ULTRASOUND-INDUCED FETAL BIOEFFECTS

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Abstract

When diagnostic ultrasound started being used more routinely for fetal imaging in the 1970's, it motivated an interest in the question of whether diagnostic ultrasound might induce biological effects in the fetus. As a result a great number of studies, primarily in animal models, have been performed over the last 30+ years to investigate the possible effects of *in utero* ultrasound exposure. These studies demonstrated that ultrasound could induce biological effects via both thermal and mechanical processes. However, most experts have concluded that the threshold for adverse effects was above the exposure conditions presented by diagnostic ultrasound devices. Epidemiological studies of fetal exposure to diagnostic ultrasound have renewed a scientific interest in potential effects induced by exposure to diagnostic ultrasound, particularly since the subjects studied were exposed to acoustic output levels several times lower than current diagnostic devices are capable of producing. The experimental and epidemiological evidence for potential effects of fetal exposure to diagnostic ultrasound are discussed.

Introduction

The potential effects of ultrasound on pregnant animals were extensively investigated during the 1970's and 1980's due to the increased use of obstetrical ultrasound and the recognized susceptibility of the embryo or fetus undergoing active development to chemical and physical insults. These investigational studies used many different ultrasound outputs and exposure conditions which contributed to contradictory results and complicated extrapolation of the animal data to the potential human effects [1].

Experimental Studies

The mechanisms of action by which ultrasound interacts with tissues and induces biological effects include both thermal and mechanical processes [2-7]. Many of the early studies used average ultrasound intensities that probably resulted in significant fetal heating. Because hyperthermia was a recognized cause of developmental defects, we designed our studies to focus on developmental effects induced by mechanical processes. Hyperthermia was controlled in our early experiments by reducing the body temperature of pregnant ICR mice by anesthesia and performing the exposures in a 30º C water bath. Body weight and survival were used as endpoints in a large screening study (> 13,000 mice and > 1,100 pregnancies) because they were easily obtainable and indicative of a variety of dysfunctions. Animals were exposed to spatial average temporal average intensity levels of 0 mW/cm^2 (sham), 75 mW/cm^2 and 750 mW/cm^2, 1 MHz continuous wave ultrasound, for 2 minutes. Animals were exposed on day 4, 10 or 14 *post coitus* (pc). For the first six experiments, subjects were exposed at each stage of gestation and euthanized on either day 18 pc or day 200 pc. A seventh experiment was conducted in which animals were exposed on day 10 pc and euthanized on day 21 pc (early postpartum period). *In utero* survival was not affected by these exposure conditions. A few statistical differences were observed in body weight, however the magnitude of the changes was small and no discernable pattern was observed. We did observe an increase in early deaths (days 21-35 postpartum) in the 75 mW/cm^2 exposure groups, but not in the 750 mW/cm^2 exposure groups exposed in early or mid-gestation. This finding did prompt us to investigate whether more subtle early effects might be induced by ultrasound exposure during pregnancy [1].

A teratology study was conducted to evaluate the effects of exposure of pregnant mice on gestational day (gd) 8, a highly susceptible developmental stage. Animals were exposed to 0 mW/cm^2, 50 mW/cm^2, 500 mW/cm^2 and 1000 mW/cm^2, 1 MHz continuous wave ultrasound, for 2 minutes in a 30º C water bath. Animals were euthanized on gd 17 and the fetuses were weighed and examined for external, visceral and skeletal defects. Slight, but statistically nonsignificant, increases in the general incidence of malformations were observed [8]. To confirm that the results of this study were indeed nonsignificant and to increase the possibility of inducing effects by a non-thermal mechanism of action, a study was conducted using 1 MHz pulsed ultrasound with a 6.5 µsec pulse duration and a 90 W/cm^2 spatial peak, pulse average intensity at the surface of the abdomen. Animals were exposed to 0 mW/cm^2, 50 mW/cm^2, 500 mW/cm^2 and 1000 mW/cm^2 spatial average, temporal average intensities by varying the pulse repetition frequency. The corresponding spatial peak, temporal average intensities were 0 W/cm^2, 0.12 W/cm^2, 1.2 W/cm^2 and 2.4 W/cm^2. The number of animals in each exposure group was doubled from 30 to approximately 60 and the exposure time was increased to 20 minutes. Animals were exposed in a 30º C water bath on gd 8 and were euthanized on gd 17. The fetuses were weighed and examined for external, visceral and skeletal defects. No detectable effects were observed [9].

In the last decade, epidemiological studies of human exposure to diagnostic ultrasound during pregnancy in Norway and Sweden have yielded results that raise questions about potential developmental effects associated with ultrasound exposure. Salvesen et al. [10] studied 2,161 subjects that had been exposed in Norway between 1979 and 1981. They reported increased non-right handedness in diagnostic ultrasound-screened children. However, they found no association with impaired neurological development (attention, motor control, perception). Based on these findings, Kieler et al. [11] examined later data from Sweden (1985-1987) on 3,265 subjects. They found no differences between diagnostic ultrasound screening and non-screening groups, but in a separate analysis on diagnostic ultrasound exposure and non-right handedness among boys, a significant difference was found. The authors concluded that "*…we cannot rule out a possible association between non-right handedness among boys and ultrasound exposure in early fetal life. However, the association was confined to analyses comparing exposed and non-exposed boys and no associations were found when the comparisons were performed according to randomized groups. Our results emphasize the need for more studies on the subject before any conclusions are drawn.*" Salveson and Eik-Nes [12] performed a meta-analysis of Norway (1979-1981) and Sweden (1985-1987) data. They examined data from 4,715 subjects (Norway, 1,663; Sweden, 3,052) and found no differences between diagnostic ultrasound-screened children and the controls. However, there was a difference in a subgroup analysis among boys. The authors concluded: "*A conservative approach indicates no association between ultrasound in utero and subsequent non-right handedness. The results from exploratory analysis must be interpreted with caution. There is still a need for further research*." Kieler *et al.* [13] then examined data from 6,858 exposed and 172,537 unexposed male subjects from Sweden during the 1973 to 1978 time period. During the introductory phase (1973-1975), which primarily involved one scan at 28 weeks, there was no difference in left-handedness between exposed and unexposed men. However, when scanning was offered more widely (1976-1978) and a second trimester scan at 32 weeks was introduced, the risk of left-handedness was higher among those exposed to diagnostic ultrasound. The authors controlled for several possible confounders (e.g., maternal age, low birth weight, birth stress) in the analyses. The authors concluded that "*… ultrasound exposure in fetal life increases the risk of left-handedness in men, suggesting that prenatal ultrasound affects the fetal brain.*"

First of all, it should be emphasized that left-handedness is not a public health problem, although some medical conditions have been associated with increases in left-handedness, e.g., low birth weight and neonatal asphyxia. It should also be emphasized that no associations with diagnostic ultrasound exposure during pregnancy and childhood maldevelopment have been substantiated. Although some studies have reported an association between diagnostic ultrasound exposure and a biological effect, e.g., dyslexia and delayed speech, subsequent studies were unable to reproduce these findings. Experimental variables are much more difficult to control in human studies, for example, none of the studies controlled for ultrasound exposure conditions (time and acoustic output). Editorial and review comments regarding the feasibility of diagnostic ultrasound exposure inducing sinistrality changes are mixed. In general, they suggest more study and raise concerns about women avoiding beneficial diagnostic ultrasound exams during pregnancy.

Summary

Most expert groups conclude that: (1) available evidence, experimental or epidemiological, is insufficient to conclude that there is a causal relationship between diagnostic ultrasound exposure and adverse effects, and (2) the use of diagnostic ultrasound for medical purposes is not contraindicated. However, there are several factors which indicate a need for further research. Many of the studies on which this conclusion is based were designed to investigate the possible effects of diagnostic ultrasound devices that were limited to a derated temporal average intensity (SPTA) of 94 mW/cm^2 and a derated temporal peak intensity (SPPA) of 190 W/cm^2 for fetal applications. Current limits in the U.S. allow a temporal average intensity (SPTA) of 720 mW/cm^2 and, in lieu of a derated temporal peak intensity (SPPA) of 190 W/cm^2, a mechanical index (MI) of 1.9. This author is unaware of any epidemiological studies conducted to determine if these higher acoustic output limits are associated with adverse effects. Routine diagnostic ultrasound scanning during pregnancy has increased and fetuses are often exposed in the first trimester. Because of the widespread, routine use of diagnostic ultrasound during pregnancy, it may be difficult to design a study with proper controls. And finally, low intensity pulsed ultrasound has been shown experimentally [14] and clinically [15] to shorten the bone fracture repair process and induce healing of nonunions. The ultrasound emission parameters for these devices are in the range of pulsed diagnostic ultrasound devices, except they utilize a longer pulse duration. Low intensity pulsed ultrasound also has been reported to enhance repair of soft tissue damage [16] and accelerate nerve regeneration [17] in animal models. The mechanism of action of these low intensity pulsed ultrasound effects is not clear. These effects do raise questions about potential effects of fetal exposure. It should be cautioned that any study, experimental or epidemiological, to detect adverse fetal effects will be difficult; subtle effects and small changes in incidence are not easy to identify and measure.

Statements contained in this article are the opinions of the author and do not represent Department of Health and Human Services policy.

References

[1] M.E. Stratmeyer, "Ultrasound-induced experimental fetal bioeffects," 17th International Congress on Acoustics, Rome, Italy, 1-8 September 2001, vol. VII, pp. 124-125.

[2] American Institute of Ultrasound Bioeffects Committee, Bioeffects and Safety of Diagnostic Ultrasound, American Institute of Ultrasound in Medicine, Laurel, MD, 1993.

[3] American Institute of Ultrasound in Medicine, "Mechanical Bioeffects from Diagnostic Ultrasound: AIUM Consensus Statements," Journal of Ultrasound in Medicine, vol. 19, pp. 68-168, 2000.

[4] World Federation for Ultrasound in Medicine and Biology, "Symposium on Safety and Standardisation in Medical Ultrasound," Ultrasound in Medicine and Biology, vol. 18, pp. 731-814, 1992.

[5] World Federation for Ultrasound in Medicine and Biology, "Symposium on Safety of Ultrasound in Medicine. Conclusions and Recommendations on Thermal and Non-Thermal Mechanisms for Biological Effects of Ultrasound," Ultrasound in Medicine and Biology, vol. 24, pp. S1-S58, 1998.

[6] National Council on Radiation Protection and Measurements, Exposure Criteria for Medical Diagnostic Ultrasound: I. Criteria Based on Thermal Mechanisms, NCRP Report No. 113, Bethesda, MD, 1992.

[7] National Council on Radiation Protection and Measurements, Exposure Criteria for Medical Diagnostic Ultrasound: II. Criteria Based on all Known Mechanisms, NCRP Report No. 140, Bethesda, MD, 2002.

[8] C.A. Kimmel, M.E. Stratmeyer, W.D. Galloway, J.B. LaBorde, N. Brown, and F. Pinkavitch, "The embryotoxic effects of ultrasound exposure in pregnant ICR mice," Teratology, vol. 27, pp. 245-251, 1983.

[9] C.A. Kimmel, M.E. Stratmeyer, W.D. Galloway, N.T. Brown, J.B. LaBorde, and H.K. Bates, "Developmental exposure of mice to pulsed ultrasound," Teratology, vol. 40, pp. 387-393, 1989.

[10] K.A. Salvesen, L.J. Vatten, S.H. Eik-Nes, K. Hugdahl, and L.S. Bakketeig, "Routine ultrasonography in utero and subsequent handedness and neurological development," British Medical Journal, vol. 307, pp. 159-164, 1993.

[11] H. Kieler, O. Axelsson, B. Haglund, S. Nilsson, and K.A. Salvesen, "Routine ultrasound screening in pregnancy and the children's subsequent handedness," Early Human Development, vol. 50, pp. 233-245, 1998.

[12] K.A. Salvesen, and S.H. Eik-Nes, "Ultrasound during pregnancy and subsequent childhood non-right handedness: A meta-analysis", Ultrasound in Obstetrics and Gynecology, vol. 13, pp. 241-246, 1999.

[13] H. Kieler, S. Cnattingius, B. Haglund, J. Palmgren, and O. Axelsson, "Sinistrality – A side-effect of prenatal sonography: A comparative study of young men," Epidemiology, vol. 12, pp. 618-623, 2001.

[14] L.R. Duarte, "The stimulation of bone growth by ultrasound," Archives of Orthopaedic and Trauma Surgery, vol. 101, pp. 153-159, 1983.

[15] S.J. Warden, K.L. Bennell, J.M. McMeeken, and J.D. Wark, "Acceleration of fresh fracture repair using the sonic accelerated fracture healing system (SAFHS): A review," Calcified Tissue International, vol. 66, pp. 157-163, 2000.

[16] Y. Takakura, N. Matsui, S. Yoshiya, H. Fujioka, H. Muratsu, M. Tsunoda, and M. Kurosaka, "Low-intensity pulsed ultrasound enhances early healing of medial collateral ligament injuries in rats," Journal of Ultrasound in Medicine, vol. 21, pp. 283-288, 2002.

[17] A.R. Crisci, and A.L. Ferreira, "Low-intensity pulsed ultrasound accelerates the regeneration of the sciatic nerve after neurotomy in rats," Ultrasound in Medicine and Biology, vol. 28, pp. 1335-1341, 2002.