Ultrasound Markers for Aneuploidy: “Soft Markers” can be Squishy others Indicate Intrinsic Conditions. A Reminder that the Comprehensive Sonogram Remains Key in the NIPS Era

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Given @ Benton Convention Center WS, NC, 4.9.16
Disclosure Information

I have no financial relationships to disclose and will not discuss off label use and/or investigational use in my presentation.

“Son, if you really want something in this life, you have to work for it. Now quiet! They’re about to announce the lottery numbers.”
- Homer Simpson
Disclosures: None Unfortunately...patent pending.
Objectives

- To be able to recognize common ultrasound markers of aneuploidy and acknowledge that SOME are “soft”
- To associate markers with increased risk for aneuploidy
- To have awareness patient perspective
- To be able to place in context of screening
Expectation

Yep. There it is... It's definitely a boy.
Patient Needs

• Looking for reassurance but ...

• Unrealistic expectations
  – Want to know *everything* is “normal”
  – Want a worry to be dispelled
  – Want guarantees
1st trimester u/s screening

- NT: defined as a collection of fluid under the skin behind the neck;
- Measured between 11-14 weeks gestation
- Increased thickness confers increased risk for aneuploidy (e.g., T13, T18, T21, XO), major defects (e.g., heart defects), and FD
- Etiology: lymphatic drainage, heart failure, extracellular matrix
- Screen-positive rate of 5% yields 77% sensitivity (T21).
Does Size Matter?
Hypoplastic Nasal Bone:

- 1-2% unaffected pregnancies
  (Caucasian; 5% Asian; 9% AA)
- 60% T21 fetuses
Second-Trimester Ultrasound Markers for Down Syndrome

- Brachycephaly
- Increased nuchal thickness
- Short/absent nasal bone
- Hyperechoic bowel
- Shortened femur
- Shortened humerus
- Renal pyelectasis/UTD
- Echogenic intracardiac focus

- Hypoplasia of midphalanx of 5th digit
- “Sandal gap”
- Foot length

More Definitive Findings/Markers:
- AV canal defect
- Duodenal atresia
Increased nuchal fold

- ≥6mm in 2\textsuperscript{nd} trimester
- Most distinctive of the "soft" markers
- Present in 35\% T21 but 0.7\% normal fetuses
Cystic Hygroma

- Usually septate
- 66% assoc’d w/chromosomal abnormality:
  - Turner (most)
  - T21, 18, 13
  - Noonan syndrome
Brachycephaly:
- Round cranial contour
- 63-98% T21 fetuses
- Premature closure of coronal suture
Echogenic Intracardiac Focus

- 5-8% normal pregnancies*
- More common in Asians
- 1 in 5-6 of T21
- LR of T21: 1.8-2.8
- By itself, it minimally changes risk.
AV Canal Defect:

- Missing the “crux” of the heart on 4CH view
- T21 found in 40% of those with this finding! (get an amnio)
- 20% have some other chromosomal anomaly or syndrome
Echogenic Bowel:

- Normal bowel echogenicity is $\geq$ liver but $\lt$ bone
- hence, “bright as bone”
- Caveat: high frequency U/S increases false positive (turn down the gain)
- Present in 1% fetuses
Echogenic bowel

• LR (T21): 5.5 to 6.7

• Other assoc’s:
  – Fetal CF
  – CMV
  – IUGR
  – Abruptio Placenta, Invasive procedure (CVS) or Swallowed SCH (Swallowed blood)
Duodenal Atresia (DA):

- “double bubble” on u/s
- Found in association with polyhydramnios
- Lack of normal duodenal canalization
- 50-70% have other anomalies
- 30% have T21
- All fetuses should be karyotyped
Urinary Tract Dilation (formerly known as pelviectasis)

- 3% normal fetuses
- transient/idiopathic
- LR 1.5 to 1.9 of T21 when isolated
- 0.46% fetuses w/isolated case have aneuploidy
- Renal pelvis diameter:
  - <4mm (<32wks)
  - <7mm (>32 wks)
  - >10mm ~always pathologic (UPJ obstruction/VUR)
Short proximal extremities (humerus and femur)

• Relative to expected length for BPD

• Ratio of observed to expected length < 0.91 or BPD/femur ratio of >1.5 has a LR 1.5-2.7 when present as an isolated finding

• Short humerus is more strongly related to T21 (LR 2.5 to 7.5)

FitzSimmons and Droste
- Tip of 5th finger turns inward
- NS Associated with T21
- 60% T21 have it
- 2-4% of normal hands
- Amniocentesis if not isolated or high risk (eg, AMA or abnormal screen test)
• Remember: usually normal
• Etiology: delayed or absent ossification of the middle phalanx
Sandal Gap Toe

- B/W 1\textsuperscript{st} & 2\textsuperscript{nd} toe
- Most normal variant (positional; or look at the family’s feet)
- 45% fetuses with T21
- If isolated, minimal increase in background risk = SOFT!
2nd trimester u/s and risk of T21

- Sonographic finding observed in 68.8% fetuses with T21 compared with 13.6% of control fetuses (p<0.001; n =8914 pregnancies, 186 with T21)
- 1/3 T21 fetuses have no marker on u/s
- When “genetic u/s” = normal, estimated risk of T21 decreases by 60-65%. (Nyberg et al); can be combined with markers as well.
Trisomy 18

- Micrognathia
- Choroid plexus cysts
- Strawberry-shaped head
- Absent corpus callosum
- Enlarged cisterna magna
- Facial cleft
- Nuchal edema
- Esophageal atresia
- Exomphalos

- Renal defects
- Myelomeningocele
- Growth restriction
- Shortening of the limbs
- Radial aplasia
- Overlapping fingers
- Talipes/club foot
- Rocker bottom feet
Profile
Micrognathia

- Small mandible
- Jaw index (AP mandible/BPD): <21 (100% PPV)
- 70% polyhydramnios
- >50% airway difficulty at birth
- 30% feeding problems
- 66% abnormal chromosomes
Choroid Plexus Cyst (CPC)
Choroid Plexus Cysts (CPCs)

• 1% fetuses (16-24 wks) = MOST NORMAL VARIANT
• 1/3 T18 fetuses
• 3% fetuses with CPC have T18;
• when isolated, it has an increased risk for T18 of 9...given low incidence, typically remains SOFT
• Size, location or persistence does not alter risk
Still Awake?
Cleft Lip
Palate
Cleft Lip & Palate

- Failure of lip/palate closure
- Aneuploidy rate related to type CL/CP
- Bilateral or midline CL/CP is most commonly associated with aneuploidy
- Most common aneuploidy = T13 or T18
Ventriculomegaly
Myelomeningocele
Lower Extremities
Club Feet
Trisomy 13

- Holoprosencephaly
- Microcephaly
- Facial abnormalities
- Cardiac abnormalities
- Enlarged and echogenic kidneys
- Omphalocele
- Post axial polydactyly
Microcephaly/ Holoprosencephaly

[Ultrasound images of fetal brain with measurements and labels]
Hypotelorism, Probocis, Strawberry Skull
Polydactyly
<table>
<thead>
<tr>
<th>US finding</th>
<th>Population prevalence</th>
<th>Background risk multiplier</th>
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<tbody>
<tr>
<td>Nuchal fold &gt;6mm</td>
<td>0.5</td>
<td>10</td>
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<td>Echogenic bowel</td>
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<td>6</td>
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<td>EICF</td>
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<td>CPC</td>
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<td>Pyelectasis/UTD</td>
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<td>Clinodactyly</td>
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<td>NS (~1)</td>
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<td>Short Humerus</td>
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<td>Short Femur</td>
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<td>No. of Markers or Major Abnormality</td>
<td>LR</td>
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<td>Major Abnormality</td>
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# Cell Free DNA: Perspective for T21

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<tr>
<th>Maternal Age (Years)</th>
<th>Prevalence at 10 weeks GA</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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# Cell Free DNA: Perspective for T18

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# Cell Free DNA: Perspective for T13

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Thank You
Happy Spring!