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An Angiopoietin-2 gene polymorphism in unexplained intrauterine fetal death: a multi-center study

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Abstract

Objective: Angiopoietin-2 (Ang-2) is a potent regulator of angiogenesis and vascular tone. As vascular processes have been proposed to be involved in the pathogenesis of pregnancy associated complications such as late unexplained intrauterine fetal death (IUFD), we determined whether a common G/A polymorphism of the Ang-2 gene (*ANGPT2*) is associated with this condition.
Methods: In a multicenter case-control study, we evaluated the common G/A polymorphism within exon 4 of the *ANGPT2* gene using PCR in 90 women with IUFD and 90 healthy women with at least one uncomplicated full term pregnancy and no history of IUFD.
Results: Genotype ($p = 0.2$; OR = 1.4 [0.8–2.6]) and allele frequencies ($p = 0.1$; OR = 1.4 [0.9–2.1]) of the *ANGPT2* polymorphism did not differ between women with IUFD and healthy women. A multivariate regression analysis with smoking habits and preexisting diabetes as covariates did not change the results.

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Conclusions: We are the first to report on a common polymorphism of the *ANGPT2* gene in patients with late IUFD. The investigated *ANGPT2* poylmorphism does not seem to be a candidate gene for IUFD in Caucasian women.

Keywords: Angiopoietin-2; Intrauterine fetal death; Gene; Polymorphism

1. Introduction

Late intrauterine fetal death (IUFD) occuring in 5–8/1000 pregnancies represents a tragic event for pregnant women (Martinelli et al., 2000). Several conditions including malformation of the fetus, chromosomal aberration, maternal or fetal infections, and preterm premature rupture of membranes (PPROM) are known to predispose to this condition. However, in most cases of IUFD, the etiology remains unknown (Hefler et al., 2001a).

The normal development of pregnancy is dependent on an adequate uterine and placental circulation (Regnault et al., 2002; Kaufmann et al., 2004). The development of a functioning placental vascular network with optimal fetal nutritional supply requires extensive coordination and cross-talk between vascular endothelial cell-specific growth factors and cell types (Smith, 2000; Leach et al., 2002; Regnault et al., 2002; Kaufmann et al., 2004).

Thrombophilia and vasoconstriction have been shown to be crucially linked with various pregnancy associated diseases such as recurrent miscarriage, intrauterine growth restriction (IUGR), preeclampsia, and IUFD in animal models (Hefler et al., 2001b; Tempfer et al., 2000). The same is thought to be true in humans (Martinelli et al., 2000; Hefler et al., 2004).

The angiopoietin family has been shown to be critically involved in angiogenesis, especially in the female reproductive tract (Davis et al., 1996; Maisonpierre et al., 1997; Valenzuela et al., 1999; Geva and Jaffe, 2000). To date, three human angiopoietin isoforms have been identified: angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), and angiopoietin-4 (Ang-4) (Davis et al., 1996; Valenzuela et al., 1999). All angiopoietins bind to the endothelial cell-specific receptor tyrosine kinase Tie2 with similar affinity (Valenzuela et al., 1999).

Ang-2 seems to exert vasodilatative effects in hypoxic conditions, possibly stimulated by the most prominent mediator of angiogenesis, vascular endothelial growth factor (VEGF) (Oh et al., 1999; Dunk et al., 2000). Of note, under normal conditions, in the absence of hypoxia or VEGF, Ang-2 exerts its properties by destabilizing and regressing blood vessels (Maisonpierre et al., 1997).

Characterization of the structure of the human gene encoding Ang-2 (*ANGPT2*) has shown that *ANGPT2* is located on chromosome 8p23.1. The most common polymorphism of *ANGPT2* is a G/A polymorphism in exon 4, which is detectable by *Eco57*I restriction enzyme cleavage (Ward et al., 2001). The *ANGPT2* polymorphism is thought to alter protein expression and might subsequently inhibit angiogenesis (Pietrowski et al., 2003). To date, the *ANGPT2* polymorphism has only been linked to obstetric conditions/diseases.