Ultrasound Screening for Down Syndrome

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Patient EH

- 35 y/o G0P0
- IVF treatment; now pregnant with di/di twins, GA by LMP = 13 weeks, 0 days
- Presents with bleeding
- Undergoes transabdominal ultrasound
- Presenting fetus is “ultrasonically somewhat increased risk for Down” due to increased nuchal translucency
Down Syndrome: Background I

- Trisomy 21: most common chromosome abnormality among live births (1/730)
- Clinical Manifestations:
  - Mental Deficiency (Average IQ 25-50)
  - Flat facial profile (90%)
  - Hypotonia (80%)
  - Hyperflexibility of joints (80%)
  - Upward slanting palpebral fissures (80%)
  - Simian crease (45%)
  - Congenital heart disease (e.g. Endocardial cushion defect, VSD – 40%)
Down Syndrome: Background II

- Pathogenesis: Meiotic non-disjunction → increasing risk with advanced maternal age

From www.uptodate.com, adapted from Cuckle, HS et al. BJOG 1987; 94:387
Screening I: AMA

- 97% of Down pregnancies occur in families with no previous history of the syndrome.
- Amniocentesis: Effective diagnosis but 1% risk fetal loss.
- Only 12.9% of all children are born to mothers age > 35 → only about 30% of Down babies are born to “AMA” mothers.
- Goal: isolate highest risk pregnancies for amniocentesis/CVS.
Screening II: Serum

- Serum Screening:
  - "Triple Test": Free B-hCG, AFP, uE3
    -- 2nd trimester
    -- 69% sensitive
    -- 9.3% false positive
  - "Quadruple Test": Triple Test + inhibin A
    -- 2nd trimester
    -- 80% sensitive
    -- 6.2% false positive
Screening III: Nuchal Translucency

- Best overall screening test:
  Quadruple test (2nd trimester) + PAPP-A (1st trimester) + NT at 10 weeks → 85% sensitivity, 1.2% false-positive rate

Ultrasound: Basics I

- Current is applied to a transducer made of piezoelectric crystal, generating high-frequency sound waves which pass through the soft tissue.
- Interface of different densities (acoustic impedance) reflects some of the energy, proportional to the difference in densities.
- The reflected energy generates small voltage, amplified and represented by light/dark on screen.
  - Bone, air, fat: white
  - Fluid: dark
  - Solid organs: grey
Ultrasound: Basics II

- **Advantages:**
  - No ionizing radiation \(\rightarrow\) pregnancy
  - Any plane
  - Inexpensive
  - Portable - bedside
  - Real-time images

- **Disadvantages:**
  - Fuzzy images
  - Skill-dependent
Routine Ultrasound

- 11-14 weeks
- Assess:
  -- Viability, number, size
  -- Anatomy:
    -- Head/Brain (BPD, HC)
    -- Cardiac
    -- Abdomen (stomach, bowel, AC)
    -- Urinary (bladder, kidneys)
    -- Limbs (FL, HL)
Nuchal Translucency Measurement

- Increase in the size of the normal, clear area behind the fetal neck (>2.5 mm or 95th percentile)
- Optimal time: 11-13 weeks
- Transabdominal or transvaginal
- Sagittal Section
- Magnification: Fetus should occupy 75% of the image
- Distinguish between fetal skin and amnion
- Fetus in neutral position (i.e. not flexed/extended)

From http://www.nuchalscans.co.uk/images/scan2.gif
NT Pathophysiology

- Cardiac malformation/dysfunction
- Alterations in the extracellular matrix
- Lymphatic abnormalities
- Precise etiology remains unknown
Patient EH
Patient EH: Twin A
Patient EH: Twin B
NT: “Dose Response”

- Increased incidence of trisomies 21, 18, and 13:
  
  \[
  \begin{align*}
  \text{NT} &= 3\text{mm} \rightarrow 3\times \\
  \text{NT} &= 4\text{mm} \rightarrow 18\times \\
  \text{NT} &= 5\text{mm} \rightarrow 28\times \\
  \text{NT} &= >6\text{mm} \rightarrow 36\times
  \end{align*}
  \]

- Patient EH, Twin A: Only mildly increased NT (2.6mm) \(\rightarrow\) mildly increased risk

- Recommend “quadruple test”
Other US “soft markers”

- Frequently found among normal fetuses; should not be used in isolation for Down screening
- Useful in combination with serum screening and NT to modify risk
  - Shortened humerus/femur
  - Hyperechoic bowel
  - Hypoplastic nasal bone
  - Endocardial cushion defect
  - Pyelectasis
“Soft Markers”

Patient LG

PACS, BIDMC

Echogenic Bowel
Patient LG

Short femur

PACS, BIDMC
Patient LG

Renal dilatation
Normal 4-Chamber Heart
Patient SS

Endocardial Cushion Defect
Patient SS

Normal nasal bone
Nasal Bone Hypoplasia

- Present in 62% of trisomy 21 fetuses, 1.2% chromosomally normal fetuses


http://www.femalepatient.com/html/arc.sel/sept02/article01.asp
Differential Diagnosis

- Smith-Lemli-Optiz syndrome
- Meckel syndrome
- Iniencephaly
- Cardiosplenic syndromes
- TORCH infections
- Normal pregnancy
## Integrated screening

### Sonographic Scoring for Down Syndrome

<table>
<thead>
<tr>
<th>Marker</th>
<th>Likelihood ratio</th>
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<tbody>
<tr>
<td>Structural anomaly</td>
<td>25</td>
</tr>
<tr>
<td>Nuchal thickening</td>
<td>18.6</td>
</tr>
<tr>
<td>Echogenic bowel</td>
<td>5.5</td>
</tr>
<tr>
<td>Shortened humerus</td>
<td>2.5</td>
</tr>
<tr>
<td>Shortened femur</td>
<td>2.2</td>
</tr>
<tr>
<td>Echogenic intracardiac focus</td>
<td>2</td>
</tr>
<tr>
<td>Renal pyelectasis</td>
<td>1.6</td>
</tr>
<tr>
<td>Normal examination</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Integrated Screening

- Maternal age
  - Previous history
- Fetal nuchal translucency
- Maternal β-hCG & PAPP-A
- Counselling
- Chorionic villus sampling
Patient EH

- Age = 35 → 1:274
- Increased NT → 1:15

→ Advise quadruple serum screen
→ Amniocentesis/CVS
Patient LG

- Age = 40 → 1:74
- Echogenic bowel → 1:13
- + Short femur → 1:4.5

→ Amniocentesis/CVS
Patient SS

- Age = 28 → 1:855
- Endocardial cushion defect → 1:34.5

→ Advise quadruple serum screen
→ Amniocentesis/CVS
ACOG Recommendations (2001)

- “A combination of one major or two minor ultrasound markers of Down syndrome substantially increases risk and warrants further counseling regarding invasive testing”

- “The use of ultrasonographic screening for Down syndrome in high-risk women (e.g., women age 35 years and older) to avoid invasive testing should be limited to specialized centers”
Summary

- The challenge of screening for Down syndrome is one of risk-assessment.
- Ultrasonographic markers such as NT can significantly alter a patient’s risk assessment.
- Integrated screening -- US combined with maternal age and serum screening -- provides a sensitive and specific screen for Down syndrome.
References

- Benacerraf, B. Prenatal Diagnosis 2002; 22: 798-801
- Jameson, L. J. Harrison’s Textbook of Internal Medicine.
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