

The Basics of Prenatal Diagnosis

Cori Feist, MS, CGC
Prenatal Diagnosis Program
Doernbecher Children's Hospital

Genetics Education

- For information and educational opportunities related to genetics and your career, please see the website for the National Coalition for Health Professional Education in Genetics (NCHPEG)
- <http://www.nchpeg.org/>

Prenatal Diagnosis

- Identify pregnancies at increased risk for genetic conditions/birth defects
- Explain to families what the risk would be
- Offer testing options, if available
- Help families make decisions about the pregnancy
- Identify resources for support/education

Common Indications

- **Maternal age >34 years at delivery**
- **Positive maternal serum screening**
- **Family history of genetic condition/birth defect**
- **Abnormal ultrasound**
- **Exposure to medications and infectious agents**
- **Maternal conditions (epilepsy, diabetes)**
- **Ethnic background**

General Population Risk

- The general population risk for birth defects is 3-5%
 - Both physical and developmental
- All risk assessments add to this baseline risk

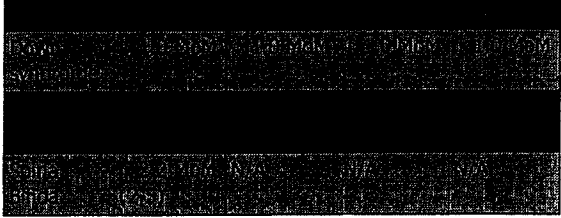
Options for PNDx

- Maternal Serum Screening
- Ultrasound
- Amniocentesis
- Chorionic Villus Sampling
- Percutaneous Umbilical Blood Sampling
- Pre-implantation Genetic Diagnosis

Maternal Serum Screening

- Non-invasive screen to determine risk for:
 - Down syndrome (Trisomy 21)
 - Trisomy 18
 - Spina Bifida (open neural tube defect)
- Valid between 15 - 20 weeks gestation
- Measure raw values of AFP, ue3, hCG, and inhibin and compare to median value for the appropriate gestational age (MoM)

Quadruple Marker Results



Maternal Serum Screening

- Is this a diagnostic test? **NO!**
- It detects:
 - 85% of ONTDs with 2% positive
 - 70% of Down syndrome with 2-5% positive
 - 60% of Trisomy 18 with .2% positive

What does an elevated AFP really mean?

<ul style="list-style-type: none"> ■ ONTD ■ Ventral wall defect ■ Esophageal atresia ■ Cystic hygroma ■ Fetal demise ■ Placental anomaly 	<ul style="list-style-type: none"> ■ Normal pregnancy ■ Multiple gestation ■ Incorrect dating ■ Fetal blood contamination
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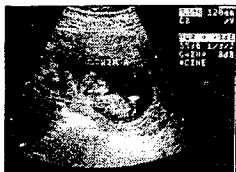
Quadruple Marker Screen

- For a positive screen
 - Verify gestational age, rule out multiple gestation (AFP only is valid for multiple gestations)
 - Offer counseling to explain results
 - Offer targeted ultrasound and amniocentesis
 - Ultrasound is not diagnostic for Down syndrome or Trisomy 18, but is 90-95% accurate for ONTDs
 - Amniocentesis is the most commonly used diagnostic test for Down syndrome and Trisomy 18

Ultrasound/Sonogram

- Non-invasive screening test
- Uses sound waves to visualize fetal anatomy
- Fetal anatomy - 18-20 weeks
- Cardiac abnormalities - 20-22 weeks
- Not a diagnostic tool - a normal ultrasound does not guarantee a healthy baby

Ultrasound/Sonogram



Fetus at 11.5 weeks gestation



Fetus at 19 weeks gestation

Fetal Anatomy Scan – Level II US

- Growth
- Physical Development
- Soft Markers including:
 - Choroid plexus cysts
 - Intracardiac echogenic focus
 - Increased nuchal thickness
 - Echogenic bowel
 - Clenched, unusually positioned hands

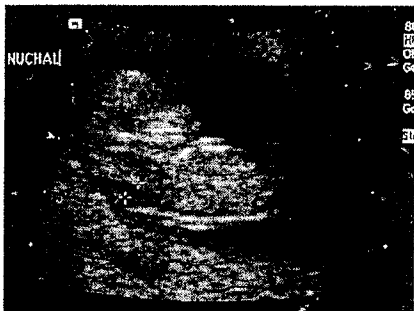
Nuchal Translucency (NT)

- Fluid accumulation between the skin and the soft tissue overlying the cervical spine
- Measured between 11.1-13.9 weeks
- Typically between 1 – 3 mm
- Increased NT is an indication of a chromosomal abnormality, single gene defect or birth defects, commonly cardiac defects

Ultrasound image of NT



Increased NT

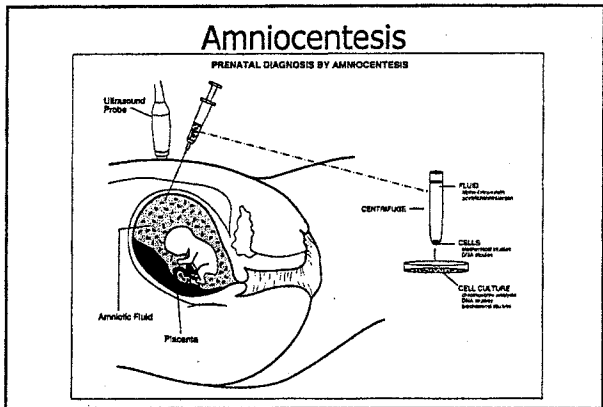


Ultra-Screen

- Combines nuchal translucency with serum screening for PAPP-A and free β -hCG
 - Detects 90% of Down syndrome with a 5% positive rate
 - Detects 98% of Trisomy 18 with a 1% positive rate
 - Does not screen for spina bifida
 - May be used in a twin pregnancy

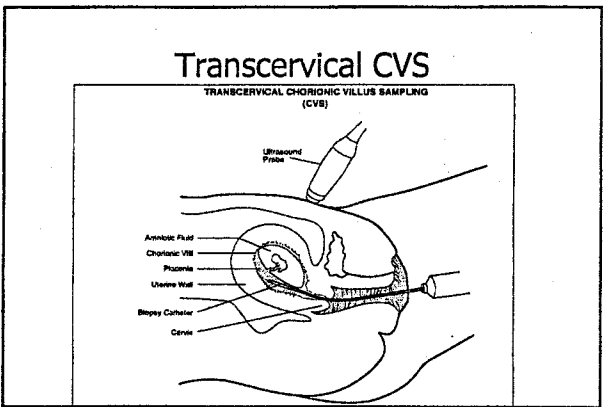
Amniocentesis

- Invasive diagnostic procedure
- Routinely done from 15 weeks
- Obtains amniotic fluid to measure:
 - AFP/acetylcholinesterase
 - Biochemical markers
- Obtains fetal cells for:
 - Chromosomal analysis (karyotype)
 - Single gene/DNA testing



Chorionic Villus Sampling (CVS)

- Invasive diagnostic procedure
- Routinely done from 10-12.5 weeks
- Obtains chorionic villi for:
 - Chromosome analysis(karyotype)
 - Single gene/DNA testing
 - Biochemical studies on fetal cells



Amnio vs CVS

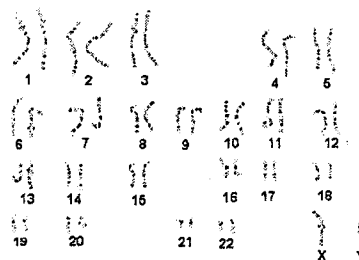
- | Amniocentesis | CVS |
|------------------------------------------|------------------------------------------------------------|
| ■ 99.9% accurate | ■ 99.9 % accurate |
| ■ 2-3 week turnaround | ■ 2-3 week turnaround |
| ■ 0.5% risk for miscarriage | ■ 1% risk for miscarriage |
| ■ Begin at 15 weeks | ■ 10-12 weeks gestation |
| ■ Can test fluid for biochemical markers | ■ Must measure MSAFP to screen for ONTDs |
| ■ Direct test of fetal cells | ■ 1-2% chance for mosaic results due to placental sampling |

Common reasons to offer an Amnio/CVS

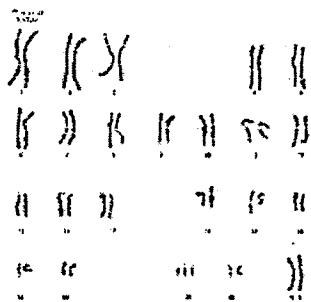
- AMA
- Anomaly seen on ultrasound
- Positive maternal serum screen
- Family history of a genetic condition with mutation previously identified
- Family history of a biochemical defect

Risk for Chromosomal Abnormality by Maternal Age

Normal karyotype 46, XY normal male



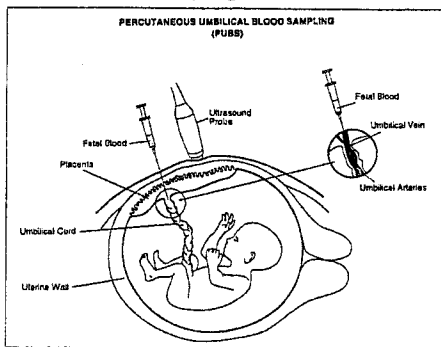
Trisomy 21 (Down syndrome)



PUBS

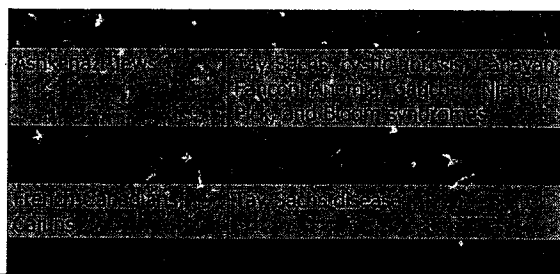
- Percutaneous Umbilical Blood Sampling
- Performed after 17 (20) weeks gestation
- Used for:
 - Rapid karyotyping and DNA studies
 - Detection of isoimmunization/fetal infection
 - Fetal blood transfusion
 - Introduction of drugs/therapies
- 1-2% chance of miscarriage

PUBS

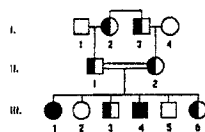


Ethnic background

- Certain populations have an increased risk to be carriers of specific genetic conditions



Autosomal Recessive Inheritance



- Both males and females affected
- Siblings at risk to be affected
- Increased incidence of consanguinity
- 25% recurrence risk

Carrier Screening

- In many cases carrier screening can not identify all carriers of a condition (cystic fibrosis, Tay-sachs)
- A negative screen may only reduce the likelihood of being a carrier
- Useful in further refining the chance the fetus could be affected

Teratogens - Epilepsy

- Recommend monotherapy at lowest possible doses for seizure control
- Risk to pregnancy is dependant upon the anti-seizure medication used
- In general risk to the pregnancy is 2-3 times the general population risk

Insulin Dependent Diabetes Mellitus

- Increases the risk for birth defects 2-3 times above the general population risk
- The spectrum of birth defects is broad
- Better control is thought to decrease the overall risk
- HgbA1c levels are a good measure of control

What happens when something goes wrong?

- Parents can choose to:
 - Continue the pregnancy with education and support about the outcome and impact of the diagnosis
 - Terminate the pregnancy either by D&E or induction of labor
 - Adoption is an option in some cases (Down syndrome)

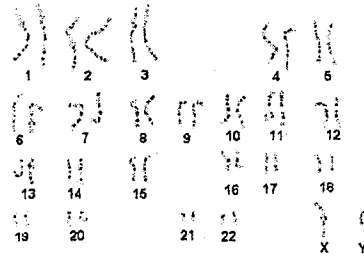
Pre-implantation Genetic Diagnosis

- Combining IVF with genetic testing
- Can reduce the likelihood of implantation of an affected conception
- Sample one cell at the six to ten cell stage to test for genetic condition at increased risk for:
 - Chromosomal abnormalities
 - Some single gene disorders

PGD for AMA

- Limited look at the chromosomes using FISH
- Only looks at chromosomes 13, 18, 21, X, and Y for number not for structure
- Does not look at any of the other chromosomes
- Can help enrich for chromosomally healthy conceptions used for implantation

Standard karyotype



FISH for chromosome 13

