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Current Topic

Connective Tissue and Related Disorders and Preterm Birth: Clues to Genes Contributing to Prematurity

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ABSTRACT

To identify candidate genes contributing to preterm birth, we examined the existing literature on the association between known disorders of connective tissue synthesis and metabolism and related diseases and prematurity. Our hypothesis was that abnormal matrix metabolism contributes to prematurity by increasing risk of preterm premature rupture of membranes (PPROM) and cervical incompetence. Based on this review, we identified gene mutations inherited by the fetus that could predispose to preterm birth as a result of PPROM. The responsible genes include *COL5A1*, *COL5A2*, *COL3A1*, *COL1A1*, *COL1A2*, *TNXB*, *PLOD1*, *ADAMTS2*, *CRTAP*, *LEPRE1* and *ZMPSTE24*. Marfan syndrome, caused by *FBN1* mutations, and polymorphisms in the *COL1A1* and *TGFB1* genes have been associated with cervical incompetence. We speculate that an analysis of sequence variation at the loci noted above will reveal polymorphisms that may contribute to susceptibility to PPROM and cervical incompetence in the general population.

1. Introduction

Preterm birth has multiple etiologies but among these, preterm premature rupture of membranes (PPROM) is the leading identifiable cause, occurring in 1% of all pregnancies [1]. The human fetal membranes are composed of an inner layer, the amnion, and an adherent outer layer, the chorion. The amnion has five distinct layers (the epithelium, basement membrane, compact layer, fibroblast layer, and an intermediate layer), while the chorion is made up of a reticular layer, basement membrane, and trophoblast cells. Although the chorion is thicker than the amnion, the amnion is the main contributor to structural integrity [1–3]. The strength of the fetal membranes is thought to be influenced by both synthesis and degradation of the components of the extracellular matrix [4,5]. The fibrillar collagens (type I, III and V) are presumed to be the critical components lending tensile strength to the amnion [5,6]. However, other extracellular membrane proteins are also present including type IV collagen, type VI collagen, elastic components, fribronectin and laminin [6–8]. Consequently, connective tissue disorders that involve defects in fibrillar collagen synthesis or altered collagen or other extracellular matrix protein structure may affect fetal membrane tensile strength and result in preterm birth from unscheduled rupture. Cervical incompetence is another cause of preterm birth [9]. Since the extracellular matrix is critical to cervical function, and its remodeling, a necessary event in normal parturition, abnormalities in maternal matrix metabolism affecting cervical integrity could also contribute to prematurity.

Women with connective tissue disorders and related diseases are at an increased risk for complications during pregnancy. These complications include rupture of maternal viscera, including blood vessels, bowel and uterus, defects in fetal connective tissue formation, recurrent miscarriage and PPROM leading to preterm delivery. Heritable disorders associated with preterm delivery include Ehlers–Danlos syndrome, osteogenesis imperfecta and restrictive dermopathy. Some of these disorders are caused by mutations that affect fibrillar collagen synthesis or structure.

We reasoned that a critical analysis of the existing literature on pregnancy outcomes in disorders affecting extracellular matrix, particularly those involving known matrix components of the fetal membranes and cervix, could be informative in that disorders of matrix metabolism with known genetic causes would implicate or exclude the respective genes as candidates for PPROM and cervical incompetence [9]. Indeed, studies on pregnancy outcome in women with Ehlers–Danlos syndrome have reported an increased risk of PPROM and preterm birth if the fetus is affected [10,11]. Case reports of pregnancies in which the fetus is affected with restrictive dermopathy [12–14] and epidermolysis bullosa [15–17] have also described instances of PPROM or preterm birth. However, studies that reported on pregnancy outcome in women with Marfan

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syndrome, another heritable connective tissue disorder, found no increase in risk of PPROM whether or not the fetus was affected [18,19].

The purpose of this work was to assess the effect that heritable connective tissue disorders and related diseases in pregnancy have on preterm birth, and derive, based on the established genetics of these conditions, a list of candidate molecules and genes critical to fetal membrane and cervical integrity and risk of preterm birth. Many of the mutations in these disorders are newly identified, and the list may expand as more information regarding these diseases becomes known. The list of candidate genes for preterm birth derived from our analyses is based on what is currently known about these collagen and related disorders and does not preclude the involvement of other genes and pathways such as mutations in pro-inflammatory cytokine and matrix degrading metalloproteinase genes that are associated with preterm birth.

2. Methods

Medline and Google Scholar searches of studies and case reports on pregnancy outcome in heritable connective tissue disorders and related diseases were conducted. Disorders examined were Ehlers–Danlos syndrome, Marfan syndrome, osteogenesis imperfecta, epidermolysis bullosa, restrictive dermopathy and cutis laxa. For each condition different combinations of the search words 'in pregnancy', 'preterm birth', 'prematurity' and 'case reports', in addition to the name of the condition were used.

3. Results

3.1. Ehlers–Danlos syndrome

Ehlers–Danlos syndrome encompasses a group of heritable connective tissue disorders characterized by hyperelasticity of the skin, joint hypermobility, tissue fragility and cardiac valvular defects [20]. There are six major types of Ehlers–Danlos syndrome – Classical (types I and II) in which there is a defect in type V or rarely type I collagen; Hypermobility (type III) in which the cause is still largely considered unknown, however a defect in the extracellular matrix protein tenascin X (*TNXB*) has been reported in a subset of patients; Vascular (type IV) where there is defect in type III collagen; Kyphoscoliosis (type VI) where there is deficiency of lysyl hydroxylase; Arthrochalasia (a subgroup of type VII) where there is deficiency of type I collagen caused by mutations in the *COL1A1* and *COL1A2* genes that affect recognition sites for the processing enzyme ADAMTS2; and Dermatosparaxis (also a subgroup of type VII) in which there is deficiency of the enzyme ADAMTS2, which excises the N-propeptide of type I, type II and type V procollagens [21–23] (Table 1). The prevalence for all types of Ehlers–Danlos syndrome is estimated to be 1 in 5000 [24]. People of all racial backgrounds are equally affected [25].

Data collected from members of Ehlers–Danlos Associations/Foundations have consistently revealed higher rates of preterm birth and PPROM [11,26,27] (Table 1). A 1966 study of birth outcome among mothers with Ehlers–Danlos syndrome provided strong evidence of an increased risk for PPROM and preterm delivery, if the fetus is affected [10]. Among 18 patients with Ehlers–Danlos syndrome whose birth histories were available 14 (77.8%) were born prematurely. In 13 of the 14 preterm births, labor was preceded by PPROM [10].

In a survey of patients in the Ehlers–Danlos Foundation, Ainsworth and Aulicino [26] reported premature rupture of membranes rates of 26–75%, depending on the type of Ehlers–Danlos syndrome. Ehlers–Danlos syndrome types I and III had the highest and lowest incidences, respectively. Premature rupture of membrane rates for types II and IV were 40% and 58%, respectively. The incidence of PPROM in these subjects exceeds the prevalence of PPROM in the general population of 1–3%, supporting the notion that the defects in extracellular matrix predispose to unscheduled fetal membrane rupture [1].

Lind and Wallenburg [11] reported a preterm birth rate of 22% among 45 Dutch women affected with Ehlers–Danlos syndrome. In cases where both mother and fetus were affected with Ehlers–Danlos syndrome, 35% of the deliveries were preceded by PPROM. In affected women with a non-affected fetus, the preterm delivery rate was 12.5%. Among non-affected mothers who delivered an infant with Ehlers–Danlos syndrome, the preterm delivery rate was 40%, with one-half of all preterm cases preceded by PPROM.

In a clinical survey of obstetric histories of 43 women affected with Ehlers–Danlos syndrome, Sorokin et al. [27] reported a preterm delivery rate of 23.1% (22/95). Fifteen of the infants (15.7%) were small-for-gestational age. Yen et al. [28] reviewed the medical records of 16 Ehlers–Danlos patients and reported a preterm delivery rate of 19% (3/16). The prevalence of premature rupture of membranes was also 19% (3/16).

Most articles on pregnancy outcome in Ehlers–Danlos patients are case reports or reviews of case reports. These case reports are prone to publication bias yet, review of the articles listed in Table 1 shows that a pregnancy with an unaffected child [29–40] may proceed to term whereas an individual affected with Ehlers–Danlos syndrome [41–44] is more likely to be born preterm following PPROM. Table 1 also lists reports where the diagnosis in the offspring was either unknown at the time of delivery or confirmed to be Ehlers–Danlos syndrome, and yet the pregnancy proceeded to term [33,45]. Cases where maternal complications necessitated earlier delivery [46,47] are also reported. Morales-Rosello et al. [34] reviewed the obstetric outcome in 39 published cases of Ehlers–Danlos syndrome type III and reported a preterm/premature rupture of membranes rate of 15% (6/39).

In 32 out of 36 healthy women who presented with recurrent miscarriage following PPROM, using immunohistochemical and electron microscopic studies, changes in the dermal collagen architecture similar to those in patients with Ehlers–Danlos syndrome were found [48]. A control group that comprised of 33 women with uneventful pregnancies and 33 non-pregnant women showed no differences in dermal matrix structure. The findings, according to the authors, suggest a link between recurrent preterm premature rupture of membranes and connective tissue abnormalities.

Based on the observations that PPROM rates are highest when the fetus is affected with classical Ehlers–Danlos syndrome (types I and II) and type IV, the *COL5A1*, *COL5A2* and *COL3A1* genes are implicated as contributors to PPROM risk. Mutations leading to a non-functional *COL5A1* allele, leading to haploinsufficiency of type V collagen, or mutations that result in a structural alteration in the type V collagen proteins are among the more common causes of classical Ehlers–Danlos syndrome [49]. Mutations in the *COL3A1* gene causing type IV (vascular) Ehlers–Danlos syndrome encompass multiple exon deletions, skipping of a single exon or a point mutation resulting in the substitution of a glycine by another amino acid [50]. While PPROM appears to be a significant obstetrical complication when the fetus is affected, maternal Ehlers–Danlos syndrome is widely thought to facilitate vaginal delivery due to more compliance of the birth canal.

3.2. Osteogenesis imperfecta

Osteogenesis imperfecta is a heterogeneous group of inherited connective tissue disorders. Among the most common signs of the disorder are increased bone fragility, blue sclera and thin skin [51]. The disease has an overall incidence of approximately 1 in 10,000