Prenatal Genetics

OG200 - 2009
Supplemental Information
Drs. Deborah Driscoll, Michael Mennuti and Lorraine Dugoff
Objectives

• Describe the strategies used to screen for Down syndrome
• Understand the advantages and disadvantages of screening versus diagnostic genetic testing
• Discuss the prenatal evaluation and prevention of neural tube defects
• Discuss genetic screening recommendations based on ancestry
Risk Factors for Aneuploidy

- Advanced maternal age
- Previous child with DS
  - 1% recurrence risk until >40 yrs
- Robertsonian translocation carrier
Maternal Serum Screening General Concepts

• Used to adjust risk for Down syndrome based on maternal age
• Voluntary
• Screening tests are not diagnostic tests and cannot detect all chromosome abnormalities or congenital anomalies
  – Sensitivity or detection rate <100%
• 5% Positive Screen Rate is considered acceptable
Maternal Serum Screening

- **Advantages**
  - Avoids an invasive test
  - Avoid potential for fetal loss
  - Identifies a fetus at risk

- **Disadvantages**
  - Anxiety
  - False reassurance

- **Limitations**
  - Provides a revised risk assessment not a diagnosis
  - Sensitivity <100%
  - Misses other chromosome abnormalities
Second Trimester Maternal Serum Screening for Aneuploidy

- Performed at 15-20 weeks
- Singleton gestation
- Adjusts age risk based on levels of
  - AFP
  - hCG
  - Unconjugated estriol (uE3)
  - Inhibin-A
- Detection rate in women
  - <35: 60-75% for DS
  - >35: 75% or more
  - >80% for trisomy 18
- Positive screening rate 5%

“Triple”

“Quad”
Alpha-fetoprotein (AFP)

- Glycoprotein of unknown function
- Used to screen for open NTDs
  - 15-22 weeks gestation
  - Detection rate 80-85%
- Used to screen for trisomy 21
  - 15-20 weeks gestation
  - Detection rate 20-25%
Human Chorionic Gonadotrophin

- Serum levels in DS often $\geq 2.5$ MoM
- hCG or free b-hCG used
- Elevated levels found in hydatiform molar pregnancies
  - partial molar pregnancies associated with triploidy
Unconjugated Estriol (uE₃)

• Synthesized from DHEAS, converted to 16αOH-DHEAS in fetal liver and then to uE3 by placenta
• Low levels associated with:
  – Trisomy 21
  – Trisomy 18
  – Triploidy
  – Smith Lemli Opitz
  – Steroid sulfatase deficiency
  – Fetal demise
  – Congenital adrenal hypoplasia
Inhibin-A

- Polypeptide hormone
- Secreted by granulosa & Sertoli cells
- In pregnancy secreted by fetoplacental unit, peaks at 8-10 weeks then declines until 20 and rises gradually until term
# Maternal Serum Screening for Trisomy 21 and 18

<table>
<thead>
<tr>
<th>Serum marker</th>
<th>Trisomy 21</th>
<th>Trisomy 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>hCG</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>uE3</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Inhibin-A</td>
<td>↑</td>
<td>N/A</td>
</tr>
</tbody>
</table>
First-trimester screening

- Performed at 10 wks 3 days - 13 wks 6 days
- Singleton gestation
- Nuchal translucency
- Serum screening
  - PAPP-A
  - Free β-hCG
Pregnancy associated plasma protein A

- Glycoprotein of unknown function
- Only reliable for detection of DS between 10-13 weeks
- Levels are 60% lower in DS
- Highest detection rate of any marker (42%)
First-trimester screening

• Advantages:
  – Sensitivity comparable to quad screen
  – Performed earlier
  – If positive option of CVS
  – Option of earlier TAB if fetus affected
  – Increased privacy

• Disadvantages:
  – Does not test for NTDs
Sequential Screening for DS

Offer 1st trimester screen (NT, PAPP-A, hCG)

- DS risk >1 in 50
  - Offer counseling & CVS

- DS risk <1 in 50
  - 2nd trimester screen with Integrated Result (NT, PAPP-A, AFP, hCG, uE3, Inhibin)
    - DS risk >1 in 270
      - Offer counseling & amnio

Uses both 1st and 2nd trimester results to adjust maternal age risk for DS and takes advantage of higher detection rate
Prenatal Diagnosis by Amniocentesis

Ultrasound Probe

Amniotic Fluid

Placenta

FLUID
- alpha-fetoprotein
- acetylcholinesterase

CELLS
- biochemical studies
- DNA studies

CELL CULTURE
- chromosome analysis
- DNA studies
- biochemical studies

CENTRIFUGE
CVS vs Amniocentesis

- Performed at 10-12 wks
- Results available earlier
- May lower anxiety
- Privacy
- If results abnormal option of earlier TAB preferable to some couples
- Risk SAB <1%

- Performed at 15-17 wks
- 10-14 days for results
- SAB rate <1/300-600
- Test amniotic fluid AFP for NTD
Sonographic Screening for Aneuploidy

- Performed at 18-20 weeks
- Look for major malformations often seen in fetus with aneuploidy (trisomy 21, 18, 13)
- Risk for aneuploidy increases with finding of major anomaly or 2 or more minor abnormalities
- Detection rate for trisomy 21: 60-75%
- FPR: 4-15%
Sonographic findings in Trisomy 21

- Cardiac defect
- Duodenal atresia
- Thick nuchal fold
- Renal pyelectasis
- Echogenic bowel
- Echogenic intracardiac focus
- Sandal gap
- CP cyst
- Short mid-phalanx 5th finger
- Short femur/humerus
- Flat facies with maxillary hypoplasia
- Macroglossia
Detection of Neural Tube Defects

• Maternal serum alphafetoprotein (AFP)
• Ultrasonography
• Amniocentesis
  – AFP
  – Acetylcholinesterase
Interpretation of Maternal Serum Screening Tests

- Gestational age-dependent

Prevention of NTD

• Recurrence
  – Folate 4 mg/day 3 months prior to conception and through 1st trimester

• Occurrence
  – Multivitamin with folate 0.4 mg/day
Genetic Screening based on Ethnicity

• Caucasians
  – Cystic fibrosis

• African Americans
  – Sickle cell disease
    • Hemoglobin electrophoresis

• Asian
  – Thalassemia
    • MCV

• Mediterranean
  – Thalassemia
    • MCV
Genetic Screening Recommendations for Jewish Ancestry

• Tay Sachs disease*
  – Hexosaminidase A levels
  – Mutation screening
• Canavan disease*
  – Mutation screening
• Familial dysautonomia*
• Cystic Fibrosis*
• Gaucher, Niemann-Pick, Bloom, Fanconi’s pancytopenia, mucolipidosis type IV

*standard of care