DO WE NEED TO RESTRICT THE USE OF DOPPLER ULTRASOUND IN THE FIRST TRIMESTER OF PREGNANCY?

GAIL R. TER HAAR,* JACQUES S. ABRAMOWICZ,† IWAKI AKIYAMA,‡ DAVID H. EVANS,§ MARVIN C. ZISKIN,‖ and KAREL MARŠÁL‖

*Joint Department of Physics, Division of Radiotherapy and Imaging, Institute of Cancer Research, Royal Marsden Hospital, Sutton, Surrey, UK; †Department of Obstetrics and Gynecology, Rush University, Chicago, IL, USA; ‡Department of Biomedical Information, Faculty of Life and Biomedical Sciences, Doshisha University, Kyoto, Japan; §Department of Cardiovascular Sciences, School of Medicine, University of Leicester, Leicester, UK; ‖Center for Biomedical Physics, Temple University Medical School, Philadelphia, PA, USA; and ♂Department of Obstetrics and Gynecology, Clinical Sciences Lund, Lund University, Lund, Sweden

INTRODUCTION

During the past decade, an increasing interest in using Doppler ultrasound in the first trimester of pregnancy could be noticed among clinicians who perform fetal ultrasound for estimation of the risk for aneuploidies and for diagnosis of fetal malformations. Considering the potential for high-output ultrasound energy levels in color and spectral Doppler modes and the sometimes lengthy examination time, this new clinical application might expose the fetus to Doppler ultrasound during its early development when it is sensitive to external influences. Therefore, it is important to carefully evaluate the risk-benefit relationship before Doppler ultrasound is used widely in early gestation.

In Summer 2009, a group of experts on bioeffects and safety aspects of diagnostic ultrasound met for a 3-day workshop* to discuss the use of Doppler ultrasound in early pregnancy. This workshop provided a platform for further work by the World Federation for Ultrasound in Medicine and Biology (WFUMB) Safety Committee that resulted in recommendations for the use of Doppler ultrasound in the first trimester of pregnancy, approved by the WFUMB and the International Society for Ultrasound in Obstetrics and Gynecology (http://wfumb.org/about/statements.aspx). The following text summarizes the background information and rationale for these recommendations.

THE ARGUMENT FOR THE USE OF FETAL DOPPLER ULTRASOUND IN THE FIRST TRIMESTER OF PREGNANCY

During the embryonic period, the human heart develops in the cardiogenic plate derived from the splanchnopleuric mesoderm. Three weeks after conception (i.e., 5 wk after the first day of the last menstrual period), the primitive heart tube starts to pulsate. In the subsequent development the heart tube grows and bends, septa begin to grow, the four chambers are formed and, finally, the two outflow tracts separate. At 8 wk after conception, the development of the heart is completed.

On a transvaginal ultrasound scan, the heart activity can be identified in the real-time 2-D image of the pregnant uterus when the crown-rump length of the embryo is ≥5 mm. This occurs at 5 wk 3 d to 6 wk 3 d of gestational age, calculated from the last menstrual period. After 6 wk of gestation, spectral and color Doppler signals of pulsating blood flow in the fetal heart and large vessels can be detected. During the latter part of the first trimester of pregnancy, ultrasound imaging and Doppler recording can be performed transabdominally.

Obstetric ultrasound examinations to detect fetal developmental disorders are usually performed in the second trimester of pregnancy. During the past decade, technical developments have profoundly improved the
resolution of ultrasound images, thus enabling detection of fetal anomalies at 11–13 wk with high accuracy (Becker and Wegner 2006; Ndumbe et al. 2008). The first reports of ultrasound detection in the first trimester of the fluid collection in the nuchal region of fetuses with trisomy 21 (Bronshtein et al. 1989; Cullen et al. 1990) showed that by measuring the nuchal translucency (NT) thickness with ultrasound, it is possible to screen for fetuses with aneuploidies (trisomies 21, 13 and 18) at this time of gestation (Nicolaides et al. 1994). Furthermore, the increased NT was found to be associated with cardiac defects (Hyett et al. 1999). Screening for Down syndrome and other major aneuploidies at 11 wk to 13 wk 6 d of gestation, using NT measurement in combination with maternal age and analysis of biochemical markers in maternal serum (pregnancy-associated protein-A and free β-human chorionic gonadotrophin), was reported to have a detection rate of ~90%, with a false positive rate of 5% (including a necessity for an invasive procedure, such as chorion villi biopsy or amniocentesis; Ndumbe et al. 2008; Nicolaides 2011). Currently in many countries and regions, the ultrasound measurement of NT is offered routinely to pregnant women as a way of estimating the risk for chromosomal abnormalities.

In 1998, the first studies were published demonstrating that a large proportion of fetuses with aneuploidies have abnormal blood flow pattern in the ductus venosus as recorded using spectral Doppler ultrasound (Borrell et al. 1998; Matias et al. 1998). The ductus venosus (DV) is a vessel that is present during fetal life and connects the umbilical vein to the inferior vena cava. Normally the DV flow is pulsatile, with positive blood velocities throughout the cardiac cycle. In up to 90% of aneuploid fetuses, the wave corresponding to atrial contraction (A wave) is absent or reversed (Matias et al. 1998). The finding of abnormal DV flow in fetuses with trisomies has been confirmed in several studies (Borrell 2004). It has also been reported that aneuploid fetuses have an increased frequency of tricuspid regurgitation (Falcon et al. 2006; Huggon et al. 2003). Furthermore, the results of Doppler ultrasound examinations of other fetal vessels indicate associations between the abnormal findings in hepatic arteries (increased flow) and Down syndrome (Bilardo et al. 2011), the intra-abdominal section of the umbilical vein (decreased flow) and subsequent development of intrauterine growth restriction (Rizzo et al. 2010) and abnormal DV flow and complications in monochorionic twin pregnancies (Matias et al. 2010).

In first-trimester fetuses with normal chromosomes (euploid fetuses), an increased NT (Hyett et al. 1999) and an abnormal DV Doppler finding (Matias et al. 1999) might indicate an increased risk for cardiac defects. This risk was subsequently confirmed by the same research group in a larger patient cohort. The authors proposed that Doppler assessment of the DV flow pattern might improve the results of screening for cardiac malformations (Chelemen et al. 2011).

THE ARGUMENT AGAINST THE USE OF FETAL DOPPLER ULTRASOUND IN THE FIRST TRimestER OF PREGNANCY

Ultrasonic energy considerations

B-mode and Doppler ultrasound imaging use different pulsed regimes with consequent different power outputs. When considering the potential for harmful thermal effects, it is the spatial peak temporal average intensity (I_SPTA) that is important. Past surveys showed that this intensity was considerably higher in pulsed Doppler or color-flow modes than in B-mode (Whittingham 2000). A more recent survey, based on outputs declared by manufacturers (Martin 2010), shows that there is considerable overlap in these values between modes, but the mean intensity remains higher for the pulsed Doppler and color-flow modes. The median intensity for B-mode (273 mW/cm²) is 36% of that for pulsed Doppler and 61% of the mean for color-flow imaging. The range of reported intensities is shown in Figure 1. Both transabdominal and transvaginal probes are included in this survey.

Modern scanners display safety-related information in the form of mechanical and thermal indices. These indices are defined in the Output Display Standard, a document produced jointly by the American Institute of Ultrasound in Medicine and the National Electrical Manufacturers Association (1992). The thermal index (TI) gives an indication of the temperature rise that might be expected in tissue during the acquisition of the scan on the screen, whereas the mechanical index (MI) reflects the potential for mechanical effects such as cavititation. There are three forms of TI: soft tissue thermal index (TIS) reflects the temperature rise in soft tissue, bone thermal index (TIB) reflects the temperature when the ultrasound focus coincides with bone, and cranial thermal index (TIC) reflects when there is bone close to the skin (e.g., in the neonatal skull). The British Medical Ultrasound Society has issued guidelines for the safe use of clinical ultrasound based on these indices (www.bmus.org). The guidelines state that TIS should be monitored up to 10 wk after the last menstrual period, and TIB should be monitored thereafter. Once the TI exceeds 0.7, the scanning time should be limited. For example, scanning times less than 15 min are recommended for 1.5 < TI < 2 (Table 1).
Ultrasound in Medicine and Biology

Volume 39, Number 3, 2013

use of clinical ultrasound (www.bmus.org). From the British Medical Ultrasound Society guidelines for the safe exposure of 30 min or longer, a small but statistically significant number of neurons failed to reach their proper position in the brain. The amount of faulty dispersion of labeled neurons increased with the duration of exposure to ultrasound. There was also an increase in abnormal cell migration in animals exposed to a 420-min sham experiment over that in normal controls. This finding might be the result of stress experienced by pregnant animals during prolonged exposure to the experimental procedure. Shorter durations of sham exposure had no effect on cell migration compared with normal controls. In an independent sham-exposure experiment, ultrasound exposure did not affect oxygenation or body core temperature in pregnant mice; therefore, the authors speculate that the mechanism for the disturbed neuronal migration resulting from ultrasound is a nonthermal, noncavitational, mechanically mediated effect, perhaps involving radiation force, microstreaming or shear effects on cellular walls. These mechanical effects might interfere with the delicate adhesion between the migratory neurons and the surface of migratory substrates, such as the radial glial shafts, which serve as guides.

Schneider-Kolsky et al. (2009) investigated whether the effects of B-mode or pulsed Doppler-mode ultrasound close to the time of hatching could affect memory in newly hatched chicks. The results suggest that extended exposure to pulsed Doppler ultrasound could adversely affect cognitive function in the chick. The chick brains were exposed on day 19 of a 21-d incubation period to a 5- or 10-min ultrasound examination, 5 or 10 min of B-mode ultrasound, or to 1, 2, 3, 4 or 5 min of pulsed Doppler ultrasound in ovo. The derated $I_{SPTA}$ of the clinical transducer used was 97.2 mW/cm² for B-mode and 576 mW/cm² for pulsed Doppler mode. The TI was 0.1, and MI was between 0.39 and 0.55. Learning and memory function (shown by a discrimination task) were assessed 2 d after hatching. The chicks were exposed to red or blue beads, the red ones being drenched with a bitter fluid. Chicks quickly learned to associate the red color with a bitter taste. In addition, if memory formation proceeded normally, they would avoid pecking at red beads in future tests. B-mode exposures of up to 10 min did not impair memory function in the chick model, whereas exposure to pulsed Doppler ultrasound lasting ≥4 min resulted in significant deficits in long-term memory. Short-term and intermediate-term memory were significantly impaired after 5 min of exposure to Doppler ultrasound, as was the ability to relearn.

The aim of the study by Pellicer et al. (2011) was to investigate whether pulsed Doppler exposure of the DV in fetal rats could cause damage to their livers, as assessed using the cleaved caspase 3 apoptosis test. This study is important because in clinical practice, markers for Down syndrome measured with Doppler in early pregnancy include blood flow in small vessels, such as the DV and across the tricuspid valve. Pregnant female rats (gestational day 18) were anesthetized, and fetuses in the proximal position from each uterine horn were exposed to ultrasound. Pulsed wave and color Doppler from a clinical ultrasound scanner were used. For the pulsed Doppler exposures, a frequency of 5.8

### Table 1. Recommended exposure time for Doppler ultrasound examinations during pregnancy

<table>
<thead>
<tr>
<th>Thermal index*</th>
<th>Maximum exposure time for an embryo</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.7</td>
<td>Unlimited</td>
<td>Recommended range provided adequate images/s signals can be obtained</td>
</tr>
<tr>
<td>&gt;0.7–1.0</td>
<td>60 min</td>
<td>Observe ALARA</td>
</tr>
<tr>
<td>&gt;1.0–1.5</td>
<td>30 min</td>
<td>Observe ALARA</td>
</tr>
<tr>
<td>&gt;1.5–2.0</td>
<td>15 min</td>
<td>Observe ALARA</td>
</tr>
<tr>
<td>&gt;2.0–2.5</td>
<td>4 min</td>
<td>Observe ALARA</td>
</tr>
<tr>
<td>&gt;2.5–3.0</td>
<td>1 min</td>
<td>Observe ALARA</td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>Not recommended</td>
<td>Not to be used for obstetric scanning</td>
</tr>
</tbody>
</table>

ALARA = output energy as low as reasonably achievable.
* Monitor thermal index for soft tissue up to 10 gestational wk after the last menstrual period, and thermal index for bones thereafter. Adapted from the British Medical Ultrasound Society guidelines for the safe use of clinical ultrasound (www.bmus.org).

Fig. 1. Range of spatial peak temporal average intensities reported by manufacturers of ultrasound scanners. It is these intensities that have the most relevance for thermal effects. The median values are also shown. (Adapted from Martin 2010.)
and potentially irreversible biological effects. Although there is uncertainty about the biological effects that can be induced by pulsed Doppler exposures of the embryo or fetus, it is particularly important to observe the ALARA (as low as reasonably achievable) principle.

**FIRST-TRIMESTER DOPPLER IN SCREENING FOR ANEUPLOIDIES: DOES THE BENEFIT OUTWEIGHT THE RISK?**

By including additional ultrasound markers (e.g., the absence of nasal bone) into the models of first-trimester screening for fetal aneuploidies, it is possible to achieve detection rates exceeding 90% with false-positive rates of 5% or less (Cicero et al. 2001). A similar effect was reported when Doppler examinations of the DV or tricuspid valve, or both, were incorporated into the screening models (Kagan et al. 2009; Maiz et al. 2009).

By various combinations of biochemical tests and ultrasound markers, several models have been developed for estimating the risk for trisomy 21 in the first trimester of pregnancy (Table 2). The combination of maternal age and biochemical markers in maternal serum gives a relatively low detection rate. Including ultrasound measurements of the NT thickness in the models significantly improves the efficacy of the test (Kagan et al. 2009; Maiz et al. 2009). Recently, a model combining NT and biochemical tests in two steps gave a detection rate of 92% and a false-positive rate 1.4% (Habayeb et al. 2010). By performing Doppler examination of flow in the DV or tricuspid valve, or both, in all fetuses, detection rates of 96% were achieved (Kagan et al. 2009; Maiz et al. 2009). However, using the Doppler measurements in

---

**Table 2. Efficacy of first-trimester screening for trisomy 21**

<table>
<thead>
<tr>
<th>Screening model</th>
<th>False-positive rate (%)</th>
<th>Detection rate (%)</th>
<th>Exposure to Doppler ultrasound (% of population)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA + biochemical tests*</td>
<td>4.8</td>
<td>62</td>
<td>0</td>
<td>Kagan et al. 2010</td>
</tr>
<tr>
<td>MA + NT</td>
<td>1.9</td>
<td>76</td>
<td>0</td>
<td>Kagan et al. 2010</td>
</tr>
<tr>
<td>MA + NT + biochemical tests</td>
<td>2.3</td>
<td>89</td>
<td>0</td>
<td>Kagan et al. 2010</td>
</tr>
<tr>
<td>MA + NT + FHR + biochemical tests</td>
<td>5</td>
<td>94</td>
<td>0</td>
<td>Maiz et al. 2009</td>
</tr>
<tr>
<td>Model 4 + DV</td>
<td>5</td>
<td>97</td>
<td>100</td>
<td>Kagan et al. 2009</td>
</tr>
<tr>
<td>Model 4 + TD</td>
<td>5</td>
<td>96</td>
<td>100</td>
<td>Kagan et al. 2009</td>
</tr>
<tr>
<td>Contingent DV screening (model 4 as the first line screening)</td>
<td>2.6</td>
<td>96</td>
<td>15</td>
<td>Maiz et al. 2009</td>
</tr>
<tr>
<td>Contingent TD screening (model 4 as the first line screening)</td>
<td>2.4</td>
<td>96</td>
<td>15</td>
<td>Kagan et al. 2009</td>
</tr>
<tr>
<td>Contingent biochemical screening (MA + NT + nasal bone as the first line screening)</td>
<td>2.6</td>
<td>90</td>
<td>0</td>
<td>Kagan et al. 2010</td>
</tr>
<tr>
<td>Contingent biochemical screening (MA + NT + DV as the first line screening)</td>
<td>2.7</td>
<td>96</td>
<td>100</td>
<td>Kagan et al. 2010</td>
</tr>
<tr>
<td>Contingent biochemical screening (MA + NT + TD as the first line screening)</td>
<td>2.6</td>
<td>94</td>
<td>100</td>
<td>Kagan et al. 2010</td>
</tr>
</tbody>
</table>

DV = ductus venosus Doppler; FHR = fetal heart rate; MA = maternal age; NT = fetal nuchal translucency; TD = tricuspidal valve Doppler.

Reports are from the King’s College Hospital research group based on retrospective application of various screening models on a series of 19,614 pregnancies.

* Biochemical tests: maternal serum free β-human chorionic gonadotrophin and pregnancy-associated plasma protein-A.

† Contingent screening: a subgroup of pregnancies with intermediate risk for aneuploidy (1:51–1:1000) according to the first-line screening is submitted to the second-line test.
a contingent manner, \textit{i.e.}, in a preselected group of pregnancies with intermediate risk for aneuploidy [risk 1:51 to 1:1000]) on the basis of the first line screening (maternal age, NT, fetal heart rate and serum biochemistry) gave almost identical results. Detection rates in this case were 96\% for tricuspid regurgitation and 97\% for DV with false-positive rates of 2.6\% and 2.4\%, respectively \citep{Kagan2009, Maiz2009}. In the latter two models, if DV or tricuspid valve measurements were included as the second line test, only 15\% of pregnant women were exposed to Doppler ultrasound in the first trimester (Table 2). In contrast, if biochemical markers are used only as the secondary test, the whole population would be exposed to Doppler examinations as a part of the first line screening \citep{Kagan2010}.

**SAFE USE OF DOPPLER ULTRASOUND IN THE FIRST TRimestER OF PREGNANCY**

To be able to follow the ALARA principle, the ultrasound operator must be able to understand the information provided about ultrasound energy exposure, to know where to find it and how to control the energy emitted by the ultrasound equipment. Unfortunately, it has been shown clearly that such knowledge is anything but satisfactory among the experts on fetal ultrasound in Europe (Maršál 2005), the United States \citep{Houston2011, Sheiner2007a} and in Asia \citep{Akhtar2011}. Without a doubt, there is a need for intensified continuous education of ultrasound users in questions of ultrasound safety. The international and national societies of medical ultrasound must coordinate their teaching efforts and provide guidelines for the safe use of diagnostic ultrasound and especially of Doppler ultrasound in pregnancy.

One possible way to encourage the ultrasound users, especially those using Doppler ultrasound in the first trimester, to acquire the necessary knowledge of safety issues is to require adequate reporting of the information on ultrasound exposure when submitting reports on research studies to scientific journals or to congresses \citep{Campbell1999, terHaar2011}. Better adherence to the guidelines would then be expected \citep{Salvesen2009}. If Doppler ultrasound were used properly, including safety considerations in the research context, then it might be expected that such practice would also be carried over into clinical implementation of research results in patient care.

There are a few studies that have evaluated the levels of TI and MI and the exposure time during standard obstetric ultrasound examinations \citep{Deane2000, Sheiner2005, Sheiner2007b}. These studies have shown that the TI values occasionally exceed 2.0 when color or spectral pulsed wave Doppler modes are applied. This is despite the fact that in most obstetric examinations, fully satisfactory images and/or Doppler signals can be obtained at low levels of TI and MI. The surveys cited in this article were performed for examinations in the second half of pregnancy; to our knowledge, no such surveys have been performed for Doppler examinations in the first trimester.

To adhere to the recommendation of TI \(\leq 1.0\) for Doppler use in the fetal examination at 11 wk to 13 wk and 6 d \citep{Salvesen2011b}, the ultrasound operator must control the factors that influence ultrasound exposure. In brief, the following influence output energy in color Doppler mode: the width of the color box, how deep the box is located, and the color scale. For spectral pulsed wave Doppler, the corresponding factors are the velocity scale related to the pulse repetition frequency and the depth location of the sample volume \citep{gate}. For both color and spectral Doppler, there are overall output intensity (power) controls. The recommended procedure is always to use low default output settings and only to consider an increase in the overall output energy when optimization of the “receive parameters” of the image and Doppler signals does not give satisfactory results.

The duration of an examination is important for the resulting ultrasound exposure. According to practical experience, most Doppler examinations indicated in the first trimester can be performed within 5–10 min, as has been recommended in the International Society of Ultrasound in Obstetrics and Gynecology \citep{ISUOG} statement \citep{Salvesen2011a}. However, on some occasions it may be difficult to receive good signals from the tiny vessel structures of the first trimester fetus. For example, if the reason is the obesity of the mother, a controlled and short-lasting increase in the output intensity may be justified; this might enable easier acquisition of good signals and, consequently, shortening of the total examination time. The time needed for a Doppler examination is dependent on the experience and skill of the examiner \citep{Nicolaides2011}. It has been shown that to achieve a 95\% success rate in examining the DV in early pregnancy, on average a minimum of 80 examinations is necessary \citep{Maiz2008}. Thus, extensive supervised training is needed, which in itself speaks against including the DV and tricuspid valve examinations as a routine part of all screening examinations in the first trimester.

As mentioned earlier, a properly indicated Doppler examination of fetuses in early gestation can give important and clinically useful results. Applied to all pregnancies as a routine part of the screening for fetal aneuploidies, DV and tricuspid valve Doppler studies can increase the detection rate of Down syndrome. However, fully comparable results have been obtained when Doppler examinations were applied in a contingent model as the second-line test in preselected pregnancies.
with intermediate risk for aneuploidy (Table 1; Kagan et al. 2010; Maiz et al. 2009; Nicolaides 2011). This application is preferable for safety reasons. It should also be mentioned that, probably in the near future, the screening for chromosomal defects in early gestation might be based on a completely different concept (e.g., on analysis of the free fetal DNA in maternal blood; Ehrich et al. 2011; Hahn et al. 2011), thus making biochemical and ultrasound screening for aneuploidies superfluous. One recent report has shown that the first-trimester Doppler might improve the early detection of cardiac defects (Chelemen et al. 2011), which would be desirable. The safety aspects and the necessity of expertise for execution of these examinations again speak against an application of Doppler in early pregnancy as a routine part of screening for cardiac defects. Doppler ultrasound will probably be useful as the second-line examination in high-risk fetuses, such as those with normal chromosomes and increased NT.

The consideration presented here, regarding the use of Doppler ultrasound in the first trimester, provides the background to the joint WFUMB-ISUOG statement on the safe use of Doppler in the fetal ultrasound examination at 11 wk to 13 wk and 6 d. The Bioeffects and Safety Committee of the ISUOG, in their recent opinion article, summarized these concerns as follows: “The main reason for advocating precautionary use of Doppler ultrasound in early 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” (Salvesen et al. 2011b).

REFERENCES


Salvesen KA, Lees C. Ultrasound is not unsound, but safety is an issue. Ultrasound Obstet Gynecol 2009;33:502–505.


