

Overview of Prenatal Screening

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Objectives

- Identify specific reasons for genetic counseling or prenatal diagnosis
- Distinguish between prenatal screening and diagnostic procedures
- Review prenatal screening procedures
- Review ethnicity carrier screening

Referral Indications for Genetic Counseling and/or Prenatal Diagnosis

- Advanced maternal age (>34 at delivery)
- Abnormal Quad or first trimester screen
- Ultrasound abnormalities
- Exposure of current pregnancy to known or suspected teratogen
- Maternal illness or infection

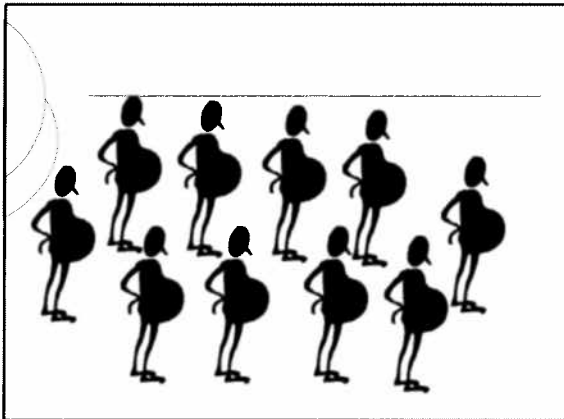
Referral Indications for Genetic Counseling and/or Prenatal Diagnosis

- Family history of a chromosome abnormality, single gene disorder, or birth defects
- History of multiple spontaneous miscarriages, stillbirth, neonatal death or infertility
- Risk for genetic disease due to ethnic background
- Consanguinity (couple is related)

Prenatal Screening

Prenatal Screening vs. Diagnosis

- Prenatal Screening: Quick, inexpensive tests that flag individuals who should be offered diagnostic testing
- Diagnostic Testing: Any procedure performed to determine whether a genetic change is causing or may cause a specific condition



Prenatal Screening vs. Diagnosis

- Screening test examples:
 - Quad screening (or MSAFP screening)
 - First trimester screening
- Diagnostic test examples:
 - Chorionic Villus Sampling (CVS)
 - Amniocentesis

Prenatal Screening Tests

- Benefits
 - Screens low risk populations
 - Usually test results are fairly quick
 - Inexpensive compared to more invasive, diagnostic testing

Prenatal Screening Tests

- Risks
 - Raises maternal anxiety
 - Generates false positives and false negatives
 - Positive result cannot diagnose abnormality
 - Negative result does not eliminate the risk of abnormality

What are we screening for?

- Open neural tube defects
- Down Syndrome (Trisomy 21)
- Trisomy 18



Neural tube defects

- Incomplete development of the spine or brain
- Occurs before the 28th day of pregnancy
- Includes spina bifida and anencephaly
- Maternal health conditions such as diabetes and epilepsy increase risk
- **Can only screen for in 2nd trimester**

Down syndrome and Trisomy 18

- Caused by the presence of an extra chromosome

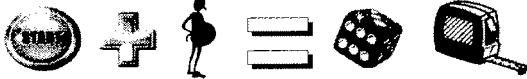


Aneuploidy

- An incorrect number of chromosomes
- Trisomy/monosomy of any chromosome is possible
- Major cause of miscarriages
- Occurs by chance
- More likely to occur as a woman gets older

How does screening work?

- Start with a baseline risk
- Gather information specific to the pregnancy
- Calculate a new personalized risk
- See where risk is compared to cut-offs
- Risk is above cut-off = screen Positive
- Risk is below cut-off = screen Negative



Quad Screening

Also known as maternal serum screening, AFP test, or 2nd trimester screening

What is the Quad screening?

- Blood test performed between the 15th and 20th week
- Screens for neural tube defects, Down syndrome, and trisomy 18
- Has been standard of care

Baseline Risk



Neural Tube Defects

- General population risk = 1/1000

Down syndrome & Trisomy 18

- Maternal age-related risk

Maternal Age Related Risk




- Every woman regardless of age has a risk
- The risk goes up with age
- The risk goes down through the pregnancy due to chance of miscarriage
- Most labs use the age that a woman will be at time of delivery
- Advanced maternal age (> 34)

Pregnancy specific information




- Begins when you fill out the screening requisition form
- Information that helps interpretation including:
 1. Maternal Age
 2. Gestational age
 3. Weight
 4. Ethnicity
 5. Diabetes Status

How does the test work? 


Detects 4 markers in the mother's blood

1. Alpha fetoprotein (AFP)
2. Human chorionic gonadotropin (hCg)
3. Unconjugated estriol (uE3)
4. Inhibin (DIA)

Converts to Multiples of the Median (MoMs)

Multiples of the Median (MoMs) 

- o Allows comparison across labs
- o Defined as the patient's raw value divided by the median value at a specific gestational age
- o Ideal score is 1.0
- o 2.0 MoMs means twice the expected
- o 0.5 MoMs means half the expected

Calculating the new risk 

- o Use MoMs to detect patterns linked with the different conditions

Condition	AFP	hCG	uE3	DIA
NTDs	↑	N/A	N/A	N/A
Down syndrome	↓	↑	↓	↑
Trisomy 18	↓	↓	↓	N/A

Cut-offs for NTDs



- High AFP
 - Screen positive if > 2.0-2.5 MoM
 - Repeat MSAFP if 2-3 MoM
 - Greater than 3 MoM, offer ultrasound and amniocentesis
- Other explanations of high AFP
 - Ventral wall defects
 - Kidney defects
 - Fetal death
 - Multiple gestation

Cut-offs for Down syndrome



- Most labs use risk of a 35 year old woman during the second trimester
- Approximately 1/270 risk
- Greater than 1/270 risk = Screen positive
- Lower than 1/270 risk = Screen negative

Cut-offs for Trisomy 18



- Much rarer than Down syndrome
- Most labs have a set cut-off
- Approximately 1/100 risk
- Greater than 1/100 risk = Screen positive
- Lower than 1/100 risk = Screen negative

How well does the Quad screen work?

Condition	Quad Detection rate
NTDs	80-85%
Down Syndrome	75-80%
Trisomy 18	60%

Example

Age: 35
Gestational Age: 18.7 weeks by U/S
Maternal Age Related Risks
Down Syndrome: 1 in 336
Trisomy 18: 1 in 1010

Screen Results

Marker	MoM	Pattern
AFP	0.72	↓
hCG	1.02	↔
uE3	1.28	↑
DIA	2.17	↑


Screen Positive for Down Syndrome
Personalized Risk is 1 in 196

Example

Age: **25**
Gestational Age: 18.7 weeks by U/S
Maternal Age Related Risks
Down Syndrome: 1 in 1313
Trisomy 18: 1 in 3941

Same MoMs
Screen negative for Down Syndrome
Personalized Risk is 1 in 765

First Trimester Screening (FTS)

First Trimester Screening 

- o Done between 11-14 weeks gestation
- o Involves blood test and ultrasound
- o Screens for Down syndrome and Trisomy 18
- o Does NOT screen for NTD
- o Baseline risk is maternal age-related risk

Pregnancy Specific Information



- o Nuchal Translucency
- o Blood test
 1. Pregnancy-associated protein (PAPP-A)
 2. Human chorionic gonadotropin (hCG)

Nuchal Translucency



Nuchal Translucency



- o Measurement of fluid at the back of the baby's neck
- o Increased fluid is seen in pregnancies with chromosome differences
- o Specific guidelines about measurement
- o If measurement is greater than 95th percentile or a specific cut-off, diagnostic testing is offered

Calculating New Risk



- Convert raw blood data into MoMs
- Looking for patterns

Condition	hCG	PAPP-A	NT
Down syndrome	↑	↓	↑
Trisomy 18	↓	↓	↑

- Calculate new risk of 1/X

Cut-offs



Down syndrome

- Cut-off based on risk of a 35 year old
- Approximately 1/240

Trisomy 18

- Cut-off of 1/150

Patients who choose FTS should be offered AFP only screening in 2nd trimester

How well does FTS work?

Condition	1 st trimester	Quad screening
Down Syndrome	80-85%	75-80%
Trisomy 18	>90%	60%

Limitations of FTS

- Requires early prenatal care
- Not accessible to all due to location and/or cost
- Special training for ultrasonographers
- The center has to be skilled at CVS
- Does not provide neural tube defect screening
- Time consuming!

Benefits of FTS

- Psychological (?reduce anxiety)
- Earlier termination if desired
- Increased nuchal translucency can be associated with cardiac or other defects
- Better detection rates

Other Prenatal Screening Options

For Down Syndrome and Trisomy 18,
NOT Neural Tube Defects

Components of FTS and Quad

- First trimester serum screen (FTSS)
- Quad serum screen (Q)
- Nuchal Translucency (NT)



Other Options



- Serum integrated (FTSS + Q)
- Integrated screen (FTSS + NT + Q)
- Step-wise sequential (FTSS + NT then Q if other two are negative)
- Contingent sequential (FTSS + NT then Q if risk is intermediate)

Confused yet?

What is a health care professional to do?

ACOG Recommendations

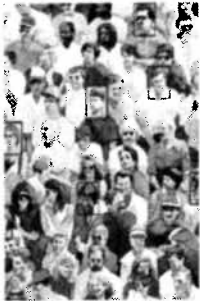
- Screening options should be available to all women who present before 20 weeks
- Decide on options you can perform in house
- Locate other prenatal screening options available in your geographic area
- Be aware of where diagnostic testing is offered

Points to make to patients

- Screening identifies pregnancies that are at an increased risk
- What we screen for
- Maternal age-related risk
- Screening positive will lead to counseling and additional test options
- Screening negative does not eliminate all risk

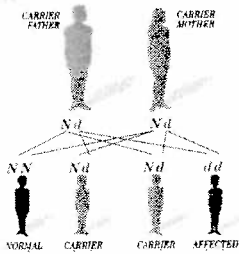
Ethnicity Carrier Screening

Ethnic Carrier Screening



- o Every person is a carrier of 5-10 different recessive gene mutations or changes
- o Ethnicity influences which genes are changed
- o Autosomal recessive inheritance

Autosomal Recessive Inheritance



- o Parents are unaffected "carriers" of genetic condition
- o Equal numbers of males and females affected
- o 25% (1 out of 4) risk with each pregnancy to have an affected child

Caucasian Ancestry

- o Increased risk for cystic fibrosis
- o CF affects lungs, digestive tract, and reproductive tract
- o Carrier frequency = $1/25$



Cystic Fibrosis Screening

- ACOG and ACMG guidelines (2005)
- o Screening of 23 common mutations
- o Should be available to all couples
- o Should be offered early in pregnancy to couples who are of Caucasian, European, or Ashkenazi Jewish ancestry
- o Couples with a family history of CF should be offered genetic counseling

Cystic Fibrosis Screening

- o More than 2000 mutations have been described
- o Most labs offer panels with 32-40 mutations
- o Detect approximately 90% of mutations in Caucasians
- o Price is between \$250-300
- o NC screens for CF in newborn period

Cystic Fibrosis Carrier Frequencies

Ethnicity	Carrier Frequency
Caucasian	1 in 25
Ashkenazi Jewish	1 in 29
Hispanic	1 in 46
African American	1 in 65

African American Ancestry

- Increased risk for sickle cell disease
- Causes red blood cells to be distorted
- Interrupts blood supply
- Carrier frequency = 1 in 10



Sickle Cell Disease

- HbS is most common mutation
- Hemoglobin electrophoresis is gold standard
- Detects other mutations to the hemoglobin molecules
- Solubility tests will not detect all mutations that can cause sickle cell disease

Ashkenazi Jewish Ancestry

- Eastern European Jewish population
- At risk for multiple genetic disorders
 1. Cystic Fibrosis (1 in 29)
 2. Canavan disease (1 in 41)
 3. Tay Sachs disease (1 in 31)
 4. Familial dysautonomia (1 in 31)

Ashkenazi Jewish Ancestry

- Panels of Jewish disorders are available
- Can include many more diseases than the four recommended
- If one only person is of AJ ancestry, that person should be screened first

Hispanic Ancestry

- No specific screening recommendations
- 1 in 46 chance to be CF carrier
- CF carrier screening panels are less effective in Hispanic population



Hispanic Ancestry

- Risk for Sickle Cell disease varies greatly
- As high as 1/8 (Brazil)
- As low as 1/67 (Mexico)
- Hemoglobin electrophoresis recommended for all prenatal patients

Supplemental Information

- Regional Genetic Counselor Maps
- Maternal Age-Related Risk Table
- Resources
 1. Teratogens and Exposures
 2. Prenatal Screening/Ethnicity Screening

Thank you for your attention!
