Mannose-binding lectin may affect pregnancy outcome

Şebnem Çalkavur[1], Gülin Erdemir[1], Hüseyin Onay[2], Özge Altun-Köroğlu[1], Mehmet Yalaz[1], Osman Zekioğlu[3], Güzide Aksu[4], Ferda Özkınay[2], Fuat Akercan[5], Nilgün Kültürsay[1]

Divisions of [1]Neonatology, and [4]Immunology Department of Pediatrics, and Departments of [2]Medical Genetics, [3]Pathology, [5]Obstetrics and Gynecology, Ege University Faculty of Medicine, İzmir, Turkey. E-mail: mehmetyalaz35@gmail.com
Received: 22 April 2014, Revised: 14 November 2014, Accepted: 28 November 2014

SUMMARY: Çalkavur Ş, Erdemir G, Onay H, Altun-Köroğlu Ö, Yalaz M, Zekioğlu O, Aksu G, Özkınay F, Akercan F, Kültürsay N. Mannose-binding lectin may affect pregnancy outcome. Turk J Pediatr 2015; 57: 26-33.

Mannose-binding lectin (MBL) is a component of the innate immune system and acts as a complement activator through the lectin pathway. Genetic variations of MBL and low MBL levels cause several infection problems, which may also be related to pregnancy problems. We aimed to investigate the role of MBL gene codon 54 polymorphism and serum MBL levels in pregnancy problems and premature delivery.

In this prospective study, MBL gene codon 54 polymorphism and serum MBL levels were studied in 45 mothers who delivered earlier than 35 gestational weeks.

The frequency of MBL gene codon 54 variant allele B was much higher (homozygous 4.4% and heterozygous 33.3%) in the study group mothers than the previously reported frequency in the healthy Turkish population (homozygous 2-6%, heterozygous 12-20%). MBL variant allele B frequency was closely related to low MBL levels (<0.1 μg/ml), vaginitis and increased IL-6 levels. The median MBL levels were lower than the critical level of 0.1 μg/ml in study mothers who had recurrent miscarriage, infertility, preeclampsia, gestational diabetes mellitus, preterm premature rupture of membranes with duration of longer than 72 hours, tocolysis, histological chorioamnionitis, urinary tract infection and vaginitis.

MBL gene codon 54 variant allele B is related to low serum MBL levels, increased IL-6 levels, genitourinary infections and may cause pregnancy-related problems such as infertility, recurrent miscarriage and preterm delivery.

Key words: mannose-binding lectin, gene, polymorphism, pregnancy, outcome.

Mannose-binding lectin (MBL) is a plasma protein produced mainly in the liver. It is a component of the innate immune system and acts as a complement activator through the lectin pathway. MBL binds to carbohydrate structures on microbial surfaces and activates MBL-associated serine proteases 1 and 2 (MASP-1 and MASP-2) to initiate complement activation[1].

Mannose-binding lectin deficiency is the most frequent immunodeficiency, with a prevalence of 10-12% in Caucasians[2]. Human plasma levels of MBL are determined genetically, and three different mutations coding for structurally abnormal protein have been identified in codons 52, 54 and 57 of exon 1, which are designated as the D, B and C alleles of the MBL gene on chromosome 10[1,2]. Prevalence of the mutations varies widely according to ethnic origin. The B allele is found in 80% of the healthy population in South Africa, and in 25% of Caucasians and Europeans. The C allele is rarely found in Europeans, but its frequency reaches 50% in Africans[2,3].

Individuals who are homozygous or compound heterozygous for MBL gene mutations have plasma concentrations of less than 1% of the wild-type levels and heterozygotes have plasma levels about 10% of the wild-type levels. Variant alleles of MBL have been associated with increased susceptibility to infectious and some noninfectious conditions in humans[4,5].

The genetic basis of MBL deficiency and its effects on pregnancy outcome have not been clearly understood yet. Recently, several authors have proposed that MBL deficiency may be related to pregnancy problems such as histologic chorioamnionitis, recurrent abortus, preeclampsia and prematurity, and also to neonatal outcome[6,7,8,9,10]. In another study, genotypes conferring very low serum MBL concentrations were associated with perinatal infections, and high-MBL-conferring genotypes were associated with prematurity[11].

Most intrauterine infections represent as an ascending infection from the vagina. The premature rupture of membranes and vaginitis are the main risk factors for development of chorioamnionitis. Perinatal infection and inflammation is closely related to the increased risk of poor pregnancy outcome such as abortus, stillbirth and preterm delivery [11-13]. Preterm delivery is more common in mothers with clinical or histological chorioamnionitis[14]. Besides increased IL-6 levels which is indicative of inflammation is commonly reported in perinatal infections and is an early marker of labor induction.

In the present study, we analyzed the effect of MBL codon 54 variant allele B and serum MBL levels on pregnancy outcome.

Materials and Methods

Forty-five mothers who gave birth before 35 gestational weeks due to the higher risk of underlying chorioamnionitis in this gestational age group were enrolled in this study after obtaining their informed consent. The study was performed at Ege University Hospital between October 2004 and May 2005. Pregnant women with previously known genital pathology or chronic systemic diseases which could lead to preterm delivery and those women who did not give consent were excluded from the study. A detailed maternal history, including previous premature delivery, infertility treatment, gestational diabetes, fever during labor, uterine sensitivity and characteristics of vaginal discharge, was taken. Two milliliters of blood samples were obtained from mothers during labor or in the first hour after delivery. In addition, peripheral blood samples of 500 μl were collected in EDTA tubes and genomic DNA was isolated. Serum acute phase reactant C-reactive protein (CRP), IL-6, whole blood count and MBL levels during labor were studied in all mothers. The diagnosis of clinical chorioamnionitis was based upon the presence of maternal fever of >38°C plus at least two of the following conditions: maternal leukocytosis (WBC>15,000 cells/mm3), maternal tachycardia (>100 beats/min), fetal tachycardia (>160 beats/min), uterine tenderness and/or foul-smelling amniotic fluid[10,12].

Preterm premature rupture of membranes (PPROM) was defined as membrane rupture and the onset of labor before 37 weeks. The diagnosis of vaginitis was made on the presence of vaginal discharge with foul odor[13].

Placentas and umbilical cords were evaluated in the laboratory of the Pathology Department, all by the same pathologist, who was not previously informed about the patients' clinical findings. The diagnosis of histological chorioamnionitis was made based on identification of polymorphonuclear leukocytes on examination of the placenta and fetal membranes[14].

MBL genotyping

DNA was extracted from blood samples using standard techniques[15]. Codon 54 polymorphisms in exon 1 of the MBL gene were genotyped in 45 mothers using the polymerase chain reaction (PCR) and sequence-specific primers. The primer sequences were 5-TAGGACAGAGGGCATGCTC-3 and 5-AGGCAGTTTCCTCTGGAAGG-3. The PCR product (349 bp) was digested with Ban I for codon 54. Ban I digestion was performed at 50° C for 60 min with 5 U enzyme. The normal allele (allele A) was cut with Ban I into 2 fragments, 260 and 89 bp. The variant allele (allele B) remained uncut. Products were projected through electrophoresis on 2% agarose gel[15].

Mannose-binding lectin serum levels were measured with ELISA (Oligomer ELISA Kit, Antibody Shop, Denmark). The results were interpreted according to the manufacturer's instructions, and levels >0.1 mcg/ml were accepted as normal. Serum CRP levels were determined by a nephelometric method (Behring, Marburg, Germany). IL-6 serum levels were measured with ELISA (Bender MedSystems GmBH, Vienna, Austria). The

results were interpreted according to the manufacturer's instructions.

All statistical analyses were performed using the SPSS® statistical package, version 17.0 (SPSS, Chicago, IL, USA) for Windows®. Allelic and genotypic frequencies were determined from observed genotype counts, and the expectations of the Hardy–Weinberg equilibrium were evaluated by Pearson's χ^2-test. The frequency of gene polymorphisms in patients was compared using Fisher's exact test. A χ^2 test, Fisher's exact test, the Mann–Whitney U test, the Wilcoxon signed-rank test and an independent samples t-test [with 95% confidence interval (CI)] were performed to determine differences between the study groups and correlation of MBL genotype and clinical variables as appropriate. A P value < 0.05 was considered to be statistically significant.

Ethical Considerations

The local hospital ethics committee approved the study (Date: 19 04 2005; No: 05-1/05) and informed consent was obtained from all mothers.

Results

The study included 45 mothers aged 20-42 years (mean 29.6±5.5 years). The clinical characteristics of the group are shown in Table 1. MBL gene codon 54 variant allele B was studied in all members of the group (n=45), and the results correlated well with the Hardy–Weinberg equilibrium (x^2=0.87646, p=0.3491). The distribution of MBL gene codon 54 variant allele B is shown in Table II. Fifteen (33.3%) mothers were found heterozygous and two (4.4%) were homozygous for codon 54 variant allele B. A total of 17 (37.7%) mothers had at least one mutant codon 54 allele.

Serum MBL levels could be studied in only 25 mothers due to financial and laboratory limitations. Sixteen mothers (64%) had serum

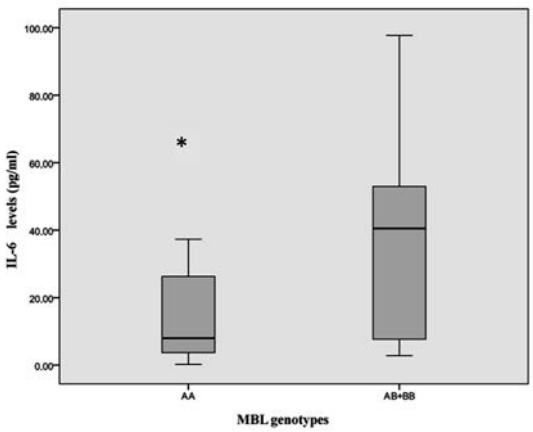

Fig. 1. Relationship between serum IL-6 levels and MBL genotypes. (*p=0.046)

Table I. Clinical Characteristics of the Study Population

	Study group (n=45)	
Clinical characteristics	mean±SD* (min-max)	n (%)
Maternal age (years) *	29.62±5.548	
Gestational age (weeks) *	30.6±2.941	
History of recurrent miscarriage		10 (22.22)
Infertility		16 (35.6)
Preeclampsia		6 (13.3)
Gestational diabetes mellitus		6 (13.3)
PPROM		15 (33.3)
PPROM duration of > 72 hrs		7 (15.6)
Tocolysis		31 (68.9)
Histological chorioamnionitis		15 (33.3)
Clinical chorioamnionitis		2 (4.4)
Urinary tract infections		19 (42.2)
Vaginitis		7 (15.6)
Antenatal antibiotics		23 (51.1)
Antenatal steroids		35 (77.8)
Total		45 (100)

PROM: preterm premature rupture of membrane

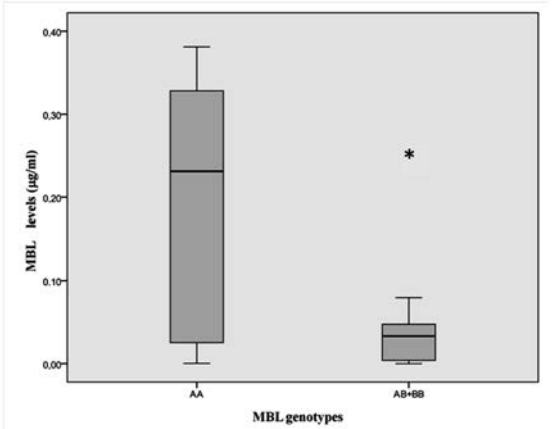

Fig. 2. Relationship between serum MBL levels and MBL genotypes. (*p=0.005)

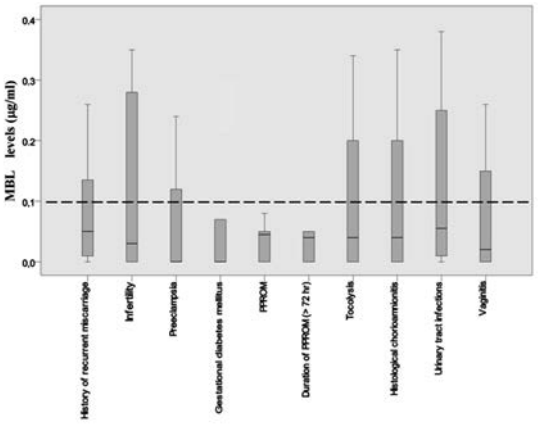

Fig. 3. Median serum MBL levels of mothers with various pregnancy problems in relation to the normal MBL level of 0.1 µg/ml.

MBL levels lower than 0.1 µg/ml, considered to be the cutoff level for normal according to the test manufacturer's instructions.

The relationship of MBL gene codon 54 variant allele B with pregnancy complications and serum CRP, IL-6 and MBL levels is shown in Tables III and IV.

The presence of MBL gene codon 54 variant allele B was not associated with increased risk of recurrent abortus, infertility, preeclampsia, gestational diabetes, any PPROM, PPROM with duration longer than 72 hours, tocolysis, histological or clinical chorioamnionitis, urinary tract infection, antenatal antibiotic use during the third trimester, antenatal steroid use and serum CRP level during labor. However, the presence of MBL codon 54 variant allele B was significantly associated with vaginitis during pregnancy (p=0.018, OR=14.727 CI 95 %:1.583-136.97) (Table III), with high serum IL-6 levels (p=0.046) and with low serum MBL levels (p=0.005) (Table IV) (Figs. 1 and 2).

The relationship of serum MBL levels with pregnancy complications was not statistically significant (Table V). However, median MBL levels of mothers who had recurrent miscarriages, infertility, preeclampsia, gestational diabetes mellitus, PPROM, duration of PPROM greater than 72 hours, tocolysis, histological chorioamnionitis, urinary tract infection and vaginitis were all under the normal MBL level limit of 0.1 µg/ml (Fig. 3).

Table II. Distribution of MBL Gene Codon 54 Polymorphism in the Study Group (n=45).

Codon 54 mutation	n (%)
AA (No mutation)	28 (62.3)
AB (Heterozygous mutation)	15 (33.3)
BB (Homozygous mutation)	2 (4.4)
AB + BB (B allele frequency)	17 (37.7)
Total	45 (100)

Discussion

Our results show that MBL codon 54 variant allele B and the related low serum MBL levels may be responsible for perinatal infection problems leading to preterm delivery.

Previously, recurrent bacterial infections, tuberculosis and invasive aspergillosis in immunocompromised patients have been reported in association with MBL deficiency[15,16].

Intrauterine infection is a major cause of spontaneous preterm birth, and immune system defects causing susceptibility to infection have a genetic basis[17,18]. Since MBL is a component of innate immunity, polymorphisms of the MBL gene are associated with susceptibility to infections, which may also lead to preterm labor in pregnant women[4]. The association between the risk of preterm delivery and MBL gene codon 54 variant allele B has been recently suggested[19,20,21]. Our data showed a B allele homozygosity of 4.4% and a B allele heterozygosity of 33.3% in mothers who delivered before the 35th gestational week. In recent studies, homozygous and heterozygous B allele frequencies in the healthy Turkish population have been reported as 2-6% and 12-20%, respectively [15,16]. Therefore the total

Table III. Relationship of MBL Gene Polymorphism with Pregnancy Complications

Clinical characteristics	AA n (%) 28 (62.8)	AB / BB n (%) 17 (37.8)	P	OR	95 % CI	p
History of recurrent miscarriage	4 (14.3%)	6 (35.3%)	0.143	3.273	0.766-13.988	0.110
Infertility	8 (28.6%)	8 (47.1%)	0.214	2.222	0.632-7.808	0.213
Preeclampsia	2 (7.1%)	4 (23.5%)	0.179	4.000	0.646-24.768	0.136
Gestational diabetes mellitus	3 (10.7%)	3 (17.6%)	0.658	1.768	0.317-10.061	0.511
PPROM	10 (35.7%)	5 (29.4%)	0.667	0.750	0.205-2.748	0.664
PPROM duration of >72 hrs	3 (10.7%)	4 (23.5%)	0.399	2.564	0.497-13.220	0.260
Tocolysis	18 (64.3%)	13 (76.5%)	0.397	1.806	0.463-7.045	0.395
Histological chorioamnionitis	9 (32.1%)	6 (35.3%)	0.830	1.152	0.323-4.109	0.828
Clinical chorioamnionitis	2 (7.1%)	0 (0%)	0.519	0	-	-
Urinary tract infections	10 (35.7%)	9 (52.9%)	0.262	2.025	0.594-6.905	0.260
Vaginitis	1 (3.6%)	6 (35.3%)	0.008	14.727	1.583-136.971	0.018
Antenatal antibiotics	15 (53.6%)	8 (47.1%)	0.675	0.770	0.230-2.578	0.672
Antenatal steroids	22 (78.6%)	13 (76.5%)	0.871	0.886	0.210-3.737	0.869

PPROM: preterm premature rupture of membranes

and, in particular, the heterozygous B allele frequency is much higher in our study group than in the healthy Turkish population. In addition, our results revealed significantly lower serum MBL levels in mothers carrying the B allele, which may show a possible cause–result relationship in regard to preterm delivery.

Geijn et al.[22] showed that MBL serum concentrations significantly increase during pregnancy beginning from the first trimester and decline at 6 weeks post-partum. They suggested that sufficient MBL levels during early pregnancy are essential for maintaining the pregnancy and for protecting pregnant women against infections. The involvement of the innate immune system, particularly MBL, in the development of recurrent vaginal infections was documented by Babula et al.[24] and Eisen et al.[25] in 2003. They suggested that decreased levels of vaginal secretory MBL in women with MBL gene codon 54 variant allele B are associated with increased susceptibility to vaginal infections[22,23]. We similarly observed a higher incidence of vaginitis in mothers with MBL 54 variant allele B.

Prolonged PPROM is accepted as a risk factor for ascending infection, but it is also a result of membrane damage caused by vaginal infections during pregnancy. Microorganisms in the genital tract produce proteolytic enzymes and are often isolated in pregnancies complicated by PPROM [24]. In our study, we did not observe any relation of PPROM and MBL allele B.

Annells et al.[5] evaluated 181 women with spontaneous preterm birth prior to 35 weeks and demonstrated the association of MBL gene codon 54 variant allele B with the development of histological chorioamnionitis. We did not observe such a relationship, possibly due to the limited number of study patients. However, serum mean MBL levels of mothers with vaginitis, PPROM and histological chorioamnionitis, and of mothers who received tocolysis, were under the normal MBL level limit of 0.1μg /ml (Fig. 3).

Mannose-binding lectin has inhibitory effects on the release of proinflammatory cytokines, resulting in a decreased inflammatory response[25,26,27]. Our data accordingly showed

Table IV. Relationship of MBL Gene Polymorphism with Serum CRP, IL-6 and MBL Levels During Labor (n=25)

Parameters	Statistical Data	MBL gene polymorphism		p
		AA	AB / BB	
CRP (mg/dl)	n	24	17	0.314
	median	0.965	1.17	
	mean±SD	2.98±4.89	2.98±4.06	
	SEM	0.9994	0.985	
	min-max	0.26-16.10	0.32-15.10	
IL-6 (pg/ml)	n	16	14	0.046
	median	7.96	4.5	
	mean±SD	15.76±18.05	38.83±33.85	
	SEM	0.514	9.048	
	min-max	0.20-65.93	2.78-97.72	
MBL (μg/ml)	n	12	13	0.005
	median	0.23	0.0	
	mean±SD	0.19±0.14	0.04±0.06	
	SEM	0.042	0.018	
	min-max	0.00-0.38	0.00-0.24	

CRP: c-reactive protein, IL-6: interleukin-6 MBL: mannose binding lectin SD: standard deviation, SEM: standart error of mean

Table V. Relationship of Serum MBL Levels During Labor with Pregnancy Complications

Conditions	n (%)	Serum MBL levels (mm/ml)	p	Range	Interquartile range	Percentiles		
						25th	50th (Median)	75th
History of recurrent miscarriage	7 (70)	0.08±0.10	0.65	0.26	0.19	0.0039	0.0475	0.1972
Infertility	12 (75)	0.11±0.15	0.65	0.35	0.29	0.0040	0.0277	0.2971
Preeclampsia	4 (66.66)	0.06±0.12	0.068	0.24	0.18	0.0000	0.0018	0.1824
Gestational diabetes mellitus	5 (83.33)	0.06±0.11	0.40	0.38	0.24	0.0021	0.0043	0.1667
PPROM	6 (40)	0.03±0.14	0.24	0.08	0.06	0.0002	0.0414	0.0555
PPROM duration of > 72 hrs	5 (71.42)	0.03±0.02	0.148	0.05	0.05	0.0002	0.0371	0.0466
Tocolysis	17 (54.83)	0.09±0.12	0.17	0.34	0.22	0.0038	0.0371	0.2196
Histological chorioamnionitis	10 (66.66)	0.09±0.12	0.56	0.35	0.21	0.0036	0.401	0.2140
Clinical chorioamnionitis	1 (50)	0.0048	-	-		-	-	-
Urinary tract infections	12 (63.15)	0.13±0.14	0.78	0.38	0.25	0.0075	0.0560	0.2587
Vaginitis	4 (57.14)	0.07±0.12	0.54	0.26	0.21	0.0012	0.0235	0.2090

MBL: mannose binding lectin,
PPROM: preterm premature rupture of membranes.

higher proinflammatory cytokine IL-6 levels in mothers having MBL gene codon 54 variant allele B.

Kilpatrick et al.[20] studied maternal and paternal serum MBL levels of couples who experienced recurrent miscarriages and showed that serum MBL levels less than 0.1 μg/ml were a clinically significant risk factor for spontaneous abortion. Conversely, Baxter et al.[28] suggested that there was no association between recurrent miscarriage and variant alleles of MBL. In our study group, an increased MBL B allele frequency was not seen among mothers with a history of recurrent abortus, but there was seen among them a greater frequency of MBL levels below the normal limit of 0.1 μg/ml (Fig. 3).

Some studies suggested a minor role for MBL in the development of preeclampsia[28,29]. We observed low MBL levels in mothers with preeclampsia. Gestational diabetes mellitus has been shown to be related to MBL gene codon 54 variant allele B[30]. Serum MBL levels of the mothers in our group with gestational diabetes mellitus were lower than normal; but no association could be shown regarding MBL gene codon 54 variant allele B.

Since most studies so far have reported on either the genetic variations of MBL codon 54 or MBL levels, but not both, our study combining both factors in relation to poor pregnancy outcome is important. Limitations of this study are the small size of the study group and the evaluation of MBL codon 54 only, it being the most common MBL polymorphism in the Turkish population. In addition, while MBL gene codon 54 variant allele B was studied in the entire study group, serum MBL levels could be studied in only 25 mothers. As a result of this limitation, no statistically significant relationship could be demonstrated between serum MBL levels and pregnancy complications, although the presence of MBL gene codon 54 variant allele B had a strong association with vaginitis, high serum IL-6 levels and low serum MBL levels.

It is apparent that mothers delivering before 35 weeks can have certain kinds of pregnancy complications. However, in the present study, we failed to show a significant association between MBL deficiency and perinatal complications on a one-by-one basis. Future studies with larger populations may give further information about the relation of the MBL gene to pregnancy outcome.

Conclusion

MBL codon 54 variant allele B is related to low serum MBL levels, increased IL-6 levels and genitourinary infections, and may cause pregnancy-related problems such as infertility, recurrent miscarriage and preterm delivery.

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