A Review of Potential Adverse Effects of Antenatal Ultrasonography

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Abstract

This report examines the recent evidence for potential adverse effects of antenatal ultrasonography on the fetus.

1 Introduction

The routine use of ultrasound for antenatal examination is today a virtually universal procedure. For example, Backe *et al.* (1990), in Norway, note that ultrasound screening has become more widespread; in New Zealand its use is almost routine, see Buckenham *et al.* (1991); in the United States, by 1990, 52% of mothers were receiving ultrasound, see Ewigman *et al.* (1993b); and Rushworth *et al.* (1994), in a study of women in New South Wales, report that almost all had an ultrasound examination.

Not only do the majority of women receive antenatal ultrasound examination but its use is rarely restricted to a single scan. Dowswell and Hewison (1994) found that the mean number of scans received was 2.6, suggesting that many women receive an early dating scan followed by one or more routine scans. Jorgensen (1993) notes that women offered screening had a significantly increased number of ultrasound examinations than those not receiving such an offer. Similarly, Ewigman et al. (1993a) found that women in an ultrasound-screening trial had a mean of 2.2 scans, whereas those only receiving scans if medically indicated received a mean of 0.6 scans. The implication is that women generally opt for an ultrasound examination if it is offered.

Moore *et al.* (1990) in a US study note that the most common indication for an ultrasound examination was to establish the gestational age. Other uses include estimation of fetal weight, location of the placenta, detection of multiple gestation, detection of anomalies, guiding amniocentesis and CV sampling. Bottoms (1995) advocates its use to check for major malformations prior to preterm delivery, while Seeds (1996) suggests that this is its least likely benefit.

Despite its widespread use, many authors continue to express concern about the potential risks to the fetus. For example, Lewis and Mocarski (1987), cautioning against indiscriminate ultrasound exposure, advocate following recommended guidelines. They await long-term follow-up studies.

Miller (1991) reviewed the then existing literature and conceded that concern exists about the thermal effects of ultrasound, particularly in fetal examinations with pulsed-Doppler beams. He contends that the threshold nature of any damage, and new techniques and equipment, will resolve these problems. He also observes that non-thermal cavitational bioeffects create a problem in risk assessment and also serve as reminders of potential low-level risks.

Butnariu (1992) reviews the existing literature and considers ultrasonography low-cost, reproducible, informative, and having "minor if any" long-term side-effects. Terinde (1992) considers ultrasound safe, though he qualifies this as being "below clearly defined intensity levels". However, he does caution against routine use of duplex sonography.

Ewigman *et al.* (1993a,1993b) conclude that routine ultrasound screeing does not improve perinatal outcome when compared with its selective use as determined by clinical necessity. However Skupski *et al.* (1995), in a critical review of this RADIUS study conclude the opposite, namely that routine use of ultrasound is supported by the scientific data. Seeds (1996) similarly is critical of the RADIUS study in suffering from inherent biases arising from the restrictions imposed upon the study group. He suggests that routine ultrasound examination between 18 and 22 completed weeks is acceptable provided the patient is aware of the "goals and limitations" and the scan is competently performed and properly recorded. Waldenstrom (1995) similarly advocates providing information to the patient.

Dowswell and Hewison (1994) express concern that insufficient is known about the safety and efficacy of ultrasound scans and question how cost effective they are. They further observe that little is known about the possible psychological effects of early scans.

Despite the concern about its widespread use the prospects for the future are for an increasing number of ultrasonography examinations for detecting a wide range of anomalies. For example, Duchatel *et al.* (1993) suggest that ultrasonography is a good prenatal diagnostic aid for detecting cystic fibrosis. They advocate routine ultrasonography at 17-29 weeks gestation. Guibaud *et al.* (1996) claim that ultrasonography gives a highly accurate diagnosis of, and accurate prognosis for once diagnosed, fetal congenital diaphragmatic hernia. However it should be noted that this study only demonstrated its diagnosis in a retrospective study.

The chief contention in this report is that the claimed safety of antenatal ultrasonography is a dubious one, though it is conceded that the available studies do give conflicting results. The animal studies which give grounds for concern about the use of ultrasound are reviewed in Sections 3 and 4. The studies on fetuses and neonates which suggest adverse effects are presented in Section 5.

Section 2 presents evidence of the measurement errors associated with the use of ultrasound. These errors place limits on the effectiveness of ultrasound examinations. Partly the errors arise due to observer error. There would appear to be inherent limitations in the ability to accurately detect fetal abnormalities or to measure supposedly important variables.

2 Measurement Variation

As noted in Section 1, a key use of ultrasonography is to estimate gestational age and to detect fetal anomalies. Unfortunately these goals are compromised by the errors which can arise through ultrasonography. One key problem is that of intra-observer error. Thus Flack *et al.* (1994) report such errors are significant when obtaining certain measurements using ultrasonography. They suggest that one major source of error is transducer pressure.

Baronciani *et al.* (1995) examined the sensitivity of ultrasound scanning as a screening test for detecting major congenital abnormalities. They reported sensitivity rates of between 4% and 75%. Overall, only 18% of the defects diagnosed *in utero* were detected before 24 weeks' gestation. They advocate the abandonment of ultrasound as a screening test in the general population, though they suggest that better equipment and training should improve matters. Sensitivity rates were 4% for congenital heart diseases, 17% for gastrointestinal tract defects, 23% for skeletal abnormalities, 24% for diaphragmatic hernia, 47% for abdominal wall defects, 49% for central nervous system anomalies, and 75% for urinary tract anomalies. The low rate for congenital heart disease causes Buskens *et al.* (1995) to propose abandonment of routine prenatal screening for this condition.

These sensitivity rates are similar to those reported by Roberts *et al.* (1993) who found that the ultrasonography detection rate of cardiovascular, facial and gastrointestinal major abnormalities was low, but high for abnormalities of the central nervous system, renal tract and abdominal wall. They note that this is similar to other studies and suggest that it could be improved by better training and equipment. Similarly Cullen *et al.* (1992) suggest that an effective ultrasound screening programme requires major training and careful timing of the screening.

Saari-Kemppainen *et al.* (1994), in a study on Finnish women, record that 40% of major fetal anomalies were detected by a systematic screening for fetal abnormalities. Ultrasound between the 16th and 20th weeks of gestation detected 27% of the major abnormalities. As in other studies, ultrasound was most successful in detecting abnormalities of the central nervous system, genito-urinary tract, and cases with multiple abnormalities. It was less satisfactory in detecting anomalies of the heart and gastrointestinal tract. Interestingly, though they have similar results to those of Baronciani *et al.* (1995), they reach the opposite conclusion, namely that a systematic search for fetal anomalies should be included in the routine ultrasound screening.

A consequence of such sensitivity rates is misdiagnosis of potentially healthy fetuses, with the concomitant risks of such action. Thus Schei (1991) estimates that screening for congenital anomalies in Norway during the second trimester might, through misclassification, lead to the yearly elimination of 300 desired fetuses, some of which might have otherwise been born as healthy children. A similar dissatisfaction with ultrasound use is expressed by Cameron and Malmo (1993) who dismiss its use as a diagnostic tool for pregnancy in cattle because of its poor accuracy, with sensitivity 93% and specificity 76%.

A further problem of over-reliance on results of ultrasound examinations is illustrated by Larsen and Larsen (1991), who report several cases of incorrectly diagnosed ectopic pregnancies following ultrasound examination. In one case a twin pregnancy was missed, with subsequent clinical examinations not questioning the results of the ultrasound examination.

Wojak *et al.* (1995), in a study of ectopic pregnancy, report that examiner experience has a strong effect on the diagnostic accuracy of ultrasound examination.

Fetal weight estimation provides a case study of the kinds of problems which can arise through ultrasonography measurements.

The work of Rogers *et al.* (1993), reporting that ultrasound fetal weight estimation had similar standardized absolute error as estimation methods based on multiple regression of birth-weight on maternal age, parity, height and weight would suggest little advantage is gained from the use of ultrasound.

Chang *et al.* (1993), in a study of inter- and intra-observer errors, claim that fetal weight estimates are reproducible. However their work shows that 95% prediction intervals for inter-observer comparisons are slightly negatively biased, though including zero, with a spread of the order of 300 g., depending on the formula used to estimate fetal weight. The intra-observer standard deviation was not negligible.

A consequence of inaccurate prediction of fetal weight is that it can result in unnecessary obstetric intervention; see for example Sandmire (1993), who observes that ultrasonic estimation of fetal weight is not accurate enough for detecting macrosomia as defined by weight criteria.

Shamley and Landon (1994) examine the accuracy of several formulae for estimating fetal weight at labour. They conclude that any of the four used formulae gave good estimation of fetal weight, though for all four equations at most 80% of the fetal weight predictions were within 10% of the actual birth weight. Thus more than one in five predictions was in error by more than 10%. Sensitivities for detecting birth weights greater than 3800 g varied between 11% and 76% while specificities for detecting birth weights less than 3800 g exceeded 88%. However Scott *et al.* (1996) find errors in the Warsof formula for ultrasound estimation of fetal weight for low fetal weights, with a consistent negative bias in the predicted weight.

Wilcox *et al.* (1993) show that birthweight curves are a function of the method of derivation, whether dated from menstrual history or through ultrasonography. Clearly, using the wrong standard reference curves would lead to invalid conclusions.

Similarly, prediction of gestational age, another key use of ultrasound, is found to be imprecise.

Thus, while Alonso and Portman (1995) suggest that the biparietal diameter, as determined using ultrasound, is an excellent predictor of gestational age, and its measurement correlates well with the actual measurement, Shamley and Landon (1994) report that it could not be measured in approximately two-thirds of the patients examined.

Bottoms (1995) advocates the use of both biparietal diameter and femur length to date the gestational age in the absence of reliable dates derived from menstrual history. Similarly, Rosati *et al.* (1995) suggest that only these two measurements allow correct weekly growth evaluation to be made. However Alonso and Portman (1995) report that femur length measurements had a large coefficient of variation (23%), which suggests that the predicted gestational ages will have large variability. Alonso and Portman also found a comcomitant large coefficient of variation (17%) in the calculated fetal weight.

3 Adverse effects observed in animals

The research group of Hande and Devi and other co-workers, based in the Department of Radiobiology at Kasturba Medical College in India, consistently report findings of adverse effects of ultrasound in studies on mice and rats.

For example, Hande and Devi (1995), in a study of Swiss mice, found that the group exposed to 3.5 MHz ultrasound, at approximately 65 mW, (spatial peak, temporal peak intensity) ISPTP = 1 W/cm^2, (spatial average, temporal average intensity) ISATA = 240 mW/cm^2, on days 6.5 and 11.5 of gestation showed an increase in the percentage of growth retarded fetuses, although the animals recovered during the post-weaning period. Postnatal mortality was significantly higher in this group. There was also a significant change in their locomotor activity, with a reduction in the total activity at 3 and 6 months of age. Latency in learning capacity was also noticed in this group. The results suggested that repeated exposures to ultrasound, or its combination with X-rays, could be detrimental to the embryonic development and impair adult brain function when administered at certain stages of fetal development.

Devi *et al.* (1995) exposed pregnant Swiss albino mice to diagnostic ultrasound at 3.5 MHz, 65 mW, ISPTP = 1 W/cm^2, ISATA = 240 W/cm^2, for 10, 20 or 30 minutes on day 14.5 of gestation. No change in the physiological reflex in the adult was detected when compared with sham-exposed controls. However they did observe a significant alteration in behaviour for all three exposed groups as revealed by decreased locomotor and exploratory activity and in the increase in the number of trials needed for learning. They conclude that ultrasound exposure during the early fetal period can impair brain function in the adult mouse.

Hande *et al.* (1993) reported anxiolytic activity and latency in learning in ultrasound-treated Swiss mice, exposed to diagnostic levels of ultrasound, at 3.5 MHz, ISPTP = 1

W/cm^2, ISATA = 240 mW/cm^2, for 10 minutes on day 11.5 or 14.5 post-coitus.

Hande and Devi (1992) found a small increase in the resorption rate and a significant reduction in fetal body weight after ultrasound exposure on day 3.5 of gestation in Swiss mice exposed to diagnostic levels of ultrasound.

In contrast to these findings, the research group located at the Children's Hospital Research Foundation in Cincinnati, comprising Vorhees, O'Brien, Fisher, and other co-workers, generally report no adverse effects arising from ultrasound treated animals and much of their work is presented in Section 4. However, two of their studies did show small adverse effects.

Vorhees *et al.* (1994) studied rats exposed prenatally to continuous-wave ultrasound. While no effect was found on growth, physical or behavioural landmarks of development, or adult tests of passive avoidance or startle, effects were obtained at the highest intensity, (spatial peak, temporal average intensity) ISPTA = 30 W/cm^2, on corner and side locomotor activity and in a multiple-T water maze on measures of errors and time spent finding the goal. No consistent evidence of neurobehavioural effects were observed at lower ultrasound intensities.

Fisher *et al.* (1994) exposed rats to 3 MHz pw ultrasound for approximately 10 minutes per day at up to 30 W/cm^2 ISPTA at gestational ages 4-19 days. No evidence of an increase in skeletal or visceral malformations was found, nor any evidence of a weight affect. They did find a small but significant increase in resorptions in the group receiving highest exposure levels.

Other studies continue to report a steady stream of adverse findings.

Bretzlaff (1993) reported that 3% of ewes in a flock examined for pregnancy using ultrasonography developed hydrometra. Most of such diagnoses (40 of 41) were made at the time of a second ultrasound examination (7% of those examined a second time). Of 15 ewes with hydrometra examined a third time, 14 had resolved the condition. They conjecture that the increased prevalence of hydrometra at the second examination may have arisen due to the stress of the first examination.

Tarantal *et al.* (1993a) document the maximum temperature rise (0.6°C) from diagnostic ultrasound *in vivo* in gravid macaques. Tarantal *et al.* (1993b) also found transient physiological effects of ultrasound exposure on macaques, affecting body weight, white blood count, and muscle tone, though no significant effect on muscle tone was found after a larger study was undertaken.

Iannaccone *et al.* (1991) report adverse effects of short ultrasound exposure on mouse blastocysts subsequently transferred to surrogate mothers which included decreased implantation rate, increased resorption rate, and increased stillbirth rate.

Norton *et al.* (1991) demonstrated damage to the developing cortex of fetal rats 24 hours after exposure to ultrasound. A decrease in cortical thickness was present postnatally for 28 days, but this decrease was not statistically significant. Other of his findings suggested that there was no significant adverse effect, and these are reported in section 4 below.

See also Pepper (1994).

4 No adverse effects observed in animals

In Section 3 above it was noted that the group comprising Vorhees and Fisher and other co-workers generally report no adverse effects of ultrasound exposure in animals.

Vorhees *et al.* (1994) studied rats exposed prenatally to continuous-wave ultrasound. They found no effect on growth, physical or behavioural landmarks of development, or adult tests of passive avoidance or startle, although neurobehavioural effects were observed at high intensity levels as discussed in section 3.

Fisher *et al.* (1994) exposed rats to 3 MHz pw ultrasound for approximately 10 minutes per day at up to 30 W/cm^2 ISPTA at gestational ages 4-19 days. No evidence of an increase in skeletal or visceral malformations was found, nor was there evidence of a weight affect.

Vorhees *et al.* (1991) exposed rats to varying levels of ultrasound up to 30 W/cm^2 and found no evidence of embryotoxicity in fetuses examined for malformations nor any increase in resorption.

After exposing groups of rats to varying levels of ultrasound, Jensh *et al.* (1994) subjecteded them to five reflex tests and observed them for four physiological parameters. Postnatal growth was also monitored. No significant alterations in neonatal development or postnatal growth due to exposure to 5 MHz ultrasound below an intensity (ISPTP) of 1500 W/cm^2 was found.

Norton *et al.* (1991), although reporting damage to the developing cortex of fetal rats after exposure to ultrasound, examined the performance of ultrasound-exposed rats in several behavioural studies. Though in one test they performed slower, in another test they performed faster when compared with unexposed rats. There was no consistent pattern. No decrease in postnatal weight or growth was found.

5 Adverse effects in humans

5.1 Growth

Newnham *et al.* (1993), in a major study of 2834 women which generated much correspondence, found that intensive ultrasound for imaging and Doppler-flow studies, resulted in significantly higher intrauterine growth restriction. While they note that this may have been a chance result they caution against unnecessary frequent ultrasound exposure.

Evans *et al.* (1996) compared two groups of ultrasound examined pregnancies. One group received intensive examination and the other group received one examination at 18 weeks and other imaging scans if clinically required. While no statistically significant differences were found, the intensive group did have differences when compared with the regular group. The babies tended to be shorter at birth and after 2-3 days. There were reductions in the circumference of the chest, abdomen and mid-arm, as well as other reductions. The reductions tended to be associated with the skeleton rather than soft tissue. They concluded that if multiple ultrasound scans did affect fetal growth it was more likely to be an effect on bone growth rather than an effect to the placenta.

Geerts *et al.* (1996) examined the cost and effect of obstetric ultrasonography in patients with no risk factors for congenital anomalies. They found more babies of low birthweight born in the group receiving ultrasound examination between 18 and 24 weeks. More suspected postdate pregnancies occurred in the control patients, perhaps suggesting that estimation of gestational age in these patients was imprecise. There was no difference in the incidence of adverse perinatal outcome. Routine ultrasonography resulted in a considerable increase in cost.

5.2 Speech and neural development

Cambell *et al.* (1993) report that children with delayed speech were twice as likely as a child without delayed speech to have been exposed to prenatal ultrasound. They suggest that physicians could consider cautioning their patients about the adverse effects of in-utero ultrasonography.

5.3 Maternal response

Kelley (1992) suggests that maternal-fetal attachment is initially enhanced in those women undergoing ultrasound examinations whose fetal gender could not be determined or who chose not to learn the fetal gender.

5.4 Microscopic tissue damage

Huang *et al.* (1994) examined the biological effects of diagnostic ultrasound on the embryo with gestational age of 6-8 weeks prior to induced abortion. They found various degrees of change in four lysosomal enzymes studies, malondialdehyde (MDA), superoxide dismutase (SOD), and in the ultrastructure of the chorionic villi in those exposed to ultrasound for between 10 and 30 minutes, with the most significant changes in those exposed for 30 minutes.

Gao *et al.* (1996) examined villus structure of early pregnancy after exposure to ultrasound for 30 minutes. The main injured sites were found to be the plasma membrane and suborganelles, though the changes disappeared after three days.

Feng-Zeping *et al.* (1996) irradiated fetuses at 20-28 week gestation with diagnostic ultrasound prior to abortion. Those irradiated for 30 minutes showed microscopic damage to the fetal testes. No damage was observed with 10 minutes exposure.

Ueda *et al.* (1996) demonstrate that ultrasound has a biological effect on the skin barrier.

5.5 Other biological effects

Watkin *et al.* (1996), in a study of the position of induced tissue damage in ultrasound surgery, find lesions forming under some exposure conditions ahead of the geometric focus. They suggest that a possible explanatory mechanism is bubble formation as a result of acoustic cavitation.

Cheng-Shuqun *et al.* (1996), in a study of high intensity focused ultrasound of 1.1 MHz at an intensity of 500 W/cm^2 for 20 seconds duration, suggest that thermal damage (rapid elevation of local tissue temperature to over 80°C) and cavitation may be the main mechanisms for tissue destruction.

Bly *et al.* (1992) estimated upper limits of fetal temperature elevations in Doppler mode ultrasound at 1°C in the first trimester, and less than 4°C in the second and third trimesters in the majority of cases.

Stone *et al.* (1992), in studies of dead lamb brain, found that the heating effect of pulsed Doppler ultrasound occurred at the skull bone-to-brain interface, not in the brain tissue.

Recent work attempts to establish the thresholds for bioeffects of ultrasound in organs. Suhr *et.* (1996) suggest that such a threshold effect exists in vitro. Holland *et al.* (1996) provide direct evidence in vivo of cavitation effects produced by diagnostic ultrasound.

5.6 Miscellaneous

Bronshtein and Blumenfeld (1995) report a husband's head trauma resulting from obstetric ultrasound use!

6 No adverse effects detected in humans

Vogel (1996) reviewed recent epidemiological studies and concluded that no negative late effects exist for routine ultrasonography, though he noted that a similar conclusion could not be made for Doppler flow ultrasound because of a lack of study. He claims that routine ultrasonography is of great value. He reviews postnatal mortality and morbitity effects of ultrasound, and its effect on birth weight, cancer incidence, and neural development.

Salvesen and Eik-Nes (1995) conclude that there is no proven association between ultrasound exposure *in utero* and childhood maldevelopment (birth weight, malignancies, and neural development, dyslexia, left-handedness, delayed speech development).

Grisso *et al.* (1994) examined 13000 pregnancies and found no adverse effect of ultrasound performed during the first two trimesters of pregnancy on birth weight.

Shu *et al.* (1994) found no evidence of a link between antenatal ultrasound exposure and increased risk of developing three major types of childhood cancer (acute leukaemia, lymphona and brain tumours) or all childhood cancers combined.

Tikkanen and Heinonen (1992) found no evidence of a link between ultrasound examination and harm to the developing fetal heart.

Cardinale *et al.* (1991) detected no morphological or structural changes in liver fragments of aborted fetuses exposed to ultrasound at 9-12 weeks gestation.

Salvesen *et al.* (1992) found no evidence of a link between reading and writing ability at age 8 or 9 years and whether the mother had been offered ultrasound.

Sulovic *et al.* (1991) compared human placental lactogen levels in women before and after ultrasound exposure and found no significant difference in the concentration of the hormone.

7 Doppler ultrasound exposure

Vogel (1996) was unable to reach a firm conclusion about the value and risks of Doppler flow ultrasound because of a lack of available evidence.

Salvesen and Eik-Nes (1995) have reviewed the effect of Doppler ultrasound exposure and reach no firm conclusion on possible effects in childhood, including left-handedness and low birth weight after frequent Doppler ultrasound exposure. They advocate further studies.

8 Discussion

DeVore (1994) demonstrates that the cost of routine ultrasound scans per detected malformed fetus as being critically dependent upon the competence of the individual conducting the screening examination.

Leivo *et al.* (1996), in a Helsinki study, conclude that longer ultrasound examination time and more numerous advanced examinations were more cost-effective in reducing perinatal deaths.

Geerts *et al.* (1996) examined the cost and effect of obstetric ultrasonography in patients with no risk factors for congenital anomalies. There was no difference in the incidence of adverse perinatal outcome between those receiving routine ultrasound scans and those receiving no routine scan. Routine ultrasonography resulted in a considerable increase in cost.

Montenegro *et al.* (1993) report a promising tool in "essential studies" of embryonic-fetal haemodynamics, namely transvaginal endosonography.

The chief contention in this report is that the safety of antenatal ultrasonography is a dubious claim, though it is conceded that the available studies do give conflicting results. However it must surely be unwise to be complacent and await conclusive evidence of harm before being cautious about the use of ultrasonography.

There appears to be little evidence that routine ultrasound scans benefit patients, but evidence that they increase the cost of health care.

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