Preconception Counseling: From a Genetics Perspective

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Preconception Health Care

The care a woman of childbearing age receives before or between pregnancies

- Choosing to have a baby includes the responsibility to prepare for pregnancy. It goes without saying that as mothers, every one of us want to have a healthy baby and a good birth experience. That is why, more than ever before, preconception has become a recognizable part of almost every pregnancy.
- Our goal is to provide our patients with information and treat conditions that can improve their health and help reduce the risks to their future baby

Conditions That Can Increase Risk

- High Blood Pressure
- Diabetes
- Up to date Vaccinations
- Review of Medications that patient is currently taking
- Lifestyle factors
  - Nutrition information regarding reaching a healthy weight
  - Smoking
  - Drinking alcohol
  - Occupational exposures
Genetic Concerns that should be addressed

- Ethnicity Based Carrier Screening
- Advanced Maternal Age
- Family History of Genetic Disorders
- Recurrent Pregnancy Loss
- Folic Acid Supplementation

Ethnicity Based Carrier Screening

- To detect couples at risk for prenatally diagnosable genetic diseases
- Targeted population-based screening
  - Carrier screening limited to particular groups of people determined to be at higher risk for specific genetic disorders

Carrier Frequencies of Common Conditions

<table>
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<tr>
<th>Disorder</th>
<th>Condition</th>
<th>Carrier Frequency*</th>
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| Ashkenazi Jewish | Beta Thalassemia | 1 in 31
|          | Beta Hemoglobin | 1 in 31
|          | Cystic Fibrosis | 1 in 30
|          | Tay-Sachs Disease | 1 in 90
|          | Phenylketonuria | 1 in 20
|          | Canavan Disease | 1 in 90
|          | Alpha Thalassemia | 1 in 23
|          | Beta Thalassemia | 1 in 30
|          | Friedreich Ataxia | 1 in 27
|          | Beta Thalassemia | 1 in 30

*Carrier frequencies vary by ethnicity.
Principles of Carrier Screening

Should be offered to patients:

- Seeking preconception counseling
- Seeking infertility care
- During the first or early second trimester of pregnancy

Informed Consent

Counseling before screening should include:

- Purpose, voluntary nature of screening
- Range of symptoms and severity of each disease
- Risk of carrier status and affected offspring
- Meaning of positive and negative results
- Factors to consider in decision-making
- Further testing would be necessary for prenatal diagnosis

Ethnicity Based Screening

- Most carrier tests are for autosomal recessive conditions that are predominant in a given population
- In general, carriers of autosomal recessive conditions are asymptomatic and remain unaffected
- Both partners must be carriers to have a child with an autosomal recessive condition
Autosomal Recessive Inheritance

Cystic Fibrosis

- Chronic lung disease with GI malabsorption
- Incidence of 1/3300 in Caucasian and AJ populations
- Age of onset early childhood. Variable symptoms. Life expectancy now 20-35 years
- Treatment: daily respiratory therapy, digestive enzymes, medication to promote lung function

CF Carrier Screening

- Carrier screening by DNA mutation analysis
- ACOG Recommendations:
  - Offer CF screening to:
    - Individuals with a family history of CF
    - Reproductive partners of carriers/persons with CF
    - Couples in whom one or both partners are Caucasian and are planning a pregnancy or seeking prenatal care
  - "Make CF screening available" to couples in other racial or ethnic groups at lower risk
- Detection rate in Ashkenazi Jewish population is 97%
- Detection rate in Caucasian population is 80-90%

Ashkenazi Jewish Patients

Standard of care to offer to persons of AJ background and/or their partners:

- Cystic Fibrosis
- Tay-Sachs disease
- Canavan disease
- Familial Dysautonomia

All autosomal recessive genetic conditions

Tay Sachs Disease
- Hexosaminidase A deficiency causing accumulation of ganglioside in brain
- Progressive weakness, loss of motor skills, decreased attention, and increased startle response beginning at 3-6 months of age

Canavan Disease
- Large head, lack of head control, severe hypotonia, and developmental delay by 3-6 months of age
- Life expectancy usually in the teens

Familial Dysautonomia
- Progressive neuronal degeneration throughout life
- Gastrointestinal problems, vomiting, recurrent pneumonia, episodic hypertension, scoliosis, cardiovascular disease


Ashkenazi Jewish (and anyone who has AJ ancestry)

If both patient and husband are AJ
- Order Ashkenazi Genetic Panel 4 (Health Connect: 207276)
  - CF
  - Tay-Sachs (DNA test)
  - Canavan
  - Familial dysautonomia

If patient is AJ, but husband is not
- Order Ashkenazi Genetic Panel 2 (Health Connect: 207275)
  - CF
  - Tay-Sachs (DNA test)
Specific Ethnic Backgrounds

• Hispanic Patients
  - No standard protocol for CF carrier testing due to low carrier frequency and decreased detection rates

• African American Patients
  - Standard to offer Sickle Cell screening
    - Use Hb electrophoresis (NOT sickle dex)
  - Standard to review MCV
    - If MCV <80, offer thalassemia screen w/quantitative Hb electrophoresis
  - No standard protocol for CF carrier testing due to low carrier frequency and decreased detection rates

• Asian Patients
  - Standard to review MCV
    - If <80, screen for thalassemia w/quantitative Hb electrophoresis
  - No standard protocol for CF carrier testing due to low carrier frequency and decreased detection rates

When Should Patients Be Referred to Genetics?

• If a patient and/or her partner receives a positive result for any screening test
• Low MCV with normal iron studies, and normal hemoglobin electrophoresis
• Abnormal hemoglobin electrophoresis
• Family history of these genetic conditions
Advanced Maternal Age

- Maternal age 35 or older at time of delivery has an increased risk for chromosome abnormalities
- Options for prenatal testing/screening:
  - CVS
  - Amniocentesis
  - Multiple marker screening
    - 1st or 2nd trimester, or combined
  - Ultrasound

Family History of Genetic Disorders

- Referral to Genetics when there is a family history of a genetic condition or birth defect
- Examples:
  - Nephew with Duchenne Muscular Dystrophy
  - Brother with Fragile X syndrome
  - Previous child with spina bifida, etc.
Recurrent Pregnancy Loss

- Recurrent Pregnancy Loss is usually defined as two or more pregnancy losses at any gestational age.

- Chromosome abnormalities are found in 60% of spontaneous abortions.
  - Of these abnormalities, approximately 6% are due to unbalanced translocations.

Translocations

- Defined as a chromosome abnormality caused by the rearrangement of parts between nonhomologous chromosomes.
- Translocations are the most common inherited chromosome abnormality occurring in couples who experience multiple miscarriages.
Types of Translocations

- Reciprocal translocations between chromosomes N and M
- Two acrocentric chromosomes
- Robertsonian translocation
Risks to an Individual with a Translocation

Dependent on ascertainment:
• Birth of a child with a chromosome abnormality
  ▪ 5-30% risk of unbalanced karyotype resulting in a child with a chromosome abnormality
  ▪ Risk of miscarriage is increased
• Recurrent Loss
  ▪ 5% risk of unbalanced karyotype if father is carrier resulting in a child with a chromosome abnormality
  ▪ 10-15% risk of unbalanced karyotype if mother is carrier resulting in a child with a chromosome abnormality
  ▪ Risk of miscarriage is increased

Identifying a Translocation Carrier helps:
• Determine the cause of some of the losses
• Identifies the carrier’s risk of having a reproductive loss, a liveborn unaffected or an affected baby with future pregnancies
• Identifies other members of the family who may also be carriers of the translocation
Folic Acid Supplementation

1991 - MRC Vitamin study
- 72% protective effect (recurrence)

1992 - Hungarian study
- ~ 50% protective effect (first occurrence)

1992 - CDC recommendation
- 0.4 mg/day folic acid

1998 - FDA mandated supplementation
- 18-20% decrease predicted

2000 - cases of NTD decrease 19%

The Importance of Folic Acid

Scientists are not completely sure of why folic acid is crucial in the closure of the neural tube, but they have postulated the following:
- Folic acid is needed in the development of DNA
- Plays a large role in cell growth and development
- Plays a role in tissue formation

Folic Acid Absorption

- Mothers of children with an NTD may have lower blood levels of folate but generally are not folate “deficient”
- Genetic variations/mutations may affect the ability of absorption of folate in the baby or mother
- Supplementation of extra folate may compensate for the inability of absorption
CDC Recommendations

For optimum risk reduction, CDC recommends patients take the following amounts of Folic Acid 3 months prior to conception through at least the first trimester of pregnancy.

Patients with:
- no family history
  - 0.4 mg/day
- previously affected child with NTD
  - 4 mg/day
- Family history of affected relative (greater than 1st degree relative to the fetus)
  - 0.4 mg/day