Maternal Genetic Conditions Affecting Pregnancy and the Fetus

Ben Li, MD
University of California, San Francisco,
Department of Obstetrics, Gynecology &
Reproductive Sciences, San Francisco, CA

June 9, 2016

Speaker Disclosure:

Nothing to Disclose

Outline

• Background
• Learning objectives
• Key points
• Disorders
  • Things to think about during pregnancy (and before pregnancy!)
• Summary points

Background

Advances in early detection (i.e.: newborn screening), medical care and artificial reproductive technology have allowed conception in an increasing number of women who in previous generations would have been unable to reach childbearing age or have the ability to become pregnancy
Background

- The number of women with various genetic syndromes who are undergoing pregnancy is increasing
- This represents an important issue for obstetric care providers
- Potentially serious complications exist for the mother and fetus

Learning Objectives

- Understand the influence of some of the more common disorders on both the mother and fetus
- Be able to recognize potentially serious medical issues specific to each disorder
- Understand that the fetus may face issues related to risk for inheritance of the genetic disorder itself, as well as risks related to the chronic disease status of the mother

Key Points

- Preconception counseling
- Baseline evaluations and surveillance during pregnancy
- Multidisciplinary team approach
  - MFMs and OBs
  - Anesthesiologists
  - Subspecialists
    - Geneticists and Genetic Counselors
    - Cardiologists
    - Hematologists
    - Etc

Marfan Syndrome

- Autosomal dominant (AD)
- \textit{FBN1} gene
- Occurs in 2-3 per 10,000 individuals
- Skeletal: long bone overgrowth causing tall stature, anterior chest deformity, loose joints
- Ocular: ectopia lentis
- Cardiovascular: valve dysfunction, aortic aneurysm/dilation
Marfan Syndrome

What is the most serious pregnancy complication of Marfan Syndrome?

A. Preterm labor  
B. Aortic dissection  
C. Postpartum hemorrhage

Potential pregnancy issues:

• Significant morbidity due to cardiovascular complications
• Risk for maternal mortality increases significantly if aortic root diameter > 40 mm, with 10% risk for dissection (ESC Task Force)
• Need echocardiogram to evaluate aortic root size and evidence of valvular abnormality

Management considerations:

• Beta blocker
• Cardiology consultation with close echo surveillance
• Anesthesia consultation
• Trial of labor and vaginal delivery ok if stable aortic root diameter < 40 mm (Rossiter 1995)
• Risk of having affected child is 50%
Ehlers-Danlos Syndrome (EDS)

- Heterogeneous group of connective tissue disorders
- Various inheritance patterns and differing genetic mutations
- Occurs in 1 per 5000 as a group
- Cardinal manifestations include joint hypermobility, skin hyperextensibility, connect tissue fragility
- Risk factor for cervical incompetence, aortic root dilation

Ehlers-Danlos Syndrome 3 (EDS 3)

- EDS type 3, most common type, and least severe
- EDS type 3 has AD inheritance
- Causative gene has not been identified in the majority of cases

Potential pregnancy issues:

- Subluxations and dislocations are common; they may occur spontaneously or with minimal trauma and can be acutely painful
- Risk factor for cervical incompetence, aortic root dilation
**EDS 3**

Management considerations:

- Cardiology consultation with close surveillance
- Anesthesia consultation
- Peripartum risks include postpartum hemorrhage and abnormal wound healing and scarring
- Safe to have a spontaneous vaginal delivery and there is no clear advantage to vaginal versus cesarean delivery
- Risk of having affected child is 50%

---

**Ehlers-Danlos Syndrome 4 (EDS 4)**

- EDS type 4 carries significant risk for obstetric complications due to fragility of arteries, intestines, uterus
- Characteristic translucent skin and easy bruising
- EDS type 4 has AD inheritance
- *COL3A1* gene

---

**What is the most serious pregnancy complication of EDS 4?**

A. Preterm labor  
B. Uterine rupture  
C. Postpartum hemorrhage

- Preterm labor: 59%  
- Uterine rupture: 36%  
- Postpartum hemorrhage: 5%

---

**EDS 4**

Potential pregnancy issues:

- Pregnancy mortality with EDS type 4 ~12% due to uterine or great vessel rupture during labor (Pepin 2000, Murray 2014)
- Risk factor for cervical incompetence and PTL, aortic root dilation, vessel aneurysms, PPH, poor wound healing
**EDS 4**

Management considerations:
- Cardiology consultation with close surveillance
- Anesthesia consultation
- Increased risk of uterine rupture has contributed to general recommendation for cesarean delivery before onset of labor
- Risk of having affected child is 50%

---

**Achondroplasia**

- Most common form of short limbed dwarfism
- AD inheritance
- FGFR3 gene
- Occurs in 1 per 26,000 individuals
- Skeletal: short stature, short extremities, macrocephaly, frontal bossing

---

**Achondroplasia**

Potential pregnancy issues:
- Respiratory difficulties related to decreased functional residual capacity from increased uterine size and kyphoscoliosis
- Narrowed nasal passages and hypoplasia of the pharynx and maxilla contributing to difficult endotracheal intubation (Kuczkowski 2003)
- Shortened anteroposterior diameter of pelvic inlet results in risk for cephalopelvic disproportion (Allanson 1986)

---

**Achondroplasia**

Management considerations:
- Baseline pulmonary function testing
- Anesthesia consultation
- Cesarean delivery advised
- Risk of having affected child is 50% if one affected parent
- If both parents affected, 25% chance of having child with homozygous achondroplasia, a perinatal lethal condition
Turner Syndrome

- Complete or partial absence of the second X chromosome
- Affects approximately 1 in 2500 live-born females
- Congenital heart defects, growth failure, primary infertility
- Pregnancy rates are similar to other women who undergo infertility treatments (Bondy 2007)

Potential pregnancy issues:

- Increased risk of preeclampsia, GDM, and thyroid dysfunction (Boissonnas 2009)
- Increased risk of aortic dilation and dissection/rupture (2%)
- Coarctation, aortic size index > 25 mm/m², suggested as contraindications to pregnancy (Beauchesne 2001)
- Short stature increases risk for cephalopelvic disproportion (Hadnott 2011)

Management considerations:

- Cardiology consultation with close echo surveillance
- Anesthesia consultation
- Number of reported spontaneous pregnancies is low and precise risk of transmission to offspring is unknown

Phenylketonuria (PKU)

- Maternal deficient activity of the enzyme phenylalanine hydroxylase (PAH gene), responsible for hydroxylation of the amino acid phenylalanine to tyrosine
- Accumulation of phenylalanine and its metabolites are neurotoxic
- Autosomal recessive (AR)
- Occurs in 1 per 10,000 individuals of Northern European descent
PKU

Potential pregnancy issues:

- Phenylalanine is teratogenic: congenital heart defect, microcephaly, neurodevelopmental disability
- Progressive mental retardation and irreversible neurologic impairment
- In untreated pregnancies in which the maternal blood phenylalanine concentration was ≥20 mg/dL, microcephaly and intellectual disability occurred in 73 to 92% of the offspring, 12% had CHD, 26% IUGR (Platt 2000)

What is the most important preconception goal for PKU?

A. Metabolic genetics/nutritionist consult to optimize nutrition in preparation for pregnancy
B. Strict adherence to a phenylalanine restricted, low protein diet with supplementation
C. Goal for phenylalanine levels (2-6 mg/dL) to begin at least 3 months before conception
D. All of the above

PKU

Management considerations:

- Metabolic genetics consultation
- Metabolic nutritionist consult to optimize adequate pregnancy weight gain
- Strict adherence to a phenylalanine restricted, low protein diet with supplementation
- Goal for phenylalanine levels (2-6 mg/dL) to begin at least 3 months before conception (Koch 2000)

Management considerations continued:

- Fetal echocardiogram given risk for CHD
- Ultrasound growth surveillance given risk for fetal growth restriction
- Maternal decompensation during times of stress, prolonged fasting, or over-restriction of protein -> catabolic state
- If partner is carrier, 25% chance of having affected child
Fatty Acid Oxidation (FAO) Disorders

- Group of autosomal recessive (AR) disorders characterized by deficiency of various enzymes necessary for conversion of fats to energy
- Medium chain acyl-CoA dehydrogenase deficiency (MCAD, ACADM gene) is the most common with carrier frequency as high as 1 in 40
- Naming is based on enzyme defect of specified fatty acid chain length (i.e.: short, medium, long chain)

Potential pregnancy issues:

- Maternal decompensation during times of stress and prolonged fasting (hypoketotic hypoglycemia)
- Maternal acute fatty liver of pregnancy (AFLP) and HELLP have been associated with affected fetuses; 15% to 20% of AFLP are associated with fetal LCHAD deficiency (Ibdah 2000)
- 18-fold increase in maternal liver disease in pregnancies complicated by any fetal fatty oxidation disorder (Browning 2006)

Management considerations:

- Metabolic genetics consultation
- Metabolic nutritionist consult to optimize adequate pregnancy weight gain
- Avoid prolonged fasting
- Newborn testing for FAO disorder is recommended in cases of AFLP

Summary Points

- Increasing numbers of women with inherited genetic disorders are reaching reproductive age and pursuing pregnancy, either spontaneously or through assisted reproduction
- In many cases, relatively few pregnancies have been reported with a given condition, and there are few data available on which to base management decisions
- Benefit from an integrated, multidisciplinary approach to management
Thank you!