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The effect of VDR gene polymorphisms and vitamin D level on blood pressure, risk of preeclampsia, gestational age, and body mass index

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Abstract

We investigated the influence of vitamin D receptor (VDR) polymorphisms and vitamin D level on the blood pressure and the risk of preeclampsia. In a case-control study, 200 pregnant women, including 100 individuals with preeclampsia along with 100 healthy pregnant women, were studied for VDR FokI, TaqI, and BmsI polymorphisms and serum 25 (OH)-D level using polymerase chain reaction-restriction fragment length polymorphism method and commercial kit, respectively. The mean level of 25 (OH)-D in preeclamptic patients was significantly lower (16.6 ± 4.2 ng/mL, $P < 0.001$) compared with controls (19.6 ± 3.8 ng/mL). Among all women, a significantly higher systolic blood pressure and before-pregnancy body mass index and also lower gestational age were observed in the presence of 25 (OH)-D level < 20 ng/mL compared with the 20 to 30 ng/mL. A significantly higher frequency of VDR FokI C allele in preeclamptic patients (83%) than controls (74%) was associated with a 1.72-fold increased risk of preeclampsia. In all the studied individuals, the systolic and diastolic blood pressures were significantly higher in the presence of the FokI CC genotype compared with the TC and TT+TC genotypes. Neither VDR Taq1 nor VDR BmsI was associated with the risk of preeclampsia. The haplotype FokI C, TaqI C and BmsI A (CCA) compared with haplotype CTG increased the risk of preeclampsia by 1.4-fold ($P = 0.33$). Our study suggests an association between VDR FokI polymorphism and an insufficient serum level of 25 (OH)-D with the risk of preeclampsia and also the influence of insufficient 25 (OH)-D level and VDR FokI polymorphism on maternal factors, including blood pressure.

KEYWORDS

25 (OH)-D, body mass index (BMI), gestational age, hypertension, preeclampsia, VDR polymorphism

1 | INTRODUCTION

Preeclampsia is the most common and serious complication in pregnancy, which is significantly associated with maternal and fetal morbidity and prenatal mortality.[1] This pregnancy complication occurs with a frequency of 5% to 7% in most parts of the world.[2] In a referral hospital of Kermanshah (Western Iran), a prevalence of 7.5% has been reported for preeclampsia.[3]

Abnormal placentation and uteroplacental circulation, along with endothelial cell dysfunction, are known risk factors to be involved in the pathogenesis of preeclampsia.[4]

It has been suggested that vitamin D might play a key role in the pathology of preeclampsia by influencing blood pressure through calcium homeostasis and/or by modulating inflammation and immunity.[5] Also, an inverse relationship between plasma 1, 25 (OH)2-D3 level and blood pressure has been found.[5] However, studies related to the association between vitamin D status and preeclampsia are inconsistent.[6-8]

1, 25 (OH)2-D3 binds to a corresponding nuclear receptor, named the vitamin D receptor (VDR), and works on the target tissues. For effective interaction of VDR with DNA, the receptor requires heterodimerization with auxiliary proteins known as the retinoid-X receptors.[9]

The VDR gene consists of two promoter regions, eight coding exons (namely, 2-9), and six untranslated exons (1A-1F). There are frequent single nucleotide polymorphisms in the VDR gene. Four precise di-allelic polymorphisms have been described for the VDR gene, including the BsmI (A>G, rs1544410) and ApaI (A>C, rs7975232) on the last intron, and FokI (C>T, rs10735810) and TaqI (T>C, rs731236) on the coding exons.[10]

In one available study, neither VDR polymorphisms nor haplotypes were associated with preeclampsia or gestational hypertension.[11]

The aims of the current study were to investigate the frequency of VDR FokI, TaqI, and BmsI polymorphisms and serum 25-hydroxyvitamin-D (25 (OH)-D) levels in preeclamptic patients compared with healthy individuals in a population from Western Iran to find the possible influence of VDR gene variants and vitamin D level on the risk of preeclampsia and maternal factors.

2 | MATERIALS AND METHODS

2.1 | Sample

In a case-control study, 100 women with preeclampsia (the mean age of 31.4 ± 6.4 years), including 64 patients with mild preeclampsia and 36 patients with severe preeclampsia, and 100 women with normal pregnancy with the mean age of 29 ± 6 years were investigated. The samples were obtained from the Imam Reza Hospital of Kermanshah University of Medical Sciences, and sampling was performed between March and September 2017. All studied individuals were from Western Iran with a Kurdish ethnic background.

The criteria for defining preeclampsia were systolic blood pressure equal to or higher than 140 mmHg, diastolic blood pressure equal or higher than 90 mmHg, the presence of proteinuria by 24-hr urinary excretion exceeding 300 mg, a urine protein: creatinine ratio of >0.3 and equal or higher than 30 mg/dL protein in a random urine sample (1+ reaction on a standard urine dipstick). For the definition of severe preeclampsia, a blood pressure more than 160/110 mmHg, proteinuria >3 +, headache, visual disturbances, upper abdominal pain, serum creatinine and transaminase elevation, thrombocytopenia, and fetal-growth restriction were used.[12]

Early-onset preeclampsia, defined as preeclampsia before 34 weeks of gestation,[13] was detected in 23 patients.

2.2 | Vitamin D

Vitamin D status was determined by the measurement of the serum level of 25 (OH)-D, which is the circulating form of the vitamin D using the immunodiagnostic systems limited EIA kit. Vitamin D was considered adequate when 25 (OH)-D levels were above 50 nmol/L (20 ng/mL). A level between 30 and 50 nmol/L (12-20 ng/mL) was considered insufficient, and less than 30 nmol/L (12 ng/mL) was detected as deficient.[5]

2.3 | Genotyping

DNA was extracted from the leukocyte of the EDTA-treated whole blood using the phenol-chloroform method.[14]

Detection of FokI T>C (rs2228570) polymorphism in exon 2 of the VDR gene was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method using the forward primer of 5′-AGC TGG CCC TGG CAC TGA CTC TGC TCT-3′ and the reverse primer of 5′-ATG GAA ACA CCT TGC TTC TTC TCC CTC-3′.[15]

The TaqI T>C (rs731236) polymorphism in exon 9 of the VDR gene was identified by the forward primer of 5′-CAG AGC ATG GAC AGG GAG CAA G-3′ and the reverse primer of 5′-GGA TGT ACG TCT GCA GTG T G-3′ using the PCR-RFLP method.[15]

The polymorphism of BmsI G>A (rs1544410) in intron 8 was detected by the PCR-RFLP method using

the forward primer of 5′-CAA CCA AGA CTA CAA GTA CCG CGT CAT GA-3′ and the reverse primer of 5′-AAC CAG CGG GAA GAG GTC AAG GG-3′.[15]

Informed written consent was obtained from each individual before participation in the study. The study was approved by the Ethics Committee of Kermanshah University of Medical Sciences and was in accordance with the principles of the Declaration of Helsinki II.

3 | STATISTICAL ANALYSIS

The allelic frequencies were calculated by the chromosome counting method. The significance of differences in genotype and allele frequencies of FokI, TaqI, and BmsI polymorphisms between patients and controls were calculated using the χ^2 test. The Odds ratios (OR) were calculated as the estimates of relative risk for the disease, and 95% confidence intervals (CI) were obtained by SPSS logistic regression software. A two-tailed Student *t* test was used to compare quantitative data. The SPSS (SPSS Inc., Chicago, IL) statistical software package version 22.0 was used for statistical analysis. Haplotype analysis was performed by using SNPSTATS software (http://bioinfo.iconcologia.net/snpstats/start.htm).

4 | RESULTS

The characteristics of preeclamptic patients and controls are demonstrated in Table 1. As indicated in Table 1, the before and the after pregnancy body mass index (BMI) (26.6 ± 5.9 and 30.5 ± 7.6 kg/m^2, respectively) among patients was significantly higher compared with those in controls (22.1 ± 9.9 and 24.7 ± 12.3 kg/m^2, respectively). The mean level of 25 (OH)-D was 16.6 ± 4.2 ng/mL (41.5 ± 10.5 nmol/L) in all preeclamptic patients compared with 19.6 ± 3.8 ng/mL (49 ± 9.5 nmol/L) in controls ($P < 0.001$) (Table 1). Among patients, 75% had a 25 (OH)-D < 20 ng/mL compared with 53.7% in controls ($\chi^2 = 9.1$, $P = 0.003$). Among patients, 6% had 25 (OH)-D level less than 10 ng/mL. Comparing systolic blood pressure between all studied individuals that had 25 (OH)-D level < 20 ng/mL with those had 25 (OH)-D level

TABLE 1 Characteristics of patients and controls

Variables	All Patients n = 100	Severe Preeclampsia n = 36	Mild Preeclampsia n = 64	Controls (n = 100)
Age, y	31.4 ± 6.4; P = 0.01	29.8 ± 6.9; P = 0.57	32.3 ± 6; P = 0.001	29 ± 6
Gestational age, w	35.3 ± 2.5; P < 0.001	35.1 ± 2.3; P < 0.001	35.4 ± 2.7; P < 0.001	37.4 ± 2.3
Before pregnancy weight, kg	71.5 ± 10.9; P = 0.042	70.7 ± 12.9; P = 0.3	72 ± 9.6; P = 0.028	68.1 ± 11.3
After pregnancy weight, kg	82.4 ± 13; P = 0.1	81.1 ± 14.5; P = 0.51	83.1 ± 12.1; P = 0.062	79.2 ± 12.1
Before pregnancy BMI, kg/m^2	26.6 ± 5.9; P < 0.001	26.1 ± 7.1; P < 0.032	26.9 ± 5.2; P = 0.001	22.1 ± 9.9
After pregnancy BMI, kg/m^2	30.5 ± 7.6; P < 0.001	30.5 ± 8; P = 0.012	30.5 ± 7.4; P = 0.002	24.7 ± 12.3
Systolic blood pressure, mm Hg	152.5 ± 16.5; P < 0.001	165.8 ± 18.3; P < 0.001	144.8 ± 8.9; P < 0.001	113.6 ± 7.6
Diastolic blood pressure, mm Hg	92.5 ± 14.3; P < 0.001	102.2 ± 11.4; P < 0.001	87 ± 12.9; P < 0.001	73.3 ± 6.6
25 (OH)-D, ng/mL	16.60 ± 4.2; P < 0.001	17.3 ± 4.5; P = 0.012	16.3 ± 4.1; P < 0.001	19.6 ± 3.8
Urea, mg/dL	25.6 ± 7.8; P = 0.2	27.4 ± 7.5; P = 0.046	24.6 ± 7.8; P = 0.53	23.5 ± 9.8
Creatinine, mg/dL	0.79 ± 0.23; P = 0.28	0.84 ± 0.26; P = 0.33	0.77 ± 0.21; P = 0.26	1.32 ± 3.3
AST, U/L	36.6 ± 41.7; P = 0.002	39.1 ± 45.6; P = 0.039	35.1 ± 39.7; P = 0.018	22.7 ± 8.3
ALT, U/L	31.7 ± 62.9; P = 0.047	43.8 ± 98.2; P = 0.13	24.8 ± 26.1; P = 0.09	18.8 ± 9.7
Alkaline phosphatase, U/L	331.5 ± 133; P = 0.001	330 ± 134.9; P = 0.016	332.4 ± 132.9; P = 0.003	260.4 ± 116.4
Direct bilirubin, mg/dL	0.35 ± 0.35; P = 0.13	0.36 ± 0.48; P = 0.45	0.35 ± 0.26; P = 0.11	0.29 ± 0.12
Total bilirubin, mg/dL	0.80 ± 0.59; P = 0.44	0.91 ± 0.89; P = 0.28	0.74 ± 0.31; P = 0.99	0.74 ± 0.38

between 20 to 30 ng/mL indicated a significantly higher systolic blood pressure (137.8 ± 22.3 mmHg, $P = 0.029$) in individuals with 25 (OH)-D level below 20 ng/mL than those with 25 (OH)-D level more than 20 ng/mL (129.8 ± 25 mmHg). Comparing diastolic blood pressure between the first group (85.5 ± 15 mmHg) with the latter group (81.2 ± 13.8 mmHg) did not reach a statistical significance ($P = 0.066$). Also, the before pregnancy BMI was significantly higher in the first group (25.8 ± 7 kg/m^2, $P = 0.019$) compared with the latter group (22.4 ± 9.6 kg/m^2). After pregnancy, BMI was 29 ± 9.4 kg/m^2 in the first group compared with 25.5 ± 11.5 kg/m^2 in the latter group ($P = 0.063$). The gestational age in the first group was significantly (36 ± 2.6 weeks, $P = 0.025$, OR = 1.51, 95% CI, 1.02-1.3) lower than the latter group (36.9 ± 2.5 weeks).

The systolic blood pressure was higher in patients with early-onset preeclampsia (159.8 ± 22.6 mm Hg, $P = 0.066$) compared with those with late-onset preeclampsia (150.3 ± 13.6 mm Hg). Although, 87% of patients with early-onset preeclampsia compared with 72.4% of patients with late-onset preeclampsia had 25 (OH)-D less than 20 ng/mL, the difference did not reach a statistical significance.

Distribution of FokI genotypes was in the Hardy-Weinberg equilibrium in severely preeclamptic patients ($\chi^2 = 1.44$; $P > 0.1$) and in controls ($\chi^2 = 1.44$; $P > 0.1$).

Table 2 indicates the frequency of FokI genotypes and alleles in patients and controls. As demonstrated in Table 2, the frequency of C allele in all preeclamptic patients (83%) was significantly higher than those in controls (74%; $P = 0.028$) and was associated with a 1.72-fold increased risk of preeclampsia (95% CI, 1.05-2.78; $P = 0.029$). In all studied individuals, the systolic and diastolic blood pressures were significantly higher in the presence of the FokI CC genotype (137.3 ± 23.7, 85.2 ± 15.8 mm Hg, respectively) compared with the carriers of TC (127.1 ± 21, 79.5 ± 12.3 mm Hg, $P = 0.004$, and $P = 0.009$, respectively) and TT+TC genotypes (129 ± 22.2, 80.6 ± 12.8 mm Hg, $P = 0.018$, and $P = 0.031$, respectively).

In preeclamptic patients, the distribution of TaqI genotypes was in the Hardy-Weinberg equilibrium ($\chi^2 = 1.65$; $P > 0.1$). Distribution of TaqI genotypes and alleles among preeclamptic patients and controls is depicted in Table 3. The frequency of C allele was 34.5% in patients and was 32.5% in controls ($P = 0.67$).

Distribution of BmsI genotypes was in the Hardy-Weinberg equilibrium only in severe preeclampsia

TABLE 2 Distribution of FokI genotypes and alleles in preeclamptic patients and controls

Parameters	All preeclamptic patients n = 100 n, %	Severe preeclampsia n = 36 n, %	Mild preeclampsia n = 64 n, %	Controls n = 100 n, %
FokI genotypes				
TT	6 (6)	2 (5.6)	4 (6.2)	7 (7)
TC	22 (22)	8 (22.2)	14 (21.9)	38 (38)
CC	72 (72)[#] $\chi^2 = 6.53$; $P = 0.011$ OR = 2.27, 95% CI (1.2-4.35, $P = 0.011$) $\chi^2 = 6.23^{\#\#}$, $P = 0.013$ OR = 2.11, 95% CI (1.17-3.79, $P = 0.013$)	26 (72.2)[#] $\chi^2 = 3.23$; $P = 0.072$ OR = 2.24, 95% CI (0.91-5.49, $P = 0.076$) $\chi^2 = 3.26^{\#\#}$, $P = 0.071$ OR = 2.12, 95% CI (0.92-4.87, $P = 0.074$)	46 (71.9)[#] $\chi^2 = 4.99$; $P = 0.025$ OR = 2.27, 95% CI (1.1-4.7, $P = 0.027$) $\chi^2 = 4.7^{\#\#}$, $P = 0.03$ OR = 2.09, 95% CI (1.07-4.1, $P = 0.032$)	55 (55)
TT + TC	28 (28)	10 (27.8)	18 (28.1)	45 (45)
Alleles				
T	34 (17)	12 (16.7)	22 (17.2)	52 (26)
C	166 (83) $\chi^2 = 4.8$; $P = 0.028$ OR = 1.72, 95% CI (1.05-2.78, $P = 0.029$)	60 (83.3) $\chi^2 = 2.57$; $P = 0.11$ OR = 1.76, 95% CI (0.87-3.5, $P = 0.11$)	106 (82.8) $\chi^2 = 3.47$; $P = 0.063$ OR = 1.69, 95% CI (0.97-2.97, $P = 0.064$)	148 (74)

*Overall χ^2 comparing three genotypes between all preeclamptic patients and controls is 6.61, $P = 0.037$.
**Overall χ^2 comparing three genotypes between severe preeclamptic patients and controls is 3.5, $P = 0.18$.
***Overall χ^2 comparing three genotypes between mild preeclamptic patients and controls is 5.04, $P = 0.081$.
[#]Compared with TC genotype, [##]compared with TT + TC genotype.

TABLE 3 Frequencies of TaqI genotypes and alleles in preeclamptic patients and controls

Parameters	All preeclamptic patients n = 100 n, %	Severe preeclampsia n = 36 n, %	Mild preeclampsia n = 64 n, %	Controls n = 100 n, %
TaqI genotypes				
TT	40 (40)	12 (33.3)	28 (43.8)	40 (40)
TC	51 (51)	20 (55.6)	31 (48.4)	55 (55)
	$\chi^2 = 0.065$; $P = 0.8$	$\chi^2 = 0.21$; $P = 0.64$	$\chi^2 = 0.42$; $P = 0.51$	
CC	9 (9)	4 (11.1)	5 (7.8)	5 (5)
	$\chi^2 = 0.97$; $P = 0.32$	$\chi^2 = 1.8$; $P = 0.17$	$\chi^2 = 0.27$; $P = 0.59$	
TC + CC	60 (60)	24 (66.7)	36 (56.2)	60 (60)
	$\chi^2 = 0$; $P = 1$	$\chi^2 = 0.49$; $P = 0.48$	$\chi^2 = 0.22$; $P = 0.63$	
Alleles				
T	131 (65.5)	44 (61.1)	87 (68)	135 (67.5)
C	69 (34.5)	28 (38.9)	41 (32)	65 (32.5)
	$\chi^2 = 0.18$; $P = 0.67$	$\chi^2 = 0.96$; $P = 0.32$	$\chi^2 = 0.008$; $P = 0.92$	

*Overall χ^2 comparing three genotypes between all preeclamptic patients and controls is 1.29, $P = 0.52$.
**Overall χ^2 comparing three genotypes between severe preeclamptic patients and controls is 1.8, $P = 0.4$.
***Overall χ^2 comparing three genotypes between mild preeclamptic patients and controls is 0.96, $P = 0.61$.

($\chi^2 = 2.38$, $P > 0.1$). The frequency of A allele of the BmsI was 44% in patients and was 39.5% in controls ($P = 0.36$), as demonstrated in Table 4.

Haplotype analysis of three VDR polymorphisms is demonstrated in Table 5. The presence of haplotype FokI C, TaqI C, and BmsI A (CCA) compared with haplotype CTG increased the risk of preeclampsia by 1.4-fold ($P = 0.33$).

5 | DISCUSSION

In the current study, we found a significantly lower level of 25 (OH)-D in preeclamptic patients than controls. However, the severity of preeclampsia was not related to the vitamin D level. Also, a significantly higher percentage of patients (75%) had an insufficient level of 25 (OH)-D compared with controls (53.7%, $P = 0.003$).

TABLE 4 Distribution of BmsI genotypes and alleles in preeclamptic patients and controls

Parameters	All preeclamptic patients n = 100 n (%)	Severe preeclampsia n = 36 n (%)	Mild preeclampsia n = 64 n (%)	Controls n = 100 n (%)
BmsI genotypes				
GG	20 (20)	10 (27.8)	10 (15.6)	28 (28)
GA	72 (72)	22 (61.1)	50 (78.1)	65 (65)
	$\chi^2 = 1.68$; $P = 0.19$	$\chi^2 = 0.015$; $P = 0.9$	$\chi^2 = 3.5$; $P = 0.06$	
AA	8 (8)	4 (11.1)	4 (6.3)	7 (7)
	$\chi^2 = 0.63$; $P = 0.43$	$\chi^2 = 0.42$; $P = 0.51$	$\chi^2 = 0.42$; $P = 0.52$	
GA + AA	80 (80)	26 (72.2)	54 (84.4)	72 (72)
	$\chi^2 = 1.75$; $P = 0.18$	$\chi^2 = 0.001$; $P = 0.98$	$\chi^2 = 3.36$; $P = 0.067$	
Alleles				
G	112 (56)	42 (58.3)	70 (54.7)	121 (60.5)
A	88 (44)	30 (41.7)	58 (45.3)	79 (39.5)
	$\chi^2 = 0.83$; $P = 0.36$	$\chi^2 = 0.1$; $P = 0.74$	$\chi^2 = 1.08$; $P = 0.29$	

*Overall χ^2 comparing three genotypes between all preeclamptic patients and controls is 1.75, p = 0.41.
**Overall χ^2 comparing three genotypes between severe preeclamptic patients and controls is 0.61, $P = 0.73$.
***Overall χ^2 comparing three genotypes between mild preeclamptic patients and controls is 3.5, $P = 0.16$.

TABLE 5 Haplotype analysis of VDR polymorphisms in studied individuals

FokI	TaqI	BmsI	Haplotype frequencypatients	Haplotype frequencycontrols	OR (95% CI, *P*)
C	T	G	0.4148	0.4406	1
C	C	A	0.1826	0.2523	1.40 (0.71-2.79, 0.33)
T	T	G	0.1422	0.0944	0.70 (0.30-1.60, 0.4)
C	T	A	0.1179	0.1071	1.07 (0.49-2.32, 0.87)
T	C	A	0.0945	0.0677	0.81 (0.32-2.07, 0.67)
C	C	G	0.0246	0.03	1.12 (0.26-4.84, 0.88)
T	C	G	0.0233	0	0 (-, 1)

Further, the insufficient level of vitamin D (<20 ng/mL) compared with sufficient level (20-30 ng/mL) resulted in significantly higher systolic blood pressure. Consistent with our findings, it has been reported that there is a significant inverse association between systolic blood pressure and the level of 25 (OH)-D among adults.[16]

The renin-angiotensin system (RAS) plays a central role in the regulation of blood pressure during pregnancy. In a normal pregnancy, RAS is induced.[13] But in preeclampsia, the stimulation of this system fails, and the circulating serum levels of angiotensin I, angiotensin II, and aldosterone are lower than normotensive women. However, the levels of plasma active renin and autoantibodies to the angiotensin II type 1 receptor, which stimulate receptor signaling, are higher, resulting in increased systemic blood pressure.[5] An inverse relationship between the plasma levels of 25 (OH)-D and increased risk of developing hypertension[17] and essential hypertension have been reported.[5] In a study from India, the maternal 25 (OH)-D concentration was negatively associated with blood pressure and the risk of preeclampsia; although, the severity of preeclampsia was not associated with vitamin D status.[18]

Case-control and cross-sectional studies indicated an association between vitamin D status and the risk of preeclampsia, although there are inconsistent reports.[5] Among Colombian women, low maternal concentrations of 25 (OH)-D increased the risk of preeclampsia.[6] While in a randomized controlled trial, supplementation of vitamin D in the deficient pregnant women decreased the risk of preeclampsia.[7] Another study did not detect an association between exposure to vitamin D fortification during pregnancy with the risk of preeclampsia and hypertension pregnancy.[8]

In a case-control study in women with early-onset severe preeclampsia, the total level of 25 (OH)-D decreased at diagnosis of the disease.[19] In another study, maternal vitamin D deficiency was a risk factor only for severe preeclampsia, but it was not associated with preeclampsia overall or mild preeclampsia.[20]

Our study suggests an association between vitamin D level and the risk of preeclampsia and also hypertension. Vitamin D is a potent endocrine suppressor of the renin biosynthesis through a VDR-dependent mechanism and regulates the RAS.[21] So, normal levels of serum vitamin D can prevent hypertension through suppression of the RAS. Also, vitamin D can affect blood pressure through the suppression of vascular smooth muscle cell proliferation.[9] It seems that the low level of vitamin D through enhances the renin level, and vascular smooth muscle cell proliferation might be involved in the pathogenesis of preeclampsia. This hypothesis needs to be confirmed.

Our study found an association between VDR FokI C allele with the risk of preeclampsia. Also, considering all studied individuals, the FokI CC genotype was associated with significantly higher systolic and diastolic blood pressures compared with TC and TT+TC genotypes. A strong association between the common VDR polymorphisms of FokI and BsmI and the hypertension risk outside pregnancy have been detected.[10] The polymorphism of FokI influences the plasma renin activity and might be associated with a reduced risk of hypertension.[10] In mice, knock out of either the VDR or the 1 α-hydroxylase gene, which converts 25 (OH)-D to 1, 25 (OH)2-D, upregulates the RAS activity and induces hypertension.[17]

Regarding VDR polymorphism, no significant association has been found between VDR polymorphisms (FokI, ApaI, and BmsI) or haplotypes and preeclampsia or gestational hypertension.[11] The C allele of VDR FokI polymorphism (restriction site absent, ACG) lacks the first ATG, and translation starts at the second ATG, producing a shorter VDR protein by 3 amino acids compared with T allele that starts at the first ATG. It seems the C allele of the VDR FokI polymorphism to be more effective than the T allele in transactivation of the 1, 25 (OH)2-D3 signal.[22]

We detected that haplotype FokI C, TaqI C, and BmsI A (CCA) compared with haplotype CTG non-significantly

increased the risk of preeclampsia ($P = 0.33$). The VDR gene polymorphism may influence the VDR gene expression and function and might affect the binding of 1, 25-(OH)2- D3 to VDR.[23]

Briefly, our study suggests an association between VDR FokI polymorphism and insufficient serum level of vitamin D with the risk of preeclampsia. Also, the insufficient serum level of 25 (OH)-D influences maternal blood pressure, the before pregnancy BMI, and gestational age. Further, VDR FokI polymorphism was associated with high maternal systolic and diastolic blood pressures.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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