

ISUOG statement on ultrasound exposure in the first trimester and autism spectrum disorders

Recently, a study that suggests that heterogeneity in autism spectrum disorder (ASD) symptoms results from exposure to diagnostic ultrasound during early pregnancy has been published¹. The ISUOG Safety Committee has reviewed this paper and other related epidemiological literature, and has found no scientifically proven association between ultrasound exposure in the first or second trimesters and ASD.

WHAT THE STUDIES SHOW

ASD is a neurodevelopmental disorder of mainly genetic origin, but there is evidence that environmental factors may play a role, and that the initiating process leading to ASD originates during fetal life². Reported registered prevalence rates are increasing, but it seems that much of the increase reflects better awareness of the disorder rather than a true rise in prevalence³.

There is a hierarchy of studies used for interpretation of epidemiological data, based on study design and quality of the research methods. The highest value should be placed on randomized controlled trials, with less value (in decreasing order) on cohort studies, case-control studies and other observational studies, such as case series and cross-sectional studies.

Webb *et al.*¹ reported a case series of 1749 children with ASD aged 4–18 years. ASD severity was characterized using measures of cognitive ability, social ability and repetitive behaviors. Genetic predisposition was characterized by the presence of ASD-associated copy-number variations (CNV). The occurrence of ultrasound exposure in the first trimester was determined only by parental recall. No information was provided on the details of the exposure, including indication for the scan, type of ultrasound examination (transabdominal or transvaginal), exposure duration, exposure during other trimesters or imaging modality. The authors compared 84 exposed and 41 non-exposed children with ASD and CNV, and a subsample of 73 exposed and 38 non-exposed boys with ASD and CNV. They concluded that

the combination of first-trimester ultrasound and presence of CNV in male children with ASD correlated with poorer cognitive outcomes and increased repetitive behaviors.

In a case-control study at Kaiser Permanente®, California, USA, Grether *et al.*⁴ identified 362 singletons born between 1995 and 1999 with a diagnosis of ASD. Three hundred and ninety-three controls without ASD were selected randomly from the same database and frequency matched to cases by gender, hospital and year of birth. Data on ultrasound exposure were available from prospectively registered antenatal records and included gestational age at exposure and number of ultrasound examinations received. The type of ultrasound device and intensity output levels were not available. Cases with known use of pulsed Doppler ultrasound were excluded. This study found no association between antenatal ultrasound exposure and ASD. This was true even for specific analyses of each trimester and increasing number of scans.

Stoch *et al.*⁵ used an existing randomized controlled trial to investigate whether multiple ultrasound scans were associated with the autism phenotype. From 2834 singleton pregnancies, 1415 were selected at random to receive ultrasound imaging and continuous-wave Doppler flow studies at five time points throughout pregnancy and 1419 to receive a single imaging scan at 18 weeks with further scans only as indicated on clinical grounds. In a follow-up of 1181 (42%) of the children at age 19–20 years, there was no difference in the rate of ASD between the two groups, nor a difference between groups in the level of autistic-like traits in early adulthood. The authors concluded that there is no clear link between the frequency and timing of prenatal ultrasound scans and the autism phenotype.

Höglund Carlsson *et al.*⁶ performed a long-term follow-up of 14726 children born to women who underwent a 12-week scan (range 12–14 weeks) and 14596 children born to women who had an 18-week scan (range 15–20 weeks), in a randomized controlled trial

conducted in 1999–2003. Information on ASD diagnoses was based on data from the Swedish social insurance agency concerning childcare allowance granted for ASD. A validation study of 200 children was done, and a blinding technique was used until all children with ASD had been identified and included in the study. The study demonstrated that ultrasound exposure at around 12 weeks' gestation did not appear to cause more cases of ASD than did exposure at around 18 weeks' gestation. The total number of children with ASD in this study was no higher than the current prevalence rates of ASD in Sweden.

INTERPRETING THE EVIDENCE

The ISUOG Safety Committee has carefully reviewed the evidence and this included rating the available studies. The study by Webb *et al.*¹ was rated as poor quality due to several factors that introduce a high risk of bias: it was a case series with no control group; exposure information was collected by recall 4–18 years after the pregnancy; multiple testing without correction of statistical significance level was undertaken; possible confounding factors were not taken into account; and indications for the scan, an important determinant of outcome, were not reported. Given the high risk of bias, the conclusions were unjustified and implied causation when, at best, association was shown which needs to be interpreted with caution in the light of Hill's criteria of causation⁷.

The study by Grether *et al.*⁴ was rated as medium quality, being a case–control study with a fairly large number of children included and prospectively recorded ultrasound exposure data.

The studies by Stoch *et al.*⁵ and Höglund Carlsson *et al.*⁶ were judged to be of high quality as they reported long-term follow-up of a large number of children, from randomized controlled trials.

CONCLUSION

Based on the available data, the ISUOG Safety Committee has concluded that there is no scientifically proven association between ultrasound exposure in the first or second trimesters and ASD, or its severity. Sonograms can be performed safely during pregnancy by trained and accredited sonologists, when medically indicated and when the 'as low as reasonably achievable' (ALARA) principle on the use of ultrasound intensities is employed⁸. Since, in Doppler mode, relatively high intensities are usually transmitted, ISUOG (and other ultrasound organizations) recommends that pulsed Doppler (spectral, power and color-flow imaging)

ultrasound not be used routinely in early pregnancy⁹. When performing Doppler ultrasound in the first trimester on clinical grounds, the displayed thermal index should be ≤ 1.0 and exposure time should be kept as short as possible.

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