First Trimester Screening for Down Syndrome

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First Trimester Screening
- Nuchal translucency sonography
- Serum screening
- NT quality assurance
- Cystic hygroma
- Nasal bone sonography
- Ductus venosus evaluation
- Other sonographic markers

Faster: First And Second Trimester Evaluation Of Risk

Research to Improve Down Syndrome Screening

1st Trimester Nuchal Translucency

1st Trimester Nuchal Translucency FASTER

5% FPR

11/9/2009
**1st Trimester Serum Markers**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Median MoM</th>
<th>11wk</th>
<th>12wk</th>
<th>13wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>fβhCG</td>
<td></td>
<td>1.89</td>
<td>2.05</td>
<td>2.23</td>
</tr>
<tr>
<td>PAPP-A</td>
<td></td>
<td>0.42</td>
<td>0.47</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Trisomy 21

<table>
<thead>
<tr>
<th>Marker</th>
<th>Detection Rate</th>
<th>11wk</th>
<th>12wk</th>
<th>13wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>fβhCG</td>
<td>22%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAPP-A</td>
<td>51%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Detection Rate at 5% FPR

- Including maternal age

**1st Trimester Combined Screening**

First Trimester Screening

- Nuchal translucency sonography
- Serum screening
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- Other sonographic markers

Standards with NT

- Difficult to do well
- Fractions of mm make difference
- Poorly performed NT worse than no NT at all

NT Sonography: Maintaining Standards

11/9/2009

**NT Sonography: Maintaining Standards**

1. NT margins clear
2. Mid-sagittal plane
3. Adequate zoom
4. Neutral fetal neck
5. Amnion seen separately
6. + calipers used
7. Calipers placed on the NT borders, not in space
8. Calipers perpendicular to long axis fetus
9. NT measured at its widest space

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**NTQR Process: Initial credentialing**

- **Track A:**
  - Theoretic course / online exam / submit 5 images
- **Track B:**
  - Online exam / submit 5 images
- **Track C:**
  - Prior FASTER / BUN / FMF Credentialing

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**NTQR Process: Ongoing credentialing**

- Pay annual fee ($150 / $35)
- Submit NT data to participating labs
- 30 measurements per year needed
- Median NT data monitored
- May need further image review or re-training

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**NTQR Process: Participating Providers**

- Sonographers
- Physicians
- Unknown
- Total
**NTQR: Participating Labs**
- ARUP Labs, UT
- FBR, ME
- Genzyme Genetics, MA
- LabCorp, NC
- NTD Labs, NY
- Quest Diagnostics, NJ
- Strong Health, NY
- UCONN, CT
- Yale New Haven, CT

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**1st Trimester Sonography**

**Cystic Hygroma**

**1st Trimester Sonography**

**Cystic Hygroma (1:285)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Simple Enlarged NT</th>
<th>Segmented Cystic Hygroma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>32</td>
<td>132</td>
</tr>
<tr>
<td>Aneuploidy</td>
<td>10 (1:3)</td>
<td>6 (1:5.5)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0</td>
<td>2 (1:11)</td>
</tr>
<tr>
<td>IUFD</td>
<td>3 (1:11)</td>
<td>4 (1:32)</td>
</tr>
</tbody>
</table>

| Aneuploidy               | 22 (1:6)          | 51 (1:21)                |
| Cardiac                  | 3 (1:43)          | 11 (1:98)                |
| IUFD                     | 4 (1:32)          | 7 (1:145)                |

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**Table 3. Comparative Outcome of Segmented Cystic Hygroma versus Simple Increased Nuchal Translucency**

- *Malone et al, Obstet Gynecol 2005;106:288*

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**Cystic Hygroma Vs Simple NT**

- Is septated cystic hygroma different to simple enlarged nuchal translucency, or are they part of a spectrum?
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11/9/2009

1st Trimester Sonography
Normal nasal bones

1st Trimester Sonography
Absent nasal bones

Nasal Bone Sonography: Criteria

1. Magnify until only head and upper thorax visible
2. Mid-sagittal plane
3. Angle insonation 45° to facial profile
4. Tilt probe side-to-side
5. 3 lines visible at nose:
   - Top line = nasal skin
   - Bottom line more echogenic = nasal bone
   - Front line above nasal skin = tip of nose
6. Nasal bone absent if not visible or less echogenic than skin

Nasal Bone Sonography: 45° Angle Insonation

1st Trimester Sonography
Absent nasal bone

Study  | n  | Trisomy-21 (%) | Euploid (%) |
-------|----|---------------|-------------|
Cicero et al | 701 | 73% (42/59)   | 11% (3/28) |
Otano et al | 194 | 50% (3/6)     | 3% (1/30)  |
Cicero et al | 3,829 | 67% (161/242) | 1% (2/235) |
Orlandi et al | 1,089 | 67% (10/15)  | 3% (1/31)  |
Zoppi et al | 5,532 | 70% (19/27)  | 0.2% (9/4,682) |
Viora et al | 1,906 | 60% (6/10)   | 0.2% (3/12,550) |
Total | 12,550 | 64% (199/300) | 1.4% (43/3,030) |

* Otano et al, Prenat Diagn 22:930, 2002
* Orlandi et al, UOG 22:36, 2003
* Orlandi et al, UOG 22:36, 2003
**Absent Nasal Bone**

FASTER

- Present: 4,779 (99.5%)
- Absent: 4,769

**Successful** 9 T18

- 4,801 (70%)
- 6,324

**Failed**

- 0.5%
- 22

- 0 T18
- 1,523 (24%)

**Absent Nasal Bone**

- Absent: 0 DS
- T18: 1

**FASTER**

- DS = Down Syndrome
- T18 = Trisomy 18

**Selective screening**

- Risk assessment in high risk patient is very different from population screening
- Second-line tests may be of value in special populations under direction of special referral centers
- Nasal bone sonography classic example of screening test which is valuable in select high risk cases, but not for general population screening

**Nasal Bone Sonography: Contemporary role**

- Evaluate nasal bones in intermediate risk patients
- Only performed at select centers
- May improve performance of combined screening for Down syndrome:
  - 90%-93% detection rate
  - 2.5%-3% false positive rate

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**Ductus Venosus Sonography**

**Normal DV**

**Abnormal DV**

- Reversed a-wave

**1st Trimester Ductus Venosus**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Aneuploid</th>
<th>Euploid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matias et al</td>
<td>486</td>
<td>81%</td>
<td>3%</td>
</tr>
<tr>
<td>Biliardo et al</td>
<td>186</td>
<td>65%</td>
<td>21%</td>
</tr>
<tr>
<td>Antolin et al</td>
<td>1,371</td>
<td>65%</td>
<td>4%</td>
</tr>
<tr>
<td>Zoppi et al</td>
<td>330</td>
<td>70%</td>
<td>12%</td>
</tr>
<tr>
<td>Murta et al</td>
<td>372</td>
<td>93%</td>
<td>2%</td>
</tr>
<tr>
<td>Mavrides et al</td>
<td>256</td>
<td>59%</td>
<td>5%</td>
</tr>
</tbody>
</table>

**1st Trimester Ductus Venosus**

Abnormal Flow Velocities and Aneuploidy

- Zoppi et al, 2002
- Murta et al, 2002
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**First Trimester Tricuspid Regurgitation**
Abnormal Regurgitation and Aneuploidy

- 1,557 high risk pregnancies, 11-13 weeks
- Tricuspid regurgitation > 60 cm/sec
  - 58 / 1323 (4%) normal pregnancies
  - 77 / 114 (68%) Trisomy-21

**First Trimester FMF Angle:**
Increased angle in Trisomy 21

- Fronto-maxillary facial angle
- Larger in T21
- Limited data

**First trimester screening:**
Current status

- 1st Trimester combined NT/serum most effective screening for T21
- Poorly performed NT is worse than no NT measurement
- Either cystic hygroma or simple NT ≥3.0mm indication for immediate CVS

**First trimester screening:**
Current status

- Secondary screening tools may have role in selected populations, but only in specialist hands:
  - Nasal bone sonography
  - Ductus venosus evaluation
  - Tricuspid regurgitation assessment
- NT Quality Control must be essential part of all screening programs