PRENATAL GENETIC SCREENING

Background
1. Definition of prenatal genetic screening
   o Tests done to determine if unborn child at risk for genetic disorder
2. Testing types
   o Noninvasive/mildly invasive
     ▪ Ultrasound
     ▪ Maternal serum testing
   o Invasive
     ▪ Chorionic villus sampling
     ▪ Amniocentesis
     ▪ Percutaneous umbilical cord sampling

Pathophysiology
1. Pathology of Disease
   o Aneuploidy
     ▪ Klinefelter syndrome
     ▪ Trisomy 13 (Patau syndrome)
     ▪ Trisomy 18 (Edward’s syndrome)
     ▪ Trisomy 21 (Down’s syndrome)
     ▪ Turner’s syndrome
   o Autosomal dominant
     ▪ Huntington’s chorea
   o Autosomal recessive
     ▪ Cystic fibrosis
     ▪ Alpha-thalassemia
     ▪ Beta-thalassemia
     ▪ Familial dysautonomia
     ▪ Phenylketonuria (PKU)
     ▪ Sickle cell anemia
     ▪ Tay-Sachs disease
   o Polygenic
     ▪ Cleft faces (lips, palate)
     ▪ Neural tube defects
   o X-Linked dominant
     ▪ Fragile X syndrome
   o X-Linked recessive
     ▪ Duchenne’s muscular dystrophy
     ▪ Hemophilia A
   o Spontaneous mutation
2. Incidence
   o Alpha-thalassemia- 1:2500 in Southeast Asian descent
   o Beta-thalassemia- 1:2500 in Greek/Italian descent
   o Cleft faces (lips, palate)- 1/100 to 1/20 with an affected parent or after having one previous affected child
o Cystic fibrosis- 1:2500 in whites of European or Ashkenazi Jewish descent
o Duchenne’s muscular dystrophy- 1:3600-6000 live male births
o Familial dysautonomia- 1:2500 in Ashkenazi Jewish descent
o Fragile X syndrome- 1:4000 live male births, 1:6000-8000 live female births
o Hemophilia A- 1:5000 live male births
o Huntington’s chorea- incidence not available; prevalence is estimated to be 4.1-8.4/100,000
o Klinefelter’s syndrome- 1/1000 live male births
o Neural tube defects- 1/100 to 1/20 with an affected parent or after having previously affected child
o Phenylketonuria (PKU)- approximately 1:15,000
o Sickle cell anemia- 1:2500 African American descent
o Spontaneous mutation- 1/100 chance of phenotypical abnormalities with a single gene mutation
o Tay-Sachs disease- 1:2500 in Ashkenazi Jewish descent
o Trisomy 13 (Patau syndrome)- 1/20,000 live births
o Trisomy 18 (Edward’s syndrome)- 1/8000 live births
o Trisomy 21 (Down’s syndrome)- 1/800 live births
o Turner’s syndrome- 1/10,000 live births (>99% end in early pregnancy loss)

3. Risk Factors
   o Ethnic background\(^3\)
     - African American descent increases risk for Sickle Cell Anemia
     - Ashkenazi Jewish descent increases risk for Canavan disease, Familial dysautonomia, Tay-Sachs disease
     - Cajun descent increases risk for Tay-Sachs disease
     - Mediterranean descent increases risk for beta-thalassemia
     - Southeast Asian, Cambodian, Chinese, Filipino, Laotian, and Vietnamese descent increases risk for alpha-thalassemia
   o Known hereditary disease\(^3\)
   o Maternal age\(^3\)
     - Increased age increases risk for chromosomal abnormalities, especially Down’s syndrome
   o Previous child with neural tube defect/cleft face and/or affected parent\(^3\)

4. Morbidity / Mortality
   o Fetal risk with invasive testing
   o Maternal pain/infection at phlebotomy/procedure site

Diagnostics
1. History- Thorough history for hereditary diseases, congenital defects, ethnic background is crucial for determining what screening tests should be reasonably offered
2. Physical Examination- No specific findings; may see evidence for previous cleft face repair or other physical anomalies in parent(s)
3. Diagnostic Testing/Imaging and Laboratory Evaluation
   o First Trimester Optional Routine Screening
      ▪ Combined test
         • Maternal serum beta-hCG (total or free)
         • Pregnancy-associated plasma protein A (PAPP-A)
         • Fetal nuchal translucency (by ultrasound)
      ▪ Maternal serum DNA analysis for cystic fibrosis carrier status; if positive, father may also be tested
      ▪ Notes:
         • Down syndrome typically associated with high levels of beta-hCG, low levels of PAPP-A, and enlarged fetal nuchal translucency
         • Down syndrome sensitivity 78.7-89% with false-positive rate of less than 3-5%
         • Since these tests are done in first trimester, allows time for chorionic villous sampling to be done for definite diagnosis and termination of pregnancy (safer in first trimester), if desired
   o First Trimester Additional Testing Options
      ▪ Chorionic villous sampling
         • Performed between 10-13 weeks GA
         • Chorionic villi aspirated into syringe by passing catheter through cervix or by inserting needle through mother’s abdominal wall; cultured for chromosomal analysis; DNA can be extracted for molecular analysis
         ▪ Notes
            • Sensitivity for Down syndrome 97.8% with false-positive rate of 1-2%
            • Risk of fetal loss about 0.2% (about the same as amniocentesis)
            • Transverse limb defects and oromandibular-limb hypogenesis have been attributed to procedure, but are exceedingly rare
            • Must give Rhogam to unsensitized Rh-negative mothers after procedure
      ▪ Maternal serum DNA analysis for other carrier status disorders
   o Second Trimester Optional Routine Screening
      ▪ Quad screen
         • Maternal serum alpha-fetoprotein (MSAFP)
         • Maternal serum beta-hCG
         • Maternal serum unconjugated estriol
         • Maternal serum inhibin A (if this component is excluded, it is known as Triple screen)
Notes
- Most accurate if done between 16-18 weeks GA, although can be done between 15-20 weeks GA
- Screening results calculated using algorithm based on maternal age, race, weight, and diabetic status
- Usual cut-off of 95th to 98th percentile; about 80% sensitive for open spina bifida and 90% sensitive for anencephaly (closed neural tube defect not normally detected)
- Triple screening sensitivity for Down syndrome about 60-69% with 5% false-positive rate
- Quad screening sensitivity for Down syndrome 67-81% (and up to 90% with ultrasound) with less than 3-5% false-positive rate
- Second Trimester Additional Testing Options
  - Amniocentesis
    - Performed after 14-15 weeks gestation
    - Needle inserted transabdominally under ultrasound guidance into amniotic sac
    - Withdraw amniotic fluid for measurement of substances such as AFAFP, hormones, and enzymes
    - Fetal cells grown in culture for chromosomal, biochemical, and molecular biologic analysis
    - Notes
      - Sensitivity for Down syndrome 99.4% with 0.1-0.6 false-positive rate
      - Maternal morbidity (symptomatic amnionitis) rare
      - Risk of fetal loss is about 0.1-0.2%
      - Vaginal spotting or amniotic fluid leakage occurs in 1-2%, but generally self-limited
      - Must give Rhogam to unsensitized Rh-negative mothers after procedure
  - Percutaneous umbilical blood sampling
    - Performed after 16 weeks gestation
    - Needle inserted transabdominally into umbilical vein to collect fetal blood for rapid chromosome analysis and genetic diagnosis
    - May be used for evaluation of fetal metabolism and hematologic abnormalities
  - Targeted ultrasound
    - High resolution ultrasound used to provide more detailed images
    - Can identify structures that are statistically associated with increased risk of fetal chromosomal abnormalities
4. Recommendation
- Pregnant women should be offered screening and invasive diagnostic testing regardless of age (SOR:B)
- Combined testing is recommended for first-trimester screening (SOR:A)
• Patients who have a fetal nuchal translucency measurement of 3.5 mm or higher in the first trimester, despite a negative aneuploidy screen, or normal fetal chromosomes, should be offered a targeted ultrasound examination, fetal echocardiogram, or both (SOR:B)\textsuperscript{5}

• Nuchal translucency testing and serum screening can be performed in multiple gestations, but they are less sensitive than first-trimester screening in singleton gestations. (SOR:B)\textsuperscript{1}

• Quadruple screening is recommended for second-trimester screening (SOR:A)\textsuperscript{1}

• Combined first- and second-trimester screening offers superior detection rates while maintaining low false-positive rates (SOR:B)\textsuperscript{1}

• Genetics counseling and chorionic villus sampling or amniocentesis should be offered to all women with elevated risk, as determined by serum screening (SOR:A)\textsuperscript{1}

• Women who pursue first-trimester screening alone should be offered maternal serum AFP testing in the second trimester to screen for neural tube defects (SOR:A)\textsuperscript{1}

• An abnormal finding on second-trimester ultrasound examination identifying a major congenital anomaly significantly increases the risk of aneuploidy and warrants further counseling and the offer of a diagnostic procedure (SOR:B)\textsuperscript{5}

• Carrier screening for Tay-Sachs disease (TSD), Canavan disease, and familial dysautonomia (FD) should be offered to Ashkenazi Jewish couples (SOR:A)\textsuperscript{6}

• Carrier screening for other disorders seen with increased frequency in Ashkenazi Jewish individuals (e.g., Bloom syndrome, Fanconi anemia, Gaucher disease, glycogen storage disease type 1a, mucoloidosis type IV, Neimann-Pick disease type 1A, and cystic fibrosis (CF) should be offered when there is positive family history (SOR:A)\textsuperscript{6}

• When only one member of a couple is of Askhenazi Jewish ancestry, screening should be offered for TSD only (SOR:A)\textsuperscript{6}

• When both partners are carriers of the same autosomal recessive condition, they have a 25% risk of having an affected child. They should be referred for genetic counseling, either before conception or prenatally. Prenatal diagnosis would be offered and performed according to the patient’s informed decision. Prenatal diagnosis would consist of DNA analysis done on cells obtained by chorionic villus sampling or amniocentesis (SOR:A)\textsuperscript{6}

**Therapeutics**

1. **Acute Treatment**
   
   ○ Elective termination of pregnancy

**Follow-Up**

1. **Return to Office**
   
   ○ Routine prenatal care

2. **Refer to Specialist**
   
   ○ Genetic counseling for high risk couples
Prognosis
1. Depends on specific genetic disorder/congenital abnormality

Prevention
1. The U.S. Preventive Services Task Force recommends that all women planning or capable of pregnancy should take a daily supplement containing 0.4 to 0.8 mg (400 to 800 mcg) of folic acid (SOR:A)

References

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