Safety of ultrasonography in pregnancy: WHO systematic review of the literature and meta-analysis

Torloni MR, Vedmedovska N, Merialdi M, Betran AP, Allen T, Gonzalez R, Platt LD

CRD summary
The review found that exposure to diagnostic ultrasonography during pregnancy appeared to be safe. The authors’ conclusions may require a degree of caution in interpretation, due to unexplained statistical heterogeneity and limited information about RCT quality.

Authors’ objectives
To assess the safety of human exposure to ultrasonography in pregnancy.

Searching
MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restriction for articles published from 1950 to October 2007. The search strategy was reported. Definitive reviews, textbooks, published letters and reference lists of relevant primary studies and reviews were checked. Experts in the field were consulted.

Study selection
Controlled clinical trials, cohort and case-control studies that assessed long- or short-term effects of ultrasound exposure during pregnancy were eligible for inclusion. Participants were required to be low-risk or unselected women exposed at least once during any period of pregnancy to static or B-mode ultrasound and/or continuous or pulsed-wave Doppler, using any type of equipment or transducer frequency. Studies were required to include a control group that received no or fewer exposures to ultrasound and to report data that allowed calculation of odds ratios (ORs), risk ratios (RRs) or weighted mean differences (WMDs). The review reported a large number of maternal, perinatal and childhood outcomes, which were listed in a table. Studies restricted to high-risk women and studies of continuous Doppler foetal heart monitoring were excluded.

Participants in the review were women who received maternity care in a variety of settings (primary care, public or private hospital) or cases identified from registers, such as national and hospital birth records. B-mode ultrasound was used in most cases (where reported). The type of equipment used and the frequency, duration and intensity of exposure varied across studies (where reported). The gestational age of the exposed foetus ranged from under eight weeks to 38 weeks (where reported). The intervention group received up to nine exposures to ultrasound; controls received none in most studies and up to three in others (where reported). Studies were conducted in a variety of settings that included Europe, North America, China and South Africa.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Randomised controlled trials (RCTs) were assessed by their method of allocation concealment. Observational studies were assessed by the following criteria: design (prospective/retrospective), dropouts, sample size, selection method, group equivalence and reporting of exposure and outcomes. A single reviewer assessed study quality and checked with a second reviewer when considered necessary.

Data extraction
Data were grouped by outcome. Unadjusted odds ratios and 95% confidence intervals (CIs) were calculated from the numbers of events in the two groups of each study. Weighted mean differences and 95% CIs were calculated for continuous data. Two reviewers independently extracted the data using a structured data extraction form.

Methods of synthesis
Studies were combined with a fixed-effect model to calculate pooled odds ratios and weighted mean differences, with
95% CIs. Analyses were stratified by study design. Heterogeneity was assessed with the Q-test and $I^2$ statistic ($I^2 \geq 50\%$ indicated moderate or high heterogeneity). Prespecified subgroup analyses of controlled trials were undertaken to investigate the effect of ultrasound type, number of exposures and gestational age at first exposure.

**Results of the review**

Forty one studies (61 articles) were included: 16 randomised controlled trials and 13 cohort and 12 case-control studies. Most were of regular or good quality. Nine out of 16 controlled trials did not give details of allocation concealment. Among observational studies, 88% scored at least 8 points out of a maximum of 16 (range 7 to 13).

**Maternal adverse outcomes:** Pooling of nine RCTs (n=25,200) found that ultrasound during pregnancy did not significantly increase maternal hospital admissions. There was moderate to high heterogeneity for this finding ($I^2=63.8\%$).

**Perinatal birth weight, length and head circumference:** Pooling of RCTs found that ultrasound did not significantly increase the rate of low birth weight (nine RCTs, n=24,271) or very low birth weight (two RCTs, n=1,509), nor did it significantly affect mean birth weight (nine RCTs, n=35,894), length (RCT, n=7,431) or head circumference (RCT, n=7,393). There was moderate to high heterogeneity for all these findings ($I^2=50.9\%$ to 88.6%).

**Other perinatal outcomes:** Ultrasound did not significantly influence rates of preterm birth, low Apgar scores, need for neonatal resuscitation, seizure, intensive care admission, neonatal, foetal or perinatal mortality and small-for-gestational-age infant; there was moderate heterogeneity for the last outcome ($I^2=50.6\%$).

**Infant outcomes:** RCTs or RCT follow-up studies found no statistically significant long-term effect from foetal ultrasound exposure on childhood growth, dyslexia, speech development, behavioural scores, school performance and neurological outcomes. Although ultrasound did not significantly affect the overall risk of non-right handedness, when boys were considered separately in subgroup analysis, there was a small but statistically significant increase in risk in the exposed group (OR 1.26, 95% CI 1.03 to 1.54; two RCTs). No RCTs reported childhood malignancy. Pooling of eight case-control studies found no increased risk from foetal exposure to ultrasound.

The results of cohort and case-control studies and of other subgroup analyses were reported in the review.

**Authors' conclusions**

Exposure to diagnostic ultrasonography during pregnancy appeared to be safe.

**CRD commentary**

The objectives and inclusion criteria of the review were clear. Relevant sources were searched without language restriction for studies. It was unclear whether the search was restricted by publication status, so there may have been a risk of publication bias; it did not appear that this was formally assessed. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently select studies and extract the data. However, not all stages of validity assessment involved two reviewers. It appeared that allocation concealment was the only component of quality that was assessed in RCTs; important components of RCT validity (such as follow-up rates) were not reported. Appropriate statistical methods appeared to be used to combine data and assess for heterogeneity. Potential differences between the studies were explored in subgroup analyses. Higher-quality studies were prioritised in the interpretation of results. Potential biases in observational studies were explored. However, the high levels of statistical heterogeneity in many of the RCT analyses were acknowledged only in passing and no explanations were suggested. The authors’ conclusions may require a degree of caution in interpretation, due to unexplained statistical heterogeneity and limited information about RCT quality.

**Implications of the review for practice and research**

**Practice:** The authors stated that patients should be exposed to the minimum possible amount of ultrasound energy required to make a diagnosis.

**Research:** The authors stated that large studies were needed to investigate the safety of ultrasound scans using current equipment; such studies may not be feasible in developed countries. Studies should include long-term follow up of exposed and unexposed infants.
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