Processes that can produce a biological effect with some degree of heating (i.e., about 1°C above the physiologic temperature) act via a thermal mechanism. Investigations with laboratory animals have documented that pulsed ultrasound can produce elevations of temperature and damage in biological tissues in vivo, particularly in the presence of bone (intracranial temperature elevation). Acoustic outputs used to induce these adverse bioeffects are within the diagnostic range, although exposure times are usually considerably longer than in clinical practice. Conditions present in early pregnancy, such as lack of perfusion, may favor bioeffects. Thermally induced teratogenesis has been shown in many animal studies, as well as several controlled human studies; however, human studies have not shown a causal relationship between diagnostic ultrasound exposure during pregnancy and adverse biological effects to the fetus. All human epidemiologic studies, however, were conducted with commercially available devices predating 1992, that is, with acoustic outputs not exceeding a spatial-peak temporal-average intensity of 94 mW/cm². Current limits in the United States allow a spatial-peak temporal-average intensity of 720 mW/cm² for fetal applications. The synergistic effect of a raised body temperature (febrile status) and ultrasound insonation has not been examined in depth. Available evidence, experimental or epidemiologic, is insufficient to conclude that there is a causal relationship between obstetric diagnostic ultrasound exposure and obvious adverse thermal effects to the fetus. However, very subtle effects cannot be ruled out and indicate a need for further research, although research in humans may be extremely difficult to realize. Key words: bioeffects; fetus; obstetrics; safety; thermal effects; ultrasound.
This article analyzes thermal effects of fetal ultrasound exposure. The normal core human body temperature is generally accepted to be 37°C with a diurnal variation of ±0.5°C to 1°C, although 36.8°C ± 0.4°C (95% confidence interval) may be closer to the actual mean for large populations. During the entire gestation, the temperature of the human embryo/fetus is higher than the maternal core body temperature and gradually rises until, in the final trimester (near term), it exceeds that of the mother by 0.5°C. Thermally induced teratogenesis has been shown in many animal studies, as well as several controlled human studies. Edwards and others have shown that hyperthermia is teratogenic for numerous animal species, including the human, and suggested a 1.5°C temperature elevation above the normal value as a universal threshold. An elevated maternal temperature in early gestation has been associated with an increased incidence of congenital anomalies. Tolerance to increased temperature (thermotolerance) is an important aspect of thermal teratogenesis. Thermotolerance is induced by the production of heat shock proteins (HSPs), which occurs (up to a limit) during a relatively slow (10- to 15-minute) temperature increase of the whole body. Diagnostic ultrasound exposures of mammalian embryos or fetuses in vivo and in vitro do not cause a whole-body temperature increase in the mother but can potentially do so in the embryo. In principle, heating with ultrasound could occur so rapidly that the protective effects of HSPs might not come into play. There are data on effects of hyperthermia and measurements of in vivo temperature induced by pulsed ultrasound but not in the human. These data have been widely reviewed. However, there is a serious lack of data on the effects of ultrasound while rigorously excluding other confounding factors. A number of epidemiologic studies of possible developmental effects of obstetric ultrasound were performed before 1992, when exposures of the fetus, if anything, were lower on average than they are today. The results overall were negative. Around 1992, the maximum permitted acoustic output of clinical ultrasound instruments operating in the obstetric mode was allowed to increase by a factor of almost 8. Potentially of even greater significance, no report clearly defines the duration of actual exposure. Epidemiology, of course, cannot be expected to reveal subtle effects. Today, ultrasound is so much a part of obstetric care that it would be very difficult to design an ethically acceptable epidemiologic study.

The material in this article will be presented in the following manner: “Definitions,” “Mechanisms of Tissue Heating,” “Measured Temperature Rise in Human Fetal Tissue,” “Intracranial Temperature Elevation,” “Epidemiologic Data,” “Clinical Studies,” “Discussion Regarding Obstetric Issues in the Human,” and “Conclusions and Recommendations.”

Definitions

bioeffect—Any biological change occurring as the result of an exposure, whether physiologic or harmful.
damage—An irreversible adverse outcome that has occurred.
embryo—The conceptus from fertilization through organogenesis (late third through eighth weeks’ gestation). This embryonic period is the time of greatest sensitivity.
fetus—The conceptus from organogenesis to delivery; in common usage, the term fetus encompasses the entire gestational period.
harm—An adverse outcome, whether reversible or irreversible.
hazard—A possible source of harm.
risk—The combination of the probability of occurrence of harm and the severity of that harm.
safety—Freedom from unacceptable risk; absolute safety cannot be achieved.

Mechanisms of Tissue Heating

Two widely accepted facts are that ultrasound has the potential to elevate the temperature of the tissues being scanned and an elevated maternal temperature, whether from illness or exposure to heat, can produce teratologic effects. The major question is whether diagnostic ultrasound can induce a harmful temperature rise in the fetus. Some believe that this temperature rise is, in fact, a major mechanism of ultrasound bioeffects. The temperature elevation in the insonated tissue can be calcula-
ed and estimated fairly accurately\textsuperscript{33,34} if the field is sufficiently well characterized. A temperature change in insonated tissues depends on the balance between heat production and heat loss. Local heating is proportional to the temporal-average intensity. Acoustic power is more appropriate for the prediction of a temperature rise within the ultrasound beam, and this fact forms the basis of the thermal index (TI). Physical characteristics of the ultrasound beam modify the temperature rise. These characteristics include ultrasound frequency, focusing (which determines the beamwidth), whether the beam is scanned, and the duration of exposure. Some properties of the exposed tissues (eg, acoustic impedances and absorption) also influence, respectively, how much ultrasound energy is reflected and how much is transformed into heat.\textsuperscript{33} Conduction and convection influence the rate at which heat is transported locally from the sites of its generation.

One other tissue property that strongly influences the amount of heat transported is local perfusion, a form of convection, which very clearly diminishes the risk, if present. Similar experimental conditions caused a 30% to 40% lower maximal temperature increase in live versus dead sheep fetuses exposed in the near field,\textsuperscript{13} while in guinea pig fetuses exposed at the focus, the difference was approximately 10%.\textsuperscript{14} These results were thought to be secondary to vascular perfusion in live animals. A significant cooling effect of vascular perfusion was observed only when the guinea pig fetuses reached the stage of late gestation near term, when the cerebral vessels were well developed. In the midterm, there was no significant difference when guinea pig fetal brains were exposed, alive (perfused) or postmortem (nonperfused), in the focal region of the ultrasound beam.\textsuperscript{35} The loss of heat due to perfusion is more important in those parts of the beam close to the transducer and beyond the focus, where the beam has a large cross-sectional area. In the focal region, where the beam is narrow, the effect of perfusion (in the absence of thermally significant vessels) is much less\textsuperscript{36} because conduction radially down the large thermal gradient is the dominant mechanism for heat transport away from the focal region. It is worth noting here that in early pregnancy (<6 weeks), there appears to be minimal maternal-fetal circulation, that is, minimal fetal perfusion, which may potentially reduce heat dispersion.\textsuperscript{37}

The lack of perfusion is one reason why the spatial-peak temporal-average intensity ($I_{SPA}$) for ophthalmic applications has been kept very low, in fact, much lower than peripheral, vascular, cardiovascular, and even obstetric scanning, despite the general increase in acoustic power that was allowed after 1992. Herman and Harris\textsuperscript{38} have provided the rationale for the ophthalmic exposure output limit of the US Food and Drug Administration (FDA), initially 17 mW/cm$^2$ but increased to 50 mW/cm$^2$ in the 1997 revised 510(k) guidance to the industry.\textsuperscript{39} The FDA's rationale was based on the relatively large absorption in the lens and orbital fat and the poor perfusion in the eye. The FDA initially based its findings on using (calculating) 720 mW/cm$^2$ but applied it to physical characteristics of the eye (no perfusion and some protein) and noted that temperature increases in the 8°C to 10°C range were obtained. The FDA then calculated that if the output was kept at or below 50 mW/cm$^2$, the temperature rises were all less than 1°C, hence the output limit of 50 mW/cm$^2$ for the eye.

There are some similarities in physical characteristics between the early first-trimester embryo and the eye. Neither is perfused; they can be of similar size; and protein is present (in an increasing proportion in the fetus). The present TI values for first-trimester scanning are based on the usual perfusion rate for tissue. At about weeks 4 to 5, the gestational sac is about the size of the eye (2.5 cm in diameter), and by week 8, it is around 8 cm in diameter. There is no perfusion in very early gestation. Only at about weeks 10 to 11 does the embryonic circulation actually link up with the maternal circulation.\textsuperscript{40} At that stage, there is a switch from previously hypoxic conditions to normo-oxic conditions and a cascading of radical scavengers (eg, superoxide dismutase) to help deal with the free radicals.\textsuperscript{37} It appears there may be some underestimation of the actual diagnostic ultrasound-induced temperature in early gestation, mainly because of the absence of perfusion. For example, at week 5, the oxygen tension in the embryonic sac is about 10 mm Hg, which is well below normo-oxic levels\textsuperscript{41}; the ten-
sion in the eye is about 15 mm Hg. These values are surrogate indicators of the absence of perfusion. Only when the embryonic circulation links up with the maternal circulation does this value change and substantially increase.42,43

The perfusion issue is in addition to modifications of tissue temperatures due to ambient maternal and fetal temperatures. The questions of tolerance development and the cumulative effect have not been fully evaluated. Furthermore, motions (even very small) of the examiner’s hand as well as the patient’s breathing and body movements (in the case of obstetric ultrasound, both the mother and the fetus) tend to spread the region being heated. However, for spectral (pulsed) Doppler studies, it is necessary to have the transducer as steady as possible. This is because, in general, blood vessels are small in comparison to the general organ or body size being scanned with B-mode imaging, and hand movements while performing Doppler studies will have more undesired effects on the resulting image. The intensity ($I_{\text{SPV}}$) and acoustic power associated with Doppler ultrasound are the highest of all the general-use categories; hence, the associated TI values and potential for heating are also the highest. Ziskin44 reported that among 15,973 Doppler ultrasound examinations, the average duration was 27 minutes (and the longest 4 hours). It is important to note at this point that no actual damage attributable to heat generation by ultrasound has been described in the human medical literature.

**Measured Temperature Rise in Human Fetal Tissue**

Those wishing to measure the temperature rise in the gravid human uterus in vivo during ultrasound scanning must contend with almost insurmountable problems, both from the difficulty in managing a controlled experiment and from ethical considerations. A recently funded project to carry out such experimental studies in the United Kingdom has not yet been reported (G. R. ter Harr, PhD, DSc, e-mail communication, 2006). In vitro studies must therefore be used. In one study, Doody et al45 reported the temperature increase generated in vitro at the surface of samples of human fetal vertebrae ranging in age from 14 to 39 weeks. The exposure conditions (3.5 MHz, a weakly focused beam, and acoustic power of 50 mW) compared well with estimated in situ exposure conditions toward the upper end of pulsed Doppler ultrasound use. For a fully ossified vertebra from a 39-week fetus, a temperature rise of 1.8°C after 5 minutes of exposure was reported. For vertebrae from less mature fetuses, lower temperature rises were observed, which were related to the lower degree of ossification. For the 14-week vertebra studied, a temperature rise of no more than 0.6°C was reported.

Another experimental approach uses tissue-mimicking materials in the form of thermal test objects (TTOs).46 Thermal test objects have been used to explore the validity of the TI as a predictor of a temperature rise in a significant study carried out by the National Physical Laboratory (Middlesex, England). Atkins and Duck47 have reported results from a more limited study using a soft tissue TTO and two pulsed Doppler beams, one of them in the color Doppler mode. When surface heating effects were ignored, the maximum temperature rises in the TTO were 2.8°C after 10 minutes of exposure in the pulsed Doppler mode (3 MHz and 290 mW/cm²) and 0.4°C in the Doppler imaging mode. When compensation was included for the attenuation of overlying tissue (the measurements being made using water coupling), the temperature rises were reduced to 0.95°C and 0.21°C, respectively. Higher temperatures were reported when a bone TTO was used. Use of such a phantom for precise fetal exposure calculations would need specific modification to the case of the fetal absorption coefficient, which is presently unknown.48

The potential for nonlinear propagation effects to enhance heating has been explored both experimentally and theoretically by, among others, Cahill et al.49 A condition was used that approximated an obstetric examination, using assumptions of a fixed attenuation near the source, transmission through a low-attenuation liquid, and a tissue-equivalent target. Both the model and experiments found that the temperature rise may be enhanced by up to 50% when compared to linear propagation calculations, but that for higher pulse amplitudes, the temperature rise may be reduced because of increased dissipation of energy by the liquid. Current clini-
cal scanners can, under some conditions, operate with a displayed TI of 6.0 or higher. If one misinterprets the TI as accurately representing the maximum possible temperature rise in vivo, one may predict a worst-case temperature rise of 6°C or a rise from an average 37°C to 43°C in vivo. Temperature increases similar to this have been shown in vitro with commercial systems. A recent publication described TI values remaining very low during routine obstetric examinations but occasionally reaching 1.5 for very brief periods.

**Intracranial Temperature Elevation**

The extraordinary growth in the use of ultrasonic imaging as a diagnostic tool in medicine has led to the development of a wide range of specialized procedures and the evolution of sophisticated and powerful modern equipment. Improvements in resolution and image quality and in gray scale definition have been particularly important in obstetrics. However, it is important to realize that some developments of novel technology have been accompanied by increased acoustic outputs, such that modern equipment is capable of emitting beams with acoustic intensities sufficient to produce measurable effects in biological tissue. Pulsed Doppler sonography, spectral flow analysis, and Doppler color flow imaging techniques offer the potential to increase diagnostic effectiveness and may be attractive for applications in early pregnancy or embryonic sonography.

During ultrasound examinations, acoustic energy is absorbed by tissue and converted into heat. The temperature rise depends on a number of factors, including tissue properties and the ultrasound exposure conditions (see above). In simple ultrasound scanning, using gray scale B-mode, modest energy levels are applied in a constantly moving beam, so that there is negligible opportunity for tissue heating to occur. On the other hand, Doppler techniques present the highest risk of inducing thermally mediated biological effects. This follows from the use of higher pulse repetition rates and longer pulse lengths than are used in gray scale imaging and from the use of a stationary beam in spectral Doppler measurement of flow. The skull bone, with its high acoustic absorption coefficient, has a significant effect on ultrasound interactions and potential bioeffects. Bone attenuates the amount of energy that penetrates into deep brain tissue; meanwhile, the absorbed acoustic energy is rapidly transformed into heat in the bone and the nearby soft tissue of the cerebral cortex.

The subject of ultrasound-induced heating and its biological consequences has been examined in detail by groups of international experts in two symposia sponsored by the World Federation for Ultrasound in Medicine and Biology (WFUMB). The first of these symposia identified the pulsed Doppler mode as being capable of producing biologically significant temperature increases in certain unperfused tissue. Two WFUMB publications have highlighted the significance of thermal bioeffects as a potential risk factor in diagnostic sonography. Since these WFUMB symposia took place, there have been several publications showing that diagnostic pulsed ultrasound can produce substantial temperature increases in live perfused fetal brains when insonated within the uterus. These findings will have an impact on the development of relevant safety guidelines.

Meanwhile, the FDA Center for Devices and Radiological Health has relaxed its regulatory limit in the United States, such that the embryo or fetus may be exposed to substantially increased acoustic intensity (nearly 8 times compared to pre-1992 limits), provided the equipment incorporates a real-time output display. The display is intended to provide an indicator of the risk of producing bioeffects for each examination in each mode of operation or whenever the equipment output controls are altered. The rationale for the output display is to alert the user to potential bioeffects. This option of self-regulation increasingly places the responsibility on the user/clinician to maximize the benefit of ultrasound examinations while minimizing the risk. The FDA-approved output display standard describes a TI as an indicator of the risk of producing thermally mediated biological effects and a mechanical index (MI) as an indicator of the risk of producing mechanically induced effects. The concept of using an index value seems simple. In practice, it often can be misleading because the calculations are based on...
various assumptions about average properties of biological tissues and ultrasound parameters as the modeled beam propagates through homogeneous tissue, whereas actual tissues are heterogeneous. Some studies have shown limitations of the TI as an estimator of a temperature rise and have shown that, in certain circumstances, the index can underestimate the potential for a temperature increase.\textsuperscript{55,57–59} An example of this limitation is described below.

There is ample published scientific evidence to show that exposure to diagnostic ultrasound can produce significant temperature increases in the fetal brain near bone.\textsuperscript{13,36,60,61} The critical questions that need to be addressed are whether there is evidence that:

1. The extent of the ultrasound-induced temperature rise is sufficient to create a hazard;
2. There are neurophysiologic effects or responses to clinically relevant exposures;
3. There are unexplained epidemiologic effects; and
4. There is a significant risk to embryonic and fetal development.

Ultimately, these data are used to establish conclusions about thresholds for temperature-mediated biological effects. The following text describes some fundamental research that has evaluated the extent of ultrasound-induced heating in the brain and further studies on the influence of changes in exposure conditions and physiologic conditions on the extent of heating.

**Experimental Evidence**

The data reviewed here are derived from a series of published collaborative studies in which one of the authors (S.B.B.) participated in different laboratories in Australasia. To facilitate comparisons of data, the same ultrasound exposure equipment was used throughout. The ultrasound exposure parameters are given together with reference to the original articles in Table 1. In all studies, the ultrasound beam was stationary so that a single-point tissue target was constantly insonated with pulsed ultrasound. This situation represents the worst case for spectral pulsed Doppler examinations. Other studies that used handheld thermocouples and ultrasound probes are not considered in this evaluation.

There are variations in the animal models used, and some studies involved insonation in the near field to explore the effects of tissue heating over a larger area of tissue using a wide beam.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Frequency, MHz</th>
<th>Power, mW</th>
<th>I\textsubscript{SPM}, W/cm\textsuperscript{2}</th>
<th>Beamwidth, cm</th>
<th>Duration, s</th>
<th>Mean ΔT, °C</th>
<th>Animal Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosward et al\textsuperscript{11}</td>
<td>3.2</td>
<td>260</td>
<td>2.9</td>
<td>0.27</td>
<td>120</td>
<td>5.2</td>
<td>Guinea pig fetus</td>
</tr>
<tr>
<td>Horder et al\textsuperscript{54}</td>
<td>3.5</td>
<td>240</td>
<td>2.8</td>
<td>0.26</td>
<td>120</td>
<td>5.1</td>
<td>Guinea pig fetus</td>
</tr>
<tr>
<td>Horder et al\textsuperscript{14,35}</td>
<td>3.5</td>
<td>240</td>
<td>2.8</td>
<td>1.60</td>
<td>120</td>
<td>1.4</td>
<td>Guinea pig fetus</td>
</tr>
<tr>
<td>Horder et al\textsuperscript{61}</td>
<td>3.5</td>
<td>240</td>
<td>2.8</td>
<td>0.26</td>
<td>120</td>
<td>4.9</td>
<td>Guinea pig fetus</td>
</tr>
<tr>
<td>Duggan et al\textsuperscript{13}</td>
<td>3.5</td>
<td>600</td>
<td>0.3</td>
<td>1.70</td>
<td>120</td>
<td>1.5</td>
<td>Sheep fetus</td>
</tr>
<tr>
<td>Duggan et al\textsuperscript{62}</td>
<td>3.5</td>
<td>200</td>
<td>1.4</td>
<td>0.30</td>
<td>90</td>
<td>1.5</td>
<td>Neonatal pig</td>
</tr>
</tbody>
</table>

The site of temperature measurement varied between studies. Intensity was measured in a free field in water, not in situ.
duce an increase of 2.6°C in the midbrain when the bony cranium was removed from 60-dga fetuses. There was no significant difference in the results obtained for formalin-fixed or fresh tissue. Most of the heating (80% of the mean maximum temperature increase) occurred within 40 seconds. The rate of heating is relevant to the safety of pulsed Doppler examinations in which the dwell time may be an important factor. The results show that the amount of the ultrasound-induced temperature increase that occurs in the fetal brain near bone is directly related to the amount of mineralization deposited in the bone, that is, the fetal age. The implications of this finding are that the worst-case heating will occur later in pregnancy (from the second trimester). Therefore, ultrasound-induced heating is not as intense during embryonic development where there is no bone.

Fetal Brain Insonated In Utero

Pulsed Doppler ultrasound examination of the fetal cerebral circulation may cause potentially harmful temperature elevations in brain tissue immediately beneath the insonated segment of the skull. Temperature increases were measured at various depths in the brain of living third-trimester (57- to 61-dga) fetal guinea pigs during in utero exposure to a narrow focused beam of unscanned pulsed ultrasound at an ISPTA of 2.8 W/cm². Mean temperature increases of 4.9°C close to the parietal bone and 1.2°C in the midbrain were recorded after 120 seconds. Cerebral blood perfusion had a negligible cooling effect on ultrasound-induced heating in these guinea pig fetuses (Figure 2).

When this study was repeated in older near-term (62- to 66-dga) guinea pig fetuses, a statistically significant but small (12%) difference was found in the mean peak intracranial temperature increase for live (perfused) versus dead (nonperfused) fetuses exposed in utero. This study was designed primarily to test the effectiveness of the thermal index for bone (TIB) as an estimator of the intracranial ultrasound-induced temperature increase. Even though the temperature was measured on the inside of the cranium (ie, not the outer surface of bone proximal to the transducer, as defined by the TIB), and the temperature was reduced by cerebral blood flow, the TIB was found to underestimate the value for the temperature increase. The ratio of the measured temperature to that estimated by the TIB was 1.3. In subsequent continuing studies, a larger difference between the TIB and the measured temperature increase was found for the outer surface of the fetal skull.

Effect of Cerebral Perfusion on Heating

A study with anesthetized neonatal pigs measured the effect of variations in cerebral blood flow (normal, double, and absent flow) on ultrasonic heating of the cerebral cortex (Table 2). Cerebral blood flow was measured using the radiolabeled microsphere technique. The study

**Figure 1.** Mean temperature elevations in fixed guinea pig fetal brain tissue during 120-second exposures to 260-mW pulsed ultrasound. A single thermocouple was placed under the parietal bone at a distance of 6.0 cm from the transducer (after Bosward et al).
also compared the temperature increases achieved for a narrow beam with those achieved for a wide beam. Pulsed ultrasound was applied to the neonatal pig brain, insonating with an ISPTA of 1.4 W/cm² at the 0.3-cm-diameter beam focus or with the brain positioned in the 1.6-cm-diameter near field of the beam, where the intensity was 3.6 W/cm². In all exposures to the focused narrow beam, there was no difference in the heating curves for normal, increased, and no cerebral blood flow, for which mean peak temperature increases of 1.5°C were recorded after 90 seconds (Figure 2). However, when insonated with the wide beam, the mean peak temperature increases in the cerebral cortex were significantly different for the 3 rates of blood flow: mean temperature increases of 1.9°C (normal flow), 1.7°C (increased flow), and 2.4°C (no flow) were recorded. There was a 20% reduction in the mean peak temperature rise after 90 seconds in the healthy live neonate when compared with the dead nonperfused neonate (Figure 3). However, it was found that an increase of 300% above the normal flow rate produced only a marginally (9%) further reduction in the mean maximum temperature increase. In another study on the possible cooling effect of cerebral perfusion,13 perfusion in the living versus the dead sheep fetuses was found to result in a 40% reduction in the mean peak temperature increase when insonation was with a similar wide beam. Ultrasound was applied to the conscious nonanesthetized near-term fetal lamb, and the temperature was measured at a depth of approximately 2 mm in the cerebral cortex under the parietal bone.

The results of these studies comparing heating in wide and narrow beams support the theory underlying the bioheat equation24,53 that perfusion affects heating by broad beams to a greater extent than that of narrow beams. The large temperature gradient in narrow, focused beams allows optimum heat dissipation so that any further cooling effects of vascular perfusion are minimal.

Effect of Ultrasound-Induced Heating on Brain Electrophysiologic Mechanisms

The temperature increase was measured deep in brain tissue adjacent to the sphenoid bone in fetal guinea pigs during in utero exposure to pulsed ultrasound at an intensity (ISPTA) of 2.8 W/cm². This is clinically relevant for Doppler flow studies on middle cerebral vessels. Sensitive important homeostatic hormone- and growth-regulating structures, such as the hypothalamus and the pituitary, lie in the region commonly targeted by transplacental ultrasound.

Table 2. Results of Ultrasound-Induced Temperature Increase in Brain Tissue Under Different Experimental Conditions

<table>
<thead>
<tr>
<th>Reference</th>
<th>Temperature Increase in Brain of Live Animals After Insonation, °C</th>
<th>Temperature Increase in Brain of Dead Animals After Insonation, °C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 s</td>
<td>60 s</td>
</tr>
<tr>
<td>Bosward et al11</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Horder et al14</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Horder et al14 (&gt;5 mm depth)</td>
<td>3.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Horder et al14</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Duggan et al13</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Duggan et al62</td>
<td>1.0</td>
<td>1.4</td>
</tr>
</tbody>
</table>

NR indicates not reported.

*Temperature measured at depth in the brain at the sphenoid bone (Refer to Figure 4).
during examination of the cerebral vessels. After 120 seconds of exposure, a mean temperature increase of 1.5°C was measured at the sphenoid bone (Figure 4). This temperature is readily conducted to the adjacent hypothalamus, which regulates the body temperature by adjusting the heart rate. However, fetal electrocardiographic measurement throughout these exposures showed that ultrasound-induced heating of the hypothalamic region by 1.5°C during a brief exposure (total time, 120 seconds) did not significantly alter the normal mean fetal heart rate of 250 beats per minute.61

Another study found no difference in the electrocortical activity in the brains of conscious nonanesthetized fetal sheep during intrauterine exposure to low-intensity (0.3 W/cm²) pulsed ultrasound.63 Ultrasound was delivered by a wide beam in the near field of a transducer that was surgically implanted onto the fetal skull. The study was designed to provide empirical data from a reliable animal physiologic model to investigate previous reports of increased fetal activity after examinations with diagnostic ultrasound. The temporal-average intensity applied was more comparable with that of B-mode scanning than current pulsed Doppler exposures. The results gave no evidence of the fetal electrophysiologic response to low-intensity ultrasound exposures.

The current published WFUMB policy statements on thermal effects of pulsed Doppler ultrasound resulted from expert interpretation of bioeffects data at the time of the last WFUMB safety symposium in April 1996. Since then, a number of publications have shown that a significant temperature increase is produced in living perfused brain tissue. Furthermore, the extent of heating is not significantly reduced by vascular perfusion during exposure to clinically relevant narrow-focused beams.

**Epidemiologic Data**

For detailed analysis of epidemiology literature, as it relates to possible fetal bioeffects of ultrasound, see a separate article related to the American Institute of Ultrasound in Medicine epidemiology statement.64

**Health, Safety, and Risk: Why Should There Be Concern at All?**

It is certain that diagnostic ultrasound has had an enormous beneficial effect on patient health and welfare. It is a noninvasive procedure, widely available, and with excellent resolving capabilities. The topic of “safety,” however, is not so easily addressed. Safety is another way of discussing “risk.” We know that great benefit has been derived from the clinical use of diagnostic ultrasound, but there is uncertainty about its risk. This uncertainty arises primarily from the fact that there has been (1) no clinical evidence of any bioeffects or “side effects” from exposure to diagnostic ultrasound and (2) uncertainty as to the relevance of (a) theoretical insights about the insonating conditions leading to the occurrence of heating and nonthermal mechanisms of action and (b) reports of bioeffects from in vitro and in vivo chemical and nonhuman biological systems apparently relevant to the topic of safety.

If there is a risk, it is, most likely, very subtle and therefore not so easily detected, even after 4 decades of use. It is important to bear in mind that throughout this 4-decade period, there has been a steady increase in acoustic outputs of diagnostic ultrasound devices (allegedly to gain better diagnostic information). There are major problems in designing appropriate (particularly human) studies.
One major question to resolve is whether a temperature threshold exists for inducing birth defects. This is a legitimate and relevant question because there is little information on this topic. This information would be useful to know from both basic science and clinical points of view. One can use the rat to illustrate the various difficulties involved with designing adequate studies. The sample size needed to detect various increments in background rates of major malformations in rat fetuses is the first parameter to consider. Rats have a background rate of 1 malformed fetus per 250 rats (i.e., the rate of occurrence of malformations in the rat is 0.004 [0.4%]%). A “2-proportions power analysis” indicates the numbers of individuals (i.e., fetuses) and litters needed to determine with reasonable statistical power normal background rates for major malformations in the rat. It is obvious that a larger effect requires a smaller sample size than a smaller effect. For instance, detection of a doubling of the background rate of malformations would require 11,370 individuals, or approximately 1138 litters. At present, data on hyperthermia-induced defects in rats are meager because the usual experiments have involved 5 to 15 litters per regimen. These sample sizes are simply far too small to gain any insights about whether temperature thresholds exist. However, exposure conditions have not been extended to determine the presence or absence of a threshold. It is unknown whether the threshold would diminish or disappear for greatly extended durations and different bioeffect end points.

Although no relevant data exist, there are many opinions about whether a temperature threshold exists. Edwards suggests somewhere between 1.5°C and 2.5°C above normal physiologic levels; Kimmel et al suggest 2°C above normal physiologic levels; WFUMB suggests 1.5°C; the National Council on Radiation Protection and Measurements suggests 1.0°C; and the International Radiation Protection Association/International Non-Ionizing Radiation Committee suggests 0.5°C. However, Carstensen and Gates state that hyperthermia-induced damage scales linearly with time and exponentially with temperature. This latter position is quite analogous to the empirically determined thermal dose concept of Sapareto and Dewey for hyperthermia-induced killing of human cells. This implies an Arrhenius relationship between thermal exposure and the rate of induction of an adverse biological effect and, therefore, that there is no threshold for biological change (namely, enzymatic reaction rates). However, the magnitude of the induced effect at low doses may be too small to be detectable in even very large sample sizes, or the biological changes might not, in fact, lead to adverse effects.

The issue is even more complicated when examining the above aspects in humans. This is precisely the domain of epidemiology. Suppose one wants to attempt to determine whether obstetric diagnostic ultrasound induces a temperature increment sufficient to cause birth defects in humans. Analyses will be limited to the first trimester because several embryologic changes (neural tube closure [NTC] in particular) have been shown in animal systems to be very heat-sensitive stages. We know that (1) the background rate for major malformations in humans is about 3%, and (2) the occurrence of diagnostic ultrasound scans during early pregnancy is increasing because of in vitro fertilization procedures and other medical reasons. The rationale for selecting a heat-sensitive stage of embryogenesis for studying this problem is that if a threshold is determined for a sensitive stage, then one can be certain that, if one remains below that threshold level when scanning during that stage as well as all other stages of pregnancy, there is reasonable assurance that diagnostic ultrasound will not induce a thermal effect on the embryo or fetus.

A simplistic statistical assessment with the usual criteria (80% power; \( \alpha = .05 \)), with a basis of a 3% background rate of major malformations in humans, will show that for detecting doubling, tripling, quadrupling, and factor-of-10 increases above the background rate, the total sample sizes (divided equally between control and “exposed”) are 1498, 490, 268, and 58, respectively. These numbers are considerably smaller than those associated with the same anticipated increments in malformations in animal model systems in which the anticipated rate of background occurrences is approximately an order of magnitude smaller than that of humans.

The problem of epidemiologically studying whether diagnostic ultrasound-induced temper-
ature increments cause an increase in birth defects is potentially complicated by the fact that some stages of pregnancy are more sensitive to hyperthermia-induced birth defects than others. In general, NTC is recognized as a heat-sensitive stage. Thus, from a retrospective approach, it would be necessary to have access to patient records of the dating of the pregnancy and the timing of the diagnostic ultrasound application as well as its thermal dose, as represented by the type and duration of exposure and the temporal-average intensity. One would also want to ensure that all patients were nutritionally comparable. It would be necessary to ensure that patients taking vitamin supplementation were not mixed in with patients not taking such supplementation. For a prospective study, it would be necessary to have the same information, except that the scans would take place given medical reasons for conducting them during NTC. An additional complication is that nearly all pregnancies are scanned with diagnostic ultrasound. Thus, a control group may not be available. It may be possible to devise a situation in which the fetal outcome results of first-trimester (NTC) scans are compared against those of subsequent diagnostic ultrasound scans. A problem with nearly all diagnostic ultrasound scans from an epidemiologic basis is the total absence of exposimetry information. Knowledge of information available about the scan (eg, temporal-average intensity, acoustic frequency, pulse length, and pulse repetition frequency, as presented in the owner’s manual) would be very useful.

There appear to be some reasons for concern that modern diagnostic ultrasound devices are capable of inducing temperature increments in soft tissue known to be teratogenic in animals and that such diagnostic ultrasound exposures are occurring at times when the mammalian embryo is known to be sensitive to thermal insult.

There are two major mechanisms by which bioeffects are known to occur: thermal and nonthermal. We do not expect to see nonthermal effects arising in the embryo or fetus simply because there appear to be no stabilized gas bodies in those structures. Mechanical phenomena may become very relevant if procedures arise by which the embryo or fetus is treated with echo contrast agents to enhance diagnostic capability. It therefore seems more likely that a diagnostic ultrasound-induced thermal mechanism could be operating because the physics (sufficient acoustic output) and the biology (thermally sensitive stages) of obstetric settings are conjoined. Furthermore, this situation may worsen because acoustic outputs of instruments are rising and will be exacerbated if the present regulated limitations on allowable SPTA acoustic emissions of diagnostic ultrasound devices are further relaxed or eliminated.

**Clinical Studies**

Several biological end points have been analyzed in the human fetus/neonate: intrauterine growth restriction (previously named growth retardation) and low birth weight, delayed speech, dyslexia, mental development or behavioral issues, and, more recently, non–right-handedness. Occasional studies report an association between diagnostic ultrasound and some specific abnormalities such as lower birth weight, delayed speech, dyslexia, and non–right-handedness. With the exception of low birth weight (also shown in monkeys), these findings have never been duplicated, and findings from most studies have been negative for any association. For further details, please see American Institute of Ultrasound in Medicine epidemiology statement. Recently, a follow-up study to the famous low-birth-weight study was published with up to 8 years’ follow-up of children who were insonated in utero, and no long-term differences were shown with controls in growth and measures of development.

A major problem with formulating hypotheses from animal data is that in vivo effects of hyperthermia seen in animals result from exposure situations that would never be encountered by the human embryo or fetus during ultrasound examination. It is all to do with the volume of exposed developing tissue. While there exist reliable data on teratogenic effects of hyperthermia in animals (mostly rodents), these data are based on whole-body exposure of both the embryo and mother in situations in which the elevated temperature is consistently maintained for relatively
long periods compared with that likely to occur in a diagnostic ultrasound examination. In the human, insonation will generally be of limited parts of the fetus and the mother. However, while this is true in the second and third trimesters, early in pregnancy (up to week 10), the entire embryo/fetus is insonated. The size of the embryo is approximately 1 to 2 mm at 5 weeks, 5 to 6 mm at 6 weeks, 10 mm (1 cm) at around 6 to 7 weeks, and about 2 cm at 8 weeks and reaches 3 cm at 10 weeks (when it is now called a fetus). These sizes are well within the range of the beamwidth at a depth of 10 to 20 cm.

With a whole-body temperature increase, the animal mother is stressed and compromised physiologically. Blood pressure, heart rate, systemic corticosteroid levels, stress hormone levels, and stress protein levels all would increase when the maternal core temperature is elevated greater than 5°C in typical hyperthermia experiments. We know from radio frequency experiments with nonhuman primates that only a 1°C increase in core temperature results in significant behavioral (and, presumably, physiologic) changes. This result forms the basis of international safety standards for radio frequency radiation. Reports from human studies show that a similar modest increase in body temperature (<1°C) elicits physiologic responses, including sweating and an increased heart rate. The National Institute for Occupational Safety and Health and the American Conference of Governmental Industrial Hygienists recommend an upper threshold limit value of a rise in body temperature of 1°C. This was endorsed by the World Health Organization. In an ultrasound examination, the maternal physiologic state is not perturbed by environmental heating, so it is unlikely that induced systemic effects would have an impact on fetal development (that is, beyond any stress-induced effects that the clinical examination might induce).

What About Synergistic Effects of Ultrasound and Raised Temperature?
In studies that were designed specifically to examine the direct effects of the combination of ultrasound mechanical interaction with bulk heating, some interesting results emerged. The collaborative research joined the expertise of growing whole embryos in culture with a custom-built and calibrated ultrasound exposure system. Whole rat embryos were grown in culture in the laboratory in a carefully controlled environment. This experimental model was well established and had been previously used in published studies on teratogenic effects of hyperthermia. Bioeffects end points and thresholds for hyperthermia had already been well established for the rat embryo when heated at a specifically sensitive stage in gestation: exactly 9.5 dga. In work that set out to examine the effects of combining hyperthermia and ultrasound exposure (culture vessel heated and pulsed ultrasound applied), a synergistic effect was implicated in the response of delayed somite development and enhanced HSP synthesis occurring with an increase in the whole-embryo body temperature (through bulk heating of surrounding culture media) of only 1.5°C above the normal culture temperature for rat embryos. The investigators found various effects at lower hyperthermic exposure levels (temperature increase × duration of application) when ultrasound was applied (as opposed to whole-body hyperthermia alone). For example, previous work with this embryo assay system showed that a temperature elevation to 40°C for 40 minutes alone had no detectable effect on embryonic growth. In contrast, adding ultrasound to modest hyperthermia produced a significant reduction in the neural protein level and an altered head-to-body surface area ratio. Exposure to ultrasound for 15 minutes at 40°C caused significant reduction in the growth of the head compared with that of control embryos. The exact mechanism was not identified.

Such an exposure situation (embryos or oocytes being pushed around by an ultrasound beam in a fluid environment) may occur in in vitro fertilization. Considering the potential ramifications of perturbed embryonic development and the extreme financial cost factor in in vitro fertilization treatments, it seems that this topic should be carefully explored.

Clinical Relevance in the Human
There are problems in relating laboratory animal studies to patients. First and foremost, one cannot necessarily extrapolate from animal studies
to humans or even from one animal species to another because differences in outcome may, in fact, be due to strain differences. Animal studies are usually performed in an attempt to obtain some effects, and the values of exposure parameters are usually “pushed” to some extreme not applicable to human scanning, such as an $I_{SPDA}$ of $10^{9}$ W/cm$^2$, or even 1500 W/cm$^2$.

On the other hand, the lack of findings is just that. It does not “prove” safety. Subtle behavioral or psychological changes would be extremely difficult to show. Even more obvious anomalies might not be directly due to one etiology but could be secondary to the presence of multiple confounding factors. In addition, even when a procedure might carry some yet unidentified risk, one has to balance the risks versus benefits. This is why most national and international medical organizations adhere to the principle of performing ultrasound only when clinically indicated and then use the ALARA (as low as reasonably achievable) principle for output power. It is important to note that if there is a threshold, and exposure is kept below this threshold, then there is no need to apply the ALARA principle. It is beyond the scope of this article to describe the clinical indications for ultrasound use, but when they are present, the advantages greatly outweigh the potential risks.

An important point to remember is that the indices, TI and MI, are estimators of relative risk based on assumed simple physical models. They are most meaningful for tracking changes of operating conditions of equipment when the operator is heeding ALARA and comparing displayed index values with those displayed immediately beforehand. The TI was not intended to indicate a temperature increase in degrees Celsius in numerous selected clinical situations, although many interested parties continue to criticize it for not doing so accurately. In fact, these indices may be underestimating the actual in situ acoustic pressure in clinical practice. This reservation is substantiated for the MI. The presence of harmonic frequencies (sound waves generated at exact multiples of the original frequency) in particular may cause overestimation or underestimation of the TI. As previously mentioned, if one misconstrues the TI as a direct temperature indicator, the underestimation can be as high as 1.4°C and 1.8°C for B-mode and color imaging, respectively, and up to 5.8°C for pulsed Doppler imaging when bone is insonated through a liquid layer with low attenuation. This needs to be kept in mind in obstetric ultrasound with studies of fetal intracranial vasculature. This question of applicability of the indices, particularly in regard to the TI, is a major concern.

The exposure variables are one part of the equation. The second component is the insonated tissue. This also poses somewhat of a quandary because the sensitivity of the target tissues is not precisely known and thus demands awareness by the operator, at least, of the acoustic output and exposure time. The issue of a long path through fluid (such as a full bladder in first-trimester scanning or polyhydramnios) has to be considered, too, because estimation of temperature elevation by invoking the TI may be an underestimation by a factor of 2 or even more. Heating at the transducer surface tends to be ignored, but clinicians have the experience of some patients reporting a warm feeling at the point of contact with their skin. This is particularly relevant in intracavitary scanning, such as transvaginal ultrasound.

**Discussion Regarding Obstetric Issues in the Human**

While above-mentioned studies present “no positive information” (which leads to the natural conclusion that there is no risk), there are a few issues that appear to be pertinent to obstetric diagnostic ultrasound that seem not to have been discussed. Some have been addressed above, to some extent, but will now be detailed as they relate to actual clinical reality.

1. For most of the first trimester, the embryo is hypoxic and the only physical mechanism for heat dissipation is diffusion. Perfusion is not a pertinent factor. The embryonic heartbeat begins about week 6, and with that begins the development of an embryonic circulatory system. By week 11, the placenta is reasonably organized, and the rudiments of a perfusion-based circulatory system are in place. For early diagnostic ultrasound scans, however, it is well to be
aware that the embryo’s main heat dissipation mechanism is diffusion, not perfusion. This has an effect on anticipated diagnostic ultrasound-induced heat removal and may mislead an operator who interprets the TI as a precise indicator of tissue temperature because the TI assumes some level of perfusion. Thus, the embryo would be expected to be a little warmer than expected because of the absence of perfusion. However, a mitigating effect is that embryonic soft tissues may be less absorbing than adult soft tissues, which would then cause the embryo to be less warm than expected.

2. Later in pregnancy (third trimester), it becomes apparent that the placental system is not a fully efficient mechanism for perfusive dissipation of heat because the fetus becomes (naturally) warmer than the mother by about 0.5°C.4

3. Whenever a pregnant woman visits her obstetrician, and the woman is febrile, the obstetrician will often scan the fetus just to be sure that “everything is OK,” thereby increasing the thermal load to the fetus.

These points are important because the Arrhenius relationship for hyperthermia-induced effects from a chemical rate perspective is linear with time but exponential with temperature. For example, a thermal effect seen at one temperature might require only one tenth the exposure time at a 2°C higher temperature. This would not be indicated by the displayed value of the TI, and because, as previously stated, there can be differences amounting to a factor of 0.5, 2, or even 6 in the TI, the problem is compounded even more.6 To our knowledge, the present literature on obstetric scanning ignores some basic obstetric facts such as lack of perfusion in the first few weeks of pregnancy, as mentioned above, which would lead to higher temperature change, ΔT, values than predicted. It should be noted however that, conversely, differences in protein and fat content between fetus and adult might change the ΔT in the opposite direction. In addition, there are some further problems with the epidemiologic literature in terms of obstetric diagnostic ultrasound scanning. When an effect is reported, considerable effort is made to scrutinize the protocol and verify whether there may be some deficiency that renders the report questionable. When no effect is reported by the investigation, the outcome is generally accepted with no or minimal criticism.

In this respect, two reports, one by Ziskin44 and the other by the Canadian Health Directorate,107 are useful to consider. The Ziskin report44 was about an international survey of clinical users and entailed about 25,000 obstetric examinations with a notation that there were no reported “bad” outcomes in terms of the obstetric diagnostic ultrasound exposure by any of the 68 respondents in more than 121,000 examinations. However, because the background rate for major deleterious birth defects is somewhere between 3% and 5%, there should have been (minimally) 750 major anomalous fetuses in the Ziskin report44 on the basis of the background rate alone. None was reported. Admittedly, it was not the goal of the survey to determine the background rate of anomalies in the general population, but the report can be misread from that standpoint. The only way one could reasonably sort out whether there is an effect would be to compare what was observed with what was expected. Similarly, the Canadian Health Directorate report107 was also a survey and entailed 1,200,000 obstetric examinations among 111 respondents. It found no bad outcomes due to ultrasound exposure. In that report, there should have been at least 3000 major birth defects on the basis of the background rate of occurrence alone. Again, none was reported. Clearly, the background rate of anomalies must have been filtered out. This is what Bello108 also expressed in an article asking whether harmful effects of ultrasound may have been missed because the wrong time frame reference is usually used. He describes two possible factors for such errors. Changes in the fetus are extremely rapid, and if one uses a term pregnancy (264 days [37–38 weeks])-to-life expectancy of 60 years (22680 days) ratio, then 7 in utero days are comparable to about 601 ex utero days. Therefore, a much shorter time interval (perhaps even 1 day) should be used to group fetuses to evaluate effects. Furthermore, Bello108 also discusses a “dilution error,” similar to what was exposed above. Assuming an event has a background rate of 10% in the general population but
occurs in 100% of fetuses exposed on day 30, if a large number (eg, 2000) of fetuses exposed on that particular day are examined, the incidence will be 100%, that is, 90% increase over the control population. However, if we assume 2000 fetuses exposed per day for 12 weeks, this represents 168,000 scans, and only 11.1% will be affected (all 2000 scanned on day 30 and 10% of all others, due to background incidence, or 18,800), an increase of only 1.1% over the background rate. A further confounding factor, which may decrease the number of reported malformations, is that when such a fetal malformation is diagnosed in utero, there is often an option for elective abortion. Elective abortions (of malformed fetuses) lower the birth defect rates because most hospitals do not include electively aborted malformed fetuses in their “birth” defects registries.

In summary, performing research on the risk of fetal malformations posed by thermal effects of ultrasound scanning in early pregnancy is extremely difficult for the following reasons:

1. If ultrasound-induced heating produced localized pinpoint damage in the beam focal zone, it would not be detectable;
2. Numbers in clinical studies are insufficient for statistical purposes unless all data are merged into a meta-analysis;
3. There is an absence of sham-exposed controls (virtually every pregnant woman is exposed at least once);
4. Numbers in animal experiments to detect low-level (in contrast to gross developmental) effects are too small; and
5. Without a hypothesis derived from experimental animal work, it is almost impossible to know where to look, and any finding would be seen as questionable.

There is, in addition, a whole ethics aspect (eg, withholding scanning to obtain a control group) that is beyond the scope of this article.

Conclusions and Recommendations

Conclusions

1. Acoustic output from diagnostic ultrasound devices is sufficient to cause temperature elevations in fetal tissue. In general, temperature elevations become progressively greater from B-mode to color Doppler to spectral Doppler applications. For identical exposure conditions, the temperature rise near bone increases with ossification development throughout gestation. Although, in general, an adverse fetal outcome is possible at any time during gestation, most severe and detectable effects of thermal exposure in animals have been observed during the period of organogenesis. For identical exposure conditions, the potential for thermal bioeffects increases with the dwell time during examination.

2. The TI, a quantity related to the calculated or estimated temperature rise under certain defined assumptions, correlates, albeit not perfectly, with temperature elevation. There are 2 TIs relevant for fetal exposure: the TI for soft tissues and the TIB.

3. Ultrasound exposures that elevate fetal temperature by 4°C above normal for 5 minutes or more have the potential to induce severe developmental defects. Thermally induced congenital anomalies have been observed in a large variety of animal species. In current clinical practice, using commercially available equipment, it is unlikely that such thermal exposure would occur at a specific fetal anatomic site.

4. The epidemiology database consists of exposures occurring before 1992, after which time diagnostic equipment capable of higher acoustic output became commercially available for fetal use. No congenital anomalies have been attributed to diagnostic ultrasound in humans.

5. Transducer self-heating is a significant component of the temperature rise of tissues close to the transducer. This may be of significance in transvaginal scanning, but no data for the fetal temperature rise are available.

Recommendations

1. The TI should not be interpreted as an actual degrees Celsius temperature rise in the region of interest. Its use should be limited to a relative indication of the maximum temperature rise.
2. Although the TI is not ideal, it should be used to assess the potential thermal risk in conjunction with the dwell time.

3. Given the fact that maternal fever early in pregnancy is known to be associated with fetal anomalies, one should be aware that ultrasound examination in a febrile patient might further increase the local temperature.

4. If it is ever clinically indicated in the first trimester, spectral Doppler examination of the fetus should be used with caution.

5. Given the present state and methods of epidemiologic research, detection of subtle effects, should they take place, is unlikely. To detect such effects, studies with sufficient statistical power to detect low-incidence occurrences would be desirable. Because of ethical, practical, and financial issues, such studies are hard to perform. Therefore, it is necessary to rely on laboratory experimentation for advancing our knowledge of ultrasonically induced bioeffects and for our understanding of the underlying mechanisms.

6. Output display indices represent important patient information and should be documented as part of the permanent record of the examination to enable future studies.

References


Fetal Thermal Effects of Diagnostic Ultrasound


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