THE 11-14 WEEK OBSTETRICAL SCAN

Jude P. Crino, M.D.

ANEUPLOIDY SCREENING AT 11-14 WEEKS

The skin is deficient in elasticity giving the appearance of being too large for the body. The face is flat and the nose is small.

Observations on an ethnic classification of idiots

Langdon Down 1866

Courtesy Kypros Nicolaides, M.D.

NUCHAL TRANSLUCENCY

• First trimester correlate of nuchal fold
• Specific measurement technique
• Standardized training
• Quality assurance

NUCHAL TRANSLUCENCY

• Gestation 11-14 wks
• Crown-rump length 45-84 mm
• Mid-sagittal view
• Image size: head and thorax
• Neutral position
• Away from amnion
• Maximum lucency
• Callipers on-to-on
NUCHAL TRANSLUCENCY CUTOFF VALUES

- NT increases w/ gestational age
  - 17% per week
- If single cutoff used false pos rate increases w/ advancing gest age

NUCHAL TRANSLUCENCY AND GESTATIONAL AGE

CONVERSION OF NT TO DOWN SYNDROME RISK

- NT measurement is compared to expected normal median value for crown-rump length or gest age
- The deviation in fetal NT from the expected value is converted into a likelihood ratio
  - delta value method – based upon difference in mm from normal regressed median for CRL
  - MoM-Gaussian method – uses multiples of the expected median (MoM) for gest age
- Risk for trisomy 21 = a priori maternal age and gestation-related risk X likelihood ratio

FIRST TRIMESTER SERUM ANALYTES

<table>
<thead>
<tr>
<th>Method of Screening</th>
<th>TRISOMY 21</th>
<th>TRISOMY 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>70%</td>
<td>50%</td>
</tr>
<tr>
<td>Nuchal translucency (NT) at 12 wks</td>
<td>80%</td>
<td>50%</td>
</tr>
<tr>
<td>Quadruple screen at 16 wks</td>
<td>80%</td>
<td>50%</td>
</tr>
<tr>
<td>Fetal NT, a-fetoprotein (AFP) at 12 wks</td>
<td>80%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Screening for trisomy 21
Effectiveness of different methods of screening
STRATEGIES TO IMPROVE TEST PERFORMANCE

↑ detection, ↓ false pos rate

- First trimester contingent screening using additional sonographic markers
- Combining 1st and 2nd trimester tests
  - integrated
  - sequential

FRONTOMAXILLARY FACIAL ANGLE

Screening for aneuploidy other than trisomy 21

ADDITIONAL BENEFITS OF FIRST TRIMESTER SCREENING

- First trimester dating
- Early diagnosis of multiples and chorionicity
- Early diagnosis of some structural anomalies
- Serum screening for adverse outcomes
- Screening for congenital heart disease
**MULTIPLE GESTATION**

**Assessment of Chorionicity**

**10-14 weeks**

• Dividing membrane – appearance of base

  - Monochorionic – "T"
  - Dichorionic – "twin peak" or "lambda"

<table>
<thead>
<tr>
<th>Ultrasound diagnosis</th>
<th>Placenta/pathology</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monochorionic</td>
<td></td>
<td>101</td>
</tr>
<tr>
<td>At 14 weeks</td>
<td>M 1</td>
<td>67</td>
</tr>
<tr>
<td>At 14 weeks</td>
<td>D 1</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>101</td>
</tr>
<tr>
<td>Dichorionic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 14 weeks</td>
<td>M 3</td>
<td>26</td>
</tr>
<tr>
<td>At 14 weeks</td>
<td>D 1</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>34</td>
</tr>
</tbody>
</table>

Assessment of Chorionicity

**Frequency of lambda sign in dichorionic pregnancies**

<table>
<thead>
<tr>
<th>Time</th>
<th>Fused placenta</th>
<th>Separate placenta</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>16 weeks</td>
<td>100%</td>
<td>91%</td>
<td>97%</td>
</tr>
<tr>
<td>20 weeks</td>
<td>93%</td>
<td>74%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Increased nuchal translucency (mm)

- <2.5 mm: 2% (risk: 20%)
- 2.5-3.4 mm: 5% (risk: 20%
- 3.5-4.4 mm: 10% (risk: 30%)
- 4.5-5.4 mm: 20% (risk: 40%)
- >5.5 mm: 70% (risk: 80%)

**OUTCOME OF INCREASED NUCHAL TRANSLUCENCY**

- Chromosomal Defects: 0.2%
- Fetal death: 1.3%
- Major fetal abnormalities: 1.6%
- Alive and well: 97%

**Major Heart Defects**

- <2.5 mm: 2% (risk: 30%)
- 2.5-3.4 mm: 5% (risk: 30%)
- 3.5-4.4 mm: 10% (risk: 40%)
- 4.5-5.4 mm: 20% (risk: 50%)
- >5.5 mm: 70% (risk: 60%)
The 11-13th week anomaly scan

- What are the embryological limitations?
- What abnormalities can be detected?
- What are the sonographic limitations?
- Develop a protocol for an early anatomic survey

Acrania / anencephaly

47 cases, prevalence 1 / 1,200
First 31 8 missed
Last 16 0 missed

In the first trimester the brain may appear normal!
Onset of ossification of the skull 11 wks

Johnson et al 1996
The 11-13th week anomaly scan

### Holoprosencephaly

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>T13</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 wks</td>
<td>1 : 3,500 65%</td>
</tr>
<tr>
<td>20 wks</td>
<td>1 : ~7,000 40%</td>
</tr>
<tr>
<td>Birth</td>
<td>1 : ~10,000 ?</td>
</tr>
</tbody>
</table>

26 cases, prevalence 1 / 3,800

### Encephalocele

- Seen after 10 weeks
- Bony defect

- 75% occipital
- 25% frontal or parietal

### Meckel Gruber Syndrome

- AR lethal disorder
- Polydactyly
- Echogenic kidneys

- Low risk group: 1 in 20,000
- High risk group: Recurrence 2/6
- None missed

- Sepulveda et al 1996

### Face

- Profile
- Nasal bone
- Orbits

- Maxilla
- Mandible
Bilateral cleft lip

Spine
- Vertebrae: neck to pelvis
- Skin intact

Spina bifida
- 29 cases in 61,972 singleton pregnancies
- Prevalence of 1 / 2,000
- None diagnosed in first trimester
- Increased NT in 1 of 29 cases
- High risk group: Lemon sign: 3 of 3

Sebire et al 1997

Cranial signs not fully evaluated in 1st trimester

Lumbosacral meningoele
- Cannot rule out spina bifida in lumbosacral region before 18 w
Lemon sign

Chiari II malformation
Banana sign & meningomyelocele

Posterior fossa
Cerebellar vermis may not close over 4th ventricle until 18 w

Intracranial translucency

Intracranial translucency

Spina bifida

Omphalocele

Physiological Omphalocele
6 wks: Onset of herniation
10 wks: Herniation in all cases
11 wks: Resolution

Spina bifida

Midline defect with bowel herniation into the base of the cord

Prevalence: 1/4,000 births
 Cause: Sporadic
 Other defects: Trisomies 18 & 13, Beckwith syndrome
 Treatment: Surgical
 Prognosis: 80% survival
Normal cord insertion

Physiologic midgut herniation

Omphalocele
Diagnosed when:
- CRL > 45 mm
- Mass > 7mm
- Contains Liver/stomach

Gastroschisis
- Birth prevalence 1 : 5,000
- Sporadic
- Not associated with aneuploidy
- Very few diagnosed in 1st trimester
**Body Stalk Anomaly**

- Birth prevalence: 1:14,000
- Sporadic, lethal
  - Major abdominal wall defect
  - Short cord
  - Kyphoscoliosis
- Early amnion rupture
- Many present with increased NT

Daskalakis et al 1997

**Diaphragmatic Hernia**

- Birth prevalence: 1:4,000
- Development completed by 9 weeks
- Intrathoracic herniation of abdominal viscera may occur when gut returns to abdomen at 10-12 weeks
- May be delayed until 2nd or 3rd trimester

Sebire et al 1997

- 19 cases: 1/4,000
- NT>95th: 7 of 19
- 5 of 6 NND

**Diaphragmatic Hernia**

- Bowel in chest, mediastinal shift, pleural effusion, polyhydramnios
- Isolated hernia: 50%
- Chromosomal defects: 30%
- Other abnormalities: 20%
- Survival of isolated: 50%
The 11-13+6 weeks scan

**Normal bladder**
- 10 wks: visible in 50%
- 11 wks: visible in 98%
- 12 wks: visible in all

Liao et al 2003

**Megacystis**
- Normal bladder
- > 7mm

90% resolution
10% obstructive uropathy
100% abnormal karyotype
25% abnormal
10% normal

Megacystis > 7mm

Liao et al 2003

**Kidneys**
- Visible in all by 12 weeks
- May appear echogenic
- Look for rim of fat

**Renal Agenesis**
- Birth prevalence 1 : 4000
- Absence of kidneys
- Absence of bladder
- 1st trimester - normal fluid

**Multicystic dysplastic kidney**
No bladder seen
Irregular mass lower anterior abdominal wall

Cloacal exstrophy

Fetal skeleton

- Femur
- Upper Limb

10 wk: Ossification centers of long bones seen
11 wk: Long bones measured with accuracy
Limb movements readily seen

Extremities
- 4 limbs
- Movements

Lethal skeletal dysplasia

- Short femur
- Hitch-hiker thumb

Diastrophic dysplasia
Club foot & polydactyly

Molar Placenta (1 in 2,500)
- Complete mole / normal twin
- Partial mole
- Mesenchymal dysplasia

The 11-13+6 weeks scan

Successful examination of fetal anatomy at 11-13+6 weeks

Transabdominal and / or transvaginal scan:

<table>
<thead>
<tr>
<th>CRL (mm)</th>
<th>6-8</th>
<th>9-11</th>
<th>12-15</th>
<th>16-19</th>
<th>20-23</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Face</td>
<td>98%</td>
<td>98%</td>
<td>98%</td>
<td>98%</td>
<td>98%</td>
<td>100%</td>
</tr>
<tr>
<td>Spine</td>
<td>85%</td>
<td>85%</td>
<td>85%</td>
<td>85%</td>
<td>85%</td>
<td>96%</td>
</tr>
<tr>
<td>Heart</td>
<td>71%</td>
<td>71%</td>
<td>71%</td>
<td>71%</td>
<td>71%</td>
<td>94%</td>
</tr>
<tr>
<td>Stomach</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>100%</td>
</tr>
<tr>
<td>Abdomen</td>
<td>46%</td>
<td>46%</td>
<td>46%</td>
<td>46%</td>
<td>46%</td>
<td>58%</td>
</tr>
<tr>
<td>Extremities</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Successful examination of fetal anatomy at 11-13+6 weeks

Screening for structural defects

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Anomalies</th>
<th>Prenatal diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Souka et al 2004</td>
<td>43 (36.1%)</td>
<td>92 (77.3%)</td>
<td>119 (8,476)</td>
</tr>
<tr>
<td>Carvalho et al 2002</td>
<td>7 (53.8%)</td>
<td>10 (76.9%)</td>
<td>13 (1,632)</td>
</tr>
<tr>
<td>Economides et al 1998</td>
<td>11 (27.5%)</td>
<td>30 (75.0%)</td>
<td>40 (3,991)</td>
</tr>
<tr>
<td>Hernandi and Torocsik, 1997</td>
<td>11 (27.5%)</td>
<td>30 (75.0%)</td>
<td>40 (3,991)</td>
</tr>
</tbody>
</table>

Total

| Head             | 8,476 | 119 |
| Exposed anomalies | 1,632 | 13  |
| Skeletal dysplasias, arthrogryposis | 3,991 | 40  |

Gynecology and Obstetrics
What anomalies do we miss?

11-14 WEEK SONOGRAM SUGGESTED GUIDELINES

- Crown-rump length
- Heart rate
- Nuchal translucency
- BPD level
- Profile
- TRV chest at heart
- TRV abdomen
- Abdominal CI
- Stomach
- Bladder
- Sag/ coronal spine
- Four extremities
- Hands
- Feet

The future...

FUTURE DIRECTIONS

- Integrating first trimester screening and cfDNA in aneuploidy screening strategies
- First trimester preeclampsia screening

CELL FREE DNA

CELL FREE DNA TERMINOLOGY

- NIDT – noninvasive DNA testing
- NIPD – noninvasive prenatal diagnosis (Y chromosome specific sequences, RHD)
- NIPT – noninvasive prenatal testing
- NIPS – noninvasive prenatal screening
**SOURCES OF FETAL DNA IN MATERNAL BLOOD**

- **Fetal cells**
  - 1 in 1 billion of total cell population
  - Require isolation via mechanical and/or biochemical means
- **Cell free DNA (cfDNA)**
  - Maternal blood contains both maternal and fetal cfDNA
  - 2-20% of total cfDNA is fetal

**CELL FREE DNA**

- Released through apoptosis
  - Fetal cfDNA likely arises from cytotrophoblast cells of placenta
- Released into bloodstream as small DNA fragments (140-200 bp)
- Reliably detected after 7 weeks of gestation
- Undetectable within hours postpartum

**TEST COMPARISON**

<table>
<thead>
<tr>
<th>Result Types</th>
<th>verifi®</th>
<th>Harmony</th>
<th>MaterniT21</th>
<th>Natera</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneuploidy Detected</td>
<td>Aneuploidy Suspected</td>
<td>Aneuploidy Detected</td>
<td>Aneuploidy Detected</td>
<td>Aneuploidy Detected</td>
</tr>
<tr>
<td>Assay Failure Rate</td>
<td>5.5%</td>
<td>4.6 – 4.9%</td>
<td>1%</td>
<td>5.5 – 12.6%</td>
</tr>
<tr>
<td>Sample</td>
<td>1 tube maternal blood</td>
<td>2 tubes maternal blood</td>
<td>2 tubes maternal blood</td>
<td>2-4 tubes maternal blood (best with paternal sample)</td>
</tr>
<tr>
<td>Egg Donors</td>
<td>Yes (with data)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Test Menu</td>
<td>T21, T18, T13</td>
<td>Y chromosome (optional)(not published)</td>
<td>T21, T18, T13</td>
<td>Sex chromosome aneuploidies (not published)</td>
</tr>
<tr>
<td>Published Clinical Validation</td>
<td>Large-scale, blinded clinical validation</td>
<td>Large-scale, blinded clinical validation</td>
<td>Large-scale, blinded clinical validation</td>
<td>Small, blinded clinical validation</td>
</tr>
</tbody>
</table>

**POSITIVE SCREENING TEST FETAL KARYOTYPE**

- Detectable by NPT
  - Trisomy 21
  - 1592 (53.2)
  - Trisomy 18
  - 511 (17.1)
  - Trisomy 13
  - 139 (4.6)
  - Sex chromosome aneuploidy
  - 247 (8.3)
  - Total
  - 2489 (83.2)

**TEST COMPARISON SENSITIVITY**

<table>
<thead>
<tr>
<th>Assay</th>
<th>T21</th>
<th>T18</th>
<th>T13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ariosa</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>80</td>
</tr>
<tr>
<td>Natera</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Sequenom</td>
<td>99.1</td>
<td>&gt;99.9</td>
<td>91.7</td>
</tr>
<tr>
<td>Verinata</td>
<td>&gt;99.9</td>
<td>97.4</td>
<td>87.5</td>
</tr>
</tbody>
</table>

*) From website

Specificities >99%

**POSITIVE SCREENING TEST FETAL KARYOTYPE**

- Not Detectable by NPT
  - Mosaicism
  - 186 (6.2)
  - Other trisomy
  - 92 (3.1)
  - Insertion/Deletion
  - 88 (2.9)
  - Structural abnormality
  - 100 (3.3)
  - Balanced rearrangement
  - 97 (3.2)
  - Unbalanced rearrangement
  - 3 (0.1)
  - Trisomy
  - 29 (1)
  - Marker
  - 9 (0.3)
  - Total
  - 504 (16.8)
FTS AND cfDNA SCREENING STRATEGIES

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Total cost of screening (k$)</th>
<th>No. of patients with risk</th>
<th>Cost of FTS (k$)</th>
<th>No. of patients with risk</th>
<th>Test results</th>
<th>No. of patients with risk</th>
<th>Cost of 10k$</th>
<th>No. of patients with risk</th>
<th>Test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTS for all</td>
<td>3,000,000</td>
<td>200</td>
<td>100</td>
<td>15</td>
<td>1</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMT for all</td>
<td>3,000,000</td>
<td>200</td>
<td>100</td>
<td>15</td>
<td>1</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Total cost of screening (k$) | 3,000,000 | 5,000,000 |
| No. of patients with risk | 100 | 200 |
| Cost of FTS (k$) | 15 | 15 |
| Test results | 1 | 1 |

CONTINGENT cfDNA ON COMBINED FTS IN THE UK

- Initial combined FTS
- High risk result (> 1:100) offered CVS, cfDNA, or no further testing
- Intermediate risk result (1:101-1:2500) offered cfDNA or no further testing
- Low risk result (< 1:2500) not offered additional testing

• Overall detection rates
  - 91.5% trisomy 21
  - 100% trisomy 18

• FTS detection rate (FPR 3.4%)
  - 87% trisomy 21
  - 93% trisomy 18

• cfDNA detection rate (FPR 0.25%)
  - 98% trisomy 21
  - 82% trisomy 18

CONTINGENT cfDNA ON COMBINED FTS IN THE UK

• 43% reduction in rate of invasive testing
• 74.4% trisomy 21 termination rate
  - 92.6% who chose invasive testing
  - 35.7% who chose cfDNA
• 31.9% trisomy 21 live birth rate

FIRST TRIMESTER PREECLAMPSIA SCREENING

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<tbody>
<tr>
<td>FSH</td>
<td>85</td>
<td>75</td>
</tr>
<tr>
<td>In</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>hCG</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>NV</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>90</td>
<td>70</td>
</tr>
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</table>

THANK YOU!