Ultrasound Soft Markers for Aneuploidy

Obstetrics Nursing Progress Lecture
February 22, 2019

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Educational Objectives

• Define ultrasound soft markers and determine their significance
• Manage soft markers in low-risk & high-risk patients

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

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

- Prenatal screening tests
  - First trimester screen
  - Quad screen
  - Integrated screen
  - Cell-free DNA
  - Ultrasound screening
Aneuploidy

• Ultrasound screening
  – Structural malformations
  – Fetal growth restriction (FGR)
  – Soft markers

Soft Markers

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


First Trimester Soft Markers
Case

- 30 yo woman presents at 12 weeks’ gestation
- Dating scan incidentally shows an increased nuchal translucency
- How should she be counseled?
- What additional testing is offered?

First Trimester Soft Markers

- Nuchal translucency
- Nasal bone

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

- 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>FTM screen</td>
<td>NT + FTM serum</td>
<td>87%</td>
</tr>
<tr>
<td>Integrated</td>
<td>NT + FTM serum + quad screen</td>
<td>95-96%</td>
</tr>
</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

### Nasal Bone

- Image of normal and abnormal nasal bones.
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

Case

- 30 yo woman presents at 12 weeks’ gestation
- Dating scan incidentally shows an increased nuchal translucency
- How is she counseled?
- What additional testing is offered?
Management of Increased NT

• MFM referral for:
  – Genetic counseling
  – Consider invasive prenatal diagnosis
    • If declined, consider cf-DNA
    • Hormone-based maternal serum screening not recommended
  – Schedule targeted scan & fetal echocardiogram

Midtrimester Soft Markers

Case

• 25 yo woman presents at 18 weeks’ gestation
• Anatomy survey shows a choroid plexus cyst
• How should she be counseled?
• What additional testing is offered?
• What about same finding in a 40 yo?
• 30% have structural malformations
  – Congenital heart disease
  – Cystic hygroma
  – Bowel atresia
• 20% have isolated soft markers
• 50% may not be detectable by US

• Soft markers
  – Nuchal fold
  – Nasal bone
  – Echogenic focus
  – Echogenic bowel
  – Shortened long bones
  – Urinary tract dilation
  – Ventriculomegaly

Nuchal Fold
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

- 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
- 20-30% of T21 vs. 3-5% normals
- Not associated with cardiac anomalies or dysfunction

Echogenic Bowel
Echogenic Bowel
- Echogenicity of fetal bowel similar to bone
- 10-20% of T21 vs. 1-3% of normals
- Other associations:
  - FGR
  - Cystic fibrosis
  - Congenital infection
  - Intraamniotic bleeding
  - Bowel obstruction

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
Shortened Long Bones

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

Benacerraf, Semin Perinatol 2005

Urinary Tract Dilation

- Renal pelvis $\geq$ 4-7 mm
- 10-25% of T21 vs. 1-3% of normals
- Can be due to obstruction or reflux
- Typically resolves in pregnancy or postnatally
**Ventriculomegaly**

- Lateral ventricles ≥ 10 mm
- 4-13% of T21 vs. 0.1-0.4% of normals
- Can also be associated with CSF obstruction, brain malformations, atrophy
- When mild, majority of outcomes are normal

*Waller, Ultrasound Clin 2011*

**Trisomy 18**

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

- Small cyst in the choroid plexus
- Trapping of CSF by entangled villi
- Variable size, number & location
- 30-50% of T18 vs. 1-2% normals
- Not associated with brain anomalies

Waller, Ultrasound Clin 2011
Two Vessel Cord

- Absent umbilical artery
- 20% of T18 vs. 1% of normals
- Can be associated with anomalies, typically urologic or cardiac
- Risk of T18 is increased when other malformations are present

Management of Midtrimester Soft Markers
Midtrimester Soft Markers

• Soft marker screening is not indicated on basic anatomy US
• Aneuploidy screening best done with maternal serum & NT
  – High detection rates
  – Low false-positive rates

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

Midtrimester Soft Markers

• Low-risk patients
  – Provide reassurance
  – Obtain quad screen
Midtrimester Soft Markers

• MFM referral indicated:
  – Thickened nuchal fold
  – Ventriculomegaly
  – Echogenic bowel
  – Persistent urinary tract dilation
  – Two vessel cord

Midtrimester Soft Markers

• High-risk patients
  – AMA
  – Abnormal serum screen
  – Family history of aneuploidy

Midtrimester Soft Markers

• MFM referral for:
  – Genetic counseling
  – Targeted ultrasound
  – Consider invasive prenatal diagnosis or cf-DNA
Case

- 25 yo woman presents at 18 weeks’ gestation
- Anatomy survey shows a choroid plexus cyst
- How should she be counseled?
- What additional testing is offered?
- What about same finding in a 40 yo?

Case

- 25 yo patient
  - Careful anatomic survey
  - Offer a quad screen
- 40 yo patient
  - MFM referral for further evaluation

Conclusions
Conclusions

• Aneuploidy may be associated with US findings including structural defects, soft markers & FGR
• Soft markers increase the risk for aneuploidy but are most often seen in normal fetuses

Conclusions

• The best soft markers for T21 are nuchal & nasal bone assessments
• MFM referral after detection of a soft marker depends on:
  – Baseline risk for aneuploidy
  – Type of soft marker
  – Additional US findings

Reference

• Society for MFM & American College of Ob/Gyn Practice Bulletin #163, May 2016