Atlas of Ultrasound Findings in Down Syndrome

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Agenda

• Background of Down Syndrome
• Patient Cases
• Menu of Tests
• Full Fetal Ultrasound
• Screening Methods for Down Syndrome
• Ultrasound Findings
• Summary
**Down Syndrome: Background**

- **Trisomy 21**: Most common chromosomal abnormality among liveborn infants (1/629)
- **Caused by chromosomal aberration**
  - Most often non-disjunction during maternal meiotic segregation
  - Strong association with increased maternal age
  - Less often via Robertsonian translocation

Down Syndrome: Clinical Features

- Mental Retardation
- Congenital heart defects (50%)
- Characteristic facies (90%):
  - upslanting palpebral fissure
  - epicanthal folds
  - flat nasal bridge
  - small ears
  - macroglossia
- Dysmorphic features:
  - transverse palmar crease
  - hypotonia
  - hyperextensible joints
- Increased rates of disease:
  - Alzheimer’s disease
  - leukemia
  - infections

Our Patient: Presentation

• 32-year-old female G1P0 presenting at 20 weeks 1 day gestational age by dates for routine full fetal survey
  – Declined genetic screening
  – No known history of inherited genetic or chromosomal disorders
Menu of Tests: Ultrasound

– Advantages:
  • Non-invasive
  • Not harmful to fetus
  • Cost-effective
  • Portable
  • Can guide procedures

– Disadvantages
  • Highly operator-dependent

http://www.umm.edu/pregnancy/000233.htm
Ultrasound: Mechanics

- Piezoelectric crystals convert electrical energy into sound waves that are released in synchronized pulses.
- Transducer then "listens" for the returning echoes.
- Real-time image created from sound waves reflected back from organs, fluids and tissue interfaces of the fetus.
Ultrasound: Safety

- Should only be performed with valid medical indication and with lowest possible exposure setting to gain necessary information
  - Recent studies show that prolonged ultrasound exposure may affect migration of brain cells in fetal mice (Rakic 2006)
- “Keepsake fetal imaging” is not condoned by FDA or AIUM!
- Routine 2nd trimester full fetal survey is current recommendation
Routine 2\textsuperscript{nd} Trimester Prenatal Ultrasound

• Purpose is to obtain information to enable provision of optimal antenatal and perinatal care
• Information Obtained:
  – Fetal viability
  – Gestational age, expected date of delivery
  – Number of fetuses
  – Fetal survey to detect congenital anomalies
  – Assessment of amniotic fluid volume
  – Placental location (2\textsuperscript{nd} trimester)
• Performed 18-20 weeks – Why?
  – Optimal balance between visualization of anatomy and time for diagnostic procedures and legal termination
2nd Trimester US Findings of Trisomy 21

1) Major Structural Defects
   – Aneuploidy often associated with anomalies
   – NB: 2-3% of infants are found to have major birth defects, not all with T21

2) “Soft-Signs”
   - Markers which increase risk but alone are of uncertain clinical significance. Previously utilized in ‘genetic sonogram’ to calculate risk based on quantity of markers found
   - Now, presence of any marker leads to referral for fetal karyotyping
   - The more soft signs evident, the higher the risk
Major Structural Defects associated with aneuploidy

- **CNS:**
  - Ventriculomegaly
  - Dysgenesis of corpus callosum
  - Abnormal posterior fossa

- **MSK:**
  - Syndactyly
  - Clinodactyly

- **Face:**
  - Cleft palate
  - Low set/small ears
  - Macroglossia
  - Micrognathia

- **Cardiac:**
  - VSD
  - Endocardial cushion defect
  - Hypoplastic left heart syndrome
  - Tetralogy of Fallot

- **GI:**
  - Esophageal/duodenal atresia
  - Diaphragmatic hernia,
  - Ompalocele

- **GU:**
  - Hydronephrosis
  - Renal Agenesis
2nd Trimester Sonographic Markers
Aka “Soft Signs”

- Nuchal fold
- Absent/hypoplastic nasal bone
- Short femur
- Short humerus
- Echogenic bowel
- Echogenic intracardiac focus
- Pyelectasis
- Heart defect
- Mild ventriculomegaly
- Hypoplasia of fifth digit
- Wide iliac angle
- Ear length
- Frontothalamic distance
Back to our Patient

- 32-year-old female G1P0 presenting at 20 weeks 1 day gestational age by dates for routine full fetal survey
  - Declined genetic screening
  - No known history of inherited genetic or chromosomal disorders
Our Patient: Fetal Ventriculomegaly on 20w US

Transverse Ultrasound
- 17mm Dilated Right Lateral Ventricle
- Dangling Chorioid
Ventriculomegaly

- Enlargement of cerebral ventricles which represents abnormal brain development
- Measurement taken at atrium of lateral ventricle; portion where body, posterior horn and temporal horn converge
  - Ventriculomegaly >10 mm width
    - Severe ventriculomegaly >15mm width
  - Dangling choroid plexus characteristic in severe cases
- DDx: Wide variety genetic and environmental causes
  - T21, 18, 13 (5-25% risk of aneuploidy)
  - CMV and Toxoplasmosis
Our Patient: Bilateral hydronephrosis on 20w US

Transverse Ultrasound
- 6 mm dilated left kidney
- 5 mm dilated right kidney
- Aorta
- IVC
- Spinal Column

Courtesy of Dr. Olga Brook
Renal Pyelectasis

- Enlargement of the fluid-filled renal pelvis (>4mm)
- DDx:
  - Commonly seen in normal fetuses (2-3%)
    - May be related to maternal hydration, fetal bladder distention
    - Look for flow at the bladder, reimage kidneys because enlargement may be dynamic
  - GU malformation
    - Fetal VUJ obstruction
    - Posterior urethral valves
    - Vesicoureteric reflux
    - Duplex kidney
  - Down Syndrome - soft sign (17%)
Companion Patient #1

• 33-year-old female G1P0 presenting at 16 weeks 2 days gestational age by dates for fetal survey after abnormal quadruple screen result
  – Abnormal quadruple screen revealed 1 in 13 risk of T21
    - Age-related risk was 1 in 625
Let’s continue to discuss screening
Aneuploidy Screening Basics

- **ACOG 2007 Practice Guidelines:**
  - All women should be offered aneuploidy screening before 20 weeks gestation
  - All women should have the option of invasive testing, regardless of maternal age

- Purpose of screening is to identify highest risk pregnancies for invasive diagnostic procedure
Aneuploidy Screening Options

- First trimester combined test
- Full integrated test
- Quadruple test
- Cell-free fetal DNA test
Screening: 1st Trimester Combined Test

• Consists of:
  – Ultrasound Measurements: 10-13 weeks GA
    • Nuchal Translucency (NT) and gestational age (GA) by crown-rump length
  – Serum Assay: 9-13 weeks GA
    • Pregnancy-associated plasma protein-A (PAPP-A)
    • Beta human chorionic gonadotropin (β-hCG)

• Pros:
  – risk assessment available early

• Cons:
  – follow-up test is chorionic villus sampling (CVS) with higher risk of procedure-related pregnancy loss compared to amniocentesis
Screening: Full Integrated Test

• Consists of:
  – Ultrasound Measurements: 10-13 weeks GA
    • Nuchal Translucency (NT)
  – Serum Assay:
    • PAPP-A: 10-13 weeks
    • β-hCG, alpha fetoprotein (AFP), unconjugated estriol (uE3), inhibin A: 15-18 weeks

• Pros:
  – highest detection rate, lowest positive screen rate

• Cons:
  – risk estimate not available until 2nd trimester
Screening: Quadruple Test

• Consists of:
  – Serum Assay: 15-18 weeks GA
    • AFP, β-hCG, uE3, inhibin A

• Pro:
  – option for women presenting in 2\textsuperscript{nd} trimester for prenatal care
    • Can be performed as late as 22 weeks

• Con:
  – risk estimate not available until 2\textsuperscript{nd} trimester
Screening: cell-free fetal DNA

- **Consists of:**
  - Maternal plasma-based test to detect trisomy 21, 18, 13 after 10 weeks of gestation.

- **Pro:**
  - >98% detection rate, false positive rate <0.5%
  - early detection

- **Con:**
  - expensive; not covered by all insurance
  - not universally recommended as of yet
## T21 Screening Method Comparison

<table>
<thead>
<tr>
<th>Method</th>
<th>Consists of</th>
<th>Gestational Age</th>
<th>Detection Rate (%)</th>
<th>False Positive Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Trimester Combined</td>
<td>• NT, PAPP-A, Beta-hCG</td>
<td>9-13 weeks</td>
<td>85%</td>
<td>4.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95%</td>
<td>21%</td>
</tr>
<tr>
<td>Full Integrated</td>
<td>• 10 wks: NT, PAPP-A, AFP</td>
<td>10-13 weeks</td>
<td>85%</td>
<td>4.4%</td>
</tr>
<tr>
<td></td>
<td>• 15 wks: uE3, hCG, inhibin A</td>
<td>15-18 weeks</td>
<td>95%</td>
<td>17%</td>
</tr>
<tr>
<td>Quadruple</td>
<td>• AFP, uE3, hCG, inhibin A</td>
<td>15-18 weeks</td>
<td>85%</td>
<td>7.3%</td>
</tr>
<tr>
<td></td>
<td>• Genomic sequencing</td>
<td>&gt; 10 weeks</td>
<td>&gt;98%</td>
<td>&lt;0.5%</td>
</tr>
</tbody>
</table>

Data per FASTER and SURUSS trials
Nuchal Translucency (NT)

- NT = increased sonolucent area at back of fetal neck representing fluid between skin and soft tissue (>3mm)

- Criteria:
  1) Crown-rump length (35-84mm at 11-13 wks)
  2) Mid-sagittal plane
  3) Fetus in neutral position without chin flexed
  4) Fetus occupies 75% of image
  5) Distinguish between fetal skin and amnion
Companion # 2: NT Measurement on US

Sagittal Ultrasound
- 6.6 mm NT
- Amnion
- Fetal Skin
- Absent nasal bone
Back to Companion Pt #1

• 33-year-old female G1P0 presenting at 16 weeks 2 days gestational age by dates for fetal survey after abnormal quadruple screen result
  – Abnormal quadruple screen revealed 1 in 13 risk of T21
    • Age-related risk was 1 in 625
Companion Pt #1: Increased Nuchal Fold on 16w US

Transverse Ultrasound
- 9.7 mm Nuchal Fold
- Cerebellar Hemispheres
- Cavum Septum Pellucidum
Nuchal Fold

• Measurement:
  – Second trimester (versus NT in first trimester)
    • ≥6mm between 15-20 weeks is abnormal
  – Distance between outer edge of occipital bone to outer margin of skin
  – Taken in transverse plane (vs NT in sagittal plane)

• DDx:
  – Down Syndrome - soft sign
    • Most sensitive (40-50% and specific (99%) single ultrasound marker for DS in second trimester
  – Other aneuploidy
  – Normal fetus (0.5%)
Companion Pt #1: Echogenic Bowel on 16w US

Transverse Ultrasound
- Echogenic Bowel
- Liver

Courtesy of Dr. Olga Brook
Echogenic Bowel

- Defined as bowel echogenicity similar or greater than adjacent bone (i.e. iliac crest)
  - Note that a higher frequency transducer can lead to overdiagnosis

- Ddx:
  - Normal variant (0.5% normal fetuses)
  - Swallowed intra-amniotic blood
  - Down Syndrome – soft sign (LR of 6.5)
  - Cystic fibrosis
  - Congenital infection
  - Gastrointestinal malformation
Companion Pt #1: Hypoplastic 5th Digit on 16w US

Sagittal Ultrasound
- Hypoplastic 5th Middle Phalanx
- Carpals
Hypoplastic Fifth Digit

- 60% of T21 infants have hypoplasia of middle phalanx of 5th digit
  - Associated with clinodactyly, curvature of fifth finger toward adjacent fourth finger

- DDx:
  - Down Syndrome - soft sign
  - Trisomy 18
  - Normal variant (3% normal patients)
  - Dwarfism
  - Brachydactylic syndromes

https://www.pediatriccareonline.org
Our Patients’ Follow Up

• Both patients underwent amniocentesis for fetal karyotyping, both demonstrating trisomy 21
• Both patients decided to terminate their pregnancies
  – 87-95% of pregnancies prenatally diagnosed with Down Syndrome are terminated
• Both patients went on to subsequently deliver euploidic infants.
  • Risk for subsequent aneuploidic fetus is double the age-associated risk
Summary

• Down syndrome, the most common chromosomal abnormality in liveborn infants

• There are many screening options; serum assay +/- nuchal translucency, cell-free fetal DNA
  – Goal of identifying highest risk patients for diagnostic testing

• Down Syndrome is associated with multiple findings on ultrasound; none are 100% sensitive and specific for T21
  – major structural defects (i.e. ventriculomegaly)
  – ‘soft signs’ (i.e. pyelectasis, EIF, echogenic bowel, nuchal fold, hypoplastic phalanx of fifth digit)
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