

Are Prenatal Ultrasounds Associated with Autism?

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Jason and his Argonauts had about as much success in finding the golden fleece as investigators have had in establishing a unified theory of autism etiology. This case-control study was an attempt that largely failed but has some lessons regarding study design and reporting.

Source: Rosman NP, Vassar R, Doros G, et al. Association of Prenatal Ultrasonography and Autism Spectrum Disorder. **JAMA Pediatr.** 2018;172(4):336-344;

doi:10.1001/jamapediatrics.2017.5634. See [AAP Grand Rounds commentary by Dr. Daniel Doherty](#) (subscription required).

Clearly there is a genetic predisposition to developing autism, but likely other environmental "hits" on top of this predisposition may influence whether a child actually develops clinically significant disease. Prior studies looking at prenatal ultrasonography generally have concluded there is no association, but the current study was designed to extend these observations. However, Dr. Doherty, the editors of AAP Grand Rounds, and I all have concerns about this study's design and reporting. For busy clinicians who might be asked about the ultrasound-autism association, you might benefit from reading the [accompanying editorial](#) to the article.

The study was a retrospective chart review at a single medical center of children at least 37 weeks gestation at birth and diagnosed with autism spectrum disorder (ASD) by a subspecialist. They were born between 2006 and 2014 and mothers must have received prenatal care at that medical center. Results were compared to 2 control groups, 1 with developmental delay and 1 with normal development, matched for sex, birthdate, and maternal age to the ASD groups. They looked at 8 separate sonography factors (e.g. number and total duration of sonography procedures, depth of the sonographic signal) and some maternal factors, though data were missing for key factors such as family history of ASD, smoking status, and others that might impact ASD risk.

The bottom line conclusion was that sonography was not associated with ASD risk, but the authors didn't stop there. In further analysis, they claimed to have found an association between time-weighted depth of

penetration of the signal and ASD, with greater values being more common in the ASD group. Looking more closely, however, I was left scratching my head about how the researchers analyzed the data.

First, the report provides scant information about the statistical analysis itself. In particular, how did they determine that the sample size was appropriate to evaluate all of those sonographic variables? Dr. Doherty in his critique suggests at least 120 different hypotheses being tested when you add up all the variables and subgroups. There are rules for determining these numbers, though statisticians disagree on which is the best rule. Simply put, I've seen cogent arguments for choosing the number of subjects per variable examined to range from 5 to 50. With about 100 ASD patients in this study, that would allow researchers to look at anywhere from 2 to 20 variables for an association without risking finding a false association purely by looking at too many variables (i.e. by chance alone). The authors should have explained all of this in the Methods section.

Second, I found myself wondering how reproducible the sonographic elements would be. Apparently there were "gaps" of time in the screenshots they reviewed, and some judgment was made in determining the final numbers used in the analysis. Who made those judgments, and were they blinded to the child's diagnostic group? How accurate are measurements of signal depth, especially when looking at differences of only a millimeter or so? If the differences they report are also within the limits of error of the sonographic measurement itself, then the differences aren't real.

Third and last, Dr. Doherty points out a cardinal sin in the report's abstract. The last sentence states, "Further research is needed to determine whether other variables of ultrasound exposure also have adverse effects on the developing fetus." This implies that the finding of an association of signal penetration with ASD is causal. As all clinicians should know, a case-control study can never determine cause and effect, only association. Including a statement in a research abstract that isn't supported by the study's findings is a real no-no and suggests extreme sloppiness by both the authors and the journal editors.

ASD, like Lyme disease and how much alcohol to drink to live for 100 years, is ripe for misinterpretation in the press and social media. Most of the online comments from mainstream media were like **this one** from NBC, which focused on the lack of association of fetal sonography with ASD. I'm glad the press more or less saw the key finding and didn't give undue emphasis to the more provocative (and shaky) parts of the report.

Regardless, pregnant women would be wise to avoid unnecessary sonography during pregnancy. The American College of Obstetrics and Gynecology **recommends** at least 1 sonogram at 18-22 weeks gestation, but the women in all 3 groups in this study went far beyond that: an average of about 6 during pregnancy, including many in the first trimester when the fetal brain is most susceptible to injury!

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