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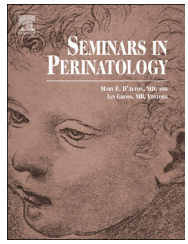

Benefits and risks of ultrasound in pregnancy

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ABSTRACT

Ultrasound is, arguably, the most commonly used diagnostic procedure in obstetrics. It is convenient, painless, yields immediate, extensive results, and is widely considered to be safe. Some (but not all) benefits described in the literature have been validated by evidence-based analysis, such as pregnancy dating. Others are considered clinically useful, although objective evidence may be less strong. As is the case with almost any medical procedure, however, its performance carries some risks: misdiagnosis on the one hand and possible undesired effects on the other. The general belief exists that diagnostic ultrasound (DUS) does not pose any risk to the pregnant patient nor to her fetus. Nonetheless, ultrasound is a form of energy and, as such, demonstrates effects in biological tissues it traverses (bioeffects). The physical mechanisms responsible for these effects are thermal or non-thermal (mechanical). It is the role of science to show whether any of these bioeffects may be harmful. A risk–benefit analysis may also be important, as well as education of the end users to assure patients' safety.

1. Introduction

Ultrasound practitioners are often asked the question of whether the technology is safe for the fetus. The answer generally given is "Of course. Ultrasound is not x-rays; it is not invasive, has been used for close to 50 years and is perfectly safe." While this answer contains some correct facts (ultrasound is not x-rays and it has been used for a long time), the concept of absolute safety is not scientifically valid, and furthermore, the level of knowledge regarding potential bio-effects of ultrasound in tissues is, by and large, very low among clinicians.

2. Definitions

When analyzing benefits and risks of DUS, particularly in obstetrics, it is important to have clear definitions. Benefit is a concept that is more easily definable than risk.

Benefit: From Old French bienfait, *good deed*, from Latin benefactum, from benefacere, *to do a service*, something that promotes or enhances well-being, an advantage.[1] For instance, performing an indicated ultrasound will offer many benefits as described below.

Risks: The ISO 31000 (2009) /ISO Guide 73:2002 definition of risk is the "effect of uncertainty on objectives."[2] This is less than a clear definition as far as clinical situations and ultrasound, in particular, are concerned. A clearer definition is the probable frequency and probable magnitude of future loss.[3] How *frequently* a loss or something bad (damage to health, environment, and objects) is likely to happen, with a certain degree of probability, as a result of an action or procedure, and *how much loss* is likely to result. These are the 3 important characteristics of risk: *probability* of occurring, *nature*, and *magnitude* of harm. It has been, specifically, applied to the use of medical instruments.[4]

3. Risk assessment

This is an issue that always needs to be addressed when discussing risks. Two approaches are possible in risk

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evaluation: how much harm is acceptable to obtain the desired results (risk–benefit ratio analysis) or how much harm can be avoided by withholding the action one is considering or modifying it (the precautionary principle). The *risk–benefit principle* is what is almost universally used in medicine to justify a medical diagnostic procedure (such as ultrasound) or a therapeutic intervention. If the benefit to be obtained from the procedure in terms of diagnosis (ultrasound) or intervention (newly discovered and not yet commercialized cancer or AIDS drug for instance) is deemed to be sufficient, then, even if this diagnostic or interventional procedure carries some risks (recognized or presumed), the benefit overrides these risks, assuming the subject understands those risks and is willing to take them. The *precautionary principle (PP)* is a diametrically opposed ethical, political, economic approach stating that if a certain action *may* cause severe damage to the public or, in the case of ultrasound, the fetal patient, in the absence of a scientific consensus that harm would not ensue, the burden of proof falls on those who would advocate taking the action.[5] As a stated principle, it is much less familiar to the medical field although it is practiced in everyday clinical situations and is very relevant when considering safety and risks of a procedure, such as prenatal ultrasound. Primum non nocere (first do no harm) and the As Low as Reasonably Achievable (ALARA) guidelines are direct applications of this principle. The simple enunciation of the principle, particularly in reference to diagnostic ultrasound, in general, and entertainment ultrasound in particular is that, even if a particular action or procedure has not been proved to be harmful, it is better to avoid it so as not to take the risk until safety is established through clear, scientific evidence, popularly expressed as "Better safe than sorry."[6] A major difference with the risk–benefit principle is that proponents of the PP believe that public action is necessary if there is any evidence of likely or substantial harm, however limited but plausible, and the burden of proof is shifted from showing the presence of risk to demonstrating its absence.[7] As such, epidemiologic research on chronic diseases and the use of surrogate for human studies (e.g., animal research or tissue cultures) have been shown to be uncertain.[8] A major goal of the PP is to help delineate (preferably quantitatively) the possibility that some exposure is hazardous, even in cases where this is not established beyond reasonable doubt.[9] The classical statistical approach to hypothesis testing is unhelpful, because lack of significance can be due either to uninformative data or to genuine lack of effect (type II error).[10] Furthermore, no moral opinion is formed of a person when treating them, but if the main focus is upon precaution, it can be deemed morally wrong not to take preventative measures. The whole precaution approach is imbued with what may appear to many as an excessively moralistic tone.[11] Furthermore, the probability of occurrence of a problem that one is trying to avoid has to be high (which does not apply, as far as we know to ultrasound) and preventative measures have to be effective. Hence, this approach may be adopted with some restrictions and this is, in fact, exactly what ALARA recommends.[12] Most scientists and professional organizations have recommended such a practice in clinical obstetrical ultrasound[13,14] most likely without the realization that the PP was the actual impetus.

4. Benefits of ultrasound in pregnancy

An extensive analysis of the benefits of ultrasound in obstetrics is beyond the scope of this article. Furthermore, clinicians are, generally, much more familiar with this aspect of DUS than with potential risks of the procedure.

Benefits that have clearly been demonstrated (evidence-based analysis) include[15,16] accurate dating (reduction in post-term by 40%), definition of exact location (when the question of an ectopic pregnancy arises), proof of viability, early diagnosis of multiple gestations, accurate follow-up of fetal growth,[17] detection of fetal anomalies[18] (although some will question whether this is a real health benefit as it will increase stress and anxiety level and may lead to termination of the pregnancy), and placental location and implantation (particularly important in cases of prior cesarean section). The American College of Obstetricians and Gynecologists (ACOG) has published guidelines for obstetrical ultrasound,[19] which include the following benefits: accurate determination of gestational age (best done in the first half of pregnancy), fetal number, viability, and placental location, diagnosis of many major fetal anomalies. In addition, ultrasonography is safe for the fetus when used appropriately (level A: good and consistent evidence); detection of fetal growth disturbances and abnormalities in amniotic fluid volume (level B: limited or inconsistent evidence); in the absence of specific indications for a first trimester examination, the optimal timing for a single ultrasound examination is at 18–20 weeks of gestation and benefits and limitations of ultrasonography should be discussed with all patients (level C: consensus and expert opinion).[19]

An additional benefit that has been reported in the literature and that relates more to the mother (or parents) than the fetus is improved bonding. This has been reported particularly since the advent of clinical 3- and 4-dimensional ultrasound[20] (although some refute that 3-dimensional ultrasound is superior[21,22]) and improved bonding was already described when 2-dimensional ultrasound became widely utilized.[23,24]

5. Risks of ultrasound in pregnancy

There are 2 categories of risks possibly associated with the use of DUS in obstetrics: diagnostic errors and possible biological effects.

Diagnostic errors can be divided into overdiagnosis, underdiagnosis, and problems with reporting of the results of the examination. Several of these misdiagnoses may be secondary to artifacts that may occur during the performance of an ultrasound exam, at acquisition, processing, or display, in both 2- and 3-dimensional ultrasound.[25] Examples of the more common artifacts include shadowing (causing "absence" of a structure), reverberation (adding a structure that is not there) but also some due to manipulation of a reconstructed volume with possible deletion of a structure by electronic scalpel.[25]

Overdiagnosis: This consists of "invented" lesions, such as presence of a mass that is not there or absence of an organ or

part of it (when the structure is perfectly normal). These false-positive findings may lead to unnecessary follow-up examinations and even therapeutic procedures, including termination of pregnancy.

Underdiagnosis: In this category, an anomaly is not visualized or only partially identified. This can take the form of missed findings (false negative): missed fetal structural anomaly (including missing part), missed fetus (in multifetal pregnancies), missed pathology of the placenta (placenta previa, accreta, etc.), missed ectopic (by confusing the pseudosac for an intrauterine gestation), or missed mass. A partial diagnosis is also part of the underdiagnosis category.

Reporting issues: Misreport, e.g., inaccurate dating, erroneous estimated fetal weight misdiagnosis (such as gender or presentation), failure to refer or to perform a scan, miscommunication ("Everything is OK" despite the fact a pathology is present or "We'll talk to your doctor"), no formal report or error in report ("there was ventriculomegaly" when it should read "there was no ventriculomegaly"), and absence of documentation.

Underdiagnosis and reporting issues may lead to worsening of the disorder or to the birth (possibly undesired, if the anomaly was prenatally known) of a fetus with anomalies and potential subsequent lawsuits.

The reason why one needs to consider *biological effects* when studying ultrasound is that ultrasound is a sound wave, a form of energy, with alternating positive and negative pressure. As such, it can have several effects in tissues it traverses (hence the term bioeffects). Two major mechanisms are known to be involved in potential deleterious effects in tissues: thermal and non-thermal (or mechanical).[26,27]

Thermal effects are an indirect result of the passage of the waveform, with acoustic energy being transformed into heat. This constitutes the major potential adverse effect in embryos and fetuses.[28] There have been many reports of harmful effects of heat in pregnancy on the embryo/fetus in animal studies from both non-ultrasound and ultrasound technology.[29–32] This seems to be the case if the temperature rise is 1.5 °C above the physiological level. At higher levels, the potential for damage increases with duration of exposure and degree of elevation. The embryo/fetus is particularly susceptible to external insult in the early pregnancy (up to 10–12 weeks) although several organs continue to develop later in pregnancy and minor effects or mild behavioral alterations, if they exist, are extremely difficult to diagnose or demonstrate.

Non-thermal mechanisms, a direct effect of the alternating pressure, can further be separated into acoustic cavitation (inertial and non-inertial) and non-cavitational mechanisms, i.e., acoustic radiation force (time-averaged force exerted by the ultrasound beam), acoustic radiation torque (producing in the insonated tissue a tendency to rotate or spin), and acoustic streaming (circulatory flow). Non-thermal mechanisms seem to not be a major concern in obstetrical ultrasound.[33] The major reason is that the presence of cavitational foci (bubbles) is necessary for cavitation to occur and the fetal lungs and bowels (areas where such effects with resulting hemorrhages have been described in neonates[34]) do not contain any air or gas.

Bioeffects have been described in animal models[35] but not in humans, particularly when epidemiological analysis is attempted.[30] The only effect that appears to be genuine is non-right handedness,[36] although it seems to be prevalent mostly in male fetuses[37] and with minimal statistical significance. Other subtle (in term of diagnosis difficulty, not in term of the severity or the impact of the condition) effects such as autism have been evoked but not unquestionably demonstrated.[38]

Early gestation is a special situation because it is well known that the fetus is most sensitive to external insults during organogenesis, mostly until 10–12 weeks,[39] although several organs continue to develop later. This is particularly important with the ever-increasing use of endovaginal ultrasound in early gestation, in reproductive endocrinology, and in early anatomy survey.

Particular caution is recommended for Doppler ultrasound, specifically pulsed (also known as spectral). Mean I_{SPTA} for B-mode is 34 mW/cm^2 and 1180 mW/cm^2 for pulsed Doppler, a major difference. A very concerning study was reported from Australia regarding possible bioeffects of Doppler.[40] Brains of chicks were exposed *in ovo* on day 19 of a 21-day incubation period to 5 or 10 min of B-mode or to 1, 2, 3, 4, or 5 min of pulsed Doppler ultrasound. Learning and memory function were assessed post-hatch. B-mode exposure did not affect memory function. Significant short-, intermediate-, and long-term memory impairment, however, occurred following 4 and 5 min of pulsed Doppler exposure. In addition, the chicks were still unable to learn with a second training session. While direct extrapolation is not necessarily valid, this study, nevertheless, raises some degree of concern regarding possible subtle effects of Doppler ultrasound. Limiting exposure of the early fetus to pulsed Doppler is strongly recommended.[41]

6. The output display standard (ODS)

From around 1985 until 1992, acoustic output of diagnostic ultrasound machines for fetal use was below a spatial-peak temporal-average value (I_{SPTA}) of 94 mW/cm^2, having first started around 46 mW/cm^2. This value was not the result of extensive safety research but of a 1976 survey of acoustic outputs of DUS equipment. No observable harmful effects were described by end users. It was concluded that the maximal derated[1] output SPTA intensity did not exceed 94 mW/cm^2 for equipment produced before 1976 for obstetric applications. Hence, 94 mW/cm^2 was chosen as the limiting (inappropriately called "safe") value of the derated SPTA intensity for future equipment.[42,43] In 1992, the FDA yielded to pressure from ultrasound clinical users as well as manufacturers, to increase instruments power output.[44] The rational for this request was that higher outputs would generate better images and, thus, improve diagnostic accuracy. To allow clinical users of ultrasound to use their

[1] Derating is a process through which allowance is made for attenuation of the ultrasound beam as it passes through tissue by introducing a reduction factor (0.3 dB/MHz) to the value that would be measured in a water bath. This is performed because it is necessary to extrapolate from ultrasound measurements performed in water, the values of acoustic field parameters *in situ*, i.e., in the tissues exposed to the beam.

instruments at higher powers than originally intended and to reflect the 2 major potential biological consequences of ultrasound (mechanical and thermal, see above), the American Institute of Ultrasound in Medicine (AIUM), the National Electrical Manufacturers' Association (NEMA), and the FDA (with representatives from the Canadian Health Protection Branch, the National Council on Radiation Protection and Measurements, and 14 other medical organizations[26]) developed a standard related to the potential for ultrasound bioeffects, the Standard for Real-Time Display of Thermal and Mechanical Indices on Diagnostic Ultrasound Equipment, generally known as the Output Display Standard or ODS.[45] This document represents the first attempt at providing to the end user quantitative safety-related information. One important result is that the end users are able to see how manipulation of the instrument controls during an examination causes alterations in the output and thus on the exposure. As a consequence, for fetal imaging, the output, as expressed by the I_{SPTA}, went from a previous value of 94–720 mW/cm^2, an almost 8-fold increase. It should be noted that the value allowed for ophthalmic ultrasound was and continues to be 17 mW/cm^2. For the output to be allowed to reach such levels, the manufacturers were requested and agreed to display, on screen, in real time, 2 types of indices with the intent of making the user aware of the potential for bioeffects, as described above. These indices are the thermal index (TI) to provide some indication of potential temperature increase and the mechanical index (MI) to provide indication of potential for non-thermal (i.e., mechanical) effects.[26,45,46] The TI is the ratio of total acoustic power in real time to the acoustic power estimated to be required to increase tissue temperature by a maximum of 1 °C. It is an estimate of the maximal temperature rise at a given exposure. There are 3 variants: for soft tissue (TIS), to be used mostly in early pregnancy when ossification is low, for bones (TIB), to be used when the ultrasound beam impinges on bone, at or near the beam focus, such as late second and third trimesters of pregnancy, and for transcranial studies (TIC) when the transducer is essentially against bone, mostly for post-natal examinations. It needs to be made clear that *TI does not represent an actual or an assumed temperature increase*. It bears some correlation with temperature rise in degrees Celsius but in no way allowing an estimate or a guess as to what that temperature change *actually* is in the tissue.[46] The MI represents the potential for non-thermal damage in tissues but is not based on actual *in situ* measurements. It is a theoretical formulation of the ratio of the pressure to the square root of the ultrasound frequency (hence, the higher the frequency, the lesser risk of mechanical effect). Both the TI and MI can and should be followed as an indication of change in output during the clinical examination. A clear extension of the above-mentioned statements is that education of the end user is a major part in the implementation of the indices. Attempts have been made to educate the end users but, unfortunately, this aspect of the ODS does not seem to have succeeded, as end users' knowledge of bioeffects, safety, and output indices is lacking.[47–51] Furthermore, several assumptions were made, which lead to some questions on the clinical value of these indices. In NCRP report number 140,[26] there is an entire chapter (Chapter 9), indicating conditions where both indices may be inaccurate, e.g., long fluid path (full bladder, amniotic fluid, ascites, or hydrocephalus) or path through increased amounts of soft tissue such as obese patients. Because of these uncertainties, the accuracy of the TI and MI may be within a factor of 2 or even 6.[44] A further disturbing and confusing element is that outputs reported by manufacturers are not necessarily equivalent to those calculated in the laboratory.[52]

7. Recommendations and conclusions

The end user of clinical ultrasound is interested in knowing how to keep the examination safe. One needs to provide recommendations based on scientific evidence. As should be apparent from the above, this is a difficult task. In terms of clinical exposure, what should be recommended? A general recommendation is that DUS should be used only when indicated and exposure should be kept as low as possible to obtain diagnostic images. Furthermore, exposure time should be kept as short as possible.[53,54] These are, of course, the components of the As Low As Reasonably Achievable (ALARA) principle. The most rigorous recommendations are from the British Medical Ultrasound Society (BMUS).[55] Their 1999 Statement reaffirmed in 2009 declares, "For equipment for which the safety indices are displayed over their full range of values, the *TI should always be less than 0.5 and the MI should always be less than 0.3*[2]. When the safety indices are not displayed, T_{max} should be less than 1 °C and MI_{max} should be less than 0.3. Frequent exposure of the same subject is to be avoided."[29,55] They have very strict recommendations for maximum allowed exposure time, depending on the TI.[55] In addition, in febrile patients, extra precaution may be needed to avoid unnecessary additional embryonic and fetal risk from ultrasound examinations. Precautions are much softer regarding mechanical phenomena, which, in the absence of gas nuclei (as is the case in fetal lungs and bowels and assuming no use of contrast agents) are probably negligible. Pulsed Doppler is an area where particular precaution is warranted, specifically in early gestation.[56–58]

Diagnostic ultrasound has been used clinically for over half-a-century without reports of harmful effects in humans, despite demonstration of such effects in cell cultures and various laboratory animals. Ideally, epidemiological studies should be performed on large populations, blindly randomizing 50% to ultrasound testing and 50% to no testing. Given the extensive indications for DUS in pregnancy and the fact that most (and in certain countries, all) pregnant patients are referred for an ultrasound examination, this would be extremely difficult to realize in a human population. New or improved indices may be necessary, particularly since TI and MI do not take time into account.[59] In the meantime, areas of uncertainty persist and while B-mode, if used when medically indicated, is, most likely, safe, caution is justified, particularly in early gestation and with Doppler mode. M-mode and 3D/4D ultrasound appear safe, if examination time is limited to what is necessary to obtain appropriate information. Education of the end users is imperative to

[2] Italics, ours.

maintain the good safety record of ultrasound and prevent possible harmful bioeffects.

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