First Trimester Screening

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Background

- 2-3% risk of birth defects regardless of risk factors
- Chromosomal abnormalities account for about 10%
- Trisomy 21 most common chromosomal abnormality at birth 1:500 pregnancies in the US
- Risk assessment changes with maternal history, age, gestational age
- ALL patient’s are at risk for fetal Down syndrome and fetal birth defects
Perspective

- Currently more than 80% of the diagnostic procedures to determine fetal karyotype are performed in the US for “AMA”
- 70% of affected pregnancies are born to women outside this group.
- Age is currently an unacceptable screening tool to determine who is offered screening vs. who is offered invasive diagnosis
Diagnostic versus Screening

- No overlap: Positive test is abnormal
- Overlap: Positive test could be normal or abnormal

History of Screening

- Era of age-based screening
  - Recommendations began in the 1970’s
    - When the statistical increase of aneuploidy started exceeding the risks of amniocentesis, that age 35 be established as a cut-off
  - 1980’s introduction of AFP screening leading to Triple Marker Serum screening which in combination with age, increased detection rates of DS to 50-70%.
    - False positive rates ranged from 10-25%, increasing with maternal age
    - Also 60% Detection rate for Trisomy 18
History of Screening

  - Detection rate for Down syndrome increased to 75-77% with a 5% false positive rate

- Around the same time, a pivotal paper was published in 1992 in the BMJ by Nicolaides (Kings College, London)
  - describing nuchal translucency (NT) which gave a 75% DR at 11-13w6d via ultrasound

History Of Screening

- 1996 – Nicolaides introduced first trimester serum (using free beta hCG and PAPP-A) to give DR with NT of 85-88% with a 4-5% false positive rate
  - called FTS or First Trimester screening
  - PAPP-A (pregnancy associated placental protein A, made by embryo and placenta, immune function, increases placental growth)

- 1996-2000 – numerous papers looking at combining 1st and 2nd trimester screening:
  - With serum (serum integrated pregnancy screening)
  - With NT (integrated pregnancy screening)
### All stacked up

<table>
<thead>
<tr>
<th>Markers</th>
<th>Detects?</th>
<th>When</th>
<th>Sensitivity</th>
<th>FPR</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Trisomy 21, 18, 13</td>
<td>@Conception /@Delivery</td>
<td>30%</td>
<td></td>
<td>Archaic</td>
</tr>
<tr>
<td>Age + TMS</td>
<td>Trisomy 21, 18, 45X, NTD’s</td>
<td>16-20w</td>
<td>50-70% (for DS)</td>
<td>10-25%</td>
<td>TMS</td>
</tr>
<tr>
<td>Age + Quad</td>
<td>Trisomy 21, 18, NTDs</td>
<td>16-20w</td>
<td>75-77% (for DS)</td>
<td>5.2%</td>
<td>Quad</td>
</tr>
<tr>
<td>Age + NT+PAPP-A + β hCG</td>
<td>Trisomies 21,18,13</td>
<td>11-13w6d</td>
<td>85-88%</td>
<td>5%</td>
<td>FTS</td>
</tr>
<tr>
<td>Age + PAPP-A + β hCG + Quad</td>
<td>Trisomies 21 +18, ONTDs</td>
<td>12w and again at 16-20w</td>
<td>84-86%</td>
<td>5%</td>
<td>Serum Integrated</td>
</tr>
<tr>
<td>Age+NT+PAPP-A+β hCG + Quad</td>
<td>Trisomies 21 +18,ONTDs</td>
<td>12w and again at 16-20w</td>
<td>92-96%</td>
<td>3-5%</td>
<td>Full Integrated</td>
</tr>
</tbody>
</table>

### Approximate Detection Rates

**Various studies**

![Graph showing detection rates across different screening methods](image)

- 5% False Positives
Approaches to Screening

- Nuchal translucency alone
- First trimester biochemistry alone
- Combined: NT and first trimester biochemistry
- Integrated first and second trimester
  - No result until both tests done
- Sequential first and second trimester
  - Results known after first test
- Second trimester screening alone

California Prenatal Screening Program

FIRST TRIMESTER COMBINED = NT Plus 1st Trimester Analytes

FULL INTEGRATED = NT Plus 1st & 2nd Trimester Analytes

SERUM INTERGRATED = 1st & 2nd Trimester Analytes Only

QUAD SCREEN ONLY = 2nd Trimester Analytes Only
Advantages to 1\textsuperscript{st} Trimester Screening

- Earlier diagnosis
  - Pregnancy less obvious, more private
    - May be less bonding
  - Pregnancy termination easier and safer
- Surveys: Many patients prefer it
- CAVEAT: Need test to have high sensitivity and low false positives
  - Account for spontaneous (and procedural) losses
    - Preferentially identify high risk for loss?

Combined screening in the first trimester

- If serum analytes drawn before NT the CPSP allows an \textbf{Instant Risk Calculation} with the addition of the NT measurement when analytes are available.

- If a woman is found to be at an increased risk for fetal aneuploidy, she can be offered genetic counseling and choose to proceed with \textbf{CVS as early as} 11 weeks providing chromosome results @ 12 weeks EGA
Problems with Second Trimester Screening

- False positives
  - Patient anxiety
    - Lessened by better pre-test counseling
  - Unnecessary amniocentesis
    - Procedural loss 0.5%
- Late diagnosis
  - Psychologically and technically more difficult to terminate
- Suboptimal sensitivity

COMPLETE THE SCREENING

- For women < 35 yo the first trimester combined result is PRELIMINARY and will detect ~ 62% of babies affected with a Down syndrome utilizing the CPSP screen positive cut off of 1 %.

- To complete the full integrated CPSP program a second blood test (Quad Screen) is required between 15 and 20 weeks which allows the test to detect an additional 20 % or more of Down syndrome babies for a final detection rate of ~ 85 %.

- Overall < 5 % of patients may have a positive test in the second trimester indicating an increased risk for a genetic birth defect.
First Trimester Screening

- 1st Trimester:
  - PAPP-A (pregnancy associated plasma protein A)
  - hCG (human chorionic gonadotropin)
  - Nuchal Translucency (NT) if available

Distribution of First Trimester Free $\beta$hCG Measurements
Distribution of PAPP-A Measurements

Down Syndrome

Unaffected

PAPP-A (MoM)

Biochemical Markers

- Pregnancy associated plasma protein A (PAPP-A)
  - Protease for IGF binding protein
  - Decreased with trisomies
- Human chorionic gonadotropin (ßhCH)
  - Increased with 21 and 18, decreased with 13
- PAPP-A and ßhCG for Trisomy 21
  - 60% sensitive, 5% false positive rate
NUCHAL TRANSLUCENCY (NT) What Is It?
NT is the sonolucent zone at the posterior aspect of the fetal neck. This space represents the sonographic appearance of subcutaneous fluid behind the fetal neck.
NUCHAL TRANSLUCENCY
“Normal” Size Changes with Gestational Age

- The “normal” nuchal translucency increases with gestational age
- The NT measurement can only be performed with a CRL of 45 mm to 84 mm.
- ~ 11 weeks to 14 weeks EGA

## NUCHAL TRANSLUCENCY Increases with Gestational Age

<table>
<thead>
<tr>
<th></th>
<th>Median (mm)</th>
<th>95 percentile (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>11 2/7 weeks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45mm CRL</td>
<td>1.2</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>14 2/7 weeks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>84mm CRL</td>
<td>1.9</td>
<td>2.7</td>
</tr>
</tbody>
</table>

*3.4 mm is the 99 percentile for all gestational ages up to 14 weeks*
Nuchal Translucency (NT)

12 week fetus with normal NT  
Trisomy 21 fetus with increased NT

Nuchal Translucency (NT)

midsagittal
-zoom
- Settings
- Calipers
- Flexion
- Amnion
- Size (CRL)
Criteria for what constitutes an adequate NT measurement

- Crown-rump length between 45mm-84mm
- Sagittal view that shows the nuchal measurement and face with the fetus in neutral position
- Magnification so that only the upper 2/3 of the fetus is included in the image
- Distinguishing nuchal membrane from the amnion
- Measuring maximal subcutaneous translucency overlying the neck
- Identifying causes of falsely increased nuchal translucency measurement including fetal, extension and nuchal cord

Nuchal Translucency
CYSTIC HYGROMA
50% RISK OF ANEUPLOIDY

NUCHAL TRANSLUCENCY
Increases Sensitivity vs Maternal Analytes alone

- **QUAD screen** < 35yo will
detect **68%** of T21 at 16 weeks.

- **SERUM INTEGRATED** < 35yo will
detect **77%** of T21 at 16 weeks.

- **FULL INTEGRATED** < 35yo will
detect **85%** of T21 at 16 weeks.
Studies examining the implementation of fetal nuchal translucency measurement at 10–14 weeks of gestation in screening for trisomy 21

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Screening cutoff</th>
<th>FPR</th>
<th>DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pandya et al, 1995</td>
<td>1763</td>
<td>NT &gt;2.5 mm</td>
<td>3.6%</td>
<td>3 of 4 (75%)</td>
</tr>
<tr>
<td>Szabo et al, 1995</td>
<td>3380</td>
<td>NT &gt;3.0 mm</td>
<td>1.6%</td>
<td>28 of 31 (90%)</td>
</tr>
<tr>
<td>Taipale et al, 1997</td>
<td>6939</td>
<td>NT &gt;3.0 mm</td>
<td>0.8%</td>
<td>4 of 6 (67%)</td>
</tr>
<tr>
<td>Hafner et al, 1998</td>
<td>4233</td>
<td>NT &gt;2.5 mm</td>
<td>1.7%</td>
<td>3 of 7 (43%)</td>
</tr>
<tr>
<td>Pajkrt et al, 1998</td>
<td>1473</td>
<td>NT &gt;3.0 mm</td>
<td>2.2%</td>
<td>6 of 9 (67%)</td>
</tr>
<tr>
<td>Economides et al, 1998</td>
<td>2281</td>
<td>NT &gt;99th centile</td>
<td>0.4%</td>
<td>6 of 8 (75%)</td>
</tr>
<tr>
<td>Zoppi et al, 2000</td>
<td>5210</td>
<td>Risk &gt;1 in 100</td>
<td>4.2%</td>
<td>33 of 47 (70%)</td>
</tr>
<tr>
<td>Theodoropoulos et al, 1998</td>
<td>11,398</td>
<td>Risk &gt;1 in 200</td>
<td>4.7%</td>
<td>16 of 21 (76%)</td>
</tr>
<tr>
<td>Schwarzler et al, 1999</td>
<td>4523</td>
<td>Risk &gt;1 in 270</td>
<td>4.7%</td>
<td>10 of 12 (83%)</td>
</tr>
<tr>
<td>Szabo et al, 1995</td>
<td>3550</td>
<td>Risk &gt;1 in 300</td>
<td>4.9%</td>
<td>10 of 11 (91%)</td>
</tr>
<tr>
<td>Total</td>
<td>44,750</td>
<td></td>
<td>3.0%</td>
<td>119 of 156 (76%)</td>
</tr>
</tbody>
</table>

**Timing**

- **1st Trimester Blood Draw:**
  10w0d – 13w6d

- **Nuchal Translucency (NT):**
  11w2d – 14w2d (CRL 45-84mm)

- **2nd Trimester Blood Draw:**
  15w0d – 20w0d
### Detection rates related to timing

<table>
<thead>
<tr>
<th>False + Rate %</th>
<th>11 weeks</th>
<th>12 weeks</th>
<th>13 weeks</th>
<th>Blood 10 weeks</th>
<th>Blood 11 weeks</th>
<th>Blood 10 weeks</th>
<th>Blood 11 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83</td>
<td>76</td>
<td>69</td>
<td>88</td>
<td>81</td>
<td>85</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
<td>83</td>
<td>75</td>
<td>92</td>
<td>87</td>
<td>90</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>92</td>
<td>85</td>
<td>79</td>
<td>94</td>
<td>89</td>
<td>92</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>93</td>
<td>88</td>
<td>81</td>
<td>95</td>
<td>91</td>
<td>94</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>94</td>
<td>90</td>
<td>83</td>
<td>96</td>
<td>92</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>97</td>
<td>94</td>
<td>89</td>
<td>98</td>
<td>96</td>
<td>97</td>
<td>94</td>
</tr>
</tbody>
</table>

### NUCHAL TRANSLUCENCY (NT)

- ABNORMAL NT IS ASSOCIATED WITH **ANATOMICAL DEFECTS** NOT DETECTED BY SERUM SCREENING
NT 3.0 mm or Greater
Detailed anatomical survey and Fetal Echo
Recommended by ACOG & CPSP

- Chromosomal abnormalities
- Genetic syndromes
- Cardiac Anomalies
- Other structural anomalies
- Fetal Infection
- Fetal Anemia
- Fetal Hydrops


## Nuchal Translucency Measurements and Adverse Outcomes

<table>
<thead>
<tr>
<th>Nuchal Translucency Measurement</th>
<th>Aneuploidy</th>
<th>Death</th>
<th>Major Anomaly</th>
<th>Alive and Well</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;95&lt;sup&gt;th&lt;/sup&gt; Percentile</td>
<td>.2%</td>
<td>1.3%</td>
<td>1.6%</td>
<td>97%</td>
</tr>
<tr>
<td>95-99&lt;sup&gt;th&lt;/sup&gt;</td>
<td>3.7%</td>
<td>1.3%</td>
<td>2.5%</td>
<td>93%</td>
</tr>
<tr>
<td>3.5-4.4mm</td>
<td>21.1%</td>
<td>2.7%</td>
<td>10%</td>
<td>70%</td>
</tr>
<tr>
<td>4.5-5.4mm</td>
<td>33.3%</td>
<td>3.4%</td>
<td>18.5%</td>
<td>50%</td>
</tr>
<tr>
<td>5.5-6.4mm</td>
<td>50.5%</td>
<td>10.1%</td>
<td>24.2%</td>
<td>30%</td>
</tr>
<tr>
<td>6.5mm</td>
<td>64.5%</td>
<td>19%</td>
<td>46.2%</td>
<td>15%</td>
</tr>
</tbody>
</table>
NUCHAL TRANSLUCENCY
Increase Size of NT
Increase Risk of Genetic Birth Defect

<table>
<thead>
<tr>
<th>NT size mm</th>
<th>½ are T21</th>
<th>½ are T 13, 18, 45x, Triploidy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>99 percentile = 3.4 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 – 3.4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>3.5 – 4.4</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>4.5 – 5.4</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>5.5 – 6.4</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>≥ 6.5</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>&gt; 8.5</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

Obstet Gynecol:2006;107:6

Nuchal Translucency Measurements and Cardiac defects in chromosomally NORMAL fetuses

<table>
<thead>
<tr>
<th>Nuchal Translucency Measurement</th>
<th>Cardiac Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;95th Percentile</td>
<td>1.6/1000</td>
</tr>
<tr>
<td>2.5-3.4mm</td>
<td>1%</td>
</tr>
<tr>
<td>3.5-4.4mm</td>
<td>3%</td>
</tr>
<tr>
<td>4.5-5.4mm</td>
<td>7%</td>
</tr>
<tr>
<td>5.5-6.4mm</td>
<td>20%</td>
</tr>
<tr>
<td>6.5mm</td>
<td>30%</td>
</tr>
</tbody>
</table>
OTHER FIRST TRIMESTER MARKERS IN PROGRESS

Nasal Bone
Nasal Bone

- nasal bone
  - 70-80% of T21 do not have nasal calcification
    (vs. 0.5% in euploidy)
  - Gives DR up to 97% with 5% FPR

Ductus Venosus

Abnormal ductus venosus
Doppler and trisomy 21
Showing retrograde flow
during atrial contractions
Ductus Venosus

Tricuspid Regurgitation
Other Anatomical Abnormalities That Can Be Detected At NT Ultrasound

Fetal Spine Abnormalities

(A) Body stalk anomaly with thoracic meningomyelocele

B Prenat Diagn. 2010
Holoprocencephaly

Spina Bifida

Prenat Diagn. 2010
Other Sono Markers to evaluate

- T13
  - MEGACYSTIS
  - 20% ANEUPLOIDY

- T18
  - OMPhALOCELE
  - 60% ANEUPLOIDY

ACRANIA
10 Weeks Anencephaly

Bilateral cleft lip associated with Trisomy 13 at 13 weeks
Omphalocele Trisomy 18 @11 weeks

CLUB FOOT
Cystic Hygroma 13 weeks

Normal Face
Normal Anatomy

Special Circumstances: Multiple Gestation

- Twin pregnancies can have quad, serum integrated, or full integrated screening.

<table>
<thead>
<tr>
<th>Quad</th>
<th>T21, NTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quad + NT</td>
<td>T21, T18, NTD</td>
</tr>
<tr>
<td>Serum Integrated</td>
<td>T21, NTD</td>
</tr>
<tr>
<td>Full Integrated</td>
<td>T21, T18, NTD</td>
</tr>
<tr>
<td>1st Trimester: Preliminary Risk</td>
<td>T21, T18</td>
</tr>
</tbody>
</table>

- Trisomy 18 risk is only calculated if NT is provided.
- Serum screening is not available for pregnancies with 3 or more fetuses. Offer NT only.
Conjoined Twins

Monochorionic/Monoamniotic Twins
Monochorionic/Monoamniotic Twins

Septuplets
Summary

- Many excellent options for screening are available
- Combined first and second trimester screening gives the greatest detection rates for aneuploidy at an acceptable screen positive rate
- Age alone should not be used for screening or used for who should be offered diagnostic testing

Summary

- Many benefits to NT and first trimester screening
- NT can be used to determine which patient’s are at greatest risk for adverse outcomes and other birth defects
- Many abnormalities can be detected during the NT ultrasound
Thank You