Use of Doppler ultrasonography to predict pre-eclampsia

We enjoyed Jeltsje Cnossen and colleagues' systematic review of the use of uterine artery Doppler ultrasonography to predict pre-eclampsia.[1] They concluded that an increased pulsatility index with notching during the second trimester is the best predictor of pre-eclampsia and strongly recommended the routine use of these measurement parameters in clinical practice. However, this recommendation is based on only 2 studies, one of which included 1757 low-risk women and the other 351 high-risk women. As the incidence of pre-eclampsia is relatively low (0.4%–6.7%), screening tests require high likelihood ratios to adequately predict the disease's probability with positive test results and very low likelihood ratios to confidently exclude the disorder with negative test results.[2] An increased pulsatility index with notching produced sufficiently positive likelihood ratios (21.0) in high-risk women but it was inadequate in low-risk populations (7.5); importantly, the negative likelihood ratios were quite poor for both populations (0.59 and 0.82 respectively).

We also have methodologic concerns. First, a valid meta-analysis should be examined for heterogeneity before one considers pooling the results of primary studies to create summary estimates with enhanced precision.[3] There is no indication in the review that the heterogeneity of the study results was formally tested. Second, there is a substantial possibility of publication bias in this area of research,[4] and there is no indication that this was assessed. Finally, although pooling of sensitivities and specificities instead of likelihood ratios has recently been encouraged,[5] we are skeptical and agree with others[6] that sensitivities and specificities are inappropriate for meta-analyses as they do not behave independently when pooled from primary studies to generate separate averages.

We therefore suggest that the authors' conclusions are premature. Doppler ultrasonography, although useful for monitoring high-risk pregnancies, should not currently be recommended for routine screening to predict pre-eclampsia.

Agustín Conde-Agudelo MD MPH
Perinatology Research Branch, Intramural Division, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md.
Marshall Lindheimer MD
Departments of Obstetrics and Gynecology and Medicine, University of Chicago, Chicago, Ill.

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[Six of the authors respond:]

We thank Agustín Conde-Agudelo and Marshall Lindheimer for giving us the opportunity to clarify the interpretation of our findings. We regret that they interpreted our words as a strong recommendation for routine use of Doppler ultrasonography in clinical practice. In the abstract we stated that "a pulsatility index, alone or combined with notching, is the most predictive Doppler index. These indices should be used in clinical practice."[1] Our intention was not to recommend the routine use of Doppler ultrasonography but rather to emphasize that if it is used then the pulsatility index, alone or combined with notching, is the best choice.

More generally, we do not think that firm clinical recommendations should be made on the basis of what might be called early-phase diagnostic studies or meta-analyses thereof.[2] A more formal economic modelling analysis on this topic, although still hampered by the use of early-phase diagnostic studies only, showed that the routine use of Doppler ultrasonography cannot currently be considered cost-effective.[3]

Conde-Agudelo and Lindheimer raise 3 methodologic concerns. First, the statistical test for heterogeneity has bad statistical properties, making such tests virtually superfluous. Although the I^2 statistic is an improvement,[4] we agree with its inventors that "quantification of heterogeneity is only one component of a wider investigation of variability across studies, the most important being diversity in clinical and methodological aspects."[5] We carefully dealt with methodologic diversity using predefined stratified analyses. Second, funnel-plot asymmetry may be caused by at least 6 different mechanisms, of which publication bias is just 1. This is why experts in the field now prefer the term small-study bias. Without firm criteria to distinguish the sources for the asymmetry, interpretation of such plots remains speculative.[6,7] Finally, the non-independence of sensitivity and specificity is a phenomenon for which the bivariate method explicitly accounts.[8] In conclusion, we concur with Conde-Agudelo and Lindheimer

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