CHAPTER 2

Discussion of Ultrasonic Safety Related to Obstetrics

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What is Safety?

Laboratory research efforts have focused on the issue of safety of diagnostic ultrasound since the inception of its use more than four decades ago. However, there are still many gaps in our understanding of the interaction of ultrasound with tissues, particularly during pregnancy. In reviewing the literature, one could readily find support for the position that it is without risk; likewise, a contrary argument could also be supported.

One of the problems inherent in this dichotomy deals with terminology, that is, the word "safe." Experimental (nonhuman) studies, by design, are frequently conducted to produce an effect, although they cannot be all-encompassing in an effort to prove "safety." Rather, what each study can provide are data that aid in the overall assessment of what could be the potential risk(s) associated with exposure. Usually, specific aspects of the safety issue are investigated rather than the issue as a whole, such as those related to the generation of heat or cavitation, and interaction of these known mechanisms with specific tissues such as bone. However, it will be exceedingly difficult to establish without a doubt that ultrasound does not place the conceptus "at risk," even at the levels employed diagnostically. Part of this problem is related to the multiple parameters that are involved when scanning, such as the length of the examination period, scanning techniques, equipment chosen for the examination, and age of the conceptus, to name a few. Based on the difficulties inherent in the application of the word "safe," a more useful and workable approach would be to examine those areas that could create the potential "risk" to which we refer. When considering these areas, benefit versus risk judgments will be required. This chapter's purpose is to provide a balanced perspective on the potential interactions associated with the use of ultrasound and issues to be considered while scanning pregnant patients.

HISTORICAL PERSPECTIVES

After the initial discovery of piezoelectricity by the Curies in the 1880s, the first use of ultrasonic energy was developed: underwater acoustic echoes were bounced off submerged objects in an effort to develop and apply the use of sound navigation ranging (sonar). During the course of these studies it was noted that high energy levels of ultrasound had a lethal effect on small aquatic animals that came within its path. Further investigation of this phenomenon confirmed these initial findings. One of the first review articles that described ultrasonically induced biologic effects of this nature evaluated the physical and chemical interactions that occurred during ultrasound exposure. Studies with isolated cells, bacteria,
and tissues were summarized, with a view toward identifying the responsible mechanism. Although the ultrasonic exposure conditions were not well characterized, it is certain that the intensity levels greatly exceeded those employed diagnostically.

Bioeffects-related studies that followed included concise documentation of all ultrasonic exposure conditions. These studies were well controlled and focused on effects specific to the central nervous system (CNS), including the production of sciatic nerve paralysis in the frog as well as lesions produced within the brain of the adult cat and rat, and adult rat and neonatal mouse spinal cord. Studies also were conducted that evaluated interactions with frog muscle in addition to rabbit blood vessel, kidney, testicle, and ocular tissues. The ultrasonic intensities incorporated in these studies were extremely high and, for the most part, were designed to cause tissue damage in an effort to identify areas of sensitivity. These studies are still significant in that they have elucidated some of the fundamental interactive processes of high-frequency sound with soft tissues and have identified those areas that appear to be more susceptible to damage. From these studies an approach to the question of assessing risk evolved. Areas of focus have included identification of biologic systems that are most sensitive to ultrasound, the exposure levels that could impose a negative impact, and the mechanisms by which these interactions can occur. There have been numerous reviews and assessments published since these first efforts to evaluate the biological effects of ultrasonic exposure were documented. However, even with these investigations, conclusions regarding risk still remain relatively elusive.

It has been almost four decades since the first ultrasonic devices for imaging the conceptus were developed. Early studies with these scanners confirmed their use for providing information about the fetus, and diagnostic ultrasonic gained wide acceptance owing to its convenience of use, level of comfort for the patient, and (relatively) limited expense. At this time, ultrasound did not appear to be associated with any known hazards, which was directly in contrast to other imaging modalities such as ionizing radiation (x-rays), known to pose a significant risk to the developing fetus. There continues to be a general belief in the medical community that ultrasound is “safe” and poses no risk to mother or fetus. However, the pursuit of more information related to this question has continued because the identification of factors involved in an unwanted interaction remains a pertinent issue. The fact that there continues to be concern for the safety of ultrasound represents an ongoing interest in maintaining that the use of this technique remains untainted and that subtle interactions that could occur are known.

### Potential Areas of Sensitivity

#### OVERVIEW

The applications of diagnostic ultrasound in obstetrics are numerous and provide reliable information whereby the health and well-being of the mother and conceptus can be readily assessed. Included within these applications are the evaluation of early pregnancy, estimation and confirmation of gestational age, monitoring fetal growth, development, and viability: in addition to its use as an adjunct to various interventional procedures such as amniocentesis, chorionic villus sampling, fetal blood sampling (cordocentesis), and fetal therapy. More recently, it has become possible to evaluate functional changes in blood flow in the uteroplacental and fetoplacental circulations in addition to the fetal heart and peripheral vasculature. Methods for diagnosing congenital heart disease, intrauterine growth retardation, twin–twin transfusion syndrome, and the evaluation of fetal arrhythmia and pregnancies complicated by maternal hypertension or diabetes have been described with the use of pulsed Doppler.

Human epidemiologic studies and numerous in vivo studies in mammals have been performed in an effort to examine the many issues related to the use of diagnostic ultrasound in regard to safety. Several reviews have described the exposure conditions and results of these studies in an effort to identify the biologic consequences of exposure and the interaction of these high-frequency sound waves (1–10 MHz) with soft tissues. Overall, some conclusions can be drawn from these reports. This includes the fact that if ultrasound were a physical agent capable of inducing gross malformations, then a rise in the occurrence of birth defects would have been documented by now. This has not been the case, as epidemiologic studies have shown no correlations between a rise in its use and the incidence of congenital anomalies. However, based on the fact that results of experimental studies have proved inconsistent, it is clear that the interaction of ultrasound with biologic systems, particularly those with rapidly dividing cells, is still not fully understood. What remains of concern are the subtle and long-term manifestations of frequent intrauterine exposure. These concerns remain pertinent owing to several factors such as the continued rise in the percentage of the prenatal population that is exposed each year.
diction, as advances in technology are made, the exposure parameters for the fetus can also change. The use of pulsed Doppler (and color flow imaging) provides good examples; these methods have been applied more recently for evaluating physiologic function and rely on time-average output parameters that are greater than those for routine imaging. The exposure time may also be increased as additional diagnostic information is sought. These points emphasize the need to pursue these questions in an effort to confirm that unwanted effects do not occur.

MECHANISMS OF INTERACTION

Some of the interactions of ultrasound with tissues are known. These include heating, acoustic cavitation, and some nonthermal, noncavitational effects. Of these interactions, only two will be considered in this chapter (see Chap. 1 by Zagzebski for a discussion of the physical aspects of ultrasound in addition to other contributions). When considering issues related to the interaction of ultrasound with tissues, the intensity of the beam is most important (because it has been most commonly reported and because the FDA regulates diagnostic ultrasound equipment based on intensity), and is described in four different combinations of spatial average (SA) or peak (SP), and temporal average (TA) or peak (TP). For bioeffects considerations, the spatial-peak temporal-average intensity (SPTA) is most important, particularly regarding thermal issues; I_{SPPA}, I_{max}, and P, are important when considering effects of cavitation.

However, it should be noted that these intensities are not dosimetric quantities and are thus flawed as exact predictors of heating and cavitation in tissue. The Output Display Standard currently considered for use on commercial imaging systems will go a long way in providing to the clinical user real-time information as to the potential for tissue heating in addition to mechanical effects during a diagnostic ultrasound examination. The specific display requirements of this standard were selected to include those quantities whose magnitudes are known or believed to be related to actual damage, or to risk of damage to biologic tissues as a result of ultrasonic exposure. The basis for this rationale lies in an understanding of the mechanisms by which it is known that ultrasound can affect living systems. Such knowledge comes from fundamental laboratory studies, as discussed earlier. These mechanisms can be classified and discussed in terms of whether heat is or is not believed to be the principal cause for the biologic effect.

Thermal Mechanisms

Whenever high-frequency ultrasonic energy is propagated into an attenuating material such as soft tissues, the amplitude or height of the wave will decrease as it traverses deeper structures. This attenuation results in an overall loss in the power of the wave that is due to either absorption or scattering. Absorption is a mechanism that represents the portion of the wave's energy that is lost by its conversion into heat, scattering can be thought of as that portion that changes direction, some of which is reflected as echoes that produce the images seen on the screen of the scanner. Since the medium interrogated is capable of absorbing energy with the resultant production of heat, a temperature rise may occur as long as the rate at which heat is produced is greater than the rate at which the heat is removed. The increase in temperature produced by ultrasound can be calculated using mathematical modeling techniques and has been estimated for a variety of exposure conditions.

Cavitation Mechanisms

Cavitation can be discussed under two general categories, namely, "transient" cavitation and "stable" cavitation, both of which involve the occurrence of gaseous bubble formation. Transient cavitation refers to a relatively violent activity (i.e., bubble collapse) in which "hot spots" of high temperature and pressure occur in short (microsecond) bursts. These bursts may be accompanied by localized shock waves or the generation of highly reactive chemical species such as hydroxyl radicals. In contrast, a much less violent form is stable cavitation, which is associated with the vibration of these gaseous bubbles. The nature of this form of cavitation consists of a micron-size gaseous body, which, because of the presence of an ultrasound field, may oscillate or pulsate. When such oscillations are established, the liquid-like medium immediately adjacent to the gas bubble flows or streams (termed microstreaming). Microstreaming has been shown to produce stresses sufficient to disrupt cell membranes.

ISSUES RELATED TO HEAT GENERATION

Hyperthermia is a proven teratogen in experimental animals and, although controversial, is considered by some investigators to be a human teratogen under certain circumstances. Because heat generated by ultrasound is a known phenomenon, the question of impact owing to a thermal interaction
is relevant. It has been shown that temperature elevations \( \geq 2.5^\circ \text{C} \) to 5.0°C can occur with ultrasound after exposures of longer than 1 hour.\(^6\)\(^{91-92}\) These studies confirm that under extreme conditions, elevations of this magnitude can occur. However, a substantial increase in intrauterine temperature has not been considered possible in a human clinical setting as the output levels of commercial systems and the methods of exposure have been considered to be significantly different from those employed in experimental studies. Based on mathematic modeling techniques it has been shown that the low intensities and short insonation times should result in negligible temperature elevations (i.e., <1.0°C). In addition, the dissipation of heat by conduction and circulating blood would further decrease the potential for a rise in intrauterine temperature. As noted earlier, there have been no reports documenting an increase in the rate of structural malformations in the human population since the incorporation of ultrasound as a diagnostic tool.\(^93\) However, the actual elevations that occur within embryonic/fetal tissues have not been sufficiently evaluated in utero. The potential effects of any change in the basal temperature of specific areas of the conceptus (particularly if repetitive) are not known. Although a temperature rise may not be great enough to result in an overall gross malformation, the impact on developmental processes such as myelination are worthy of consideration (see later discussion).

Studies by Lele have shown that a significant rise in temperature can occur in vivo in the mouse and rat fetus (ex utero) after several hours of exposure using implanted thermocouples.\(^94\) Four different intensity levels were studied (40–300 mW/cm\(^2\)) and it was noted that the temperature rise was rapid initially (i.e., an elevation of \(-1.2^\circ \text{C} \) after 6–7 minutes at 40 mW/cm\(^2\)) but stabilized with time. When the sound was turned off, the temperature diminished quickly. More recent studies in this regard include those by Abraham and colleagues where temperature elevations were measured in exteriorized viable and nonviable rat fetuses on gestational days (GDs) 15 to 20. An unfocused source transducer with a resonant frequency of 1 MHz was used, results showed that the temperature elevations produced were directly related to the ultrasonic intensity, and that after 10 minutes of exposure at I\(_\text{SPA} = 2.6 \text{ W/cm}^2\), an elevation of 6° and 8°C was observed in viable versus nonviable fetuses, respectively. The temperature rise was also shown to increase \(-2^\circ \text{C} \) when the umbilical cord was ligated in viable fetuses.

In vivo studies in gravid female macaques have been conducted to identify more accurately the elevations that can occur within the fetus in situ during a clinically relevant ultrasound examination.\(^94\)\(^95\) With the use of a commercial scanner (Advanced Technology Laboratories, Inc., Bothell, WA, MK 600, 7.5-MHz scanhead scan mode, I\(_\text{SPA} = 25.9 \text{ mW/cm}^2\), I\(_\text{SPA} = 76.4 \text{ W/cm}^2\) [I\(_\text{SPA} = 53.9 \text{ mW/cm}^2\), I\(_\text{SPA} = 15 \text{ W/cm}^2\) and PRF = 18.5 kHz (all measured in water]) and a, and acute, short-term thermoco-couple insertion via direct ultrasound guidance, fetal intrauterine temperatures (intracranially and at the muscle–bone interface [humeral, femoral]) were assessed during 10, 20, or 30 minutes (scan mode) or 5, 10, or 15 minutes (pulsed Doppler) exposure at varying stages of gestation. Measurements were obtained in ketamine-sedated gravid female macaques both during the second (GDs 70 and 90), and third trimesters (GDs 110, 130, and 150; term \(-\)GD 165). Overall, results indicated that the greatest elevation achieved in either mode was 0.6°C (range = 0.1–0.6°C), which was observed in both anatomic locations. There were no differences detected with advancing gestational age. As anticipated, these elevations quickly dissipated once the sound was turned off. Although these studies have supported the premise that any potential risks associated with a \( >1^\circ \text{C} \) elevation\(^94\) would not be anticipated, the effects, if any, of frequent, acute, low-impact exposures are unknown.

**ISSUES RELATED TO CAVITATION**

Although a known phenomenon regarding ultrasound, cavitation has been difficult to document in mammalian systems. The presence of small gaseous nuclei (bubbles) is clearly plausible as evidenced by the problems divers may encounter with decompression sickness. Many studies have been performed with *Drosophila melanogaster* because of the natural presence of air in these organisms.\(^100\)\(^101\) Although little work has been done regarding caviation and the mammalian fetus, studies performed with lithotripters help to shed some light on the potential existence of cavitation nuclei. The peak pressures generated by lithotripters (\( >10 \text{ MPa} \)) greatly exceed those for diagnostic ultrasound scanners (\(<2 \text{ MPa} \)), and it is not anticipated that currently designated peak pressure levels for diagnostic ultrasound systems will be surpassed.

Concerning in vivo studies that have addressed the presence of cavitation-like phenomenon, it has been shown that ultrasonically induced bubble activity can result in lung damage in adult mice (peak pressure threshold levels in the range of 0.8–4 MPa for various combinations of center frequency \( [1-4 \text{ MHz}] \), pulse duration \( [1 \text{ and } 10 \text{ microseconds}] \), duty cycle \( [0.001-0.0001] \), and pulse repetition frequency
These observations correlate well with the frequency-dependent, in vitro cavitation experiments of Apfel and Holland. In an effort to confirm whether the lung sensitivity observed in adult mice was related to the presence of air, Hartman and colleagues exposed in utero mouse fetuses to high-peak ultrasonic pressures (20 MPa) on the 18th day of gestation. Results indicated no significant effects on fetal tissues exposed in situ (including the lung); peak pressure levels were roughly 10 times the output required for damage in adults in prior studies. As anticipated, marked intestinal and lung hemorrhages were noted in the dams of these fetuses at the higher exposures. These observations led the authors to suggest that “lung gets its sensitivity to damage by virtue of the presence of air bodies which are potential sites for cavitation-related activity.” These studies support the hypothesis that cavitation-or bubble-like activity may not be a significant concern in relation to the fetal lung, although the potential for cavitation nuclei in other regions of the fetus is unknown. This is clearly an area of research that will require more extensive study in appropriate animal models to improve our awareness regarding the presence of these nuclei and the circumstances under which they may cause damage.

ISSUES RELATED TO THE CENTRAL NERVOUS SYSTEM

Based on early studies, it is apparent that the CNS is an area of sensitivity when considering potential biologic effects. Both structural and functional effects have been reported, and a selective capacity of the white versus gray matter for heat absorption has been shown. Studies by Hu and Ulrich have addressed the effect of low-intensity ultrasound on the nonhuman primate brain. Adult squirrel monkeys were observed to display a greater sensitivity and stimulatory effect in the parietal region of the brain when exposed to 2.25 to 5 MHz (CW) for 2 to 3 minutes. An increase in evoked potentials was noted that ceased immediately after exposure was terminated. An attempt to reproduce these findings was inconclusive, although the experimental conditions were not precisely duplicated.

Earlier studies have indicated that ultrasound at 3.2 W/cm² stimulates the CNS. The mechanisms for these effects are unknown, although a thermal mechanism is known to be responsible for the well-circumscribed brain lesions obtained with high-intensity focused ultrasound as discussed earlier. There are no data to substantiate an alteration in brain activity in utero, although the greater sensitivity and suscepti-

bility of the conceptus implies that a response of this nature is possible. This is supported by studies where chronically instrumented fetal lambs (GDs 120–125) were exposed to a commercial scanner (ISPTA = 15.5 mW/cm²) for 15 minutes to evaluate the auditory brainstem response (ABR) during exposure. A consistent decrease in the mean amplitude and an increase in the mean latency of all five wave deflections of the ABR was observed. This effect appeared to be transitory, because all values approached baseline within 30 minutes of termination of exposure. These results indicate that direct exposure of the fetal brain in vivo may temporarily influence nerve conduction along CNS axonal pathways. Functional effects of low-intensity ultrasound have also been reported by Ellisman and colleagues with the neonatal rat. Neonates from 3 to 5 days of age (roughly comparable with a third-trimester human fetus) were scanned for 30 minutes using a diagnostic ultrasound unit with an ISPTA = 0.135 mW/cm² (3.6 MHz). Electron microscopy of sections of dorsal nerve roots postexposure indicated a disruption of the nodes of Ranvier and morphologic changes ranging from vacuole formation in the paranodal regions to frank demyelination.

Effects of ultrasound on behavior have also been explored in both rodent and nonhuman primate models. Murai and colleagues reported an increase in stress response and delays in maturation in rats exposed on GD 9 to 20 mW/cm² for 5 hours (2.3 MHz). A report by Brown and colleagues indicated both accelerated and retarded response to a variety of reflex developmental tests in mice who were exposed on GD 9 to 250 mW/cm² for 3 minutes (1 MHz). Studies with nonhuman primates (Macaca fascicularis) and a commercial ultrasound unit (ATL, MK 600; ISPTA = 25.9 mW/cm²) have investigated the potential long-term manifestations of frequent exposure. Gravid macaques were scanned 5 times weekly on GDs 21 to 35 (during the early stages of organogenesis) for 10 minutes per exposure, 3 times weekly on GDs 36 to 60 for 10 minutes per exposure, and 1 time weekly on GDs 61 to 150 for 20 minutes per exposure. Sham controls were “scanned” at the same intervals with the unit placed on standby. All animals were delivered by cesarean section on GDs 152 ± 2 and reared in a nonhuman primate nursery to monitor postnatal development. Assessment of the newborn revealed an increase in simian Apgar scores (assessed at 1, 5, and 10 minutes of life) for exposed animals at 10 minutes, which was primarily attributed to increased muscle tone. A series of behavioral testing regimens were included up through the first year of life. The testing procedures incorporated were designed to assess reflex and behavior patterns, and the
development of motor and cognitive skills. Results indicated no differences between groups in behavioral state, reflex maturity, habituation, or cognitive abilities. However, a significant increase in observed tone on days 1, 2, and 4 was noted in a neurobehavioral test battery conducted during the first few weeks of life. Spontaneous gross motor behavior observed weekly from 1 to 14 weeks in an observation cage also revealed an increase in the percentage of quiet activities (laying, sitting) displayed by exposed animals. The significance of these findings is currently unknown and will require further investigation.

Epidemiologic studies in the human population have not revealed any reliably documented effects. Although Stark and colleagues reported an increase in dyslexic children exposed to ultrasound in utero, no differences between groups were observed in multiple neurologic and cognitive tests performed at 7 to 12 years of age. Studies by Lyons and colleagues have also failed to confirm any significant effects related to exposure. With the exception of the Lyons and colleagues study, epidemiologic reports have provided little insight because there is frequently limited information provided related to scanning conditions and patient history.

ISSUES RELATED TO BONE

Most sound is known to be reflected from dense structures such as bone because of its greater density, with the production of heat greatest at the soft tissue/bone interface and within the bone itself. This is a particularly relevant finding when considering the fetus, as changes in ossification over time could imply significant differences regarding a thermal impact. Drewniak and colleagues explored the temperature rise within fetal femurs ex utero in an effort to identify whether increased ossification could enhance the potential for heat generation. CW exposures at L_{500} values of 0.1 to 10 W/cm² (1 MHz) were studied in human fetal femurs from GDs 59 to 108. Thermocouples were positioned midway along the length of the femur within the diaphysis. The initial rate and magnitude of the temperature rise for a given exposure duration was shown to increase with increasing GD. On GD 59, the initial rate of rise was roughly twice the soft tissue; by GD 108 it was 30 times as great. The exposure time needed for the rise to reach 1°C was shown to decrease with increasing intensity or increasing GD. Because the femurs used for these studies were externalized, the applicability of this information to the fetus in situ is limited. As noted earlier, studies with the macaque have not, to date, revealed elevations ≥1.0°C, nor have they shown an increase in the potential for heat generation with advancing ossification. However, it should be noted that measurements were taken at the muscle-bone interface rather than within the bone itself.

When considering fetal bone, issues related to hematopoiesis must also be considered. In prior studies with the macaque conceptus, a (transient) statistically significant decrease in white blood cells (WBCs, neutrophils and monocytes) in neonates exposed to ultrasound prenatally was shown to occur. Hematologic evaluations revealed significantly lower WBCs in treated animals on days 2, 9, and 16 ± 1 of life that were no longer apparent at the later time points. The possibility of a direct effect on the fetal bone marrow is suggested by the observation that both neutrophils and monocytes were affected. Both cell populations are derived from the same immature myeloid progenitor, the colony-forming unit/granulocyte macrophage (CFU-GM). Further related studies have continued to focus on the mechanism for the observed effect and to document the reproducibility of these findings.

Takemura and Suehara observed hemolysis of maternal erythrocytes in vitro after exposure of pregnant women to a fetal monitor (CW Doppler) for ≥6 hours. Hemolysis was observed to increase in proportion to time. Maternal erythrocyte fragility was also observed after exposure via a fetal monitor during labor (1–29 hours’ duration). A shift in mean corpuscular fragility appeared significant with >7 hours of exposure. Although fetal erythrocyte fragility was not examined, it was suggested that because fetal red blood cells are generally more fragile, they may also be affected. Reports describing in vitro effects of ultrasound on blood-borne elements have appeared in the literature, readers are referred to these publications on this topic for further details.

TERATOLOGY (DEVELOPMENTAL TOXICITY)

Many of the earlier studies that focused on direct effects of ultrasound on embryonic development incorporated the fruit fly, Drosophila melanogaster, and various rodent models (i.e., rats and mice). Early continuous wave ultrasound bioeffects studies with Drosophila confirmed that specific effects regarding development and viability could occur in this species. These original studies were tainted by a lack of dosimetry information. However, later confirmations were performed under improved dosimetric conditions. The importance of this model lies in the fact that investigators can essentially reproduce on a
routine basis the earlier findings while attempting to assess the mechanism(s) responsible for the observed effects. Although distinctly different in its developmental features when compared with mammalian species, the importance of this model lies in the fact that it can provide a fundamental understanding of the causes for specifically defined biologic effects. This model has been used in the past for the development of protection guidelines for the use of ionizing radiation because a basic understanding was developed regarding the interaction mechanisms that occur with radiation and developing tissues.

The vast literature on ultrasonically induced developmental toxicity implies that we have generated a large database on which to make reliable conclusions. However, the reverse is actually more accurate because of inconsistencies in the literature. Some reports have shown that exposure of pregnant mice or rats to high levels of ultrasound have not yielded any significant effects.\(^{111,115,116}\) whereas other experiments performed with exposures at much lower intensity levels (in some cases, diagnostically relevant) have suggested the possibility of an effect.\(^{114,117-119}\) Further, there have been studies in which the original findings\(^{122,126}\) could not be duplicated, either in other\(^{116}\) or within the same laboratories\(^{120,137,138}\). One example is the occurrence of low fetal body weights after in utero exposure to ultrasound.\(^{115,117,119,116}\) Although this has been documented on several occasions in differing species, including the mouse, rat, and macaque, this has not been consistently observed.\(^{132-136,138,143}\) Studies by O'Brien\(^{132,138}\) emphasize these inconsistencies as initial studies with outbred non-Swiss albino (CF1) mice resulted in a significant dose-dependent effect on fetal weight (exposure from 10–300 seconds on GD 8, ISDTA ranged from 0.5 to 5.5 W/cm\(^2\)).\(^{139}\) whereas mouse hybrids (LAF/PI) exposed under the same conditions did not show any effect.\(^{138}\) It was hypothesized that hybrid strains may be more resistant than outbred strains, however, a similar dose-dependent response was found by Stolzenberg and colleagues\(^{142}\) with the use of outbred Carworth Farm Webster (CFW) Swiss-Webster mice (exposures on GD 1–13; ISDTA = 1 W/cm\(^2\)). An intrauterine temperature increase of 6°C after 3 minutes of exposure was also noted coincidentally within this study, which implies the effect may have been related to heating. Further follow-up studies have incorporated anesthetized pregnant female rats exposed daily to CW ultrasound (GDs 4–19, 3 MHz, ISDTPA = 0.1–30 W/cm\(^2\); 15-minute duration per exposure).\(^{157,158}\) Evaluation of fetuses on GD 20 did not indicate any developmental toxic effects including no change in fetal body weights when compared with sham controls.

Epidemiologic reports have not revealed any significant findings related to the potential for developmental toxicity of ultrasound particularly regarding growth retardation. Studies by Lyons and colleagues\(^{52}\) reported no significant differences in head circumference at birth, or in height and weight from birth to 6 years of age between 149 human sibling pairs, of which only 1 was exposed to ultrasound prenatally. Several commercial systems were included in this study, all of which used transducers with a frequency of 2.25 or 3.5 MHz. ISDTPA values were in the range of 4 to 28 mW/cm\(^2\). Prior studies have suggested the occurrence of growth retardation in the human population after exposure to ultrasound prenatally\(^{61,66}\) may have been confounded by the population of infants incorporated in the analyses. Moore and colleagues\(^{61}\) have suggested that a relationship may exist between the frequency of ultrasound exposure and reduced body weights, that is, maternal and fetal risk factors rather than the ultrasound exposure may be the primary cause of the low body weights observed postnatally.

### In Vivo Exposimetry

In the past, reports by the Food and Drug Administration (FDA),\(^{31}\) National Council on Radiation Protection and Measurements (NCRP),\(^{35}\) and the National Institutes of Health (NIH)\(^{16}\) included recommendations for bioeffects research in those areas where a paucity of information was available, such as the study of fundamental mechanisms leading to bioeffects and postnatal studies in experimental animals after in utero exposure. Most animal studies have provided limited information that can be applied to the human based on the methods incorporated for the exposures (output parameters and length of exposures), and the substantial differences physiologically in scanning a small laboratory rodent versus a confined area of an adult human. Studies with nonhuman primates can provide more relevant data because of their reproductive and developmental similarities to the human and the ability to control the conditions of exposure (i.e., number of examinations performed, time between each examination, stage of development, duration of exposure, length of time the beam is concentrated in a given area, output parameters of the ultrasound unit) so they more accurately simulate the human clinical setting.

One of the most central issues regarding bioeffects has been quantitation of the "dose" that the embryo/fetus receives during an ultrasound examination. This has become a monumental task based on the multitude of parameters that must be considered.
when attempting its assessment. Examples include factors related to attenuation (reported in decibels [dB], see Chap. 1 by Zagzebski[7]) and the volume of tissue that must be traversed before the beam reaches the conceptus. The in utero ultrasonic intensities in both the gravid and nongravid human uterus have been estimated by mathematic techniques based on these variable tissue layers (summarized in Stewart and Stratmeyer[13] and NCRP[14]). In these early studies, layers between the skin surface and gestational sac (i.e., muscle, fat, peritoneum, and urinary bladder) yielded a total attenuation in the range of 2 to 20 dB at scanning frequencies of 2 to 5 MHz. The distances between the abdominal surface and the conceptus in early pregnancy were estimated to range between 2 to 11 cm. In more recent work, similar distances were estimated to be in the range of 2-6 cm. Direct measurements of uterine intensity have been obtained in the human female[15].[16]; the average attenuation was reported to be 6.2 ± 3.5 dB under full and 7.3 ± 4.9 dB under empty bladder conditions.

Further studies have applied the "fixed-attenuation tissue model" where attenuation is dependent on the frequency (MHz) and independent of distance. Here, with a chosen center frequency of 2.4 MHz, the attenuation coefficient (described in dB/MHz) has been estimated to be 2.56 ± 1.47 for full bladder conditions. With the "overlying tissue model"—one for which attenuation is dependent on both frequency and nonfluid-filled tissues—the attenuation coefficients (in dB/cm-MHz) have been estimated to be 0.89 ± 0.71 and 0.45 ± 0.32 for full and empty bladder conditions, respectively. The FDA's Center for Devices and Radiological Health currently uses a value of 0.3 dB/cm-MHz as a factor for manufacturers in their 510(k) process (required for all ultrasound systems approved for marketing) [8]. Because the measured values for the tissue models noted previously are considerably greater than the values currently used by the FDA, it is apparent that the output requirements for ultrasound systems err on the side of safety. It is evident, however, that improved methods for identifying the attenuation that occurs in vivo will be required to assess more accurately the "dose" received by the second- and third-trimester fetus. This information will also help to confirm that the attenuation coefficient used by the FDA continues to remain relevant.

Conclusion

The current scanning conditions and information available to date suggest that the perceived risk asso-

ciated with the clinical use of ultrasound is low, provided that the length of the examination period and methods used for scanning pregnant patients are "prudent." However, it must be emphasized that, as discussed earlier, our knowledge regarding ultrasonic bioeffects and biophysical interactions with developing tissues is incomplete at this time. Several areas will require more rigorous investigations with appropriate animal models. Because of this apparent paradox, it is essential for clinicians and sonographers to be aware of the most up-to-date information on any perceived risks so that they can continue to render an informed benefit-risk judgment. The principal source of such data will be from relevant animal experimentation that can focus on defined effects and the respective mechanisms responsible for their occurrence.

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