Bioeffects and Safety of Ultrasound

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Disclosures

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Relevant Financial Relationships:
Luminary- Philips Healthcare
Writer- UpToDate

Learning Objectives

After completing this presentation, the learner will be able to:

1. Describe bioeffects of ultrasound

2. Define parameters allowing risk assessment

3. Implement ways to minimize fetal exposure

Lecture Outline

1. Mechanisms of ultrasound/tissue interaction
• Thermal: heating
• Non-thermal (mechanical): cavitation and other mechanical effects (radiation force, acoustic streaming)
2. Measures of energy exposure
• Acoustic power/spatial average intensity
• Thermal index (TI)
• Mechanical index (MI)
3. Bioeffects of ultrasound (literature review)
• Animal data
• Epidemiologic data
4. How to keep it safe

Introduction

- Ultrasound in use in obstetrics and gynecology since 1958 (Ian Donald)
- Ever expanding technologies and applications
- AIUM: Ultrasound First
- Some effects of ultrasound observed in the lab and various animal species
- No epidemiological evidence of harmful effects in humans
- So why an AIUM lecture?

What is the rate of exposure to ultrasound?

Estimates:
. "1 out of every 2 children born in the USA has been exposed" (1984)
. 80-90% of 4 million infants born in the USA (estimate, 2016)
. Close to 100% in some European, Asian, South American countries
. ART: every patient, multiple times, around fertilization and early pregnancy

Risk

Bioeffects of ultrasound

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Risk means the chance or the possibility of loss or bad consequence

These are the 3 important characteristics of risk: probability of occurring, nature and magnitude of harm

Complicating factor: personal views

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Risk analysis principles

- Risk/Benefit ratio:

How much risk is acceptable to obtain a certain benefit

- Precautionary principle:

How much harm can you avoid by not performing a certain action/procedure/test
If a certain action may cause severe damage to the public, 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

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"Better safe than sorry"

"Primum, non nocere"
("First do no harm")

ALARA
As Low As Reasonably Achievable

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"…with the frequency adjusted for resonance, the narrow beam of supersonic waves shot across the tank causing the formation of millions of minute air bubbles and killing small fish which occasionally swam into the beam. If the hand was held in the water near the plate an almost insupportable pain was felt, which gave one the impression that the bones were being heated."

Professor R. W. Wood, an American physicist from Johns Hopkins University, visiting Langevin's lab in Toulon, around 1924.

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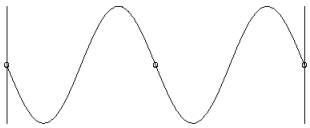
Ultrasound=energy

Ultrasound=waveform with positive and negative pressures



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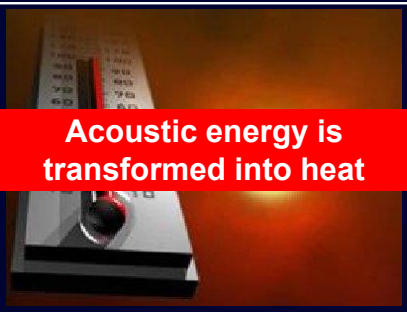
Thermal effects (indirect)



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Non-thermal effects (direct)

Positive pressure can cause:

- Radiation stress
- Acoustic streaming
- Nerve ending stimulation
- ?Release of free radicals

Negative pressure (mostly) can cause cavitation

- Inertial (a.k.a. transient): growth and violent collapse of the bubble
- Non-inertial: back and forth motion of bubbles

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So, ultrasound going through living tissues causes effects (bioeffects)…

…but there are no epidemiological studies demonstrating **harmful** bioeffects in humans

All epidemiological studies are about exposure **before 1992**

In 1992, maximal acoustic outputs for fetal applications were allowed to be **increased by a factor of 8** (from 94mW/cm^2 to 720mW/cm^2, I_{SPTA})

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FDA mandated (together with AIUM, NEMA, public representatives): **the onscreen Output Display Standard (ODS)**

Manufacturers may increase maximal output (up to 720mw/cm^2 for fetal use) on the condition that two indices appear on-screen:

- Thermal index (TI) for thermal effects
- Mechanical index (MI) for non-thermal (a.k.a. mechanical) effects
- AND: a particular effort is to be made to educate the end-users about bioeffects, safety and TI and MI

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Thermal index (TI)

Unitless estimate of possible tissue temperature rise in ^{0}C under "reasonable worst-case conditions"

$$TI = \frac{\text{total actual acoustic power } (W_p)}{\text{acoustic power needed to raise temperature by 1 } ^0\text{C } (W_{deg})}$$

Predicts po… …emperature

Not a real te… …easurement

No time (duration of exposure) information

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Thermal index

Close to 70% of the total temperature increase occurs within the first minute of exposure, but the temperature continues to slowly rise as exposure time is prolonged.

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Thermal index

TI_S: soft tissues
TI_B: bones
TI_C: cranium
} Obstetrics

Errors in calculating TI values, and the limitations of the simple models on which they are based, means that TI values can underestimate the temperature elevation by a factor of up to two (or even 6 in some cases).
Far from perfect but it's the best we have

Bigelow TA, Church CC, Sandstrom K et-al. The thermal index: its strengths, weaknesses, and proposed improvements. J Ultrasound Med. 2011;30 (5): 714-34.

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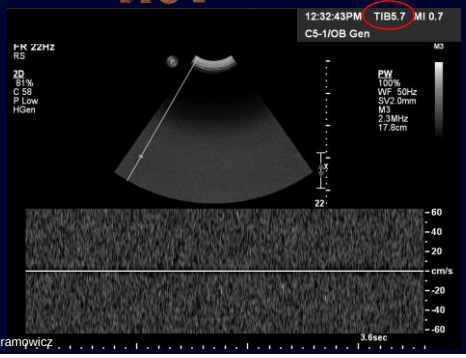
But how HOT can it get?



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Mechanical Index (MI)

MI is intended to offer a rough guide to the likelihood of the occurrence of cavitation. It is proportional to an ultrasound beam's peak negative (or peak rarefactional) pressure and inversely proportional to the center frequency of the beam. Therefore, higher frequencies have a lower MI. MI is constantly updated by the machine, according to the control settings, using the formula

$$MI = p / \sqrt{f}$$

MI expresses potential to induce inertial cavitation: bubbles must be present

No bubbles in fetal lungs or bowels

Hence, in the fetus, mechanical risk appears to be low

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Mechanical index

Per definition, MI is really strictly an index of cavitation risk, but it is more widely considered to be an indicator of tissue mechanical stress/damage

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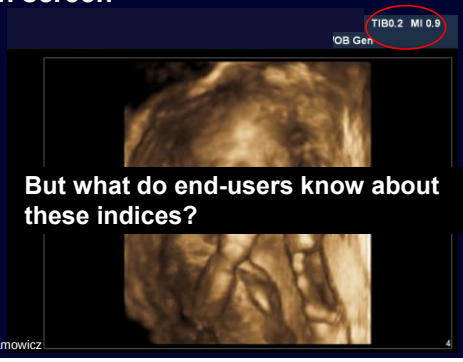
Manufacturers must display TI and MI on screen



But what do end-users know about these indices?

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Measures of acoustic intensity

Spatial Average Intensity: average intensity over the area of the transducer

Spatial Peak Intensity: peak intensity over the area of the transducer

Temporal Peak Intensity: peak intensity during on time of pulse

Temporal Average: average intensity average over the entire treatment time

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- ✓ **Spatial-peak temporal-peak (I_{SPTP}) The highest intensity measured at any point in the ultrasound beam and at any time; it is the highest value of the measured intensities (more closely related to potential mechanical bioeffects and cavitation)**
- ✓ **Spatial-peak pulse-average (I_{SPPA}) The highest intensity measured at any point in the ultrasound beam averaged over the temporal (time) duration of the pulse**
- ✓ **Spatial-peak temporal-average (I_{SPTA}) The highest intensity measured at any point in the ultrasound beam averaged over the pulse repetition period (more closely related to the magnitude of thermal bioeffects)**

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- ✓ **Spatial-average temporal-peak (I_{SATP}) The average intensity over a selected area, such as the transducer face, but at the peak in time**
- ✓ **Spatial-average pulse-average (I_{SAPA}) The average intensity over a selected area, such as the transducer face, averaged over the temporal duration of pulse**
- ✓ **Spatial-average temporal-average (I_{SATA}) The average intensity over a selected area, such as the transducer face, averaged over the pulse repetition period; this measurement of intensity is frequently quoted and is the lowest value of the measures of intensity**

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Mode	I_{SPTA} (median in mW/cm^2)
B-mode	34
M-mode	106
TV probe	
B-mode	18.8
M-mode	55.7
Color Doppler	290
Spectral Doppler	1180

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So what?
I use an FDA approved machine

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Output is mode dependent (Doppler>>B-mode)
Output is under examiner control
Output is altered by manipulating certain controls, apparently not related (focus, gate sample etc…)
Every machine behaves differently

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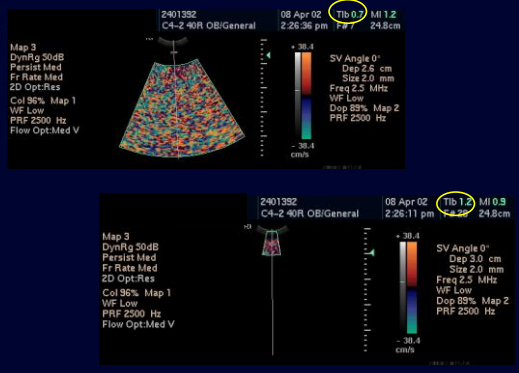

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ORIGINAL RESEARCH

J Ultrasound Med 2013; 32:1921–1932 |

Trends in Diagnostic Ultrasound Acoustic Output From Data Reported to the US Food and Drug Administration for Device Indications That Include Fetal Applications

Sarah L. Cibull, BS, Gerald R. Harris, PhD, Diane M. Nell, PhD

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***Objectives*—A survey was conducted of acoustic output data received by the US Food and Drug Administration for diagnostic ultrasound devices whose indications for use include fetal applications to assess trends in maximum available acoustic output over time.**

J Ultrasound Med 2013; 32:1921–1932

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Table 10. Ninetieth Percentile TIB During Different Periods

Period	90th Percentile TIB	Change, %
1984–1989	0.5	0
1992–1997	3.6	620
2005–2010	3.7	3

J Ultrasound Med 2013; 32:1921–1932

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***Conclusions*—The observed trends in increased acoustic output for both Doppler and non-Doppler modes underscore the widely recognized importance of adherence to the ALARA (as low as reasonably achievable) principle and prudent use in fetal ultrasound imaging.**

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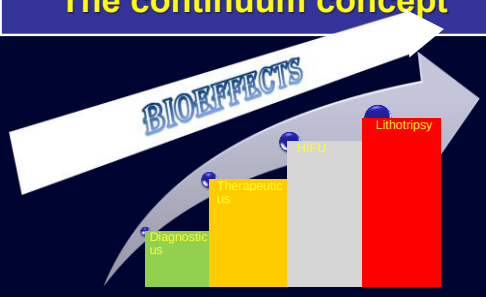
The continuum concept



Szabo, Nelson, Abramowicz: AIUM Annual Convention, Phoenix, 2012

Ultrasound bioeffects-what have we learned over the years?

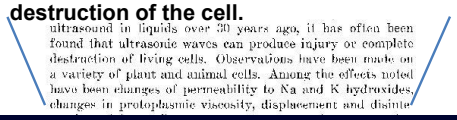
Cells/Tissue cultures
Animals
Humans

Ultrasound bioeffects Cells/Tissue cultures

- heightened fibroblast recruitment, earlier resolution of inflammation (Young & Dyson, 1990b)
- accelerated fibrinolysis (Francis, 1992, Harpaz, 2000)
- stimulation of fibroblast activity, increased protein synthesis, increased blood flow, tissue regeneration, bone healing, accelerated angiogenesis (Young, 1990)

Journal of Cellular and Comparative Physiology
Vol 40 pages 383–397, 1952

…changes in permeability to Na and K hydroxides, changes in protoplasmic viscosity, displacement and disintegration of intracellular structures, coagulation or swelling of protoplasm, dispersion of cell contents and complete destruction of the cell.


ultrasound in liquids over 30 years ago, it has often been found that ultrasonic waves can produce injury or complete destruction of living cells. Observations have been made on a variety of plant and animal cells. Among the effects noted have been changes of permeability to Na and K hydroxides, changes in protoplasmic viscosity, displacement and disinte

Ultrasound bioeffects Animals

"Older" studies:
Takeuchi et al., 1970, pregnant rats, Doppler, 150mW/cm2, no increased perinatal mortality
McClain et al., 1972, pregnant rats, Doppler, 10mW/cm² , up to 2 hrs: no effects on fetuses
Stolzenberg et al., 1980, pregnant mice, CW, 1W/cm², decreased pregnancy rate, fetal weight reduction if exposure >140s
Sikov et al., pregnant rats, 5-15min, , 15-20W/cm², Increased prenatal mortality

Ultrasound bioeffects Animals

- **335 pregnant mice, exposed to ultrasound for 30 - 420 min**
- **Small number of neurons failed to acquire their proper position and remained scattered within inappropriate cortical layers**
- **Authors mention possible consequences such as epilepsy, schizophrenia and autism**

Ang et al.: Prenatal exposure to ultrasound waves impacts neuronal migration in mice. PNAS, 2006; 103: 12903-12910.

Ultrasound bioeffects Animals

Brains of chicks 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 assessed at day 2 post-hatch.
- **B-mode exposure** did not affect memory function, nor did **1, 2, 3 min of pulsed Doppler**
- Following 4 and 5 min of **pulsed Doppler exposure** 2h after training, significant memory impairment occurred
- In separate groups of chicks, short-, intermediate- and long-term memory was equally impaired suggesting an inability to learn.
- Further, the chicks were still unable to learn with a second training session 5 min after completion of the initial testing

Schneider-Kolsky ME et al. :Ultrasound exposure of the foetal chick brain: effects on learning and memory. Int J Dev Neurosci. 2009 Nov;27(7):677-83.

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Ultrasound bioeffects Animals

- **Lung hemorrhage** in young mice and neonatal/adult pigs
- **Intestinal hemorrhage** in adult mice
- **Bleeding** near developing bone in young mice

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Effects in humans

Concerns have been raised in the past related to

- Autism
- Abnormal hearing, vision or language development
- Intrauterine growth restriction
- Childhood cancer
- Increase in non-right handedness

Abramowicz JS, UOG 29:363, 2007

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Effects in humans

Whitworth, 2010:

. Review of 11 trials totaling 37505 women with ultrasound for specific indication at less than 24 weeks gestation.

. Incidence of adverse outcome (children's physical or cognitive development) identical in both groups.

Whitworth M, Bricker L, Neilson JP, Dowswell T.: Ultrasound for fetal assessment in early pregnancy. Cochrane Database Syst Rev. 2010 Apr 14;(4):CD007058

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Effects in humans

Torloni et al, 2009: 41 different studies: 16 controlled trials, 13 cohort and 12 case-control studies

Outcomes : **perinatal outcomes** (low birth weight, SGA, preterm birth, low APGAR scores, need for neonatal resuscitation, seizures, congenital malformations, admission to NICU and fetal, neonatal or perinatal mortality), **childhood growth, neurological development and school performance** (height, weight, head circumference, dyslexia, speech development, behavioral scores, school performance [reading, spelling, arithmetic], hearing and visual impairment, cognitive function, attention deficit, motor skills), **non-right handedness, childhood malignancies and intellectual performance and mental diseases after childhood.**

Only positive correlation: weak association between ultrasound exposure and non-right handedness in boys

Torloni MR et al.: Safety of ultrasonography in pregnancy: WHO systematic review of the literature and meta-analysis. Ultrasound Obstet Gynecol. 2009 ;33(5):599-608.

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Effects in humans

Non-right handedness

Most recent analysis of randomized trials on ultrasound and handedness reaffirm "statistically significant-albeit weak-association" between *in utero* ultrasound exposure and slightly increased incidence of non-right handedness later in life

Salvesen KA. Ultrasound in pregnancy and non-right handedness: meta-analysis of randomized trials. Ultrasound Obstet Gynecol. 2011 Sep;38(3):267-71

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Ultrasound and Autism

Association, Link, or Coincidence?

Jacques S. Abramowicz, MD

There is no independently confirmed peer-reviewed published evidence that a cause-effect relationship exists between in utero exposure to clinical ultrasound and development of ASDs in childhood

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Effects in humans

We have not demonstrated harmful effects in humans ≠ there are no harmful effects.
It may simply be: we cannot detect these effects (if they exist) by our present (known) methods

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Is early pregnancy worse?

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Unclear/Unknown

Full bladder (rare in 2016)
Closer to insonated tissues (TV ultrasound)
Transducer face heating

Worst effect at bone-tissue interface
Very little bone in 1st trimester fetus (none in the embryo or the ovum)
Heat dissipating capacity??
Repeat exposure??
Cumulative effect??

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Fetus susceptibility

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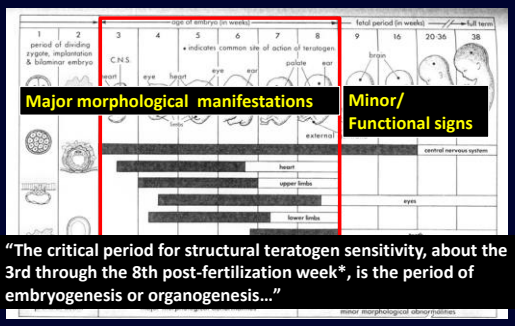

"The critical period for structural teratogen sensitivity, about the 3rd through the 8th post-fertilization week*, is the period of embryogenesis or organogenesis…"

***5-10wks GA**

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Brent, R.L., D.A. Beckman, and C.P. Landel, *Clinical teratology.* Curr Opin Pediatr, 1993. 5(2): p. 201-11.

Conclusions: First trimester B-mode examinations are associated with a negligible rise in TI

Sheiner E et al: First-trimester sonography: is the fetus exposed to high levels of acoustic energy? JCU 2007;35:245 - 249

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Is Doppler worse?

Doppler of the ductus venosus
Transvalvular blood flow, in particular tricuspid valve
Cardiac anatomy and function

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Let's assume 2 minutes each to obtain the BPD, HC, AC, FL

Total energy is (remember: 34mW/cm² for B-mode)

(34x2) x4= 272 mW/cm²

Let's now assume 5 minutes each to find the ductus venosus and the tricuspid

Total energy is (remember:1180mw/cm² for pulsed Doppler)

(1180x5)x2=11800 mW/cm²

X 43

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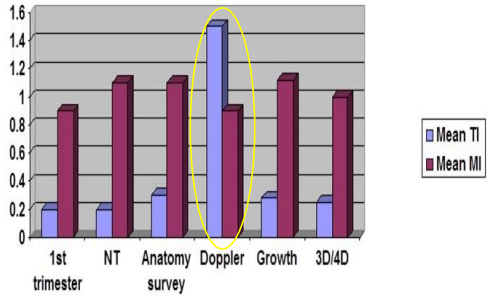

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After Sheiner & Abramowicz, 2007, 2008, 2009, 2010

How to keep it safe

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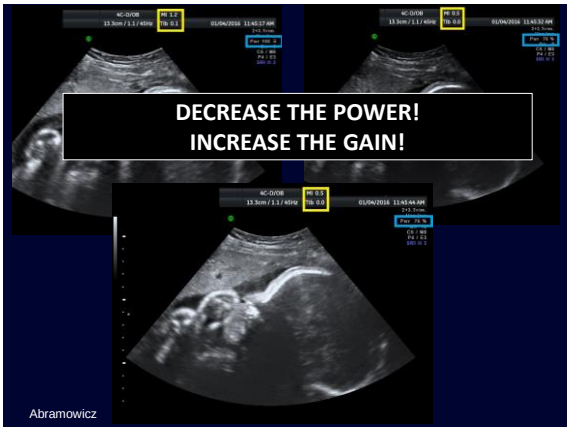

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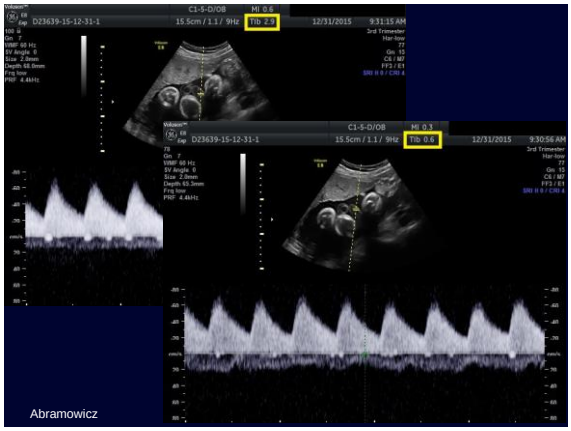

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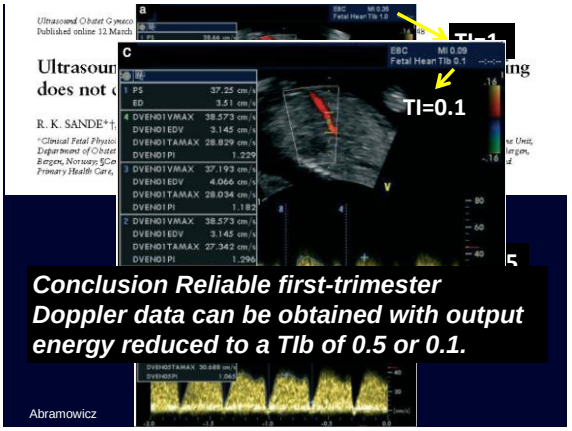

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AIUM Statement (2011)

"…Due to the increased risk of harm, the use of spectral Doppler ultrasound with high TI in the first trimester should be viewed with great caution. **Spectral Doppler should only be employed when there is a clear benefit/risk advantage** and both TI and examination duration are kept low."

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Clinical standards-diagnostic ultrasound

Guidelines from AIUM, ASUM, EFSUMB, ISUOG and WFUMB

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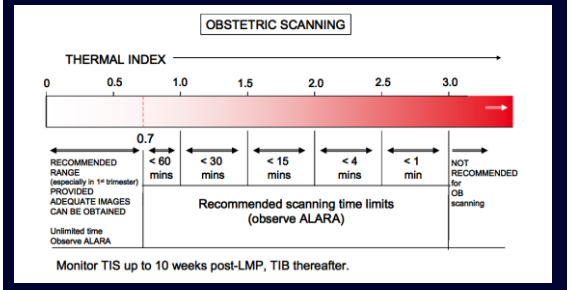
OB scanning guidelines (BMUS 2009)



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Safety statements-AIUM

http://www.aium.org/resources/statements.aspx

- As Low As Reasonably Achievable (ALARA) Principle, 2014
- Conclusions Regarding Epidemiology for Obstetric Ultrasound, 2010
- Prudent Use and Clinical Safety, 2012
- Prudent Use in Pregnancy, 2012
- Safety in Training and Research, 2012
- Statement on Mammalian Biological Effects of Ultrasound In Vivo, 2015
- Statement on the Safe Use of Doppler Ultrasound During 11-14 week scans (or earlier in pregnancy), 2016

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International Society for Ultrasound in Obstetrics and Gynecology

http://www.isuog.org/StandardsAndGuidelines/Statements+and+Guidelines/Safety+Statements/

- ISUOG statement on the safe use of Doppler in the 11 to 13+6 week fetal ultrasound examination, 2011
- ISUOG-WFUMB statement on the non-medical use of ultrasound, 2011
- ISUOG statement on the non-medical use of ultrasound, 2009
- ISUOG safety statement, 2000 (reconfirmed 2003)

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Safety statements-WFUMB

http://www.wfumb.org/about/statements.aspx

- WFUMB/ISUOG Statement on the Safe Use of Doppler Ultrasound During 11-14 week scans (or earlier in pregnancy), 2011 (This text is identical to that in the statement published by AFSUMB, AIUM, BMUS, EFSUMB and JSUMB)
- WFUMB Clinical Safety Statement for Diagnostic Ultrasound - an overview, 2012
- WFUMB Recommendations on Non-medical Use of Ultrasound, 2013

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AIUM Statement on Measurement of Fetal Heart Rate (Approved 2011)

When attempting to obtain FHR with a diagnostic ultrasound system, AIUM recommends using M-mode at first, because the time-averaged acoustic intensity delivered to the fetus is lower with M-mode than with spectral Doppler. If this is unsuccessful, spectral Doppler ultrasound may be used with the following guidelines: use spectral Doppler only briefly (e.g. 4-5 heart beats) and keep the thermal index (TIS for soft tissues in the first trimester, TIB for bones in second and third trimesters) as low as possible, preferably below 1 in accordance with the ALARA principle.

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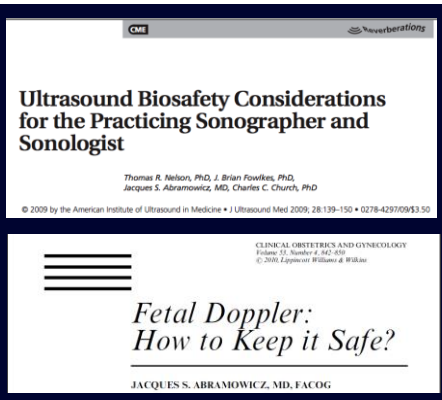
CME

reverberations

Ultrasound Biosafety Considerations for the Practicing Sonographer and Sonologist

Thomas R. Nelson, PhD, J. Brian Fowlkes, PhD, Jacques S. Abramowicz, MD, Charles C. Church, PhD

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Fetal Doppler: How to Keep it Safe?

JACQUES S. ABRAMOWICZ, MD, FACOG

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Ultrasound Bioeffects: Guidelines for Safe Use: thermal and mechanical indices

- MI> 0.3: possibility of minor damage to neonatal lung or intestine. If such exposure is necessary, try to reduce the exposure time as much as possible.
- MI>0.7: risk of cavitation if an ultrasound contrast agent containing gas micro-spheres is being used.
  - Theoretical risk of cavitation without the presence of ultrasound contrast agents.
  - Risk increases with MI values above this threshold.
- TI> 0.7: overall exposure time (including pauses) of an embryo or fetus should be restricted
- TI> 1.0: eye scanning is not recommended, other than as part of a fetal scan
- TI 3.0: scanning of an embryo or fetus is not recommended, however briefly

Nelson TR, Fowlkes JB, Abramowicz JS, Church CC.: Ultrasound biosafety considerations for the practicing sonographer and sonologist. J Ultrasound Med. 2009 Feb;28(2):139-50.

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So?

- Perform exam if indicated
- Keep output as low as possible
- Keep exam as short as possible
- Watch TI (MI) and keep <1

} Compatible with accurate diagnosis

As
Low
As
Reasonably
Achievable

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Thank you

Key References

Nelson TR, Fowlkes JB, Abramowicz JS, Church CC: Ultrasound biosafety considerations for the practicing sonographer and sonologist. J Ultrasound Med 28:139-50, 2009

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AIUM Statement on the Safe Use of Doppler Ultrasound During 11–14 week scans (or earlier in pregnancy). Approved 2016. http://www.aium.org/officialStatements/42

National Council on Radiation Protection and Measurements (NCRP) report 140, Exposure Criteria for Medical Diagnostic Ultrasound, II: Criteria Based on All Known Mechanisms. Bethesda, MD: NCRP; (2002)

WFUMB Clinical Safety Statement for Diagnostic Ultrasound - an overview. http://www.wfumb.org/about/statements.aspx

Sheiner E, Abramowicz JS: Clinical end-users worldwide show poor knowledge regarding safety issues of ultrasound during pregnancy. J Ultrasound Med, 27:499-501,2008