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Genetics of the Cervix in Relation to Preterm Birth

Jennifer E. Warren, MD, and Robert M. Silver, MD

Preterm birth is the most significant problem encountered in obstetrics in the developed world. Genetic factors are thought to play a role in a proportion of preterm births, and candidate genes have been studied in several areas relevant to parturition. Abnormal cervical function, a clinical spectrum, including cervical insufficiency (CI), is a contributing factor to the overall problem of preterm birth. There are many risk factors and etiologies for CI. However, it is becoming clear that, at least in part, a genetic predisposition to CI plays a role in the condition. Specifically, genes related to connective tissue metabolism and inflammation have been shown to be associated with CI.
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Spontaneous preterm birth is one of the most important problems encountered in obstetrics and is the leading cause of perinatal morbidity and mortality in the developed world.[1,2] The etiologies are multifactorial and no single explanation accounts for all cases. Currently, more than 60% of spontaneous preterm births are considered idiopathic. Preterm labor and preterm premature rupture of membranes represent a large proportion of spontaneous preterm birth and comprise the result of many processes taking place in the uterus, membranes, and cervix.

Abnormal cervical function has been established as a contributing factor to the overall problem of preterm birth. Under normal circumstances, the cervix functions to maintain the pregnancy until sufficient maturation of the fetus. It then must dilate, allowing the infant to deliver. Abnormal cervical function describes a clinical spectrum in which this normal sequence of events is disrupted, ranging from a mildly shortened cervix to cervical insufficiency (CI), resulting in preterm delivery.[3]

Genetics of Preterm Birth

Genetic factors have been shown to play a role in spontaneous preterm birth. For example, preterm birth is more likely in women who have had prior preterm births.[4] The influence of genetics has been born out in family and twin studies. For example, Porter et al[5] demonstrated that women who were born preterm were more likely to subsequently give birth to a preterm infant. Studies in twins have noted that genetics may account for a maximum of 36% of preterm births.[6] As a multifactorial condition, it has been difficult to study specific genes. Nonetheless, a variety of candidate genes which regulate factors relevant to parturition, including inflammation, connective tissue remodeling, uterine contractility, and placental function have been linked to preterm birth.[7] In addition, some single gene disorders have been linked to an increased risk of early delivery, including myotonic dystrophy, Ehlers–Danlos syndrome, and neurofibromatosis.[8] Another factor that argues for an underlying genetic predisposition is the long-standing recognition of racial disparity in preterm birth. Indeed, the rates of spontaneous preterm birth are much higher in black women as compared with other races, even when controlling for confounding factors, such as low socioeconomic status and low educational levels.[9] Although genes alone play a role in preterm birth, gene-environment interactions also appear to be important contributors to the risk for spontaneous preterm birth. A recent study by Macones et al[10] explored the interaction between tumor necrosis factor α and bacterial vaginosis.[10] The presence of these 2 factors together increases the risk of preterm birth above either factor alone. Taken together, these observations support the hypothesis that genetic predisposition contributes to the risk of preterm birth.

Cervical Insufficiency

Historically, CI was thought to be a dichotomous variable. Recent data incorporating sonographic assessments of cervical length, however, suggest that cervical sufficiency may function as a continuous variable, with CI occupying the

Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, UT.

Address reprint requests to Robert M. Silver, MD, Department of Obstetrics and Gynecology, University of Utah, 30 N 1900 E, Suite 2B-200, Salt Lake City, UT 84132. E-mail: bob.silver@hsc.utah.edu

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extreme of this continuum. In fact, ultrasound data have shown a correlation between shortened cervical length and an increased relative risk of preterm birth as compared with normal cervical length.[11] Despite the increased risk between shortened sonographic cervical length and preterm delivery, the correlation is not 100%. A short cervix does not always signify clinical CI or subsequent spontaneous preterm birth.

The etiology of CI is unknown and, as with spontaneous preterm birth, represents the final common pathway of a heterogeneous group of disorders. Uncertainty regarding the etiology of this condition arises from several issues. First, the pathophysiology is not well defined. Second, the condition is not always recurrent. Third, a shortened cervix does not always lead to functional insufficiency. Contributing factors to CI include genetic susceptibility and environmental factors, such as infection, inflammation, uterine activity, abnormal implantation, and gene-environment interactions.[3] A few recent studies evaluating genetic susceptibility to CI have been carried out in a cohort of women recruited in Utah.[12,13] More than one-quarter of women with CI (34 of 125 [27.2%]) recruited for those studies had a first-degree relative with the condition as compared with none in the control population. The pervasive family history in those women with CI suggests that in some cases, CI has a genetic basis.

Genetics of Connective Tissue Metabolism and CI

Differences in connective tissue constitution have been demonstrated in the cervices of pregnant women as compared with nonparous women, suggesting a normal evolution of cervical connective tissue that facilitates the dynamics of the cervix preceding and during birth. Reductions in collagen, hyaluronic acid, and sulfated glycosaminoglycans, as well as an increase in collagen extractability after parturition has been identified in the cervices of pregnant women.[14] Lower concentrations and increased extractability of hydroxyproline as well as decreases in elastin fibers have been demonstrated in women with CI.[15,16]

These observations raise the question whether genes related to connective tissue metabolism play a role in CI. Polymorphisms in the *collagen 1A1* (*COL 1A1*) and *transforming growth factor beta* (*TGF-β*) genes have both been associated with disease states characterized by perturbations in connective tissue and extracellular matrix.[17,18] The G to T single nucleotide polymorphism (SNP) affecting the Sp1 binding region of the *COL 1A1* gene alters collagen gene regulation. This polymorphism has been associated with abnormal production of the α1 collagen chain in type-I collagen, leading to the formation of homotrimers instead of the normal heterotrimers. These homotrimers in bone have been correlated with decreased mechanical strength.[18] This SNP has been associated with low bone mineral density and increased incidence of osteoporotic fracture.[15]

Polymorphisms of the *TGF-β* gene lead to changes in the levels of *TGF-β* and influence the interaction between cells and extracellular matrix. Most classes of cells in the body produce and have receptors for *TGF-β*. The *TGF-β* gene regulates proliferation and differentiation, which are involved in many functions, including embryonic development, healing, and angiogenesis. These roles for *TGF-β* have been demonstrated in "knockout" mouse models.[19] The Arg25Pro polymorphism in exon 1 of the *TGF-β1* gene alters transport of protein product across the membrane of the endoplasmic reticulum, thus affecting its concentration.[20] The known connective tissue perturbations associated with these gene pathways led to an interest in their relationship to cervical function and evaluation of polymorphisms in these genes in women with CI.[12,13] Given that both these polymorphisms are associated with abnormal connective tissue in human beings and that CI conventionally has been thought to be due to abnormalities in cervical connective tissue, it is biologically plausible that these polymorphisms may increase the risk for CI.

To assess whether the *COL 1A1* and *TGF-β* gene polymorphisms are associated with CI, we conducted a case-control study, including 121 women with CI and 165 race-matched controls.[12] The cohort included about 80% Caucasian and 20% Hispanic. Women with CI had significantly higher frequencies of the *COL 1A1* homozygous TT genotype as compared with controls (OR 3.8, 95% CI 1.4, 10.3; Table 1). The Arg25Pro polymorphism (ArgPro and ProPro) in the TGF-β gene also were increased in cases (OR 1.9, 95% CI 1.2, 3.2; Table 1). In addition, cases with a family history of the condition had higher frequencies of the homozygous TT genotype in the *COL 1A1* gene as compared with cases without a family history (Table 2). These findings indicate that CI is, in part, a genetic condition, and that polymorphisms in genes relevant to connective tissue metabolism may play a role in some cases. Subgroup analyses were performed in women with a history of "classic" CI and women with cerclage placement resulting in successful pregnancy. We hypothesized that cases with a classic history would be more likely to have connective tissue polymorphisms than those with less typical histories. However, the frequency of polymorphisms was the same in both these groups. Similarly, gene frequencies were similar in women whose cerclage placement resulted in suc-

Table 1 Genotype Frequencies of *COL 1A1* and *TGF-β* Genes in Cases and Controls

	COL 1A1			***TGF-β***		
	GG	**GT**	**TT**	**ArgArg**	**ArgPro**	**ProPro**
Cases (N = 120)	**83 (69.2%)**	**24 (20%)**	**13 (10.8%)**	**74 (61.7%)**	**43 (35.8%)**	**3 (2.5%)**
Controls (N = 165)	**107 (66.5%)**	**49 (30.4%)**	**5 (3.1%)**	**140 (85.4%)**	**22 (13.4%)**	**2 (1.2%)**
		$P = 0.04$			**$P < 0.001$**	