First trimester Uterine artery Doppler assessment and Cervical length measurement

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1. Uterine artery (UtA) doppler assessment

2. Cervical length (CL) measurement

Background

Uterine artery Doppler in the second trimester can predict 50%-85% of PE <34 weeks for a 5%-10% of false-positive rate
Background

Placental implantation: effects on UtA Doppler

Abnormal pregnant uterine a.

Non-pregnant

In pregnancy (20-24 sett.)

High vascular resistance

Reduced vascular resistance

High impedance to flow
Doppler indices

\[ RL = \frac{S-D}{S} \]

[Pourcelot 1974]

\[ PI = \frac{S-D}{A} \]

[Gosling 1976]

S/D ratio

[Stuart & Drumm 1980]

D/A ratio

[Maulik et al. 1982]

S: peak systolic frequency shift
D: end-diastolic frequency shift
A: temporal averaged frequency shifts over one cardiac cycle

Waveform characteristics

Doppler waveforms obtained at 10 weeks' gestation

UtA visualization

Uterine artery visualized by transvaginal color flow mapping at the level of the cervicocorporeal junction, as used in the first trimester

Uterine artery visualized by transabdominal color flow mapping at the crossover point with the external iliac artery, as used in the second trimester
Doppler indices before and during gestation

Anatomical and flow modification of UtA during gestation

Mean UtA PI during gestation
UtA Doppler as indicator of placental vascular pathology independent of clinical manifestations.

- Abnormal uterine Doppler
- FGR
- PE
- PIH
- Abruptio
- Uterine Doppler screening in the 1st trimester: prediction of preeclampsia

Study 1 - Cohort of 592 women with uterine Doppler at 12-16 weeks:
- Bilateral notches in 33%
  - Sensitivity = 93%
  - Specificity = 69% +LR = 3.0 (2.5-3.2)
- Adding uterine RI:
  - Specificity = 85% +LR = 6.2 (5.0-6.7)

4.7% developed PE
<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>PE Development</th>
<th>Mean Uterine PI &gt; 95th centile</th>
<th>Screen Pos. Rate</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+LR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3045</td>
<td>2.1%</td>
<td>5%</td>
<td>27%</td>
<td>95%</td>
<td>2.1%</td>
<td>5.9 (3.7-8.8)</td>
</tr>
<tr>
<td>3</td>
<td>999</td>
<td>2.2%</td>
<td>5.3%</td>
<td>24%</td>
<td>95%</td>
<td>2.2%</td>
<td>4.6 (95% CI 2.0-9.4)</td>
</tr>
<tr>
<td>4</td>
<td>3324</td>
<td>10 (0.3%)</td>
<td>5%</td>
<td>60%</td>
<td>95%</td>
<td>10 (0.3%)</td>
<td>12.2 (6.3-17.2)</td>
</tr>
</tbody>
</table>
UtA Doppler screening in the 1st trimester: for prediction of preterm PE
Study 5 - Cohort of 3058 women with uterine Doppler at 11-14 weeks
- 33 with PE delivered <37 weeks
- 57 with PE delivered >37 weeks

AUC = 0.7 (95% CI, 0.66–0.86; P < 0.001)

UtA Doppler screening in the 1st trimester: prediction of IUGR
Study 3 - Cohort of 999 women with uterine Doppler at 11-14 weeks
- 3.7% developed IUGR
- using mean uterine UtA PI > 95th centile:
  Screen pos. rate 5.3%
  Sensitivity 24.3%
  Specificity 95.4%
  +LR 5.3 (CI 2.7-9.5)

UtA artery Doppler screening in the 1st trimester: prediction of any adverse outcome
Study 3 - Cohort of 999 women with uterine Doppler at 11-14 weeks
- 6.7% developed GH, PE, BW < 5th centile, abruptio or stillbirth
- Mean uterine PI > 95th centile:
  screen positive rate 7.4%
  sensitivity 31%
  specificity 93%
  +LR 5.6 (1.8-16.6)
Recent review

- 74 studies of PE (total 79,547) and 61 studies of IUGR (total 41,131) to April 2006
- Low and high risk population, often overlap
- Low accuracy in high risk patients
- Better accuracy for severe/preterm PE than late PE and IUGR
- PI is the most predictive Doppler index in most cases


Low risk

<table>
<thead>
<tr>
<th>Trimester</th>
<th>N° cases</th>
<th>Sens</th>
<th>Spec</th>
<th>LR±</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe PE</td>
<td>15329</td>
<td>78%</td>
<td>95%</td>
<td>15.6 (13.3-17.3)</td>
</tr>
<tr>
<td>Overall PE</td>
<td>38230</td>
<td>42%</td>
<td>91%</td>
<td>4.5 (1.7-7.3)</td>
</tr>
<tr>
<td>Severe IUGR</td>
<td>1757</td>
<td>67%</td>
<td>95%</td>
<td>12.7 (10.2-16.9)</td>
</tr>
<tr>
<td>Overall IUGR</td>
<td>12097</td>
<td>18%</td>
<td>95%</td>
<td>3.4 (1.7-5.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trimester</th>
<th>N° cases</th>
<th>Sens</th>
<th>Spec</th>
<th>LR±</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe PE</td>
<td>431</td>
<td>40%</td>
<td>90%</td>
<td>4.0 (1.6-7.3)</td>
</tr>
<tr>
<td>Overall PE</td>
<td>4966</td>
<td>25%</td>
<td>95%</td>
<td>5.4 (4.1-6.7)</td>
</tr>
<tr>
<td>Severe IUGR</td>
<td>999</td>
<td>24%</td>
<td>95%</td>
<td>5.3 (2.8-9.5)</td>
</tr>
<tr>
<td>Overall IUGR</td>
<td>3045</td>
<td>12%</td>
<td>96%</td>
<td>2.7 (1.9-3.8)</td>
</tr>
</tbody>
</table>

High risk

<table>
<thead>
<tr>
<th>Trimester</th>
<th>N° cases</th>
<th>Sens</th>
<th>Spec</th>
<th>LR±</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe PE (IR)</td>
<td>28</td>
<td>80%</td>
<td>78%</td>
<td>3.7 (1.4-5.3)</td>
</tr>
<tr>
<td>Overall PE</td>
<td>547</td>
<td>39%</td>
<td>78%</td>
<td>1.8 (0.2-3.4)</td>
</tr>
<tr>
<td>Severe IUGR</td>
<td>351</td>
<td>6%</td>
<td>95%</td>
<td>11.7 (10.3-16.9)</td>
</tr>
<tr>
<td>Overall IUGR</td>
<td>445</td>
<td>58%</td>
<td>75%</td>
<td>2.3 (1.0-5.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trimester</th>
<th>N° cases</th>
<th>Sens</th>
<th>Spec</th>
<th>LR±</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall PE (only notching)</td>
<td>72</td>
<td>91%</td>
<td>46%</td>
<td>1.7 (1.1-1.9)</td>
</tr>
<tr>
<td>Overall IUGR</td>
<td>785</td>
<td>34%</td>
<td>76%</td>
<td>1.5 (1.0-1.9)</td>
</tr>
</tbody>
</table>
First trimester UtA Doppler: recent studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N (Cases)</th>
<th>PI/CVF Cut-off</th>
<th>Sensitivity</th>
<th>CPE/PreE</th>
<th>SGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin et al. 2001</td>
<td>3,045</td>
<td>PI &gt;95th centile</td>
<td>24-27%</td>
<td>PE</td>
<td></td>
</tr>
<tr>
<td>Gomes et al. 2005</td>
<td>1,091</td>
<td>PI &gt;95th centile</td>
<td>33-67%</td>
<td>Early-onset PE</td>
<td></td>
</tr>
<tr>
<td>Dugoff et al. 2005</td>
<td>1,067</td>
<td>RI 75th centile</td>
<td>12-25%</td>
<td>SGA</td>
<td></td>
</tr>
<tr>
<td>Parra et al. 2005</td>
<td>1,447</td>
<td>PI &gt;95th centile</td>
<td>1,067</td>
<td>Dugoff et al. 2005</td>
<td></td>
</tr>
<tr>
<td>Pilalis et al. 2007</td>
<td>1,123</td>
<td>PI &gt;95th centile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placencia et al. 2007</td>
<td>6,015</td>
<td>PI &gt;90th centile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meichsner et al. 2008</td>
<td>3,058</td>
<td>RI &gt;90th centile</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity
24-27% PE
33-67% Early-onset PE
12-25% SGA

2nd trimester UtA Doppler screening performs better than 1st trimester screening

<table>
<thead>
<tr>
<th>GA at Delivery (weeks)</th>
<th>Sensitivity for PE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;32</td>
<td>0</td>
</tr>
<tr>
<td>&lt;34</td>
<td>41%</td>
</tr>
<tr>
<td>&lt;36</td>
<td>54%</td>
</tr>
<tr>
<td>&lt;38</td>
<td>70%</td>
</tr>
<tr>
<td>&lt;40</td>
<td>81%</td>
</tr>
<tr>
<td>&lt;42</td>
<td>86%</td>
</tr>
</tbody>
</table>

2nd trimester UtA Doppler screening performs better than 1st trimester screening

Rationale for observed findings

<table>
<thead>
<tr>
<th>Incomplete placentation</th>
<th>Preterm/severe/complicated PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>5%</td>
</tr>
<tr>
<td>14 weeks</td>
<td>22 weeks</td>
</tr>
</tbody>
</table>

In red: true positives
In blue: false positives

Courtesy of Dr. Prefumo
How can we improve predictive ability in low risk women?

1. Add serum markers

- **PP-13**
  - Nicolaides KH Us Ob Gyn 2006
- **Neurokinin B (NKB)**
  - Page N. Nature 2000
- **PAPP-A**
  - Dugoff for FASTER
    - Spencer Prenat Diagn 2005
- **Others:** hCG, endoglin, TGF-β1, PIGF, sFlt1, sVEGFR-1

2. Add maternal cardiac function (534 nulliparous)

   - **LOW or HIGH Cardiac output?**
   - **HYPERDINAMIC status or high RESISTANCE?**

<table>
<thead>
<tr>
<th>Cardiac Output</th>
<th>Coefficient</th>
<th>Odds ratio 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW</td>
<td>-0.14</td>
<td>0.52 (0.54-0.56)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HIGH</td>
<td>0.19</td>
<td>1.05 (1.03-1.07)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

   - **Birthweight below 5th centile**
     - 15.6% (0.04-0.44) 0.001
   - **UTA Doppler at 11-14 weeks and at 19-22 in 870 women**
     - 7.3% developed gestational hypertension, PE or BW < 5th centile

3. Sequential change

   - PI
     - Table showing mean PI between complicated and normal group:
       - Differences in mean PI between complicated and normal group:
         - >0.37 (95% CI, 0.24-0.52) I trim
         - >0.25 (95% CI, 0.17-0.33) II trim
Cohort of 3107 women with uterine Doppler at 12 and at 23 weeks

- 93 (3.0%) developed PE (22 - 0.7% early <34wks and 71 -2.3% late PE), 73 (2.3%) GH, 346 (11.1%) SGA

Individual risk calculated with:
1. UtA Doppler
2. PI ratio II trimester / I trimester
3. maternal factors (CH, parity, ethnicity)

How can we improve predictive ability in low risk women?

4. Sequential change and maternal risk factors

Screening for early PE by
- UtA PI I trimester (- - -)
- maternal factors and PI I trimester (- - -)
- maternal factors, PI I trimester and ratio II / I trimester (___)

Improved DR to 91 and 100% at 5% and 10% of FP

What can we propose to women identified as at risk?

- 86 women at HR for PE (age, family Hx of PE, DM, cHTN, Hx of PE, FGR or IUFD)
- Uterine Doppler at 12-14 weeks
- If abnormal (bilat. notches, 75%) RCT of ASA 0.5 mg/kg
Conclusions 1
UtA Doppler

- Placentation is a process starting early that could be studied early
- UtA Doppler similar in I and II trimester
- Not perfect diagnostic indices, importance of false negative and false positive
- Future use of combination of tests

1. Uterine artery (UtA) doppler assessment

2. Cervical length (CL) measurement

Background
Relative risk of PTD <32 wks

Risk Factors
- Contrainctions
- Black Race
- Pelvic Infection
- BV Positive
- Vaginal Bleeding
- BMI <20
- Previous SPB
- Cervical Length <25 mm
- Fetal Fibronectin Positive

Relative Risk

Background

- Different strategies to predict preterm delivery in symptomatic and asymptomatic patients
- One of this strategy uses transvaginal sonography (TVS) to measure and examine the length and shape of the cervix

Background (corollary)

Singleton IVF pregnancies: higher risk for spontaneous PTD adjusted for age and parity

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Studies</th>
<th>nP</th>
<th>nN</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum Delay (\leq 35)</td>
<td>4</td>
<td>229/92</td>
<td>17422</td>
<td>0.05</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>4</td>
<td>170/62</td>
<td>68145</td>
<td>0.08</td>
</tr>
<tr>
<td>Intrapartum cause</td>
<td>4</td>
<td>229/92</td>
<td>17422</td>
<td>0.05</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>5</td>
<td>39/60</td>
<td>29192</td>
<td>0.06</td>
</tr>
<tr>
<td>Preterm delivery (\geq 30)</td>
<td>9</td>
<td>25/202</td>
<td>61462</td>
<td>0.19</td>
</tr>
<tr>
<td>Postdate delivery after (\geq 10)</td>
<td>5</td>
<td>150/173</td>
<td>115124</td>
<td>0.02</td>
</tr>
<tr>
<td>Distilith</td>
<td>7</td>
<td>70/595</td>
<td>218729</td>
<td>0.04</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>7</td>
<td>49/175</td>
<td>607216</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Jackson, Obstet Gynecol, 2004, 103(3), 551-83
**How to measure CL?**

- empty bladder
- dorsal lithotomy position
- placed transducer as close as possible to the cervix without pressure, to avoid any deformation or elongation of the cervical canal
- cervical canal identified by the sonolucent endocervical mucosa
- calipers measures the distance between the triangular area of echodensity at the external os and the T-shaped or V-shaped internal os

**CL and risk of PTD**

Asymptomatic women: value of CL <25 mm for prediction of PTD <34 w

<table>
<thead>
<tr>
<th>Weeks at test</th>
<th>pretest prob</th>
<th>posttest prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>4.1%</td>
<td>test+ 21.2% test- 3.3%</td>
</tr>
<tr>
<td>20-24</td>
<td>4.1%</td>
<td>test+ 15.8% test- 2.7%</td>
</tr>
<tr>
<td>&gt;24</td>
<td>4.1%</td>
<td>test+ 14.3% test- 2.6%</td>
</tr>
</tbody>
</table>

CL: Honest review for singletons  
Ultrasound Ob Gyn 2003;22:305-22*
How about TVS CL as 1st trimester screening for PTD?

- Detection of a short cervix in the late second trimester by means of TVS is a strong predictor of PTD
- Association with other tests (fibronectin)
- The role of this method before 16 weeks’ as a screening tool to predict PTD is still controversial

How about TVS CL as screening for PTD in the 1st trimester?

Study 1- prospective study
- 2469 unselected asymptomatic women with singleton pregnancies
- TVS CL measured at 13-15 weeks’ gestation
- spontaneous PTD at <37 wks (1.7%) and <34 wks (0.2%)

Study 1

<table>
<thead>
<tr>
<th></th>
<th>Term delivery</th>
<th>PTD &lt; 35 weeks</th>
<th>PTD 35-37 weeks</th>
<th>PTD &gt; 37 weeks</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cervical length</td>
<td>347*</td>
<td>43</td>
<td>36</td>
<td>6</td>
<td>No*</td>
</tr>
<tr>
<td>±1 SD</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>23-44</td>
<td>21-36</td>
<td>37-40</td>
<td>36-34</td>
<td></td>
</tr>
<tr>
<td>5th percentile</td>
<td>27</td>
<td>33</td>
<td>38</td>
<td>30</td>
<td>No*</td>
</tr>
<tr>
<td>2.5th percentile</td>
<td>21</td>
<td>26</td>
<td>30</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>95th percentile</td>
<td>44</td>
<td>44</td>
<td>44</td>
<td>45</td>
<td>No*</td>
</tr>
<tr>
<td>97.5th percentile</td>
<td>51</td>
<td>51</td>
<td>52</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

*Term delivery: none of cases of PTD; No, not significant; PTD, preterm delivery; SD, standard deviation.
How about TVS CL as screening for PTD in the 1st trimester?

Study 2 - Prospective study: 183 high risk asymptomatic women
- TVS at 10+0 wks to 13+6 wks
- 20% PD <35wks
- 5% patients had a cervix <25 mm (short cervix) before 14 weeks
- if short cervix prophylactic cerclage performed at 12-14 weeks

In high-risk patients destined to PTD

CL <25 mm rarely occurs <14 weeks (10 cases/183)

cervical changes predictive of preterm birth develop mostly after this gestational age

test sensitivity 14%
test specificity 97%
+LR 2.8 (95% CI 1.4-5.6)

How about TVS CL as screening for PTD in the 1st trimester?

Study 3 - prospective study, 152 asymptomatic women with singleton pregnancies
- TVS at 10-14 and 20-24 wks
- 10.5% PTD <35 wks (no statistically significant differences in previous history between the group that delivered at term and the preterm group)
CL measurement better predictor of preterm delivery at 20-24 weeks than at 10-14 weeks

How about sequential change of TVS CL?

Study 4- prospective study, 529 unselected women with singleton pregnancies
- TVS at 11-14 wks and 22-24 wks
- 4.3% PTD <37 wks

CL at 11-14 wks not significantly different between group delivered at term vs preterm
CL at the 22-24 wks is significantly shorter in the PTD group than in that delivered at term

The shortening is more rapid in pregnant women who deliver prematurely and have a history of previous PTD
How about sequential change of TVS CL?

Study 5- prospective study, 605 singleton gestation of high risk women
- 2601 TVS CL between 12 and 32 wks
- PTD <35 wks (17.7%), <32 wks (10.6%), <28 wks (6.7%)
- risk of PTD increases as the CL declines and as the gestational age decreases

Risk of preterm birth decreased by 6% for each additional mm of CL (OR 0.94, 95% CI 0.92–0.95)
by 5% for each additional week of pregnancy (OR 0.95, 95% CI 0.92–0.98)

Probability of delivery before 35, 32, 28 week respectively, by cervical length (mm) and week of pregnancy

Conclusions 2
Cervical length
- Before 15 weeks, cervical length is usually normal and at times artificially long (the lower uterine segment cannot be distinguished from the cervical canal).
- Short cervix in high risk women is relevant but present only in 5% of women destined to PB (i.e. multiple prior second trimester losses or large cold knife cones)
- Use of combinations of tests (fibronectin not applicable) not explored