Ultrasound Soft Markers

Obstetrics Progress Lecture
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Educational Objectives

• To define and examine various ultrasound soft markers
• To determine how to manage soft markers detected in low-risk patients
• To examine use of the genetic sonogram in patients at high risk for fetal aneuploidy

Disclosures

• I have no financial or other disclosures regarding the information presented
Aneuploidy

• An abnormal number of chromosomes
• Up to 0.5% of neonates
• Detection is a major goal of prenatal screening programs

Aneuploidy

• Most common in live-births:
  – Trisomy 21 - 1/730
  – Monosomy X – 1/2,500
  – Trisomy 18 – 1/5,500
  – Trisomy 13 – 1/10,000

Aneuploidy

• Prenatal screening tests
  – First trimester test
  – Quadruple marker test
  – Sequential or integrated tests
  – Non-invasive prenatal testing
  – Ultrasound screening
Aneuploidy

• Ultrasound screening
  – Structural malformations
  – Growth restriction
  – Soft markers

Soft Markers

• US findings of uncertain significance
• Often considered normal variants
  – Seen in 11-17% of normal fetuses
• Increase risk for aneuploidy
  – Prevalence is higher in aneuploid fetuses
• Transient & have no clinical sequelae

First Trimester Soft Markers

Case

- 30 yo woman presents at 12 weeks’ gestation
- Dating scan incidentally shows an increased nuchal translucency
- How do you counsel her?
- What additional testing is offered?

Soft Markers

- First trimester
  - Nuchal translucency
  - Nasal bone
  - Doppler studies

Nuchal Translucency
Nuchal Translucency

- NT normally increases with GA
- Abnormal is > 95th% for CRL
- Increased NT at 10-14 weeks
  - Most reliable & widely used T21 marker

Nicolaides K. BJOG 1994

Nuchal Translucency

Nicolaides AJOG 2008

NT Screening

- FASTER Trial
  - Prospective study at 15 U.S. centers
  - 38,167 singletons; 117 with T21
  - Compared 1st & 2nd trimester aneuploidy screening
  - Increased NT detected 70% of T21

Malone. NEJM 2005
**Combined Screens**

<table>
<thead>
<tr>
<th>Name</th>
<th>Test</th>
<th>T21 Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined screen</td>
<td>NT + 1st trimester serum</td>
<td>87%</td>
</tr>
<tr>
<td>Sequential or</td>
<td>NT + 1st trimester serum + quad screen</td>
<td>95-96%</td>
</tr>
<tr>
<td>integrated</td>
<td></td>
<td></td>
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</tbody>
</table>

Malone, NEJM 2005

**Nuchal Translucency**

- Increased NT is also a marker for:
  - Structural abnormalities
    - Cardiac
    - Skeletal
    - Renal
    - Omphalocele
      - Diaphragmatic hernia
  - Genetic abnormalities
  - Adverse pregnancy outcome

**Case**

- 30 yo woman presents at 12 weeks’ gestation
- Dating scan incidentally shows an increased nuchal translucency
- How do you counsel her?
- What additional testing is offered?
Case

- Management:
  - Refer to prenatal screening center
  - Genetic counseling
  - Offer invasive prenatal diagnosis
    - Can consider non-invasive prenatal testing
    - Serum screening not recommended
  - Targeted scan & fetal echocardiogram

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Nasal Bone

- Echogenic line within the nasal bridge
- Controversial use for T21 detection due to variable results
  - 65% sensitive in European studies
  - 0% sensitive in American FASTER study

- Rosen, Obstet Gynecol 2007
- D’Alton, Semin Perinatol 2005
Nasal Bone

• Important factors:
  – Training & experience of operator
  – Ethnic variation
  – Gestational age
  – Aneuploidy risk of population
• Best when combined with NT & serum

Doppler Studies

• Not used routinely but have been associated with aneuploidy
  – Ductus venosus reversed a-wave
  – Tricuspid regurgitation
  – Umbilical artery REDV

Second Trimester
Soft Markers
Case
• 25 yo woman presents at 18 weeks’ gestation
• Anatomy survey shows an **echogenic intracardiac focus**
• How do you counsel her?
• What additional testing is offered?
• What about same finding in a 35 yo?

Trisomy 21
• 30% have structural malformations
  – Congenital heart disease
  – Cystic hygroma
  – Bowel atresia
• 20% have isolated soft markers
• 50% may not be detectable by US

Trisomy 21
• Soft markers
  – Nuchal fold
  – Nasal bone
  – Echogenic focus
  – Echogenic bowel
  – Shortened long bones
  – Pyelectasis
  – Ventriculomegaly
Nuchal Fold

- Distance between the outer occipital bone & outer skin in an axial plane
- Abnormal ≥ 6 mm at 15-20 weeks
- One of the best soft markers for T21
  - Sensitivity 40%
  - Specificity 99%

Benacerraf, Semin Perinatol 2005

Nasal Bone
Nasal Bone

- Hypoplasia
  - Defined by MoM, ratio to BPD or < 2.5 mm
- Using absence or hypoplasia for T21:
  - 78% sensitive
  - 99% specific
- Absent in 0.3-1% normals

Cusick, Ultrasound Obstet Gynecol 2007

Echogenic Focus

- Bright spot in either ventricle with echogenicity similar to bone
  - Papillary muscle calcification
- 15-30% of T21 vs. 4-7% normals
- Not associated with cardiac anomalies or dysfunction
Echogenic Bowel

• Echogenicity of fetal bowel similar to bone
• 10-25% of T21 vs. 1-3% of normals
• Other associations:
  – FGR
  – Cystic fibrosis
  – Congenital infection
  – Intraamniotic bleeding
  – Bowel obstruction

Shortened Long Bones

<table>
<thead>
<tr>
<th>Biometry</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>BPD:</td>
<td>47.3 mm</td>
</tr>
<tr>
<td>OFD:</td>
<td>57.5 mm</td>
</tr>
<tr>
<td>HC:</td>
<td>166.1 mm</td>
</tr>
<tr>
<td>AC:</td>
<td>142.5 mm</td>
</tr>
<tr>
<td>FL:</td>
<td>27.9 mm</td>
</tr>
<tr>
<td>LUM:</td>
<td>28.4 mm</td>
</tr>
<tr>
<td>CER:</td>
<td>19.4 mm</td>
</tr>
<tr>
<td>NFT:</td>
<td>7.1 mm</td>
</tr>
<tr>
<td>Estimated FW:</td>
<td>277 gm. 0 lb 10 oz 51 %Tile</td>
</tr>
</tbody>
</table>

Gestational Age: 19w 0d
Clinical EDD: 19w 0d
Shortened Long Bones

- Varying definitions; typically compared to expected length for BPD
  - < .91 for femur
  - < .89 for humerus
- Ethnic variation

Nyberg, Ultrasound Obstet Gynecol 1998

Increased risk for aneuploidy
- Femur, 54% of T21 vs. 5% of normals
- Humerus, 49% of T21 vs. 2% of normals
- Severe shortening or abnormal long bones are a sign of skeletal dysplasia

Benacerraf, Semin Perinatol 2005

Pyelectasis

www.centrus.com.br
Pyelectasis

- Renal pelvis 4-9 mm
- 10-25% of T21 vs. 1-3% of normals
- Can be due to obstruction or reflux
- Typically resolves in pregnancy or postnatally
- Third trimester follow-up indicated

Ventriculomegaly

- Lateral ventricles > 10 mm
- Associated with aneuploidy, 4-14%
- Can also be associated with CSF obstruction, brain malformations, atrophy
- When mild, majority of outcomes are normal

Waller, Ultrasound Clin 2011
Other Markers

- Not currently recommended:
  - Clinodactyly
  - Sandal gap toe
  - Widened iliac angle
  - Short ear length
  - Short frontal lobe

Trisomy 18

- Ultrasound
  - Structural anomalies
    - Brain, cardiac
    - GI, renal, extremities
  - Soft markers
    - Choroid plexus cysts
    - Clenched hands
Choroid Plexus Cyst

- Small sonolucent structure in the choroid plexus
- Trapping of CSF by entangled villi
- Variable size, number & location
- 40-60% of T18 vs. 1-2% normals
- Not associated with brain anomalies

Waller, Ultrasound Clin 2011

Management
Soft Markers

• Soft marker screening is not indicated on basic US exam

• Aneuploidy screening best accomplished with serum +/- NT
  – High detection rates
  – Low false-positive rates

Soft Markers

• If a soft marker is detected:
  – Detailed anatomic survey indicated
  – Correlate the finding with baseline risk for aneuploidy
    • Age
    • Serum screen
    • Family history

Soft Markers

• Low-risk patients
  – Consider invasive prenatal diagnosis for:
    • Nuchal thickening ≥ 6 mm
    • A major structural anomaly
    • More than one soft marker
Genetic Sonogram

- **High-risk patients**
  - US can supplement serum screening
  - Genetic sonogram = targeted US for structural anomalies & soft markers
  - Used in most prenatal screening programs
  - T21 sensitivity, 59-87%


Genetic Sonogram

- **Normal US**
  - Reduces T21 risk
  - May allow avoidance of diagnostic testing
  - Reduce loss of normal fetuses from amnio

- **Abnormal US**
  - Lower false-negative serum screens
  - Improve detection of affected fetuses

Genetic Sonogram

- **Limitations**
  - Higher false-positive rates than other screening methods, 10%
  - May reduce detection of T21 if US normal
  - Markers subjective, dependent on GA & habitus

  Smith-Bindman, Prenat Diagn 2007
Genetic Sonogram

• Combining markers has been well-validated in screening programs
• Likelihood ratios used to revise baseline risk from age or serum screen
• New individualized risk used in decision-making for invasive prenatal diagnosis

Genetic Sonogram

• FASTER trial

<table>
<thead>
<tr>
<th>US Finding</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural anomaly</td>
<td>17</td>
<td>0.92</td>
</tr>
<tr>
<td>Nuchal fold</td>
<td>49</td>
<td>0.82</td>
</tr>
<tr>
<td>Femur length</td>
<td>4.6</td>
<td>0.73</td>
</tr>
<tr>
<td>Humerus length</td>
<td>5.0</td>
<td>0.90</td>
</tr>
<tr>
<td>EIF</td>
<td>6.3</td>
<td>0.75</td>
</tr>
<tr>
<td>Pyelectasis</td>
<td>5.5</td>
<td>0.94</td>
</tr>
<tr>
<td>Echogenic bowel</td>
<td>24</td>
<td>0.96</td>
</tr>
<tr>
<td>Ventricular megaly</td>
<td>25</td>
<td>0.95</td>
</tr>
</tbody>
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Aagaard-Tillery, Obstet Gynecol 2009

Genetic Sonogram

• Take T21 risk from serum screen or age:
  – Multiply this fraction by the LR+ for each US finding and by the LR- for each absent finding
  – Generate a revised T21 risk
• The presence of a structural anomaly or soft marker increases risk for T21
• A normal US reduces T21 risk by ~50%
Genetic Sonogram

- Performs best for T21 detection after a quad screen
  - Increases sensitivity from 81 to 90%
- Not as helpful after sequential screening
  - Increases sensitivity from 97 to 98%

Aagaard-Thiry, Obstet Gynecol 2009

Case

- 25 yo woman presents at 18 weeks’ gestation
- Anatomy survey shows an echogenic intracardiac focus
- How do you counsel her?
- What additional testing is offered?
- What about same finding in a 35 yo?

Case

- Low-risk patient
  - Detailed anatomic survey
  - Offer a quad screen
- High-risk patient
  - Targeted ultrasound & genetic counseling
  - Consider invasive prenatal diagnosis or non-invasive prenatal testing
Conclusions

- Aneuploidy is associated with structural defects, soft markers & FGR that may be detected by US
- Soft markers increase the risk for aneuploidy but are most often seen in normal fetuses
- The best soft markers for T21 are nuchal & nasal bone assessments

Conclusions

- Soft markers should not be used in isolation in low-risk patients
- A genetic sonogram should only be used in high-risk patients at a prenatal screening center
  – Performance is best when used to modify age or quad screen risk
The End!