

## Opinion

### Safe use of Doppler ultrasound during the 11 to 13 + 6-week scan: is it possible?

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Ultrasound has an excellent safety record. It has been used in obstetrics for five decades with no proven harmful effects. In this issue of the Journal, two new studies address ultrasound safety. Pellicer *et al.*<sup>1</sup> present a study indicating that Doppler ultrasound exposure of the ductus venosus of embryonic rats can lead to increased apoptotic activity in fetal liver tissue, while Heikkilä *et al.*<sup>2</sup> present new data regarding ultrasound and handedness.

Pellicer *et al.*<sup>1</sup> used an ultrasound device at low intensity with exposure times from 3 s to 10 min. A linear relationship between apoptotic activity and pulsed Doppler scanning time was found: the longer the exposure time, the more liver cell damage was observed. Of course, it is difficult to extrapolate the results of this animal model to humans. There are also questions about whether it matters that apoptotic activity in the fetal liver is raised transiently, and there is some difficulty in explaining the mechanisms of damage (whether due to thermal or non-thermal effects). There are, however, two other recent animal studies which have demonstrated a relationship between length of exposure to Doppler ultrasound and potentially irreversible biological effects<sup>3,4</sup>.

In many countries today, more than 70% of all pregnancies undergo nuchal translucency screening at 11 to 13 + 6 weeks. From an ultrasound safety perspective, this is not problematic as long as it is performed with low-intensity B-mode ultrasound by properly trained sonographers or sonologists. However, recent research has advocated Doppler measurement of the cardiac and infracardiac regions of the 11 to 13 + 6-week fetus<sup>5,6</sup>. Since Doppler usually generates higher intensity outputs than does B-mode ultrasound, the question of safety must be considered.

Also in this issue of the Journal, there is a new ISUOG (International Society of Ultrasound in Obstetrics and Gynecology) statement on the use of Doppler ultrasound at 11 to 13 + 6 weeks<sup>7</sup>, and this Opinion discusses some of the issues raised.

#### Should we be more worried about Doppler ultrasound safety during early than during later scans?

A first-trimester embryo is in a particularly vulnerable phase of development. If Doppler ultrasound were to have an adverse effect, we could hypothesize that this would be most likely early in gestation, when cell division is most rapid and when fetal blood flow is less well developed and hence less likely to dissipate any heat created during ultrasound examination. The proposed first-trimester Doppler examinations are at the level of the

ductus venosus or fetal heart, i.e. very close to a bone (the spine)/soft-tissue interface, where a heating effect would be greatest. However, from this specific standpoint, a 10-week embryo may be less prone to heating than is a 36-week fetus with mineralized bones (due to absorption of energy in bone tissue and reflection at bone/soft-tissue interfaces). Thus, from a heat-absorption point of view, caution is perhaps even more important during Doppler studies of the middle cerebral artery in a fetus close to term.

The main reason for advocating precautionary use of Doppler early in gestation is not because we know that it causes harm, but because we don't know that it is safe, and because the first trimester is a particularly vulnerable period of fetal life.

#### Is transvaginal ultrasound potentially more harmful than transabdominal ultrasound?

It is sometimes inappropriately assumed that transabdominal Doppler ultrasound is safer than is transvaginal ultrasound<sup>5</sup>. However, the potential for heating is not dependent on whether a transvaginal or transabdominal approach is used. What matters for thermal risk is the amount of energy absorbed in the region of interest. The intensities used in transvaginal scanning are generally lower than those used in the transabdominal route. This is because the path lengths involved are shorter, resulting in lower attenuation and thus requiring less intensity to achieve the same imaging quality. For Doppler applications, the outputs from transvaginal probes are generally somewhat lower than are those from transabdominal probes, but the large variation in exposure conditions between different systems and different transducers means that thermal risk can only be assessed on a case-by-case basis (using the thermal index (TI)). This is explained in a tutorial article published by the EFSUMB Safety Committee<sup>8</sup>.

#### How do you know the energy output levels of your machine, and can you adjust them?

The simple answer to this question is knowing where to find and how to interpret the output display indices on the screen and how to turn down the power (usually with a rotating knob or a switch found on the front panel of the device). If you understand this, you may jump to the next question.

Pulsed Doppler techniques generally involve greater temporal average intensities and powers than do B- or

M-mode, and hence have greater heating potential. This is because of the high pulse repetition frequencies and consequent high-duty factors that are often used. When the beam is held in a fixed position during spectral pulsed Doppler measurements, the temporal average intensity is increased relative to that when moving probes are used. Color flow Doppler and power Doppler involve some beam scanning and have a heating potential that lies between that of B- or M-mode and spectral pulsed Doppler.

The American Institute of Ultrasound in Medicine (AIUM) and National Electrical Manufacturers Association (NEMA) introduced the 'output display standard' (ODS) in the early 1990s. The ODS requires the use of biophysical indicators, such as the mechanical index (MI) and TI, for real time display of safety information during scanning. The Food and Drug Administration (FDA) in the USA adopted the ODS and issued regulations demanding that ODS information be provided by the manufacturers in all commercial devices available in the US market after 1992. In practice, this transferred the responsibility for the safe use of ultrasound from the manufacturer to the operator of the machine. The machines still have upper limits for energy output (intensity up to 720 mW/cm<sup>2</sup>), but it is the responsibility of the ultrasound operator to consider the output displays (MI and TI) and to scan using output levels that fulfil the ALARA (as low as reasonably achievable) principle.

Pulsed Doppler can be associated with high MI and TI. The MI is an onscreen indicator intended to offer a rough guide to the likelihood that ultrasound will induce an adverse biological effect by a non-thermal mechanism, including cavitation. For all practical purposes, this index is probably not relevant for obstetric scanning due to the relative absence of gas bubbles (air) in the fetus. The TI is, however, important in obstetrics, representing an onscreen indicator of the relative potential for a tissue temperature rise. Its relevance is related closely to the exposure time<sup>9</sup>. Although strictly an index (TI is the ratio of the power used to the power required to raise the temperature by one 1°C), TI is often thought of as indicating a temperature rise. However, errors in calculating TI values and the limitations of the simple models on which they are based mean that TI values can underestimate a rise in temperature by a factor of two or more<sup>9</sup>.

When performing a Doppler examination at 11 to 13 + 6 weeks' gestation, the displayed TI should be  $\leq 1.0$  and the exposure time should be kept as short as possible (usually no longer than 5–10 min), certainly never exceeding 60 min<sup>7,9</sup>. It is important to be aware that default Doppler settings mean that TIs of  $> 3$  are seen routinely when using Doppler presets on some new machines. However, appropriate spectral Doppler waveforms can be obtained with lower outputs and hence with lower TI. All obstetric scanners should therefore be set up so that the default (switch-on) setting of the acoustic output power control is low. The operator must also know how to turn down the machine output, and a

low setting should be selected for each new patient and each time the spectral Doppler is switched on.

### Do ultrasound operators know the meaning of output display indices?

Ten years after the introduction of the ODS, Karel Maršál surveyed the knowledge among ultrasound users of some safety aspects of diagnostic ultrasound<sup>10</sup>. A questionnaire was distributed to 145 doctors, 22 sonographers and 32 midwives from nine European countries. All of them were using diagnostic ultrasound on a daily or weekly basis. The results of this study were depressing. About one third knew the meaning of MI and TI, and only 28% knew where to find the safety indices on the screen of their own machine. More alarmingly, only 43 (22%) of 199 respondents knew how to adjust the energy output on their machine<sup>10</sup>.

A similar survey was repeated at the 2010 ISUOG World Congress in Prague. An unknown number of questionnaires was handed out at two plenary sessions on the 2<sup>nd</sup> day of the congress, and 255 questionnaires were returned. Compared with the results from the previous survey, significantly more respondents knew the meaning of TI (58%) and MI (56%), 58% knew where to find the safety indices on the screen and 44% knew how to adjust the energy output on their machine. This may be interpreted as an improvement of knowledge among ultrasound users, but the results may be biased: in the first study the response rate was 100%, whereas in the second survey the response rate was unknown.

Similar results were obtained in the USA. A survey of 130 end-users (of whom physicians constituted about 60%) demonstrated that 32% were familiar with the term TI, but of those only 18% gave the correct answer to the question about the nature of TI. These numbers were 22% and 4%, respectively, for MI. Perhaps more concerning was the fact that 80% did not know where to find the indices during an ultrasound examination<sup>11</sup>.

Thus, the ODS may well be an excellent concept in theory, but this is not helpful if the ultrasound end-users do not know where to find the output displays and how to turn down the output levels on their own machines. It is fair to say that the ODS has failed to provide a basis for safe scanning – at least when applied to obstetric examination.

### How may Doppler ultrasound at 11 to 13 + 6 weeks be used to refine risks for trisomies?

Various retrospective models of trisomy 21 screening, in which first-stage testing is based on maternal age and ultrasound and second-stage testing on biochemical analysis, have been reported from a large cohort of 19 800 pregnancies<sup>5,12,13</sup>. The use of Doppler ultrasound examination of the ductus venosus<sup>12</sup> or tricuspid valve<sup>13</sup> blood flow, used as the second-stage examination in cases with intermediate risk, exposed only 15% of the population to Doppler ultrasound in early pregnancy,

and the reported detection rates (DR) were high and false-positive rates (FPR) were low for trisomy 21 (ductus venosus: DR, 96%; FPR, 2.6%; tricuspid valve: DR, 96%; FPR, 2.4%). The latter performance should be compared to DRs of 94–96% for FPRs of 2.6–2.7% from the same cohort with contingent screening when all pregnancies were exposed to first-trimester Doppler ultrasound<sup>5</sup>. By comparison, combined screening without the use of Doppler has been reported to have a 91% DR for a 3.1% FPR for trisomy 21<sup>14</sup>. Furthermore, a recently reported two-stage nuchal translucency and biochemistry screening program, which did not require the use of Doppler, performed at least as well, with a 92% DR for a 1.4% standardized FPR for trisomy 21<sup>15</sup>.

The question to be answered is, therefore: is the additional exposure to ultrasound worth the benefit of a slight improvement in screening efficiency?

### What is known about ultrasound safety from epidemiological studies?

An updated review of the epidemiological literature was published in this Journal in 2009<sup>16</sup>. The authors searched the literature extensively and analyzed the data using the guidelines for Cochrane reviews. The results were reassuring. Apart from an unexplained weak association between ultrasound and non-right handedness in boys, they found no indications of deleterious effects from obstetric ultrasound. This was reconfirmed in a new update of the Cochrane review in 2010<sup>17</sup>.

The paper by Heikkilä *et al.*<sup>2</sup>, in this issue of the Journal, may alter the findings of these systematic reviews. In Torloni's meta-analysis there was no association between ultrasound exposure and non-right handedness among all children (odds ratio (OR), 1.13; 95% CI, 0.97–1.32), but there was an association among boys (OR, 1.26; 95% CI, 1.03–1.54)<sup>16</sup>. In a new meta-analysis<sup>18</sup>, it was found that non-right handedness among all children was statistically significantly increased when the Helsinki data<sup>2</sup> were included. While this will not change our understanding (or, more correctly, lack of understanding) of this association<sup>19</sup>, we cannot assume that the association will go away if we continue collecting more epidemiological data. There are currently three randomized controlled trials and two cohort studies all pointing in the same direction, and no epidemiological study proving otherwise. Besides, there is one more caveat regarding all the reassuring data from epidemiological studies. The acoustic outputs from modern devices have increased 10–15-fold in recent decades<sup>20</sup>, and most epidemiological evidence derives from B-mode scanners in commercial use 20–25 years ago. There is very little epidemiological data on the use of color flow or pulsed wave Doppler. If adverse effects of ultrasound during pregnancy are dose-dependent, one must acknowledge that the available epidemiological data are limited<sup>21</sup>.

### Conclusion

In accordance with the ISUOG safety statement in this issue of the Journal, Doppler examination of fetal vessels in early pregnancy should not be performed without a clinical indication. Teaching and training Doppler sessions on first-trimester fetuses should be kept short and should only be performed in fetuses in whom Doppler examination is indicated anyway.

We will have to live with uncertainty regarding ultrasound safety in the years to come. There is no such thing as zero risk, and an absence of evidence of harm is not equal to evidence of absence of harm. There is, however, much we can do to minimize any possible risks. Understanding safety indices and a knowledge of how to respect and follow the ALARA principle is a good start. In collaboration with other ultrasound societies and with the major manufacturers, the ISUOG Safety Committee proposes a dialogue on how safety indices are best displayed and furthermore on the feasibility of recording the safety indices, scan duration and mode for all scans carried out in pregnancy. As professionals involved in ultrasound, we must regulate ourselves sensibly... otherwise, someone else is likely to.

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### REFERENCES

1. Pellicer B, Herraiz S, Táboas E, Felipe V, Simon C, Pellicer A. Ultrasound bioeffects in rats: quantification of cellular damage in the fetal liver after pulsed Doppler imaging. *Ultrasound Obstet Gynecol* 2011; 37: 643–648.
2. Heikkilä K, Vuoksima E, Oksa K, Saari-Kemppainen A, Iivanainen M. Handedness in the Helsinki Ultrasound trial. *Ultrasound Obstet Gynecol* 2011; 37: 638–642.
3. Schneider-Kolsky ME, Ayobi Z, Lombardo P, Brown D, Kedang B, Gibbs ME. Ultrasound exposure of the foetal chick brain: effects on learning and memory. *Int J Devl Neuroscience* 2009; 27: 677–683.
4. Ang ES, Gluncic V, Duque A, Schafer M, Rakic P. Prenatal exposure to ultrasound waves impacts neuronal migration in mice. *Proc Natl Acad Sci USA* 2006; 30: 12903–12910.

5. Kagan KO, Staboulidou I, Cruz J, Wright D, Nicolaides KH. Two-stage first trimester screening for trisomy 21 by ultrasound assessment and biochemical testing. *Ultrasound Obstet Gynecol* 2010; **36**: 542–547.
6. Timmerman E, Rengerink KO, Pajkrt E, Opmeer BC, van der Post JA, Bilardo CM. Ductus venosus pulsatility index measurement reduces the false-positive rate in first-trimester screening. *Ultrasound Obstet Gynecol* 2010; **36**: 661–667.
7. Salvesen KÅ, Lees C, Abramowicz JS, Brezinka C, ter Haar G, Maršál K. ISUOG statement on the safe use of Doppler in the 11 to 13 + 6-week fetal ultrasound examination. *Ultrasound Obstet Gynecol* 2011; **37**: 628.
8. EFSUMB Safety Committee. Transvaginal ultrasonography – safety aspects. *Eur J Ultrasound* 1994; **1**: 355–357 or <http://www.efsumb.org/ecmus/tutpap06.asp>.
9. BMUS Safety Group. Guidelines for the safe use of diagnostic ultrasound equipment. *Ultrasound* 2010; **18**: 52–59.
10. Maršál K. The output display standard: has it missed its target. *Ultrasound Obstet Gynecol* 2005; **25**: 211–214.
11. Sheiner E, Shoham-Vardi I, Abramowicz JS. What do clinical users know regarding safety of ultrasound during pregnancy? *J Ultrasound Med* 2007; **26**: 319–325.
12. Maiz N, Valencia C, Kagan KO, Wright D, Nicolaides KH. Ductus venosus Doppler in screening for trisomies 21, 18 and 13 and Turner syndrome at 11–13 weeks of gestation. *Ultrasound Obstet Gynecol* 2009; **33**: 512–517.
13. Kagan KO, Valencia C, Livanos P, Wright D, Nicolaides KH. Tricuspid regurgitation in screening for trisomies 21, 18 and 13 and Turner syndrome at 11 + 0 to 13 + 6 weeks of gestation. *Ultrasound Obstet Gynecol* 2009; **33**: 18–22.
14. Kagan KO, Etchegaray A, Zhou Y, Wright D, Nicolaides KH. Prospective validation of first-trimester combined screening for trisomy 21. *Ultrasound Obstet Gynecol* 2009; **34**: 14–18.
15. Habayeb O, Goodburn S, Chudleigh T, Brockelsby J, Missfelder-Lobos H, Hackett G, Lees C. The NTplus method of screening for Down syndrome: achieving the 2010 targets? *Prenat Diagn* 2010; **30**: 434–437.
16. Torloni MR, Vedmedovska N, Meriardi M, Betrán AP, Allen T, González R, Platt LD on behalf of the ISUOG-WHO fetal growth study group. Safety of ultrasonography in pregnancy: WHO systematic review of the literature and meta-analysis. *Ultrasound Obstet Gynecol* 2009; **33**: 599–608.
17. Whitworth M, Bricker L, Neilson JP, Dowswell T. Ultrasound for fetal assessment in early pregnancy. *Cochrane Database Syst Rev* 2010; Issue (4): CD 007058.
18. Salvesen KA. Ultrasound in pregnancy and non right-handedness: meta-analysis of randomized trials. *Ultrasound Obstet Gynecol* 2011; DOI:10.1002/uog.9055.
19. Salvesen KÅ. Ultrasound and left-handedness: a sinister association? *Ultrasound Obstet Gynecol* 2002; **19**: 217–221.
20. Whittingham TA. The acoustic output of diagnostic machines. In *The Safe Use of Ultrasound in Medical Diagnosis*, ter Haar G, Duck FA (eds). British Medical Ultrasound Society/British Institute of Radiology: London, UK, 2000; 16–31.
21. Salvesen KÅ, Lees C. Ultrasound is not unsound, but safety is an issue. *Ultrasound Obstet Gynecol* 2009; **33**: 502–505.

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## ISUOG statement on the safe use of Doppler in the 11 to 13 + 6-week fetal ultrasound examination

Bioeffects and Safety Committee (K. SALVESEN, C. LEES, J. ABRAMOWICZ, C. BREZINKA, G. TER HAAR and K. MARŠÁL) on behalf of the Board of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)

1. Pulsed Doppler (spectral, power and color flow imaging) ultrasound should not be used routinely.
2. Pulsed Doppler ultrasound may be used for clinical indications such as to refine risks for trisomies.
3. When performing Doppler ultrasound, the displayed thermal index (TI) should be  $\leq 1.0$  and exposure time should be kept as short as possible (usually no longer than 5–10 min) and should not exceed 60 min.
4. When using Doppler ultrasound for research, teaching and training purposes, the displayed TI should be  $\leq 1.0$  and exposure time should be kept as short as possible (usually no longer than 5–10 min) and should not exceed 60 min. Informed consent should be obtained.
5. In educational settings, discussion of first-trimester pulsed or color Doppler should be accompanied by information on safety and bioeffects (e.g. TI, exposure times and how to reduce output power).
6. When scanning maternal uterine arteries in the first trimester, there are unlikely to be any fetal safety implications as long as the embryo/fetus lies outside the Doppler ultrasound beam.