UPDATE ON FIRST TRIMESTER SCREENING

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Overview

- Screening vs. diagnosis
- Types of screening
- Current state of screening
- Amniocentesis and CVS
  - Techniques
  - Loss rates
- Conclusions

What is a Screening Test?

- A test used to detect or define the risk for disease in an asymptomatic low risk population
  - Risk assessment
  - Applies to the entire population
  - e.g. You are at an increased risk of having a baby with Down syndrome

Screening vs. Diagnosis

- Diagnostic test ~ Definitive Answer
  - Determines that the fetus has T21
  - Applied to high risk population: ≥ 35 or screen positive
  - e.g. You have a baby with Down syndrome

- So my AFP is “negative” - that means my baby is normal, right?
A Screening Test

- Screening identifies risks for certain birth defects
- Some pregnancies with these birth defects are missed by screening (false negatives)
- Some pregnancies with screen-positive results do not have these birth defects (false positives)
- False negatives and false positives are inherent in any screening process

Why Do We Have False Negatives and False Positives?

- Detection rates can be increased by lowering the cutoff but will result in more false positive results
- Due to overlap of distributions
- Choice of cutoff

Who should be screened?

- All pregnant women

ACOG

- Proposed performance measure: Documentation of discussion regarding Down syndrome screening

Who should be offered diagnostic/invasive testing?

- “Maternal age of 35 years alone should no longer be used as a cutoff to determine who is offered screening versus who is offered invasive testing”
Down Syndrome at Birth

Risk of Down’s syndrome baby at term, by maternal age

- Presenting the Risk...
  - Who has the highest risk?
  - Who has the biggest increase in risk?

Question?

Who should be offered first trimester screening?
1. A 35 year old Hispanic female G3P2 at 12 weeks of gestation
2. A 21 year old caucasian G1 with family history of birth defects
3. 28 year old African American G3P2 with history of chronic hypertension
4. 38 yo G3P2 @ 13 weeks with a prior child with T21

- 1 & 2 only
- 1, 2 & 4
- All of the above

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History of Antepartum Screening

- 1972 - High MSAFP – anencephaly at 16 weeks
- 1984 - Markitz & Cuckle reported low MSAFP – T21
- 1986 - California AFP screening
- 1987 - Abnormal uE3 and hCG levels associated with T21
- 1992 - Multiple prospective studies demonstrate the efficacy of multiple marker screening
- 1990's - Professor Kypros Nicolaides and colleagues introduce the term “nuchal translucency” (NT)
- 1992 - California Expanded AFP (X-AFP) program
- 1998 - Inhibin-A proposed as a fourth analyte for Down syndrome screening (Wald, Haddow, Van Lith-92)
- 2007 - California Quad screening program
- 2009 - California Integrated screening

Types of Screening

- **First trimester options (1T)**
  - Combined screening - NT+ β hCG +PAPP-A
  - Serum screening - βhCG and PAPP-A
- **Second trimester options (2T)**
  - Triple screening (California Expanded AFP): AFP+ βHCG + unconjugated estriol (uE3)
  - Quadruple screening (Quad screen): AFP + βHCG + uE3 + Inhibin-A

MoM: Multiples of Median

- **Median**
  - 50th centile or middle number in a series = 1.0 MoM
  - Established for each gestational day/week of pregnancy
- **Convention to compare results from different labs**
- **Easier to compare the results of several markers**

Serum Analytes in T21

<table>
<thead>
<tr>
<th>Marker</th>
<th>Median MOM (95% CI)</th>
<th>DR (5% FPR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP</td>
<td>0.78 (0.73-0.84)</td>
<td>32%</td>
</tr>
<tr>
<td>uE3</td>
<td>0.70 (0.55-0.88)</td>
<td>30%</td>
</tr>
<tr>
<td>hCG</td>
<td>1.25 (1.09-1.42)</td>
<td>32%</td>
</tr>
<tr>
<td>Inhibin A</td>
<td>1.19 (1.05-1.35)</td>
<td>31%</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>0.38 (0.32-0.44)</td>
<td>52%</td>
</tr>
</tbody>
</table>

Shiner et al Ob Gyn Survey 52:2:123-127

Serum Analytes

<table>
<thead>
<tr>
<th></th>
<th>PAPP-A</th>
<th>HCG</th>
<th>ESTRIOL</th>
<th>INHIBIN</th>
<th>AFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>T21</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>T18</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>SLOS</td>
<td>↓</td>
<td></td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>ONTD</td>
<td>↓</td>
<td></td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
</tbody>
</table>

First Trimester Screening

- **First trimester options**
  - Combined screening – NT+ β hCG +PAPP-A
  - Serum screening - βhCG and PAPP-A
First Trimester Screening

**Advantages:**
- Earlier dx (CVS)
- Earlier reassurance
- Earlier termination
- Possibly easier psychologically
- Documented patient preference

**Disadvantages:**
- Separate screening needed for NTD/AWD/SLOS
- 50% of T21 and 90% of T18 result in SAB/IUFD
- 50% of T21 and 90% of T18 result in SAB/IUFD
- 50% of T21 and 90% of T18 result in SAB/IUFD
- 50% of T21 and 90% of T18 result in SAB/IUFD
- 50% of T21 and 90% of T18 result in SAB/IUFD
- 50% of T21 and 90% of T18 result in SAB/IUFD
- 50% of T21 and 90% of T18 result in SAB/IUFD

What’s involved in the test?

- Ultrasound performed by certified sonographer or MD
  - Preliminary result (based only on NT) at the time of the ultrasound
- Blood test
- Patient weight and history
- Final result in 7-10 days

Risk With Increasing Nuchal

- 1015 fetuses NT > 3 mm @ 10-14 weeks
- Karyotype available in all
- 194 trisomies (19%)

<table>
<thead>
<tr>
<th>NT</th>
<th>Age Related Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>3mm</td>
<td>3X</td>
</tr>
<tr>
<td>4mm</td>
<td>18X</td>
</tr>
<tr>
<td>5mm</td>
<td>28X</td>
</tr>
<tr>
<td>≥6mm</td>
<td>36X</td>
</tr>
</tbody>
</table>


First Trimester Screen
Beyond Down syndrome

- First trimester screening detects increased risks for:
  - Trisomy 18
  - Heart defects
  - Single gene syndromes
  - Structural abnormalities

- Multiple gestations
  - Zygosity, amnion and chorion counts

Relative risk of a congenital heart defect in % in relation to first trimester nuchal fold thickness

<table>
<thead>
<tr>
<th>NT</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>3mm</td>
<td>5 / 1000</td>
</tr>
<tr>
<td>4mm</td>
<td>27 / 1000</td>
</tr>
<tr>
<td>5mm</td>
<td>54 / 1000</td>
</tr>
<tr>
<td>6mm</td>
<td>266 / 1000</td>
</tr>
</tbody>
</table>

BUN - NI CHD
Maternal Serum Biochemistry and Fetal Nuchal Translucency Screening

- 12 centers, 8872 pts, 98% follow-up
  - Mean maternal age 33.6, 35% > 35
- NT ultrasound, PAPP-A, free β-HCG
  - NT successfully measured in 99.5%
- Down's detection rate 85.2% (9.4% SPR)
  - 61% age < 35
  - 89.8% ≥ 35 (15.2% SPR)
- 9% had invasive prenatal diagnosis

Wapner et al NEJM 2003:349:1471

Challenges for implementation

- Access to genetic counseling
- Unintended quad screens in those who had first trimester screens
- >15% of women present after 12 weeks
- NT certification and quality control
- Billing for NT sonography
- 2nd trimester screening for ONTDs

Question?

Combined first trimester screening refers to:
1. PAPP-A + β HCG levels before 14 weeks
2. PAPP-A + β HCG combined with Inhibin
3. PAPP-A + β HCG + Inhibin + Estriol
4. PAPP-A + β HCG + ultrasound for Nuchal translucency

Should patients with 1st Trimester Screening have 2nd Trimester Screening?

Quad Marker Screening

- Second trimester blood specimen: 15 wks 0 days to 20 wks 0 days
- Analytes: AFP, hCG, uE3, Inhibin
- Risk assessments: T21, T18, SCD, NTD

What happens if we combine first and second trimester screening tests?
Combined first- and second trimester screening with nondisclosure

- **Fully integrated screening**
  - 1T NT, PAPP-A and 2T quad screen at different times; results to patient after all tests completed
- **Serum integrated screening**
  - 1T PAPP-A and 2T quad screen at different times; results to patient after all tests completed (no need for NT ultrasound)

**Advantages & Disadvantages**

<table>
<thead>
<tr>
<th>Options</th>
<th>First Trimester</th>
<th>First and Second Trimester</th>
<th>Second Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits</td>
<td>FirstScreen</td>
<td>Sequential Screen</td>
<td>Integrated Screen</td>
</tr>
<tr>
<td></td>
<td>Down syndrome DR</td>
<td>Early answers and high detection rates</td>
<td>The highest detection rates</td>
</tr>
<tr>
<td></td>
<td>FPR</td>
<td>The best detection rate without NT</td>
<td>The best second trimester screen</td>
</tr>
<tr>
<td>83%</td>
<td>92%</td>
<td>87%</td>
<td>81%</td>
</tr>
<tr>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>80%</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>80%</td>
<td>---</td>
<td>80%</td>
<td>80%</td>
</tr>
</tbody>
</table>

**SURUSS Trial**

**Integrated Down syndrome screening**

- Observational study - 47,053 pts
  - No NT in 11,025 pts
- 12 weeks NT US and PAPP-A
- 16 weeks Quad screen
- Urinary markers added nothing to serum screening
- Integrate results into single risk adjustment
  - 85% detection with only 1% FPR
- Raised potential safety advantage of integrated (1st and 2nd trimester) approach

Wald et al J Med Screen 2003;10:55

**SURUSS TRIAL**


![Graph showing Down Syndrome detection @ 5% SPR](image)

**First And Second Trimester Evaluation of Risk**

**FASTER Trial**


- First-trimester screening in 38,033 patients
  - 26% AMA, 33.1% non-white
  - 117 fetuses with T21 (0.3 %)
  - 134 cases excluded for 1st trimester cystic hygroma or NT > 4.0 mm – 23 had Down syndrome
  - CRL 36-79 mm (10 3/7-13 6/7 weeks)
- Second trimester quad screen 15-18 weeks
- Combined 1st trimester screen: positive >1 in 150
- 2nd trimester Quad screen: positive > 1 in 300
- All results reported at 16 - 18 weeks
FASTER Trial - Results

- The rates of detection of Down’s syndrome were:
  - Quadruple screening 81%
  - Serum integrated screening 88%
  - Stepwise sequential screening 95%
  - Fully integrated screening with first-trimester measurements performed at 11 weeks 96%
- Fully integrated screening yielded the highest detection rates with the lowest false-positive rates vs. other forms of screening.

Independent Sequential screening

- Follow up of BUN study: 4145 1T screen negatives and 180 screen positives
- 6/7 (86%) 1T screen negative and 7/7 (100%) 1T screen positive Downs cases were detected by a 2T multiple marker screen (1/1270)
- Overall, independent sequential screen had a 98% DS detection rate, but at the unacceptable price of a 17% SPR

Platt et al Obstet Gynecol 2004;104:661-6

The Best Test?

- Nuchal translucency and first trimester biochemical markers for down syndrome screening: a cost-effectiveness analysis

A decision tree was designed that compared four possible screens for Down syndrome

<table>
<thead>
<tr>
<th>Screen Type</th>
<th># T21 Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT + 1 trimester serum</td>
<td>3833</td>
</tr>
<tr>
<td>NT only</td>
<td>3413</td>
</tr>
<tr>
<td>1 + 2 trimester serum</td>
<td>2993</td>
</tr>
<tr>
<td>2 trimester serum only</td>
<td>2446</td>
</tr>
</tbody>
</table>


ACOG Practice Bulletin

- Women who have had 1st trimester screening should not undergo independent second trimester screening in the same pregnancy (due to additive false positive rates and more unnecessary procedures)
- Women who want a higher detection rate can have integrated or sequential screening

ACOG Practice Bulletin No. 77, Jan 2007
Screening for Fetal Chromosomal Abnormalities
Overview

- Screening vs. diagnosis
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2009 California Prenatal Screening Program Goals

- Identify pregnant women with increased risk of:
  - Trisomy 21
  - Trisomy 18
  - Open Neural Tube Defects (NTD) and Abdominal Wall Defects (AWD)
  - SCD (Smith-Lemli-Opitz syndrome (SLOS), Congential anomalies, fetal Demise

California Prenatal Screening Program 2009 Available Screening Tests

- Quad Marker Screening
  - One blood specimen at 15 - 20 weeks
- Serum Integrated Screening
  - Combines first trimester blood test results (10-13 6/7 weeks) with second trimester blood test results
- Full Integrated Screening
  - Combines first and second trimester blood test results with NT results
  - Patients with first trimester blood specimens and NT get preliminary risk assessment for chromosomal abnormalities in the first trimester and this risk will be revised when the second trimester blood specimen is received

California Prenatal Screening Program 2009 Screening Timeline

First Trimester
Blood Draw
10 0/7 to 13 6/7
weeks

Second Trimester
Blood Draw
15 0/7 to 20 0/7
weeks

Nuchal Translucency
11 2/7 to 14 2/7 weeks

California Prenatal Screening Program 2009 Results Adjusted for Populations Factors

- Maternal age
- Gestational age
- Maternal weight (low levels with obesity)
- Race (AA have high AFP, Hispanic and Asians have high uE3)
- Number of fetuses
- Diabetic status (AFP lower in DM)
- Smoking status

California Prenatal Screening Program 2009 Integrated Screening Protocol - 2009

Maternal Serum (10w 0d - 13w 6d)
Nuchal Translucency ultrasound (11w 2d - 14w 6d)

Screen Positive
T21 >1:100
T18 >1: 50

Screen Negative
T21 <1:100
T18 <1: 50

Diagnostic Testing Declined

Quad Screen (15w 0d - 20w 0d)

Screen Positive
T21 >1:200
T18 >1: 100

Screen Negative
T21 >1:200
T18 >1: 100

Diagnostic Testing Accepted

Screen Positive
T21 >1:200
T18 >1: 100

Screen Negative
T21 <1:200
T18 <1: 50

Diagnostic Testing Offered
### California Prenatal Screening Program 2009

#### Detection Rates

<table>
<thead>
<tr>
<th>Age</th>
<th>First Trimester</th>
<th>Total after 2nd Tri</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SPR</td>
<td>DR</td>
</tr>
<tr>
<td>20</td>
<td>1%</td>
<td>55%</td>
</tr>
<tr>
<td>25</td>
<td>1%</td>
<td>57%</td>
</tr>
<tr>
<td>30</td>
<td>1%</td>
<td>61%</td>
</tr>
<tr>
<td>35</td>
<td>5%</td>
<td>75%</td>
</tr>
<tr>
<td>40</td>
<td>16%</td>
<td>89%</td>
</tr>
<tr>
<td>All ages</td>
<td>2.5%</td>
<td>75%</td>
</tr>
</tbody>
</table>

### Special Circumstances - Not Eligible

- Fetal reduction
- Multiple gestation of 3 or more fetuses
- Fetal demise (from 2 to one)
  - >8 weeks ineligible
  - <8 weeks ineligible for first, however, eligible for second trimester screening

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### Amniocentesis - Technique

- 20g vs. 22g needle
- 20 - 30 cc fluid, extra if FISH
- Beware unfused membranes at 15 - 16 weeks
- Local anesthetic doesn’t decrease uterine pain and it stings
- Twins: Indigo carmine dye

### Transcervical CVS

- Cook® catheter
- Significant learning curve
  - Increased loss >1 pass: 2% (1) vs 6.6% (2-3) p <0.05 Ferguson et al AJOG 1990
  - Bladder filling, especially for anterior placentas

### Transabdominal CVS

- Dominant approach in European centers
- Developed to avoid infection risk & tests
- Most recent studies show lower loss rate
- MAY be comparable to midtrimester amnio?
Amniocentesis vs. CVS

- Ideally 15-18 weeks
- Loss rate – 0.5%, may be as low as 0.06%*
- FISH for preliminary results in 1-3 days
- Most widely used and available
- Need mid-trimester termination in case of aneuploidy
- Early amnio should be abandoned

- 10-13 weeks
- Loss rate – 1-3%
- Direct prep for preliminary results in 1-2 days
- Does not assess for neural tube defects, recommend MSAFP/ Ultrasound
- May need confirmatory amnio for confined placental mosaicism (CPM)
- Earlier diagnosis
- Need >25 cases/year to maintain skills

*Eddleman et al, Obstet Gynecol 2006;108:1067-72

Conclusions

- All pregnant women should be offered prenatal screening and documented in the chart
- Genetic counseling to select patients
- First trimester serum screening alone appears to be inferior to NT or combined screening

Conclusions

- Combined 1st trimester screen and 2nd trimester Quad screen appear to have nearly similar efficacy
- Full integrated screening is the best option
- If NT screening is unavailable, serum integrated screening appears to be a most viable option