Objectives – California Prenatal Screening Program (PNS)

- Disorders included in PNS
- Efficient Screening
- Screening options
- Screen “positive”
- Included services
- Exceptions
- Test performance
- Controversies
What are we screening for?

**Goal:** Identify woman at increased risk to provide assistance in making an informed decision

- Aneuploidy
  - Trisomy 21, Trisomy 18
  - **NOT** trisomy 13
- Abdominal wall defects
- Anencephaly & open neural tube defects
- **SCD** (*Smith-Lemli-Opitz, Cong anomalies, Demise*)

PNS – Complex made simple

- **Two serum samples**
  - 10-13 6/7 wks
  - 15-20 wks
- **Nuchal Translucency**
  - 11 2/7 – 14 2/7 wks; CRL: 44.5-84.5mm
- [http://www.cdph.ca.gov/programs/pns](http://www.cdph.ca.gov/programs/pns)
  - Wheel, Calculator
PNS – Maximize screening results

- **Timing & Coordination**
  - Dating: use only one method
    - CRL/NT
    - BPD
    - LMP, clinical estimate are also acceptable
    - If re-dating → call coordinator for new calculation

- **Complete forms accurately**
  - Weight, Smoking, Age, Ethnicity, # Fetuses, Donor ovum

- **Blood draw**
  - SST – Yellow top tubes
  - Invert, Clot, Centrifuge

Types of screening

- **Quad screening**
  - (AFP, estriol, beta hCG, Inhibin)

- **Quad plus NT**
  - Miss first trimester blood draw
  - More sensitive than 1st TM combined screening

- **Serum Integrated**
  - 1st TM: PAPP-A & beta hCG
  - 2nd TM: Quad
Types of screening

- Quad screening
- Quad plus NT
- Serum Integrated
  - Results after 2nd TM draw
    - Down syndrome, T18
    - Abdominal wall, NTD
    - SLO
  - Positive – refer for counseling, diagnostic testing

Types of screening

- Full integrated screening
- Truth: Sequential
  - 1st TM blood & NT → “Preliminary” result
  - “Positive” or “negative”
    - Negative → 2nd TM serum (15-20 weeks) “Integrated”
    - Positive: counseling, offer diagnostic testing
      - Invasive: Normal karyotype → Screen NTD/SLOS
    - Positive: decline invasive testing → 2nd TM serum
PNS: Screen “positive”

After 1st TM combined screening:
- Down Syndrome: ≥ 1 in 100
- T18: ≥ 1 in 50
- Individual risk assessment

Commercial laboratories
- NTD labs:
  - ~1 in 300 for Down syndrome
  - 1 in 100 for T18/13
- Others: ~1 in 200 Down syndrome
  - ~1 in 100 T18

PNS: Screen “positive”

After 2nd TM screening:
- Down Syndrome:
  - Quad screen: ≥ 1 in 150
  - Quad plus NT/Full Integrated: ≥ 1 in 200
- Abd wall/NTDs: ≥ 2.5 MoMs; (4.5 MoMs twins)
- SLOS ≥ 1 in 250
- T18 ≥ 1 in 100
Diagnosis vs. Screening

- Women may not weigh the risk of procedure related loss and having a child with Down syndrome equally.

- Individual preferences vary widely.
- Most women view long term consequences of having a child affected with DS as worse than a procedure related miscarriage of a normal fetus.
PNS: Screen “positive”

- Must balance screen positive with DR
  - Adjusting screen positive to 1:30 or 1:40
    - May reduce anxiety-provoking screen positive
    - Without affecting the detection rate
    - CVS availability preference
    - Advantage: modify cut-offs with participation

What is covered?

- 1st & 2nd TM Screening Forms
- Education booklets with consent/refusal forms
- Supplies to draw and mail serum samples
- Coordinators to facilitate participation for patients and providers/clinicians
- Screen positive patient education booklets
- Authorized follow-up services at State-approved Prenatal Diagnosis Centers
  - Screen positive
What is not covered?

- NT is not covered
  - Medi-Cal & private insurance
    - State approved practitioner
- PSP can use NT in risk calculation
  - Important as new ultrasound measurements emerge (e.g. nasal bone)
  - Soft markers

Exceptions: Screening not performed

- Loss of a twin > 8 weeks GA
  - Reduction or Spontaneous
- > 2 Fetuses (AFP)
- Fetal demise

- Loss of a twin (2 to 1) <8 weeks
  - Ineligible for 1st TM screen
  - Quad screen eligible
Exceptions: Screen Positive

- Common referral: + screen for DS
  - US: Overestimation of gestational age
  - Risk recalculated
  - Considerable maternal anxiety
  - Importance of dating
    - If possible FT/NT component

Performance: Detection rates

NTD/AWDs
- 1% screen positive

Detection
- 97% Anencephaly
- 80% Open Spina Bifida
- 85% Abd wall defects
Performance: Detection rates

SLOS
• ↓beta HCG, ↓AFP, ↓↓ estriol
• 0.2% screen positive
• Amniocentesis: 7-dehydrocholesterol

Detection
• 60% SLOS
• IUFD, Congenital anomalies

Performance: Detection rates

Trisomy 18
• ↓AFP, ↓estriol, ↓hCG, ↓/nl inhibin
• Screen positive:
  • All women - 0.3%
  • >35 years - 1.3%

<table>
<thead>
<tr>
<th>Age</th>
<th>Quad Positive Rate</th>
<th>Quad Detection Rate</th>
<th>Serum Integrated Positive Rate</th>
<th>Serum Integrated Detection Rate</th>
<th>First Trimester Positive Rate</th>
<th>First Trimester Detection Rate</th>
<th>Total after Second Trimester(*) Positive Rate</th>
<th>Total after Second Trimester(*) Detection Rate</th>
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</thead>
<tbody>
<tr>
<td>30</td>
<td>0.13%</td>
<td>55%</td>
<td>0.10%</td>
<td>78%</td>
<td>0.07%</td>
<td>36%</td>
<td>0.19%</td>
<td>74%</td>
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<tr>
<td>All Ages</td>
<td>0.31%</td>
<td>67%</td>
<td>0.21%</td>
<td>79%</td>
<td>0.16%</td>
<td>59%</td>
<td>0.31%</td>
<td>81%</td>
</tr>
</tbody>
</table>
Performance

Down Syndrome
- ↑beta HCG, ↑Inhibin, ↓AFP, ↓estriol
- Increased risk of DS and T18 as MA increases
- Most births occur in younger women
  - Many with DS “missed”

Performance: Detection rates

Trisomy 21
- Screen positive:
  - All women - 0.3%
  - >35 years - 1.3%

<table>
<thead>
<tr>
<th>Age</th>
<th>Quad Positive Rate</th>
<th>Quad Detection Rate</th>
<th>Serum Integrated Positive Rate</th>
<th>Serum Integrated Detection Rate</th>
<th>First Trimester Positive Rate</th>
<th>First Trimester Detection Rate</th>
<th>Second Trimester Positive Rate</th>
<th>Total after Second Trimester(*) Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>3%</td>
<td>66%</td>
<td>3%</td>
<td>77%</td>
<td>1%</td>
<td>61%</td>
<td>3%</td>
<td>84%</td>
</tr>
<tr>
<td>All Ages</td>
<td>4.5%</td>
<td>80%</td>
<td>4.5%</td>
<td>85%</td>
<td>2.5%</td>
<td>75%</td>
<td>4.5%</td>
<td>90%</td>
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### Serum screening performance - DS

<table>
<thead>
<tr>
<th>Test</th>
<th>Detection</th>
<th>Notes</th>
<th>False (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadruple</td>
<td>60-83%</td>
<td>Standard</td>
<td>5%</td>
</tr>
<tr>
<td>1st TM Combined</td>
<td>86-87%</td>
<td>Immed results</td>
<td>5%</td>
</tr>
<tr>
<td>Serum Integrated</td>
<td>85-90%</td>
<td>No NT</td>
<td>5%</td>
</tr>
<tr>
<td>Fully integrated</td>
<td>93-96%</td>
<td>Results &gt;16wks</td>
<td>5%</td>
</tr>
<tr>
<td>Stepwise Sequential</td>
<td>95%</td>
<td>“high” risk predetermined</td>
<td>5%</td>
</tr>
<tr>
<td>Contingent Sequential</td>
<td>Highest?</td>
<td>Lowest?</td>
<td></td>
</tr>
<tr>
<td>Independent Sequential</td>
<td>98%</td>
<td>Not Rec</td>
<td>17%</td>
</tr>
</tbody>
</table>
Performance: Can PSP predict other chromosomal abnormalities

- Turner syndrome
  - With hydrops – similar pattern to DS
  - Without – moderately reduced levels of all analytes
- Triploidy (69XXX, 69XXY, 69XYY)
  - Diandric: ↑hCG, ↑inhibin, ↓estriol, AFP unpredictable
    - Fetal loss, cystic placenta
  - Digynic: ↓↓estriol, ↓hCG, ↓inhibin; often T18 screen +
    - Small fetus, small placenta, late fetal survival
- Trisomy 13
  - Slight reduction in estriol

Performance: Can PSP predict adverse obstetric outcomes?

- 1<sup>st</sup> & 2<sup>nd</sup> TM analytes are weakly assoc with adverse outcomes
- PAPP-A <1<sup>st</sup> or free beta hCG <1<sup>st</sup>
  - IUGR – PPV 24% or 14% (FASTER)
- PAPP-A <5<sup>th</sup>:
  - Stillbirth, Placental dysfunction – IUGR/SGA, PTB
  - Poor predictive values
Performance: Can PSP predict adverse obstetric outcomes?

- Pre-eclampsia
  - Elevated beta hCG, free beta hCG, Inhibin
  - ~20% of pre-eclampsia
- Screen + for DS, T18, AFP
  - IUGR, PTB, IUFD
- Very low estriol (≤15 MoMs)
  - Sulfatase deficiency, Early fetal death

Performance: Can PSP predict adverse obstetric outcomes?

- Elevated AFP: increased morbidity
  - Low birthweight, PTB, IUFD, Nephrotic syndrome
- ↑↑AFP/ ↑↑bHCG/ Low estriol
  - Pre-e, chromosomal, Structural, Poor outcomes
  - Association weak: PPV 1-18%
- Inhibin ≥2 MoM; hCG >2MoM
  - Multicystic dysplastic kidney

- Can these risks be refined?
Controversies

- May not “opt out”
  - New, better or more costly screening tests?
  - Legislation
- Incomplete sequential screening
  - “Negative” – no follow-up
  - Reminders for clinicians
    - Preliminary data – 90% follow-up

Controversies

- Free beta hCG vs. Total beta HCG
  - Free beta: 9-13 weeks
    - >35: decreased FP rate
    - <35: increased detection
  - Total beta: best 11-13 weeks
- PSP proponents:
  - Minimal difference in setting of multiple markers
  - Difficulty with blood spots on CA NBS
  - Long term experience (QA) with total beta hCG
Controversies

- Too few NT providers?
  - Substantial increases
  - 7/09 – 550 providers
    - Additional 170 providers certified in 6 months
- California population is unique
  - Maternal age 28.5 ± 6.5 (27±5)
  - Considerable number of women <32 and >32
- Model can be changed as time progresses

References

Eddleman et al. FASTER Obstet Gynecol 2006;103(5):1057
Wald, NJ. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). 2003
Wald, NJ et al. SURUSS in perspective. BJOG 2004; 111:521
References


