structural malformations may have benefit to the mother unrelated to the risk of chromosomal abnormality (eg, the family can anticipate the special needs of the child).[50] Second, most clinicians believe that detection of a major structural abnormality is sufficient grounds to offer invasive testing. Finally, the vast majority of examinations demonstrating isolated sonographic markers are false-positives.

We focused on second-trimester ultrasound and did not include studies of nuchal translucency screening, a first-trimester ultrasound test used at approximately 10 to 14 weeks' gestation. Currently, this test has not been embraced into clinical practice in the United States, the implications of the accuracy of this test on clinical management are far different than for markers observed on routine ultrasound at 15 to 24 weeks' gestation, and prospective studies of nuchal translucency screening are under way.

Our analysis has several limitations. We may have missed unpublished work, particularly of smaller studies, but these are unlikely to substantially affect the results. Broadening the search to include other electronic databases and articles in languages other than English may have increased the number of studies included, but it seems unlikely that it would make our results any more favorable toward ultrasound. The results may predominantly reflect the findings of specialized centers, and this may inflate the accuracy in a general community setting. The majority of included studies were confined to high-risk pregnancies, such as women referred for prenatal diagnosis because of advanced maternal age or a positive serum screening test result, and the sensitivity of the markers may be different, and probably lower, in low-risk women.

We excluded many studies on the basis of methodologic criteria. It was not possible to determine if including these studies would have had a significant impact on the overall results because most of these excluded studies (n=67) reported only a positive predictive value, without reporting the risk of Down syndrome among the population studied or the false-positive rate of the marker. The exclusion of the study that contributed 25% of the unaffected fetuses to this meta-analysis resulted in considerably lower estimates of the sensitivity, and worse estimates of screening performance of choroid plexus cyst, nuchal fold, and echogenic bowel.[63] That study collected results from an anomaly registry, and it is not clear if all of the cases with sonographic markers had been reported. In addition, we pooled the results from studies that used different designs, including case-control studies, which are likely to lead to overestimation of the sensitivity,[107] so that the true accuracy of these findings may be even lower than we report.

In summary, we found that a thickened nuchal fold may be useful in distinguishing between unaffected fetuses and those with Down syndrome, but that the overall sensitivity of this finding is low, and thus it is not practical for use as a screening test. The remaining ultrasonographic markers did not discern well between unaffected fetuses and those with Down syndrome. Because the use of these markers may be associated with more harm than benefit, clinicians should be very cautious about the use of these markers to counsel women about their risk of having a fetus with Down syndrome.

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Mr Deeks participated in analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and provided statistical expertise

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