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

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KEYWORDS: adverse effects; diagnostic imaging; diagnostic techniques; fetus; obstetric and gynecological; pregnancy; prenatal; prenatal injuries; safety; ultrasonography

ABSTRACT

Objective *In the context of the planned International Society of Ultrasound in Obstetrics and Gynecology–World Health Organization multicenter study for the development of fetal growth standards for international application, we conducted a systematic review and meta-analysis to evaluate the safety of human exposure to ultrasonography in pregnancy.*

Methods *A systematic search of electronic databases, reference lists and unpublished literature was conducted for trials and observational studies that assessed short- and long-term effects of exposure to ultrasonography, involving women and their fetuses exposed to ultrasonography, using B-mode or Doppler sonography during any period of pregnancy, for any number of times. The outcome measures were: (1) adverse maternal outcome; (2) adverse perinatal outcome; (3) abnormal childhood growth and neurological development; (4) non-right handedness; (5) childhood malignancy; and (6) intellectual performance and mental disease.*

Results *The electronic search identified 6716 citations, and 19 were identified from secondary sources. A total of 61 publications reporting data from 41 different studies were included: 16 controlled trials, 13 cohort and 12 case–control studies. Ultrasonography in pregnancy was not associated with adverse maternal or perinatal outcome, impaired physical or neurological development, increased risk for malignancy in childhood, subnormal intellectual performance or mental diseases. According to the available clinical trials, there was a weak association between exposure to ultrasonography and non-right handedness in boys (odds ratio 1.26; 95% CI, 1.03–1.54).*

Conclusion *According to the available evidence, exposure to diagnostic ultrasonography during pregnancy appears to be safe. Copyright © World Health Organization (2009).*

INTRODUCTION

In the last four decades, ultrasound has become a valuable and increasingly popular tool in obstetrics. Since ultrasound is a form of energy, it has the potential to produce biological effects that can constitute a risk for health. Animal studies suggest that ultrasound may produce adverse effects in the neurological, immunological, hematological, developmental and genetic status of the exposed fetus[1]. Thus there is a basis for concern about the safety of humans exposed to diagnostic ultrasound during fetal life. Because no clinically evident immediate adverse effects have been reported in humans, most health professionals and patients consider diagnostic ultrasound in pregnancy to be a safe procedure[2,3]. However, as with any diagnostic test, there may be some risk. There have been few studies specifically designed to evaluate the safety of ultrasound in human pregnancies, many suffer from methodological shortcomings and few have analyzed possible long-term effects of *in-utero* exposure. To the best of our knowledge, up to the present there have been no large randomized controlled trials done for the specific purpose of investigating potential bio-effects of prenatal ultrasound in humans[4,5], and it is highly improbable that such studies will ever be performed in developed countries

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owing to the almost universal use of ultrasound in modern obstetrics.

The World Health Organization (WHO) is planning to conduct a multicenter study for the development of international fetal growth standards by serial ultrasonographic examinations[6]. In this context, it is important to thoroughly review the data on safety of diagnostic ultrasonography obtained from the existing randomized trials and observational studies. In order to map current knowledge, we conducted a systematic review of the existing literature about adverse effects of ultrasound on the health of pregnant women and their fetuses.

METHODS

For randomized trials, this systematic review followed the principles of the Cochrane handbook[7] and for observational studies we followed the recommendations for reporting proposed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group[8]. We also took into consideration the framework proposed for systematic reviews of adverse effects[9].

Criteria for considering studies for this review

Types of study

This systematic review included controlled clinical trials, cohort and case–control studies that assessed any type of short- and long-term effects of at least one exposure to ultrasound during pregnancy.

Types of participant

Low-risk or unselected women of any race, ethnicity, age or parity submitted to ultrasound during pregnancy were included. Since we wanted to evaluate the safety of ultrasound on pregnant women who could be considered representative of the general population, and to avoid confounding due to the effects of intrinsic pathological conditions, we excluded studies restricted to high-risk pregnant women.

Types of exposure

Exposure to static or B-mode ultrasound alone or associated with continuous or pulsed-wave Doppler or Doppler alone. Exposures occurring during any period of pregnancy (first, second and third trimester), for any number of times, using any type of equipment and transducers of any frequency were included. Exposure to continuous Doppler for fetal heart monitoring was not considered diagnostic ultrasound, therefore studies reporting exclusively on this kind of exposure were excluded from this systematic review.

Outcomes assessed

Outcomes assessed are listed in Table 1.

Inclusion criteria

A study was included if the following criteria were met: (1) participants were from an unselected or low-risk population; (2) the study presented a control or comparison group that had not been exposed to ultrasound or had been exposed to fewer ultrasound scans than the study group; and (3) the study offered data for calculation of relative risk or odds ratio (OR) or weighted mean differences.

Search strategy for identification of studies

Two electronic databases (MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL)) were searched for articles published between January 1950 and October 29 2007. The search strategy, developed with the assistance of an expert in search strategies for systematic reviews at the WHO, is detailed in Appendix S1 (online). There were no language or country restrictions. Classic review articles, textbooks and published letters were also examined for potentially eligible studies. The reference lists of primary studies and relevant reviews were screened and experts in the area were contacted.

Screening and data extraction

All citations identified by electronic databases were downloaded into Reference Manager® software version 10 (The Thomson Corp., New York, NY, USA). The citations were organized, duplicates deleted and each

Table 1 Outcomes analyzed

Category
Maternal outcome
Admission during pregnancy or intrapartum and postpartum complications
Perinatal outcome
Low birth weight (< 2500 g) and very low birth weight (< 1500 g)
Mean birth weight, head circumference and infant length
Small for gestational age
Preterm birth
Low Apgar score at 1 and 5 minutes
Need for neonatal resuscitation or intubation
Seizures
Congenital malformations
Admission to neonatal ward or intensive care unit
Fetal, neonatal and perinatal mortality
Childhood growth, neurological development and school performance
Height, weight, head circumference
Dyslexia
Speech development
Behavioral scores
School performance (reading, spelling, arithmetic)
Hearing and visual impairment
Cognitive function
Attention deficit
Motor skills
Non-right handedness (left handedness, ambidexterity)
Childhood malignancies
Intellectual performance and mental diseases after childhood

citation was assigned a unique identification number. In a first step, two investigators (M.R.T. and N.V.) independently screened the results of the electronic searches to select potentially relevant citations based on title and abstracts. When the citation was relevant or when title/abstract were not sufficient to make a decision on inclusion/exclusion, the full texts were retrieved and evaluated.

All articles selected at first screening were read and abstracted by two reviewers (M.R.T. and A.P.B.) using a structured data-extraction form (Appendix S2 online) specifically created for this systematic review on the basis of a form developed for the WHO systematic review on maternal mortality and morbidity[10]. Differences between the two reviewers were resolved by consensus.

Information extracted from each article included: (1) general characteristics of the study such as design, population, setting and source of data; (2) method of recruitment, inclusion/exclusion criteria, number of participants, and number lost to follow-up or completeness of the records; (3) information on ultrasound exposure such as type of equipment, frequency of transducer, duration of examination and acoustic intensity output; (4) information on outcome (type of event, definition, method and timing of assessment); and (5) data to calculate unadjusted estimates of the risk or OR. If a single article reported on more than one outcome, each outcome was addressed separately. The data from the controlled trials were extracted on an intention-to-treat basis. When data in the original publication were not sufficiently detailed, the authors were contacted for additional information.

Methodological quality of included studies

Randomized clinical trials were judged on the method of allocation concealment[11]. Briefly, trials were graded as A when concealment of allocation was considered adequate, B when unclear and C when inadequate. The quality of observational studies was assessed using a checklist (Appendix S3 online) based on the criteria proposed by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) group[12]. Briefly, observational studies were graded according to the following: type of study (prospective vs. retrospective), number lost to follow-up, sample size, participant selection, comparability of groups, and details of exposure (to ultrasound) and of outcomes, including source of information. The maximum grade on this scale was 16. One reviewer (M.R.T.) assessed quality, cross-checking with a second reviewer (A.P.B.) when necessary.

Statistical analysis

In each study, for binary outcomes we calculated the unadjusted OR and 95% confidence interval (CI) for the specific adverse event evaluated. For continuous variables, we calculated the weighted mean difference and 95% CI for the outcome evaluated. The studies were combined by meta-analysis using the fixed-effects model. The RevMan 4.2 software (Copenhagen: the Nordic Cochrane Centre, the Cochrane Collaboration, 2003) was used. Pooled OR were obtained for each adverse event, stratifying by study design (randomized controlled trial, cohorts and case–controls).

Heterogeneity of pooled OR was assessed graphically using forest plots and statistically using the Q-test and the I^2 test. If the Q-test[13] was significant – i.e. the between-studies variability was higher than expected by chance – a random-effects model[14] was used. If the I^2 value – the proportion of total variation that is due to heterogeneity rather than chance – was greater than 50% it was considered an indication of moderate or high heterogeneity between studies[15,16].

For the controlled trials, subgroup analysis for the following conditions were decided *a priori*: (1) type of ultrasound (B mode alone vs. B-mode with Doppler or Doppler only); (2) number of exposures during pregnancy (one, two, or three or more); and (3) gestational age at first exposure (first, second and third trimester).

RESULTS

The electronic database search identified 5091 citations from MEDLINE and 1625 from Cochrane CENTRAL (Figure 1). In the first screening (abstracts/titles), 6650 citations were excluded and 66 underwent full-text evaluation. Forty-two articles were included from the electronic databases (36 from MEDLINE and six from Cochrane) and another 19 were included from the reference lists of other publications, resulting in a total of 61 included references.

The 61 publications included in this systematic review reported on 41 different studies that consisted of 16 controlled trials, 13 cohorts and 12 case–controls. The main characteristics of the 61 publications are presented

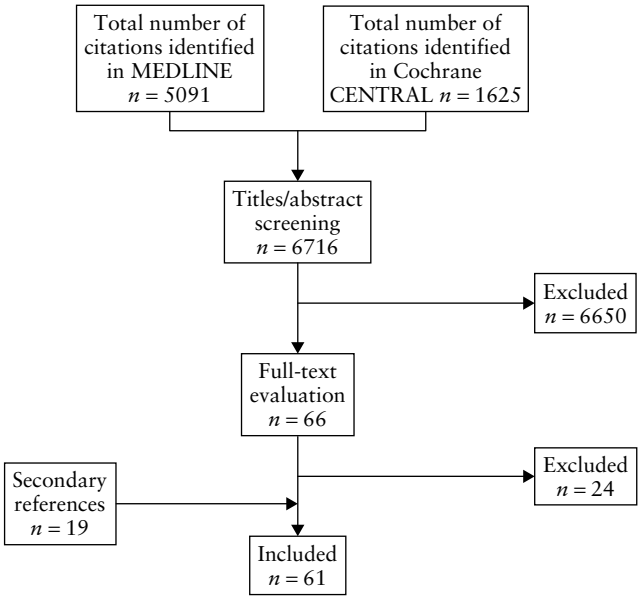

Figure 1 Flow diagram of the process of identifying and including references for this systematic review.

in Table S1 (online). Most of the 41 studies included were of regular or good methodological quality. Over half (9/16) of the controlled trials did not report in detail approaches to allocation concealment and were therefore graded as B. The quality grades of the observational studies ranged from 7 to 13, with 88% of them (22/25) scoring 8 or more points out of a maximum of 16 (Table S1 online).

Details of exposure were lacking in the majority of the studies. Details of the type of equipment used were provided in 43.9% (18/41), the frequency of transducers in 26.8% (11/41), duration of exposure in 14.6% (6/41) and the acoustic intensity in only 12.2% (5/41).

Tables S2–S7 (online) and the corresponding meta-analysis graphs (Appendix S4 online) present the main findings of the studies for each outcome category listed in Table 1. The I^2 value was < 50% in 66.7% (18/27) of the pooled OR derived from the randomized trials and in 83.3% (10/12) of the observational studies.

Adverse maternal outcome

Meta-analysis of the nine existing randomized trials involving over 25 000 women indicates that ultrasound during pregnancy does not increase the risks of maternal admission to hospital during pregnancy (Table S2 online). Only one retrospective cohort[17], involving 806 women, investigated other complications of labor and delivery and postpartum complications. Although the authors of this study did not provide details on what complications were being evaluated, they did not find any significant increase of risk in exposed women (Table S2 online).

Adverse perinatal outcome

Birth weight, length and head circumference

According to the pooled OR of the ten existing randomized trials involving over 20 000 participants, *in-utero* exposure to ultrasound does not seem to increase significantly the rate of low-birth-weight infants (pooled OR 1.06; 95% CI, 0.84–1.35). Similarly, the controlled trials indicate that exposure to ultrasound does not increase the risk of delivering infants weighing <1500 g (OR 1.26; 95% CI, 0.26–6.00) and the same was observed for the cohort studies (OR 1.24; 95% CI, 0.78–1.98) (Table S3 online).

The pooled OR derived from six cohort studies involving 18 622 individuals indicates no increase in the risk for low birth weight in those exposed to ultrasound (OR 1.11; 95% CI, 0.84–1.46). There was high heterogeneity among these cohorts ($I^2 = 72.8\%$), but only one study reported an increased risk for low birth weight[18]. The authors of this publication concluded that the indications for ultrasound examination played a significant role in the reduction of birth weight.

Grisso *et al.*[19], in a large case–control study involving 12 546 patients, reported an increased crude overall risk of having a low-birth-weight child in the exposed group (OR 1.38; 95% CI, 1.25–1.51). However, analysis according to the timing of exposure revealed that the excess risk appeared to be restricted to the group of women submitted to ultrasound in the last weeks of pregnancy and that it disappeared when only full-term, uncomplicated pregnancies were examined. The authors therefore concluded that any apparent excess risk for low birth weight in their study was probably a result of the underlying pregnancy complication for which an ultrasound scan was performed.

According to nine controlled trials involving over 35 000 participants and four cohorts with another 2000 cases, exposure to ultrasound during pregnancy did not influence significantly the mean birth weight. Similarly, the mean length and head circumference at birth did not differ significantly between exposed and unexposed infants (Table S3 online).

Other perinatal outcomes

According to the pooled crude ORs, exposure to ultrasound did not increase the risk of delivering small-for-gestational-age infants, preterm birth, low Apgar scores, need for neonatal resuscitation, seizures, admission to intensive care or neonatal, fetal or perinatal mortality (Table S3 online).

A case-control study[20] reported an increase in the risk of cardiac defects in fetuses exposed to ultrasound. However, logistic regression analysis showed that the threat of miscarriage during early pregnancy was in fact the confounding factor explaining the association between ultrasound and the risk of congenital heart disease. While a large controlled trial[21] did not find a significant association between ultrasound and any specific type of congenital malformation, the pooled OR derived from two cohort studies[22,23] indicated a possible increase in fetal malformations (OR 1.80; 95% CI, 1.16–2.78) (Table S3 online). However, in the largest of these cohorts, the rate of fetal malformations in the group exposed to four or more ultrasound scans was only 0.9% (38/4297), while it was 0.5% (38/7846) in those exposed to fewer scans[22].

Growth and neurological development during infancy

Table S4 (online) presents the results regarding child growth and neurological development. In a follow-up study of an Australian controlled trial, MacDonald *et al.*[24] reported that mean weight and height at 1 year of age were similar in the intensive (five scans with Doppler) and regular (one scan with Doppler) groups. These investigators had previously reported an increased proportion of birth weights in the lower percentiles in babies exposed to multiple prenatal ultrasound examinations[25,26]. Therefore, the authors concluded that if there is an effect of multiple ultrasound scans on birth weight, there is 'catch-up' in the infants' growth and the difference is no longer discernible at

1 year of age. Subsequent examinations of the same children done at 2, 3, 5 and 8 years of age indicated no significant differences in height, weight or head circumference measures in boys and girls exposed to multiple ultrasound examinations at between 18 and 38 weeks' gestation[27]. Similarly, the follow-up study of two Norwegian controlled trials on ultrasonic screening during pregnancy (at 19 and 32 weeks) concluded that there were no statistically significant differences in the body weight or height of screened and unscreened children at 3, 6 and 12 months or at 2, 4 and 7 years of age[28]. These findings also agree with those of Lyons *et al.*[29], who reported no significant differences in the height and weight of 149 pairs of children (exposed and unexposed to prenatal ultrasound) followed prospectively from birth to 6 years of age. Since none of these four previous studies provided values as mean and SD, we could not perform a pooled weighted mean difference for these measures.

Dyslexia

There are only two studies that evaluated this outcome. In a follow-up of a Norwegian controlled trial, the authors submitted 603 children aged 8–9 years to a specific test and did not find significant differences in the scores of the exposed and unexposed children[30]. On the other hand, on a retrospective cohort carried out in Colorado, USA[17], there was a higher proportion of exposed children with dyslexia. But as the authors point out, this finding may be explained by the higher number of pregnancy complications in the exposed group, an important source of bias.

Speech development

Although the combined results of two large Scandinavian controlled trials[31,32] did not indicate significant differences in speech development, one small Canadian case-control study[33], involving 214 children (72 cases and 142 controls), suggested that exposure to ultrasound in fetal life increased the risk for delayed speech in children. In this study, Campbell *et al.*[33] went on to explore the relationship between the trimester and number of ultrasound exposures and delayed speech, but further analysis revealed no relation to trimester of exposure or dose–response effect (1 vs. 2+ ultrasound scans in pregnancy).

Contrary to these findings, a follow-up of a controlled trial involving 2967 Australian children[27] reported that repeated exposure to ultrasound (five scans with Doppler) significantly reduced the proportion of infants with abnormal scores on a language scale at 1 year of age, thus suggesting that intensive exposure to ultrasound in pregnancy was in fact associated with earlier acquisition of language. But the authors point out that this finding may have resulted from chance, due to the many end-points tested in this study. In fact, other tests related to speech and language development did not reveal any significant differences between these exposed and unexposed children. Similarly, the Norwegian controlled trial follow-up study[32] also reported that exposed children had significantly fewer referrals to speech therapists than unexposed children (OR 0.50; 95% CI, 0.30–0.84). But, once again the authors emphasize that the statistically significant negative association between ultrasound and referral to speech therapy may be due to chance, since this was not a prior hypothesis in their study.

Behavioral scores

Two follow-up studies of controlled trials[27,31] assessed behavioral problems in children but could not be analyzed as OR because of the way in which the data were provided. Kieler *et al.* analyzed behavioral problems in 3265 children (aged 8–9 years) and reported that the mean final score on 10 items rated by the parents did not differ significantly between exposed and unexposed children[31]. In the follow-up of another controlled trial, Newnham *et al.*[27] assessed behavioral problems in 2967 toddlers (1 year of age) using a questionnaire with 97 items. There were no differences on the percentage of scores outside the normal range among children submitted to regular or intensive ultrasound during pregnancy. Using a behavioral checklist, these authors re-evaluated the same children at 2, 5 and 8 years of age and reported that there were no statistically significant differences in the scores of the exposed and unexposed children.

School performance

According to one clinical trial involving almost 2000 children, there were no significant differences in overall school performance or specific reading and arithmetic scores between children exposed or unexposed to ultrasound during fetal life[30] (Table S4 online).

Hearing and visual impairment and other neurological functions

The overall risk of having hearing, visual, neurological or developmental impairments during childhood was not increased in fetuses exposed to ultrasound during pregnancy.

Non-right handedness

There was no statistically significant association between intrauterine exposure to ultrasound and the risk of being non-right handed when male and female children were analyzed together (OR 1.13; 95% CI, 0.97–1.32) (Table S5 online). When boys were considered separately, there was a weak association between ultrasound screening and being non-right handed, both in the randomized trials (OR 1.26; 95% CI, 1.03–1.54) and in the cohort studies (OR 1.17; 95% CI, 1.07–1.28).

Childhood malignancy

According to the eight existing case–control studies[34–41] the OR for childhood malignancies was not increased in fetuses exposed to ultrasound (Table S6 online). Six of these studies had information on the number of ultrasound exposures and the occurrence of various malignancies in childhood[35–39,41]. None demonstrated a significant association between exposure to any number of prenatal ultrasound scans and the specific neoplasm analyzed.

Adult intellectual performance and mental disease

Kieler *et al.*[42] found lower intellectual performance scores and an increased risk of subnormal performance in 6026 young men born in Malmö and exposed to ultrasound in fetal life when compared with 161 033 unexposed men born in the rest of Sweden (OR 1.19; 95% CI, 1.12–1.27) (Table S7 online). However, the differences were small and men born in Malmö before the introduction of ultrasound scanning also had lower scores[42]. Another large Swedish cohort study – involving over 370 000 participants – recently reported no significant association between ultrasound exposure in fetal life and schizophrenia or other psychoses after 12 years of age[43].

Subgroup analysis of the controlled trials

Type of ultrasound exposure

Two different randomized trials (totaling five publications[24–27,44]) involved the use of B mode with Doppler, and three other trials[45–47] reported on fetuses exposed exclusively to continuous or pulsed Doppler ultrasound. According to the available data, the mean length of infants exposed to Doppler was 0.26 cm shorter (95% CI, −0.45 to −0.07 cm) than the mean length of those exposed to ultrasound without Doppler. Besides the very small magnitude of this difference, this conclusion was based on only one available study[27]. There were no other significant associations between type of exposure and outcomes (Table S8 online).

Dose–response relationship

Out of the 16 controlled trial studies, seven presented outcomes on one vs. no exposure to prenatal ultrasound, five presented outcomes comparing two with no or one ultrasound scans and four had outcomes on three or more vs. one ultrasound exposure(s) during pregnancy. There was a statistically significant association between a higher number of ultrasound exposures (3+ vs. 1) and low birth weight (OR 1.27; 95% CI, 1.02–1.58). Mean length and head circumference of those exposed to three or more scans during pregnancy were also slightly but significantly lower than those exposed to only one scan (weighed mean difference −0.26 cm; 95% CI, −0.45 to −0.07 cm and −0.15 cm; 95% CI, −0.29 to −0.01 cm, respectively). On the other hand, perinatal mortality was reduced in fetuses exposed to one vs. no ultrasound scans (OR 0.56; 95% CI, 0.40–0.78) (Table S9).

The risk of being non-right handed increased slightly in children exposed to two vs. 0–1 ultrasound scans during pregnancy (OR 1.32; 95% CI, 1.02–1.71). For boys the risk was higher, although the association was not significant (OR 1.40; 95% CI, 1.00–1.97). However, in both cases, analyses were based on only one study each (Table S9 online).

Gestational age at first exposure

There were no controlled trials that used ultrasonography during the first trimester of pregnancy and only one study[48] that randomized women to first exposure to ultrasonography in the third trimester. Therefore we could not perform subgroup analyses for any outcome according to the trimester of pregnancy at first exposure.

DISCUSSION

According to the findings of this systematic review, ultrasonography in pregnancy is apparently not associated with important adverse maternal, perinatal or childhood effects. There was a weak association between exposure to ultrasound and non-right handedness in boys only. Even though some studies (mostly observational) found some small but significant association in certain outcomes (see Tables S2–S9 online), the authors of these studies themselves presented explanations and/or potential methodological flaws that would justify the positive result.

Although there have been several narrative reviews on the safety of ultrasound, only two previous publications actually used a systematic approach to assess adverse effects of ultrasound during pregnancy. Salvesen and Eik-Nes[49] performed a meta-analysis of the randomized trials on ultrasound and non right-handedness. These authors located the same two existing publications on the topic[50,51] and also presented additional, previously unpublished, information regarding gender-specific effects of exposure vs. non-exposure to ultrasound from the Norwegian trial. Their results were identical to ours, indicating no statistically significant differences in the prevalence of non-right handedness between the screened and unscreened children in general, with a significant difference when boys were analyzed separately. While the present study only analyzed outcomes according to randomization (intention-to-treat principle), the authors of that systematic review also explored the effects of actual fetal exposure as well as the gestational age at which exposure occurred. With the use of this careful and detailed exploratory analysis, they reported an even stronger association between ultrasound exposure and non-right handedness in boys exposed to ultrasound before 19 or 22 weeks (OR 1.34; 95% CI, 1.10–1.65).

In 1999 the same authors published a second systematic review analyzing the association between ultrasound,

birth weight, childhood malignancies and neurological development[52]. While that study presented small-for-gestational-age and low-birth-weight infants in a common category and did not pool their data, we evaluated these two outcomes separately and calculated the pooled OR for each of them. Our search retrieved four more articles on low birth weight[53–56] and one more on childhood malignancies[34], besides three other studies published since that date[37,39,41].

Our systematic review provides important information necessary for the reader to understand the validity and reliability of the results[8,12]. We clearly specify how many reviewers were involved in the screening and data extraction processes, we evaluate and report on the quality of the primary studies according to predefined criteria, and we discuss heterogeneity of their pooled OR. Most of the studies included in the present systematic review were of regular or good methodological quality, therefore supporting the validity of the findings presented. Another strong point of our systematic review is that it is the first that has striven to obtain and present details of exposure such as type of equipment, frequency of transducers, duration of exposure and acoustic intensity. We also present meta-analyses of the association between ultrasound exposure and several other perinatal outcomes not presented in the previous reviews (preterm birth, perinatal mortality, low Apgar score, neonatal morbidity) as well as childhood growth. Therefore, this is the largest systematic review on the safety of ultrasound to date.

Limitations of this systematic review

A basic limitation of this systematic review is that none of the included studies stated that assessing possible adverse bioeffects of ultrasound was one of their specific objectives. Ideally, adverse effects of an intervention should be one of the objectives of any study investigating a new procedure. Unfortunately, since the introduction of ultrasound in the 1970s, the investigation of its possible side-effects in humans has been very limited.

Quantification of the intensity of acoustic exposure and duration of examination was lacking in almost 90% of the included studies. Even if these measures had been provided, research into the effects of ultrasound exposure is complicated by the fact that there is no way of objectively measuring the dose of energy absorbed[57].

Dose response is a critical issue in the study of any potential harm-inducing agent. It was not possible to determine a dose–response gradient for most outcomes since many studies included participants exposed to only one or two scans during pregnancy. Additionally, only 12 of the 41 studies provided explicit data on the number of scans vs. specific outcomes, mostly malignancies. If, as with radiation, ultrasound exposure has a cumulative effect, these data would be essential for establishing if there is a safe upper limit for the total number of ultrasound scans during pregnancy. This information would be important to obstetricians and women alike, since the availability of ultrasound equipment has produced an unjustifiably high number of fetal ultrasound scans, including those without any medical indication.

Another limitation of this systematic review is that it included mostly exposures before 1995, when the acoustic potency of the equipment used was lower than in modern machines. Over the years, there has been a continuous trend of increasing acoustic output, and the findings of this systematic review do not necessarily apply to currently used equipment. Because of weak regulation of ultrasound equipment output, fetal exposure using current equipment can be almost eight times greater than that used previously, regardless of whether gray-scale imaging, color Doppler or duplex Doppler is employed[58,59]. There is a clear need for adequately designed large studies to investigate the safety of ultrasound scans performed with the newer equipment currently in use. However, because prenatal ultrasound is now commonplace, it may be difficult to perform randomized controlled trials without significant crossover. Particularly in developed countries, it would be difficult to recruit women willing to be randomized to a possible non-exposed control group.

Protocol deviations were also reported in almost all of the controlled trials included in this systematic review, mostly involving control women being exposed to unscheduled ultrasound for various clinical reasons. Obviously this could potentially affect the results reported by these studies. Even if there had been no deviations at all, it is quite probable that many fetuses, in both arms of a controlled trial, have also been exposed to ultrasound from other sources such as heart rate detectors and electronic antepartum and intrapartum monitoring. This additional and uncontrolled exposure may weaken the estimated association between ultrasound and any of the outcomes analyzed.

The inclusion of observational studies in this systematic review is open to criticism. Although cohorts and case–control studies are more likely to be hampered by systematic error, they have the advantage that large sample sizes can be achieved, which is a prerequisite for studying rare outcomes[60,61]. However, the results of observational studies should be interpreted with caution since the possibility for confounding is large. Several studies omitted important details on the characteristics of the exposed and non-exposed women, such as age, parity, socio-economic status, drug, tobacco, and alcohol use, all of which are important determinants of perinatal outcome. Differences in the rate of obstetrical and clinical complications also often differ between the exposed and unexposed groups in cohort studies[29]. This is not surprising, since problems during pregnancy are a common reason for referral to ultrasound. Therefore, in many cohorts, the subjects exposed to ultrasound may have differed from the unexposed participants and this alone may have influenced the outcome. Consequently, the strength of inference of putative harm or absence of harm derived from observational studies will always be lower than that of randomized trials.

Implications for practice and research

Based on the available publications, diagnostic prenatal ultrasonography should continue to be considered relatively safe for both the mother and the exposed fetus. However the findings of this systematic review should be interpreted with caution. Safety implies absence of any deleterious effect, recognized or unrecognized, and it must be kept in mind that deleterious effects resulting from ultrasound may be subtle and appear many years after exposure. To answer questions about the effect of ultrasound on human development, long-term follow-up of exposed and unexposed infants is recommended[62]. However, the cost and effort needed for studies of these delayed or subtle effects have discouraged their implementation. Moreover, the various studies included in this systematic review did not necessarily assess all possible harmful biological effects produced by prenatal ultrasound. Future investigations may reveal effects that are as yet unrecognized. Furthermore, owing to the lack of sufficient detail in the existing publications, it is impossible at this time to state exactly what combination of factors (gestational age, duration and number of exposures, acoustic output and fetal position) offer the least risk to the fetus. Therefore, as stated in the ALARA (As Low As Reasonably Achievable) principle proposed almost 20 years ago[63], based on the currently available evidence it is still prudent to expose patients to the least amount of ultrasound energy necessary to obtain diagnostic information.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

(References 64–86 are cited within the supporting information)

Table S1 Main characteristics of 41 included studies (61 publications)

Table S2 Prenatal ultrasound and adverse maternal outcome

Table S3 Prenatal ultrasound and perinatal outcome

Table S4 Prenatal ultrasound and childhood neurological development and school performance

Table S5 Prenatal ultrasound and non-right handedness (NRH)

Table S6 Prenatal ultrasound and childhood malignancy

Table S7 Prenatal ultrasound and adult intellectual performance or mental disease after childhood

Table S8 Subgroup analysis: effect of type of ultrasound exposure on various outcomes (controlled trials only)

Table S9 Subgroup analysis: relationship between number of ultrasound examinations performed during pregnancy and various outcomes (controlled trials only)

Appendix S1 Search strategy

Appendix S2 Data extraction form

Appendix S3 Quality assessment of observational ultrasound studies

Appendix S4 Meta-analysis graphs for safety of diagnostic ultrasound in pregnancy