Review Is ultrasound safe?

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Key content:

- Although the general perception is that ultrasound imaging has no adverse effects on the mother or the fetus, evidence collated from laboratory studies has shown effects of potential clinical significance.
- Potential bioeffects of ultrasound can be either thermal or mechanical.
- The two safety indices most commonly used are the thermal index (TI) and the mechanical index (MI).

Learning objectives:

To learn about:

- The current thoughts on the bioeffects of ultrasound
- Types of safety indices
- Safety guidelines issued by recognised bodies
- Evidence of long-term adverse effects

Keywords bioeffects / cavitation / fetus / safety / ultrasound

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Introduction

Diagnostic ultrasound has been described as an extension of the human hand, such is our dependence on it in obstetrics. From its official introduction into the medical world in 1942 by Karl Dussick,[1] its metamorphosis into today's high-tech equipment has led to a general trend towards increased power output and the potential for associated risks.[2,3] Although the general perception is that diagnostic ultrasound has no adverse effects on the mother or fetus, evidence collated from laboratory studies has shown effects of potential clinical significance.[2,4] In addition, therapeutic uses of ultrasound, such as high-intensity focused ultrasound (HIFU) in tumour ablation,[5] haemostasis,[6] cardiac procedures[7] and treatment of various eye conditions,[8] undoubtedly suggest that it can have significant physical effects.

The principle of using the lowest acoustic power output, for the shortest duration, with the least exposure to sensitive target tissues, while achieving the optimum diagnostic information, can reduce biohazards. The ALARA (As Low As Reasonably Achievable) principle applies to diagnostic ultrasound.[9–11] Safety guidelines laid out by the British Medical Ultrasound Society (BMUS), the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) and the World Federation for Ultrasound in Medicine and Biology (WFUMB) specifically emphasise the need for competence in the safe application of ultrasound. The onus for safety is very much on the clinician. Education is, therefore, vital.

Bioeffects of ultrasound

Ultrasound is a type of mechanical energy that penetrates tissue as an oscillating wave of alternating pressure (measured in megapascals [MPa]). In B-mode, M-mode and three-dimensional imaging, this energy is transmitted in pulses, with interim pauses for image reception and display. Doppler ultrasound devices, especially pulsed spectral Doppler, produce a fixed ultrasound beam which, when directed to a fixed target tissue, cause a significant rise in temperature within a relatively short time.[3]

The hazard potential of ultrasound depends mainly on four diverse yet mutually dependent factors **(Box 1)**.[4]

Although there is no conclusive evidence of harm in human studies, reports from animal and laboratory studies of biological side effects[3,12] have led regulatory bodies to advise on precautionary measures in routine ultrasonography. It is the conglomeration of multiple factors that can cause safety thresholds to be exceeded and can lead to harmful bioeffects. These bioeffects include thermal and mechanical effects.

Thermal effects

An increase in tissue temperature is the most worrying bioeffect associated with diagnostic ultrasound in obstetric practice. User-controlled alteration of equipment settings and prolonged exposure can increase the acoustic output, generating heat, mostly in tissue interfaces.

Ultrasound energy from the transducer passes through body tissues and reflects from tissue interfaces back to the transducer to generate images of varying echogenicity. Some ultrasound energy is absorbed into the target tissue and some scatters into surrounding tissue.[2,4] In liquids and soft tissues the scattered energy dissipates longitudinally in all directions. However, in bone, transverse shear waves are generated on the surface and spread by conduction to surrounding soft tissue. This is of particular relevance to the developing brain and spinal cord in the fetus, especially in the third trimester, when there is most mineralization of bone.[4,13]

Absorbed ultrasound energy is converted to thermal energy, with a subsequent local temperature elevation.[12] Studies on laboratory animals conclude that a temperature rise of 4°C lasting for five minutes or more is potentially hazardous to a fetus or embryo.[3] Temperature elevations of less than 1.5°C present no hazard to human or animal tissue, including a human embryo or fetus, even if maintained indefinitely.[3] The fetal temperature is known to be about 0.5–1.0°C higher than maternal temperature;[3,13,14] therefore, caution is warranted in a febrile mother. Self heating of the transducer in faulty equipment, where electrical energy is converted to thermal energy instead of ultrasound energy, is more likely to occur with endoprobes and clearly could

Box 1
Factors affecting the hazard potential of ultrasound[4]

• **Ultrasound exposure**	The ultrasound energy or total acoustic output power (w) emitted by the equipment.
• **Target tissue composition**	This determines the acoustic absorption coefficients. In general, more proteinaceous tissue is more susceptible to thermal injury while higher fluid and gas content makes tissue susceptible to cavitational activity.
• **Tissue susceptibility**	Rapidly proliferating fetal or embryonic tissues are more susceptible to ultrasound effects.[3] Most adult tissues have a static cell population and safety features such as the hyperaemic reflex (an increase in blood flow through the tissue that carries the heat away).
• **Clinical settings**	The type of transducer used, the depth of penetration and overlying layers of tissue alter the acoustic output to the particular target. For example, the radiation exposure to the fetus in the first trimester differs significantly between transabdominal and transvaginal probes.

accentuate thermal injury.[3] In laboratory settings, a fixed transducer and target can lead to diminished heat dissipation, resulting in a higher than expected temperature rise. This is relevant in first trimester transvaginal scanning, where there is a smaller cushioning effect from maternal tissues. The active fetus in second and third trimester transabdominal scanning escapes this effect.

The fetal central nervous system is the most susceptible tissue to thermal injury. Hyperthermia can result in neural tube defects.[2–4,14] Arthrogryposis, disorders of muscle tone, miscarriage and intrauterine growth retardation are other known effects demonstrated in animals.[3,14,15] All of these have also been confirmed in epidemiological studies in humans.[16] Heat has a direct lethal effect on embryonic tissue. Placental infarction and increased uterine activity caused by maternal hyperthermia can result in miscarriage.[16]

While B-mode, M-mode and three-dimensional imaging are less likely to give rise to thermal injury in routine practice, Doppler ultrasound devices, which have proven immensely beneficial in the management of high-risk pregnancies, can cause significant temperature rises.[4,12] A temperature rise to above 41°C lasting for five minutes or more is potentially hazardous to a fetus or embryo and is possible with the newer modalities of diagnostic ultrasound, such as spectral Doppler and colour Doppler imaging.[3,17]

Mechanical effects

Cavitation

Cavitation refers to the development of gas bubbles in an acoustic field at high negative pressures. These bubbles may be transient (inertial) or of the stable (non-inertial) type. Once the gas bubbles reach a critical size they begin to vibrate, which results in further growth and collapse, often into smaller bubbles, causing high temperatures and pressure, release of free radicals, changes in ion transportation and sonoluminescence (emission of light).[3,4] This volatile gas bubble activity results in inertial cavitation injury. Inertial cavitation-induced free radicals have been implicated in some reports of genetic damage *in vitro*.[3,14] Non inertial cavitation injury is the consequence of oscillating gas bubbles generating streaming currents in surrounding liquids and causing mechanical damage, membrane rupture and cell lysis when shearing forces are high.[3,4,14] This has been confirmed in several laboratory experiments, but *in vivo* studies have been inconclusive. Tissues containing gas pockets are vulnerable to cavitation injury. This effect is accentuated by the use of contrast agents to enhance echogenicity and, therefore, visualisation of blood vessels and capillaries in a diagnostic image.[18–20] Contrast agents act as foci which are prone to cavitation injury.[3] At present, contrast agents have an increasing role in gynaecological oncology but there are no well defined obstetric indications.

Evidence collated from animal studies and human fetal erythrocytes *in vitro*[21] shows that ultrasound can result in cell lysis. This effect is exacerbated when ultrasound is used in combination with contrast agents,[20] presenting as haemorrhages in the lung,[18,22–25] intestine[26] and kidneys[27] in animal models. The threshold for capillary haemorrhage in animals is an acoustic pressure of 1 MPa at 2–10 MHz frequency levels, which is well within the range of outputs of the ultrasound equipment in current use.[3,28] However, the fact that the fetus is engulfed in fluid should, theoretically, spare it from cavitation injury.

Acoustic streaming and torque

Radiation forces produced by the disseminating ultrasound wave tend to push target tissue away from the transducer, leading to acoustic streaming in fluids, cell distortion and lysis.[2–4] Acoustic streaming and acoustic torque (twisting or spinning forces) are other non thermal mechanisms of injury.[14] These have been demonstrated in experimental models but are unlikely to be significant with diagnostic ultrasound in soft tissues *in vivo*, where the *in situ* adhesiveness is high.[3,4]

Safety indices

Concern over the biological effects of diagnostic ultrasound has led to the evolution of safety indices. An on-screen display of indices to guide the user to the extent of temperature rise and mechanical injury possible with a particular machine setting was formulated by the American Institute of Ultrasound in Medicine (AIUM) and the National Electrical Manufacturers Association (NEMA). It is commonly called the Output Display Standard (ODU) and was first reported in 1992.[29,30] The two indices most commonly used are the thermal index (TI) and the mechanical index (MI). The aim of the ultrasonographer should always be to keep these indices as low as possible while obtaining the best possible diagnostic images in a particular clinical scenario.

Thermal index

The thermal index is an indicator of the temperature elevation possible at a particular equipment setting. It is defined as 'the ratio of the acoustic power emitted by the transducer to the acoustic power required to produce a 1°C rise in temperature at a particular equipment setting.'[4] As the temperature rise is tissue dependent the thermal index has three subdivisions **(Figure 1)**: soft tissues (TIS); bone (TIB); and adult cranial exposure or bone at a surface (TIC). In obstetric scanning the TIS should be used for the first eight weeks after conception and the TIB should be monitored thereafter.[17]

The acoustic power of an ultrasound scanner depends on various operator-controlled parameters including focus, pressure, intensity, scan depth, mode and transducer characteristics. Various permutations and combinations of these parameters can result in varying levels of acoustic power output, with significant variations in the temperature levels **(Figures 2a, 2b, 3a, 3b)**.

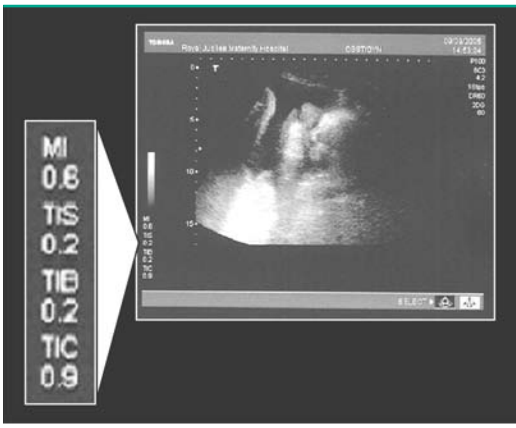

Figure 1
Safety indices (blocked arrow): mechanical index (MI); thermal index soft tissues (TIS); bone (TIB); adult cranial exposure or bone (TIC)

Figure 2a
B-mode ultrasound (TIB and MI are displayed in the top right hand corner)
TIB = 0.2, MI = 1.1

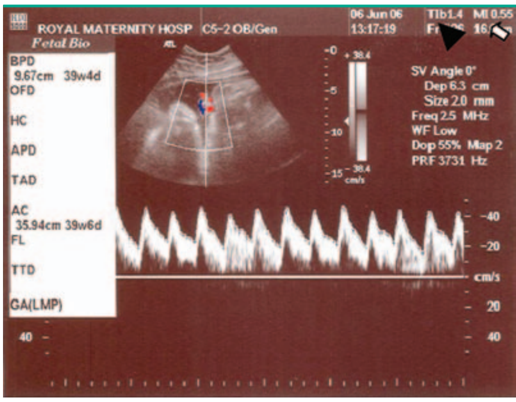

Figure 2b
Doppler mode. Note the change in TIB and MI when the settings are changed from B-mode to Doppler mode
TIB = 1.4, MI = 0.55

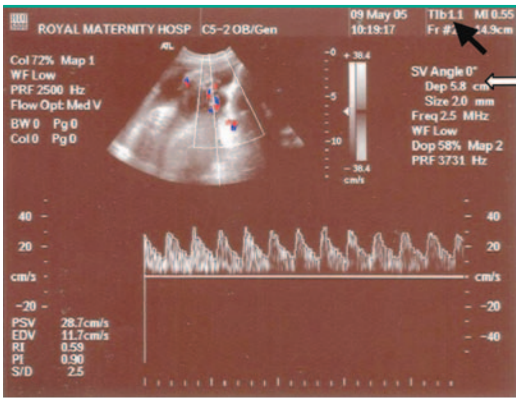

Figure 3a
Umbilical artery Doppler. TIB (solid arrow) is displayed in the top right hand corner
TIB = 1.1, MI = 0.55

Mechanical index

The mechanical index is an indicator of the likelihood of cavitation events. It is defined as the 'maximum estimated *in situ* rarefaction pressure or maximum negative pressure (in MPa) divided by the square root of the frequency (in MHz)'.[4] Thus, the mechanical index is inversely proportional to the frequency.

A mechanical index of 0.3 is considered the threshold value for haemorrhages to occur in the mouse lung.[31] Mechanical bioeffects have not been reported in humans from exposure to the acoustic power outputs currently used in diagnostic ultrasound. However, *in vitro* studies in lower organisms and animals have demonstrated the possibility of mechanical bioeffects, raising the concern that there is potential for similar injury in humans. In general use, the mechanical index should be less than 1.9.[31]

The thermal and mechanical indices do not consider factors such as duration of examination, patient temperature or presence of contrast agents.[31] Furthermore, there is probably an underestimation of temperature rise by the thermal index.[3] Jago *et al.*,[30] in a comparison of the AIUM/NEMA thermal indices with calculated temperature rises for a simple third trimester pregnancy tissue model, concluded that the thermal index may underestimate the maximum temperature rise that could occur when bone is insonated through an overlying liquid layer. It is acknowledged that, while the thermal and mechanical indices are not perfect, at present they are the most practical measurements available.[31,32]

Henderson *et al.*,[33] in a survey of the acoustic outputs of diagnostic ultrasound machines used by clinicians in the UK, found that there was a substantial increase in acoustic outputs compared with earlier surveys. They attributed this to the high output of modern, complex scanning systems and users varying control settings to their individual preferences.

The current FDA (Food and Drug Administration, Center for Devices and Radiological Health, USA) regulations allow manufacturers to increase power outputs by up to 8–10 times that used in the past, provided there is a display of safety indices on the screen.

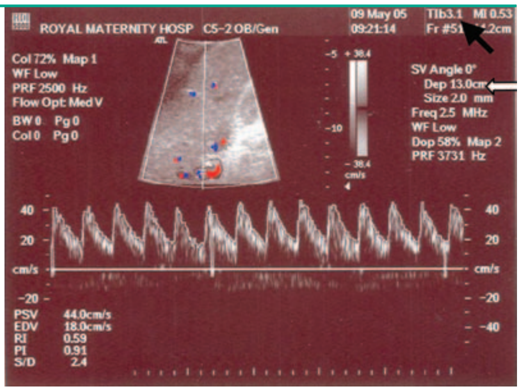

Figure 3b
Umbilical artery Doppler. TIB (solid arrow) is displayed in the top right hand corner. Note how an increase in depth from 5.8 cm (**Figure 3a**) to 13 cm (**Figure 3b**) almost triples the TIB (1.1 to 3.1)

Table 1
Maximum recommended exposure times for an embryo or fetus[17] (Reproduced with permission from the British Medical Ultrasound Society.)

Thermal index (TI)	Maximum exposure time (minutes)
0.7	60
1.0	30
1.5	15
2.0	4

Box 2
Summary of safety statements[3,17,32,46,47]

- Acoustic outputs produced by B-mode and M-mode are not high enough to produce deleterious effects and their use, therefore, appears to be safe for all stages of pregnancy. The risk of bioeffects from three-dimensional ultrasound is similar to that from regular B-mode.
- Caution is recommended in the use of spectral and colour Doppler mode as they have a high potential for bioeffects. A significant rise in temperature can occur at or near bone/soft tissue interfaces. Routine examination with Doppler ultrasound of the first trimester embryo is not advisable. This does not mean that their use should be withheld when indicated, provided the user is aware of the instrument's acoustic output or has access to the safety indices.
- A diagnostic exposure that produces a maximum temperature rise of 1.5°C above normal physiological levels (37°C) may be used without reservation in clinical examinations.
- A diagnostic exposure that elevates embryonic and fetal *in situ* temperature above 41°C (4°C above normal physiological levels) for five minutes or more should be considered potentially hazardous.
- While TIS is appropriate for diagnostic ultrasound exposure of the fetus in the first trimester, the TIB is appropriate in the second and third trimester.
- Care should be taken to avoid risk to the embryo or fetus from ultrasound examination of febrile women.
- Thresholds for non thermal bioeffects are lowest in tissues that naturally contain gas bodies (e.g. neonatal lung and intestine) and all tissues with introduced gas bodies, such as ultrasound contrast agents.
- A lower threshold of TI = 0.5 and MI = 0.3 has been recommended for non-diagnostic uses of ultrasound, including scans for operator training, equipment demonstration, production of souvenir pictures and videos of the fetus, research and 'bonding' scans.
- The safety indices should be displayed and updated regularly.
- Education on the safe use of ultrasound is paramount and responsibility should be shared between manufacturer and operator. Trainees should have a practical understanding of the machine settings and the effects changes in them can produce.
- Based on evidence to date, there is insufficient justification to conclude that there is a causal relationship between diagnostic ultrasound and long-term adverse fetal effects.

The BMUS statement[17] on the safety of ultrasound states that, with a mechanical index of more than 0.3, minor damage to neonatal lung or intestine is possible and values over a threshold of 0.7 have a propensity for cavitation injury, especially with use of contrast agents. With a thermal index of more than 0.7 the overall exposure to embryo or fetus should be restricted to less than 60 minutes; at a thermal index of 3, scanning of an embryo or fetus is not recommended. **Table 1** shows the maximum recommended exposure times for an embryo or fetus.[17]

Long-term effects

The ultrasound boom has resulted in there being few women who are not exposed to ultrasound in the antenatal period and, hence, there is a paucity of controlled studies on adverse ultrasound effects. There have been reports of intrauterine growth restriction and low birthweight[34–36] being associated with repeated prenatal ultrasound but the possibility that the cause could be the indication for the repeated ultrasound examinations cannot be ignored. Newnham *et al.*,[35] in a randomised controlled trial to assess the effect of multiple (five) ultrasound exposures in singleton pregnancies, concluded that there was an unexplained, significantly increased incidence of growth restricted newborns. However, follow-up to eight years of age showed no differences in childhood growth and development of speech, language, behaviour and neurological development compared with children who had only a single prenatal ultrasound scan.[37] These findings corroborate with the follow-up study by Keiler *et al.*,[38] who found no differences in growth, impaired vision or hearing during childhood. In contrast, others report an increased incidence of dyslexia[39] and speech delay.[40]

On follow-up, some studies have reported a significant increase of non right-handedness in boys exposed to ultrasound *in utero*.[41–44] There is an ongoing scientific debate as to whether this is due to an increased susceptibility of male fetal brains to ultrasound induced disturbances in neuronal migration and development of synapses.[45]

There is no evidence to date that ultrasound exposure increases the congenital malformation rate or that any specific anomaly can be attributed to ultrasound exposure.[2,39]

In a meta-analysis of epidemiological studies on ultrasound exposure, Salvesan and Eik-Nes[45] concluded that there was no association between diagnostic ultrasound exposure during pregnancy and reduced birthweight, childhood malignancies or neurological development. This was later endorsed in a safety tutorial issued by the EFSUMB.[44]

While these findings are reassuring and, at present, the general consensus is that diagnostic ultrasound is safe in pregnancy, with no substantiated long-term effects, caution should, nonetheless, be exercised as machines become ever more powerful.

Safety statements

Several statements pertaining to the safe use of ultrasound have been issued by recognised bodies. Some of the statements relevant to obstetric scanning issued by the BMUS,[17] EFSUMB,[46] WFUMB[3] and the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG)[32,47] are summarised in **Box 2**.

Conclusion

The general consensus is that diagnostic ultrasound is safe in pregnancy, both for the mother and fetus: no substantiated long-term effects have been demonstrated. The minimum possible acoustic power output, duration and exposure to sensitive target tissues which give the optimum diagnostic information should always be used to reduce biohazards. The application of safety indices and on-screen display is important. With many obstetricians now scanning their own patients, awareness of safety and prudent use of diagnostic ultrasound is imperative. However, it should be borne in mind that the greatest danger to the fetus in prenatal diagnostic ultrasound is misdiagnosis.

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