Ultrasound in Genetics

• Stuart Campbell diagnoses fetal hydrocephalus on ultrasound 1977
Hydrocephalus

Neural Tube Defects

- Hydrocephalus
- Meningomyelocele/Spina Bifida
- Encephalocele
- Anencephaly
Encephalocele

Anencephaly
Meningomyelocele

Ultrasound of Fetal Spine
Neural Tube Defects

- 2/1,000 population
- Genetic family of defects
- 5% recurrence risk
- Folate sensitive
Serum Marker
Alpha Fetoprotein

- 1972  Brock-high AFP in NTD pregnancy
- 1975  UK collaborative
- 19,148 pregnancies
- 95% of NTD’s diagnosed
- 1985  ACOG advisory
- 1986  California State Law – offer AFP
Ultrasound Anomalies with Genetic Implications

- Congenital Cardiac Defects
- Omphalocele
- Cystic Hygroma
- Polydactyly
- Kidney anomalies- multicystic/dysplastic, hydronephrosis, polycystic
- Cleft lip/palate
- Duodenal Atresia

Abnormal Heart
Cardiac Malformations

- 8/1,000 live births
- Chromosomal, teratogenic, multifactorial
- Up to 10% chromosomal anomaly
- 2 to 25% recurrence risk
- 25% have extracardiac malformations

Omphalocoele

- T18, T13, T21
Omphalocele

- 1 in 4,000 births
- Increases with maternal age
- 40% chromosomal anomalies
  - T18, T13, T21, XO Turners, Triploidy
- Look for other anomalies

Cystic Hygroma
Cystic Hygroma

- 1 in 4,000 ultrasound scans
- High MSAFP
- 75% chromosome anomaly
- XO Turners
- T 21
- T18
- 80% die before birth
- Survivors develop a webbed neck

Double Bubble
Duodenal Atresia
Duodenal Atresia

- 1 in 5,000 pregnancies
- 50% associated with T 21
- Polyhydramnios usually present

Ultrasound Findings
Major vs Marker

- Major finding: structural anomaly with surgical/medical impact
- Minor finding/Marker: no surgical/medical impact. Most babies with ultrasound markers are normal
Second Trimester Ultrasound “Markers”

- Echogenic cardiac focus
- Dilated renal pelvis
- Choroid plexus cysts
- Short femur
- Thick nuchal fold
- Echogenic bowel

Echogenic Cardiac Focus
Echogenic Cardiac Focus

- Present in 2% of anatomic surveys
- Calcified papillary muscle
- Physiologic, not pathologic
- Racially related
- Very positional

Dilated Fetal Renal Pelvis
Dilated Fetal Renal Pelvis

- Present in 2% of anatomic surveys
- > 4 mm
- Physiologic – not pathologic
- Weakly associated with chromosome anomaly

Choroid Plexus Cyst

- 1 in 200 sonos
- Regress at 24 weeks
- If isolated:
  - No genetic implication
Nuchal Fold

• “the skin is too large for the bodies”
• John Langdon Down
• 1866

Thick Nuchal Fold

• >5 mm
• .8% of anatomic surveys
• Most sensitive of the Markers
• 600 amnios per T21 diagnosis
**Downs Syndrome Screening**  
**Second Trimester Ultrasound**

- Second Trimester Ultrasound “Markers”
  
  - widely used
  - weakly associated with T21/T18
  - unacceptably high false positive rate
  - noted at 18 to 22 week anatomy survey

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**Second Trimester “Markers”**

Extremely common: 11% incidental finding in second trimester sonos  
Risk of abnormal karyotype in general population at 18 to 22 weeks 1 in 600  

If karyotype abnormal, 22% of associated sonos will have a “marker” identified
### Ultrasound Finding
**Minor/Marker**

- When present - risk for chromosome problem increased
- When absent – risk for chromosome problem decreased

### Second Trimester Sono “Markers”
**Current Thinking**

- Which marker?
- How many markers?
- Used in conjunction with XMSAFP to modify Downs risk
Second Trimester Serum Markers

- 1975 UK Collaborative establishes high AFP as standard screening for NTD’s with 95% detection
- 1980’s Ultrasound as screening for NTD’s has 99% detection
- 1984 Merkatz discovers low AFP is associated with chromosomal defects
MSAFP

- In 1984 AFP becomes a serum screening tool for Downs syndrome

Second Trimester Serum Markers

1984 Merkatz – 20% of T21 diagnosed on low AFP only

1988 Wald – 60% of T21 diagnosed low AFP, high HCG, low uE3

2000 75% of T21 diagnosed AFP + HCG + uE3 + Inhibin
Down Syndrome Diagnosis
Amniocentesis

30% of T21 pregnancies occur in women over 35
70% of T21 pregnancies missed
Born to women younger than 35

Down Syndrome Screening
Second Trimester Serum

- 1980’s
- MSAFP alone 20% sensitivity
- 1990’s
- AFP+HCG+Estriol 60% sensitivity
- 2000’s
- AFP+HCG+Estriol+Inhibin 75% sensitive

- Problem 15 to 20 weeks gestation
Nuchal Fold

- “the skin is too large for the bodies”
- John Langdon Down
- 1866

First Trimester Ultrasound

- Second trimester nuchal fold
  – too insensitive – too late in gestation

  1990’s
- First Trimester “nuchal translucency”
- sensitive and early
Nuchal Translucency

- Sono lucent, fluid filled area at the nape of the fetal neck
- Best seen between 10 and 14 weeks
- Increases with CRL
NT When to Measure

- CRL 45 mm to 84 mm
- Gestational Age
- 11 weeks to 13 weeks 6 days
Landmarks for NT

• True midsagittal view of fetal face
• Nasal tip
• Diencephalon
• Palate
• Nuchal translucency

Requirements

• High resolution equipment
• Upper thorax and head fill the picture
• Neutral position
• Measure the fluid space only
11w to 13w6d Nuchal Translucency

- detection
- Downs 72%
- T 18 75%
- T13 72%
- Turners 87%
- Triploidy 59%
- Other 55%
First Trimester Serum Markers

• PAPP-A is low
• Free Beta is high
• Drawn at 9 to 13 weeks

FTS Screening

• Combined MA + Free Beta + PAPP A + NT
• Downs detection = 95%
Impact of First Trimester Risk Assessment

- Earlier timing of prenatal diagnosis
- Lower rates of invasive testing
- 10 to 13 week availability of CVS
- Pregnancy termination in first trimester
- one day procedure/local anesthesia
- lower maternal morbidity/mortality

First Trimester Screening

- www.fetalmedicineusa.com
• “The skin is too large for the bodies…
• “The nose is small”
• John Langdon Down
• 1866

Nasal Bone
Absent Nasal Bone

- Normal chromosomes 3%
- T21 75%
- T18 50%

Increased Nuchal Translucency
Normal Chromosomes

- Congenital heart malformation
- Diaphragmatic Hernia
- Pulmonary defects
- Infection
- Syndromes
The Future

• CVS for Human Genome

Human Genome

Chromosomes
Genes sequences
Point mutations