

Ultrasound Markers of Fetal Down Syndrome

To the Editor: Dr Smith-Bindman and colleagues¹ have summarized a large amount of potentially useful data but, I believe, have misinterpreted or ignored data that support the use of ultrasonographic markers of Down syndrome. The results of their meta-analysis show that most ultrasonographic markers as isolated findings are statistically associated with an increased risk for fetal Down syndrome (2.8- to 17-fold greater). Furthermore, the combination of anomalies and markers were identified in 69% of fetuses with trisomy 21 (Table 3). This is consistent with other centers reporting detection rates of 59% to 82%⁴ when markers are combined with structural anomalies (observed in less than 20% of affected fetuses before 20 weeks at most centers).^{2,3} Even using outdated assumptions, the authors found a benefit for all markers except choroid plexus cyst among high-risk patients (defined as a relatively low risk of 1 in 300).

In addition, the authors assume a prevalence of 1:700 for trisomy 21. A more recent estimate is 1:504.⁵ Using this prevalence with the authors' 69% sensitivity and 8% false-positive rate for ultrasound screening, detecting 1 affected case would require screening 730 women with a loss of 0.47 normal fetuses.

The reduction of risk of detecting fetal Down syndrome applies to a normal ultrasound finding, not to an absence of any individual marker. Indeed, a negative likelihood ratio (LR) for an individual marker has little clinical relevance. Using their data (Table 3), a normal ultrasound finding has a negative LR of 0.34 (31/92). This value agrees with negative LRs reported by others in the range of 0.3 to 0.4⁶ and corresponds to a 60% to 70% reduction of risk following a normal ultrasound result.

Smith-Bindman et al also suggest that a single marker in a low-risk patient would be considered a positive screen result. Like biochemical markers, ultrasonographic markers cannot be viewed in isolation but must be interpreted together with other clinical variables, such as advanced maternal age.² For example, an isolated echogenic intracardiac focus (LR, 2.8) in a 25-year-old woman (baseline risk, 1:1040) would result in a postultrasound risk of 1:372. This result should be considered a positive finding but a negative ultrasound screen result, and it should not alter obstetric management.

Like biochemical analytes, ultrasonographic markers can provide important information about the risk of fetal Down syndrome when used appropriately but can cause confusion and needless anxiety when the results are misinterpreted.

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To the Editor: Dr Smith-Bindman and colleagues¹ concluded that ultrasound screening in the second trimester is not an efficacious screening method for fetal Down syndrome.

Their analysis and conclusions focused primarily on 6 isolated ultrasonographic markers for Down syndrome, and they did not fully consider associated fetal structural malformations, which occur in 28% of fetuses with Down syndrome or multiple markers.² Table 3 of the article shows that when multiple markers and structural abnormalities are considered together, ultrasound screening has a sensitivity of 69% and a false-positive rate of 8%. The PPVs cited also are underestimated because their prevalence rates for Down syndrome are low. In 1997, there was an overall second-trimester prevalence of Down syndrome in the United States of 1:504. For women aged 35 years or older, the prevalence was 1:134.³ Using these prevalence rates, ultrasound screening had a PPV of 1.68%, that is, 1 in 60 screen-positive women had an affected pregnancy.

Ultrasound screening is a superior method to the current standard of offering amniocentesis to all women aged 35 or older.⁴ Using a mathematical model, we determined that advanced maternal age had a sensitivity of 48.3% and a false-positive rate of 12.8% for Down syndrome in 1998. Screening the 4 >005 111 second-trimester pregnancies in the United States in 1998 by advanced maternal age would have identified 513 889 false-positive cases while detecting 3896 Down syndrome cases. Using ultrasound screening would have identified 320 409 false positive cases while detecting 5567 Down syndrome cases. Applying the quoted procedure-related loss rate of 0.8% and assuming that all risk-positive women undergo an amniocentesis, there would have been 4142 losses for advanced maternal age women and 2563 losses in women screened with ultrasound. We believe that the conclusion that ultrasound screening leads to a decrease in the prenatal detection of affected pregnancies and results in more fetal losses than cases detected is incorrect.

The efficacy of ultrasound screening in detecting Down syndrome is comparable with the widely accepted maternal serum triple marker screen that in 1998 had a sensitivity of 74.8%, a false-positive rate of 8.3%, and a PPV of 1.71%.² Using our model, ultrasound screening demonstrated greater efficacy to detect Down syndrome than advanced maternal age for every year from 1974 to 1998. The meta-analysis by Smith-Bindman et al in fact confirms the efficacy of a comprehensive second-trimester ultrasound to screen for fetal Down syndrome.

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1. Smith-Bindman R, Hosmer W, Feldstein VA, Deeks JJ, Goldberg JD. Second-trimester ultrasound to detect fetuses with Down syndrome: a meta-analysis. *JAMA.* 2001;285:1044-1055. [ABSTRACT](#) | [FULL TEXT](#) | [PDF](#) | [MEDLINE](#)

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To the Editor: The meta-analysis by Dr Smith-Bindman and colleagues¹ of the ultrasonographic markers to detect fetal Down syndrome contained a number of inaccurate assumptions. The estimate of Down syndrome prevalence of 1:300 in a high-risk population is not appropriate. The prevalence is greater than 1:86 for women aged 35 years and older,² and ranges from 1:61 to 1:85 among women with an abnormal serum triple marker screen.³ This underestimated prevalence will falsely lower the positive predictive value (PPV) of the ultrasound screen and inflate the number of normal fetuses lost per fetus diagnosed with Down syndrome.

By convention, the sensitivity of markers is generally reported a false-positive rate of 5%. In this study, the individual markers are reported at 1.0% and 2.0% false-positive rates. The sensitivity of a marker generally rises precipitously between a 1.0% and 5.0% false-positive rate. The lower false-positive rates give a misleadingly favorable impression of the sensitivity of ultrasound screening relative to serum triple markers.

Regrettably, data on structural abnormalities alone were not provided. At a gross anomaly detection on ultrasound of 33% sensitive for Down syndrome⁴ using the authors' 69% sensitivity and 8% false-positive rate for ultrasonographic markers plus structural abnormalities, then "soft" markers would add 36% sensitivity above detection based on the presence of a gross anomaly by itself, which would be a significant contribution.

The serum triple marker screen in a high-risk population (women aged ≥ 35 years) had 80% sensitivity at a 21% false-positive rate.⁵ The authors' figures of a 60% detection rate and a 7% false-positive rate are applicable only to a low- or average-risk group. Using 69% sensitivity and 8% false-positive rate, the likelihood ratio for ultrasound screen in a high-risk population would be 8.6, but for the serum triple marker screen, it would be 3.8 (80/21), indicating the superiority of ultrasound screening.

Overall, the study does not reflect the current state of the art of ultrasonographic markers for Down syndrome. Composite rather than isolated ultrasonographic markers are being used to estimate risk.⁶ Importantly, ultrasound screening must be combined with other groups of markers (eg, maternal age and biochemical analytes) to achieve optimal performance. Contrary to the authors' statement, there are data on the interaction of serum triple screen and ultrasonographic markers for the detection of Down syndrome.⁶ The addition of ultrasonographic markers improved the detection rate over serum triple marker screen alone.

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1. Smith-Bindman R, Hosmer W, Feldstein VA, Deeks JJ, Goldberg JD. Second-trimester ultrasound to detect fetuses with Down syndrome: a meta-analysis. *JAMA*. 2001;285:1044-1055. [ABSTRACT](#) | [FULL TEXT](#) | [PDF](#) | [MEDLINE](#)

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In Reply: We agree with all these authors that it would be useful to calculate an overall accuracy of ultrasound screening for fetal Down syndrome when structural abnormalities and ultrasonographic markers are used together. Unfortunately, studies that reported a composite ultrasound score (n = 18) reported statistically inconsistent results, and thus a reliable summary estimate could not be generated. The mean sensitivity (68%) and mean false-positive rate (8%) are not reliable, and we did not include them in the expected outcome data. It is meaningless to use these values to generate positive and negative LRs as the authors of these letters suggest. Although it is likely that a normal ultrasound result demonstrating no structural abnormalities or markers can reduce the likelihood of Down syndrome, the amount of this reduction is not known, and Dr Nyberg's estimate of a negative LR of 0.34 is not supported by our data.

Furthermore, there are reasons to believe that the true accuracy of the composite score is lower than we reported. First, we found significant differences in the sensitivity by study design, and if we excluded the case control studies, which are likely to overestimate accuracy,¹ the mean detection was only 58%. Second, most included studies were confined to high-risk pregnancies, and if ultrasound screening was used in a lower-risk population, the detection rate would likely be lower than we reported.²

We focused on isolated ultrasonographic markers because these results showed the most consistent data, and because in clinical practice, this is the most common occurrence. Most pregnant women are at low risk of having a fetus with Down syndrome, and markers will predominantly be identified as isolated abnormalities. We agree with Nyberg that the presence of a single ultrasonographic marker in most patients should not alter treatment. However, we strongly disagree about the nature of the current clinical practice. Detection of these markers has dramatically increased the use of invasive testing,³ and many physicians counsel their patients that they are at an elevated risk of carrying a fetus with Down syndrome based on the presence of a single marker. In addition to unnecessary invasive tests performed because of the presence of markers, the psychological impact cannot be overstated.⁴

We defined high risk as 1:300, equivalent to the risk of Down syndrome in a 35-year-old woman, and the same threshold used by many serum testing programs.⁵ If we had used the mean risk among all women older than age 35 years instead, this would have resulted in a higher PPV but would not have altered the low-detection rate or low LRs.

We agree with Dr Egan and colleagues that advanced maternal age-based screening for Down syndrome is not accurate, but there is no evidence that ultrasound screening would be as accurate as biochemical screening.⁵ If women who are at an elevated risk of carrying a fetus with Down syndrome based on serum testing results are dissuaded from undergoing amniocentesis because of the absence of ultrasonographic markers, the detection of affected pregnancies will decrease. There are no data confirming the accuracy of ultrasound screening as the primary screening test for Down syndrome. If ultrasound screening is used with serum testing, the false-positive rate will increase with no evidence whether detection will increase. Contrary to what Dr Bahado-Singh and colleagues suggest, there are no good data on whether ultrasound screening and serum markers used together would improve the performance of detection. Their study⁶ included only high-risk women, and thus it cannot be used to evaluate whether ultrasound screening can detect cases missed by other screening methods.

Finally, when continuous variables are used to define an abnormal test result, it is possible to choose

categorical variables, such as choroid plexus cysts, it is not possible to do this, and we reported the summary estimate that corresponded to that reported in the literature. Thus, it is unlikely that the sensitivity of the markers is higher than we report.

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