Maternal Genetic Disorders in Pregnancy

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KEYWORDS

• Pregnancy • Management • Genetic disorders
• Hereditary hemorrhagic telangiectasia • Tuberous sclerosis • Myotonic dystrophy
• Ornithine transcarbamoylase deficiency

KEY POINTS

- Multidisciplinary management of pregnancy in women with genetic disorders is recommended.
- Discussions of maternal and fetal risks associated with pregnancy in women with genetic disorders, including options for genetic testing, are best completed before conception.
- Continued research of pregnancy outcomes in women with genetic disorders is needed.

INTRODUCTION

As the life expectancy and quality of life improves for individuals with genetic conditions, so does the need for information regarding the management of reproductive issues. A recent review article addressed pregnancy care in women with some of the more common genetic conditions, including phenylketonuria, Turner syndrome, cystic fibrosis, connective tissue disorders, and disorders of fatty oxidation.[1] The authors, therefore, focus their review on pregnancy management and outcomes in women with hereditary hemorrhagic telangiectasia (HHT), tuberous sclerosis complex (TSC), myotonic dystrophy, and ornithine transcarbamoylase (OTC) deficiency.

HEREDITARY HEMORRHAGIC TELANGIECTASIA

Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant multisystem disease leading to the development of multiple arteriovenous malformations (AVMs). AVMs are abnormally formed vessels that lack capillaries, resulting in a direct connection of an artery with a vein. HHT is estimated to occur in approximately 1 in 5000 individuals.[2]

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HHT is caused by mutations in genes that encode proteins for the transforming growth factor-beta (TGF-ß) signaling pathway, which is involved in angiogenesis.[3] It is estimated that 75% of patients who meet the clinical criteria for the diagnosis of HHT will have an identifiable mutation in one of 3 genes, *ACVRL1, ENG, SMAD4*.[4] Additional genes, including *GDF2*, are being investigated for their role in the pathogenesis of HHT.[5] Molecular genetic testing is available to establish a genetic diagnosis in clinically suspected cases.

The presentation of HHT is highly variable. Small AVMs, also called telangiectasia, can be found on the fingers, face, nasal mucosa, lips, tongue, and gastrointestinal mucosa.[3] Telangiectasias can range from small, blanchable, pink to red lesions to large, raised, purple lesions. Because of the abnormal formation of the vessels and the close proximity to the skin surface, telangiectasias can rupture and bleed.[3] The most common presenting symptom is recurrent episodes of epistaxis, occurring in more than 95% of patients. Large AVMs can also occur within the lungs, liver, or brain. The major concern with HHT is the risk of spontaneous rupture of a large AVM leading to a catastrophic bleed.[3]

HHT is typically a clinical diagnosis, for which diagnostic criteria have been developed[6] (**Table 1**). Current management guidelines recommend that individuals with HHT undergo screening for vascular malformations at the time of diagnosis, including MRI with and without contrast for the detection of cerebral AVMs, transthoracic contrast echocardiography for the detection of pulmonary AVM with follow-up for abnormalities with unenhanced thoracic computed tomography (CT), and liver ultrasound or abdominal CT for the detection of liver vascular malformations.[7]

Pregnancy in Women with Hereditary Hemorrhagic Telangiectasia

Fertility is not typically affected, and no increased risk of miscarriage has been reported in women with HHT.[8] Most pregnancies are uneventful. However, pregnancies in women with HHT should be considered high risk given the possibility of significant morbidity and mortality associated with the risk of bleeding from AVMs.

Table 1
The Curaçao criteria

Diagnostic criteria for HHT *Definite diagnosis*: 3 criteria present *Possible or suspected diagnosis*: 2 criteria present *Unlikely*: <2 criteria present	
Criteria	
• Epistaxis	Spontaneous, recurrent nose bleeds
• Telangiectasias	Multiple, at characteristic sites • Lips • Oral cavity • Fingers • Nose
• Visceral lesions	Gastrointestinal telangiectasias Pulmonary AVM Hepatic AVM Cerebral AVM Spinal AVM
• Family history	First-degree relative with HHT

From Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler Weber syndrome). Am J Med Genet 2000;91(1):67; with permission.