The use of Doppler in early gestation

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Disclosure
I have no conflict of interest with respect to any of the material presented in this lecture. I am on the OB/Gyn advisory board of Philips and Siemens. I will not discuss off-label or unapproved uses of drugs or devices.

Is there a role for Doppler in the first trimester?

Is it safe to use Doppler in the first trimester?

Doppler uses in the 1st trimester

“Listening” to the fetal heart beat
Ductus venosus
Tricuspid valve
Cardiac physiology
Uterine arteries

“Listening” to fetal heart

Continuous (hand-held, fetal monitoring) versus pulsed Doppler
Ductus venosus, tricuspid valve
(and hepatic artery)

Helpful in screening for chromosomal anomalies in 1st trimester, as adjunct to NT (reduces false positive).

Nicolaides KH: Screening for fetal aneuploidies at 11 to 13 weeks. Prenat Diagn. 2011;31:7-15

Ductus venosus

Ultrasound Obstet Gynecol, 2008; 31: 256–260
Ductus venosus Doppler in fetuses with cardiac defects and increased nuchal translucency thickness
Maiz N, Plasencia W, Dagklis T, Faros E and Nicolaides K.

Ultrasound Obstet Gynecol, 2010;36:542-7
Two-stage first-trimester screening for trisomy 21 by ultrasound assessment and biochemical testing.
Kagan KO, Staboulidou I, Cruz J, Wright D, Nicolaides KH.

Abnormal DV waveform

Incremental benefit of adding DV waveform analysis in terms of detection for Down Syndrome: from 91% to 96% (fixed 5% FP rate) but in larger series appears to be from 76% to 85%, and combined with serum markers, from 88% to 92%.
. More importantly, DV waveform analysis reduces FP rate of NT screening (e.g. for fixed 85% detection rate, from 15 to 4.8% if used alone and from 3.2 to 1.2% in combination with NT.
. No apparent benefit for other chromosomal abnormalities

Timmerman E et al., Ductus venosus pulsatility index measurement reduces the false-positive rate in first-trimester screening. Ultrasound Obstet Gynecol 2010;36:661-7.

Also important even in the absence of abnormal karyotype.
. Fetuses with increased NT but with normal karyotype, from 11-13 weeks: absent or reversed A-wave associated with 3-fold increase in likelihood of major cardiac defect
. Normal DV flow associated with 50% reduction in the risk for such defects.
. Abnormal findings in the DV associated with increased risk of chromosomal anomalies (reverse diastolic velocity) similar to those described many years ago for fetuses at risk of hypoxia, in cases of IUGR.

Tricuspid valve
. Many fetuses with Down’s syndrome have abnormal Tricuspid valve regurgitation
. Utility: further reduce FP rate of detection

Huggon IC, DeFigueiredo OB, Allan LD. Tricuspid regurgitation in the diagnosis of chromosomal anomalies in the fetus at 11-14 weeks gestation. Heart, 2003;89

Hepatic artery
. Studies in 2nd and 3rd trim.: GR fetuses have increased flow in hepatic a, when redistribution of fetal circulation occurs, 2nd and 3rd a to hypoxemia
. Called the “hepatic arterial buffer response” (HABR).
. Observation: significantly lower hepatic a. PI in fetuses with chromosomal abnormalities, other genetic syndromes or anomalies

Ductus venosus, hepatic artery and tricuspid valve

Not screening tests!!

Cardiac physiology

- Doppler (pulsed [spectral] and color) are ideal techniques to examine heart structure and function.
- Doppler analysis of flow across cardiac valves and Doppler velocimetry of various fetal vessels have shown potential.
- It is feasible to examine the heart very soon in pregnancy, beginning at 10 or 11 weeks.
- Studies have also been published on Doppler study of flow through cardiac valves, beginning at 6 weeks, and on performing measurements of the heart diameter, heart rate and inflow and outflow waveforms “after 5 weeks”.

However, as of now (February 2011), no clinical indication

Uterine artery

Requirement for normal implantation & placental development: proliferation of trophoblast cells and invasion into decidua and myometrium
- Extravillous trophoblast invades spiral arteries and replace endothelium and smooth muscle cells by trophoblast cells.
- This causes loss of arterial elasticity, contractile ability and vasomotor tone resulting in dilatation of these vessels

Uterine artery in 1st trimester screening for preeclampsia

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- Extravillous trophoblast invades spiral arteries and replace endothelium and smooth muscle cells by trophoblast cells.
- This causes loss of arterial elasticity, contractile ability and vasomotor tone resulting in dilatation of these vessels
Increased blood flow to uterus and placenta.

Poor invasion results in maintained elevated vessel resistance and impaired flow.

- Increased 1st trimester uterine a. Doppler resistance shown to correlate with histologically proven abnormal invasion.
- Precedes onset of clinical findings

Early-onset preeclampsia

- Onset before 37 weeks (often around 25 weeks)
- Much higher incidence of complications
- Higher severity of complications
- More late-onset complications (chronic HBP, high recurrence risk [40-50%])

Uterine artery and prediction of preeclampsia

Detection rate (3107 singleton, 11-13 6/7 wks)

Uterine a. Doppler:
- Early PET: 45.5%, late PET: 15% (5% false positive)
- UA + demographic and Ob info:
  - Early PET: 90.9% (5% false positive)
**Uterine artery and prediction of preeclampsia**

Detection rate (8366 singleton, 11-13 6/7 wks)

Demographic and Ob factors:
- Early PET: 47%, late PET: 41%, Gest. HBP: 31% (10% false positive)
- Adding uterine a. Doppler
  - Early PET: 89.2%, late PET: 57%, Gest. HBP: 50% (10% false positive)

Combination of uterine a. Doppler and maternal serum markers (e.g. Placental Protein13 [PP13], Placental Growth Factor [PlGF], inhibin-A, Placenta Associated Plasma Protein A [PAPP-A]) improve prediction of preeclampsia

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**First trimester UA Doppler in IUGR**

UA Doppler useful only in IUGR secondary to preeclampsia

Conclusions

In high-risk group, helps defining very high risk group
No value as screening test in general population
No direct fetal insonation

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**Is it safe for the fetus to use Doppler in the first trimester?**
Ultrasound = Energy

Ultrasound = waveform with positive and negative pressures

Thermal energy (indirect)

Mechanical energy (direct): positive pressure causes movements, negative pressure can induce cavitation

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/cm² to 720mW/cm², ISPTA)

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

Manufacturers may increase maximal output (up to 720mw/cm² 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

Thermal index (TI)

Limitless estimate of possible tissue temperature rise in °C under “reasonable worst-case conditions”

\[
TI = \frac{\text{total acoustic power}}{\text{acoustic power needed to raise temperature by 1 °C}}
\]

Predicts potential tissue temperature increase: Not a real temperature measurement

No time (duration of exposure) information

Mechanical Index (MI)

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

No bubbles in fetal lungs or bowels

Hence, mechanical risk appears to be low
But how can it get?

<table>
<thead>
<tr>
<th>Mode</th>
<th>P(10%) (median in mW/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-mode</td>
<td>34</td>
</tr>
<tr>
<td>M-mode</td>
<td>100</td>
</tr>
<tr>
<td>TV-probe B-mode</td>
<td>18.8</td>
</tr>
<tr>
<td>TV-probe M-mode</td>
<td>55.7</td>
</tr>
<tr>
<td>Color Doppler</td>
<td>290</td>
</tr>
<tr>
<td>Spectral Doppler</td>
<td>1180</td>
</tr>
</tbody>
</table>

Is Doppler worse?

The publishing of papers on 1st trimester Doppler

Campbell and Platt
Ultrasound Obstet Gynecol, 2000

Research on the fetus using Doppler ultrasound in the 1st trimester: guiding ethical considerations

Chervenak and McCullough
Ultrasound Obstet Gynecol, 2000
**Is Doppler in the 1st trimester worse?**

**Critical Periods of Development**

<table>
<thead>
<tr>
<th>Weeks gestation from LMP</th>
<th>Central Nervous System</th>
<th>Minor/Functional signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 5 6 7 8 9 10 11 12</td>
<td>Heart</td>
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<tr>
<td></td>
<td>Teeth</td>
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<td>Palate</td>
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</tbody>
</table>

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


- Exposed the brains of chicks 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 in ovo.
- Learning and memory function were assessed at day 2 post-hatch.
- B-mode exposure does not affect memory function.
  - 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.

NT, nasal bone, maxillary angle are obtained with B-mode (low ultrasound energy). For “entire assessment” tricuspid valve and ductus venosus have to be “Doppled”

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

Total energy is (remember: $34\text{mW/cm}^2$)

$$(34\times2) \times 4 = 272 \text{mW/cm}^2$$

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

Total energy is (remember: $1180\text{mW/cm}^2$)

$$(1180\times5) \times 2 = 11800 \text{mW/cm}^2$$


Thermal Index

<table>
<thead>
<tr>
<th>TI</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>2.5</th>
<th>3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECOMMENDED</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>
| RANGE | 0.0-0.7 | 0.7-1.0 | 1.0-1.5 | 1.5-2.0 | 2.0-2.5 | 2.5-3.0 | 3.0-
| THERMAL INDEX UP TO 10 WEEKS POST-LMP, TIB THEREAFTER |

Recommended scanning time limits for these TIs (observe ALARA)

<table>
<thead>
<tr>
<th>TI</th>
<th>0</th>
<th>0.5</th>
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Statements

AIUM (aium.org)
ISUOG (isuog.org)
BMUS (bmus.org)
WFUMB (wfumb.org)

AIUM Statement

The use of Doppler Ultrasound during the first trimester is currently being promoted as a valuable diagnostic aid for screening for and diagnosis of some congenital abnormalities. The procedure requires considerable skill, and subjects the fetus to extended periods of relatively high ultrasound exposure levels. 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. Protocols that typically involve values of TI lower than 1.0 reflect minimal risk.
Bottom line: in general, use ultrasound only when medically indicated. As far as we know, B-mode is safe. Be careful with spectral Doppler.