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Mannose-binding lectin genotypes and pre-eclampsia: A case-control study

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Summary Both immunological and placental factors are involved in the pathogenesis of pre-eclampsia. The complement factor mannose-binding lectin (MBL) is associated with adverse pregnancy outcomes and has been suggested to play a role in abnormal placentation. We investigated whether MBL genotypes are associated with the systemic maternal syndrome pre-eclampsia. *MBL2* gene polymorphisms were determined in a case-control study including 157 women with pre-eclampsia (case subjects) and 157 women with uncomplicated pregnancies (control subjects). Considering MBL polymorphisms, case and control subjects were categorized in groups of high (A), intermediate (B), and low (C) MBL production. No association was found between MBL genotypes and pre-eclampsia; adjusted odds ratios and 95% confidence intervals (95% CI) for group B were 0.97 (95% CI = 0.46–2.07) and for group C were 1.44 (95% CI = 0.52–3.94). A trend was found between MBL genotype groups B and C and severe pre-eclampsia or eclampsia. MBL genotypes were not found to be associated with pre-eclampsia; however low-MBL production genotypes might be considered as disease modifier. This suggests that MBL may play a role in modulating placental inflammation by facilitating clearance of apoptotic cells and cell debris.

Introduction

Pre-eclampsia is a common but severe pregnancy disorder that is unique to pregnancy and is associated with high maternal and fetal morbidity and mortality. Pre-eclampsia becomes clinically manifest in the second half of pregnancy and is characterized by hypertension and *de novo* proteinuria [1]. Abnormal formation of the placenta (placentation) is thought to play an important role in its pathophysiology [2,3].

In uncomplicated pregnancies placentation involves trophoblast invasion and angiogenesis. Its success is dependent upon some degree of uterine inflammation, as has been

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ABBREVIATIONS

MBL mannose-binding lectin
SNP single nucleotide polymorphism

shown by several studies in human beings and in animals [4–6]. The importance of the immune system in placentation is further underscored by the detection of inflammatory cells [7] and mediators, such as cytokines [8,9] and components of the complement system [10] in placentas of normal uncomplicated pregnancies. Because of the local presence of complement regulators, deposition of complement in the placenta usually does not lead to tissue damage [11].

However if inflammation becomes excessive, it might cause pregnancy complications such as miscarriage and pre-eclampsia [6,12]. Uterine natural killer cells are the main regulators to balance the degree of inflammation at the fetal–maternal interface [13]. Trophoblast debris, apoptotic cells, and progesterone have been proposed to regulate or stimulate inflammatory cytokine production by these uterine natural killer cells [6].

Mannose-binding lectin (MBL) is a component of innate immunity. It is produced in the liver and it is an oligo- or polymeric protein that circulates in serum. Its serum concentration is strongly determined by single nucleotide polymorphism (SNP) substitutions in the structural gene and in the promoter region [14]. In exon 1 of the structural region of the *MBL*2 gene, the wild-type allele is referred to as A, and the O-alleles represent the variant alleles B, C, and D together.

Individuals with the AA wild-type genotype have higher MBL serum concentrations, whereas individuals with the AO and OO genotype show lower MBL serum concentrations. This is caused by disturbed multimer formation resulting in impaired function [15]. In addition basal MBL serum levels are influenced by the SNPs in the promoter region of the MBL gene [14].

MBL can cause activation of the lectin pathway of complement by binding to carbohydrate moieties on microorganisms and altered cells [16,17]. In addition to complement activation, the protein has several distinct functions, including promotion of complement-independent opsonophagocytosis, modulation of inflammation, and promotion of apoptosis [18]. These properties make MBL an important mediator of immunity.

During normal healthy pregnancy, MBL concentrations are increased from the first trimester onward until term, and drop sharply directly after delivery [19]. This suggests a beneficial physiologic role for high MBL levels during normal pregnancy. It was shown that this rise in MBL levels during pregnancy occurs in all pregnant women but is most pronounced in mothers with the high-production MBL genotypes.

Considering the important role of inflammation in the pathophysiology of pre-eclampsia and the suggested beneficial role of high levels of MBL in normal healthy pregnancy, it was hypothesized that women with low-MBL production genotypes are more likely to develop pre-eclampsia. To elucidate the pathogenesis of pre-eclampsia, MBL polymorphisms both in the structural gene and in the promoter region were determined in women with pre-eclampsia and healthy pregnant control subjects using a case-control design.

Subjects and methods

Study group

The subjects for this case-control study have been described previously [20,21] and are summarized in Table 1. Pre-eclampsia was defined by means of strict criteria: systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg measured on at least two occasions in women who were normotensive before 20 weeks of gestation, and proteinuria (≥2+ [1 g/l]) on a voided specimen or (≥1+ [0.3 g/l]) on a catheterized specimen, according to the criteria of the International Society for the Study of Hypertension in Pregnancy [22]. Severe pre-eclampsia was defined as an absolute diastolic blood pressure of ≥110 mm Hg and proteinuria (≥2+ (1 g/l)) on a catheterized specimen on admission. Eclampsia was clinically defined by pre-eclampsia complicated by seizures. Gestational age was calculated in days and weeks; preterm birth was defined as delivery at <37 weeks of gestation.

In brief, consecutive women who had pre-eclampsia during their first pregnancy were selected from a computer database and patient charts. Women were included who delivered on the obstetric service of the Leiden University Medical Center (n = 117) or at the St. Joseph Hospital, Veldhoven (n = 81), both in The Netherlands, from 1 January 1991 through 31 December 1996. Women (case and control subjects) who had had more than one pregnancy, multiple pregnancies, or had chronic hypertension, renal disease, diabetes, collagen vascular diseases, cancer, or thrombosis before their first pregnancy were excluded from the study

Table 1 Characteristics of study subjects.

	Control subjects	Case patients
Number of subjects	157	157
Maternal age at delivery (years)	28.5 (3.8)	28.5 (4.9)
Gestational age (days)	278 (17.8)	238 (29.7)
Gestational age <37 weeks	14 (8.9)	109 (69.4)
Gestational age <34 weeks	5 (3.2)	73 (24.8)
Body mass index	23.6 (4.2)	24.6 (4.4)
Smoking (%)	28 (17.8)	16 (10.2)
Systolic blood pressure		
<20 Weeks gestation (mm Hg)	118 (11)	127 (92)
>20 weeks gestation (mm Hg)	121 (10)	153 (16)
Diastolic blood pressure		
<20 weeks gestation (mm Hg)	69 (7)	72 (7)
>20 weeks gestation (mm Hg)	75 (7)	103 (9)
Proteinuria (mg/dl)	<30	30–100
Gender of child (male/female)	74/82*	83/71*
Race/ethnicity (% Caucasian)	96	96

Data are represented as n (%) or mean (SD).
* The genders of one child in the control group and three children in the case patients group were missing.