Association of IL-10 -819C/T, -592A/C polymorphisms with the risk of preeclampsia: An updated meta-analysis

Guanglu Che, MM, Fang Liu, MM, Li Chang, MM, Yongmei Jiang, MD

Abstract
Objective: The purpose of our study was to investigate whether IL-10 -819C/T, -592A/C polymorphisms were associated with preeclampsia (PE) susceptibility.

Methods: A comprehensive and systematic literature search was performed through online databases, including Web of Science, PubMed, EMBASE, and Chinese databases. Then eligible literatures were included according to inclusion criteria and exclusion criteria. Statistical data analysis was performed using Stata 10.0 software. Odds ratios (OR) and 95% confidence interval were applied to evaluate the association between IL-10 -819C/T, -592A/C polymorphisms and PE susceptibility.

Results: According to inclusion and exclusion criteria, 9 case-control studies, including 1423 cases and 2031 controls, were included in this meta-analysis. Our meta-analysis revealed that no association was found between IL-10 -819C/T, -592A/C polymorphisms and the risk of PE in our study.

Conclusion: Our meta-analysis suggested that IL-10 -819C/T and -592A/C polymorphisms had no association with PE susceptibility, but had a significant association with PE susceptibility in Asian and Caucasian.

Abbreviations: IL = interleukin, OR = odds ratios, PE = preeclampsia, SNP = single nucleotide polymorphism.

Keywords: IL10 -592A/C polymorphism, IL-10 -819C/T polymorphism, meta-analysis, preeclampsia, susceptibility

1. Introduction

Preeclampsia (PE) is a pregnancy-complicated hypertensive disorder, characterized by new onset hypertension and proteinuria after 20 weeks of gestation and accompanied by renal dysfunction, liver injury, pulmonary edema and multisystem dysfunction.[1,2] Currently, 2% to 8% pregnancies throughout the world are suffered from PE, a leading cause of maternal and perinatal mortality.[3] However, the etiology and pathogenesis of PE have not yet been fully elucidated. PE is thought to be an accessory of suitable interactions among immunity, inflammation, diet, and genetic factors,[4,5] leading to a decrease in trophoblast invasiveness and abnormal remodeling of uterine spiral artery. Particularly, increasing evidence suggests that genetic factors contribute to the etiology, development and complexity of PE. Copy number variations have been reported to be associated with the risk of PE.[6-8] In addition, several studies have identified that single nucleotide polymorphisms (SNPs) have been involved in the pathogenesis of PE, such as cytokines genes SNPs.[9-11]

Inflammation has been increasingly recognized as an important factor to contribute to endothelial dysfunction and to the pathology of PE.[12-14] For example, pro-inflammatory cytokine tumor necrosis factor α, by a mechanism depending on influencing the invasiveness of trophoblast cells and remodeling of the uterine spiral artery,[15] and interleukin (IL) 6, contributing to the systemic endothelial activation and vascular damage,[16,17] play an important role in the development of PE. Contrarily, IL-10, as an important anti-inflammatory factor, maintains the function of trophoblast by regulating the balance of anti-inflammatory signals, which leads to appropriate pregnancy outcomes.[18] It has reported that dysregulation of IL-10 was involved in the pathophysiology of PE.[19] Meanwhile, IL-10 is involved in regulating secretion of matrix metalloproteinases and invasiveness of trophoblast cells.[20] Taking into account the inheritable nature of PE and crucial function of IL-10 in PE, the influence of the IL-10 gene polymorphisms on PE are not negligible.

The IL-10 gene, located on chromosome 1q31-32, exhibits high polymorphisms, such as IL-10 -1082A/G (rs1800896), IL-10 -819C/T (rs1800871), IL-10 -592A/C (rs1800872), which
have been investigated to be correlated with the risk of PE, but the results remained controversial. Mehrnaz’s meta-analysis identified that IL-10 -1082G > A polymorphism was significantly associated with an increased risk of PE. However, there are several studies examining the association between IL-10 polymorphisms and PE including IL-10 -819C/T (rs1800871), IL-10 -592A/C (rs1800872), which are exhibited to be relevant to the risk of PE, characterized by deranged angiogenesis and trophoblast invasion by altering gene expression and protein production. But the results of different races and groups are contradictory and controversial. In order to attenuate the limitations of individual study, we performed a systemic review and a meta-analysis of all eligible case control studies including 1423 pregnant women with PE and 2031 normotensive pregnant women to determine whether the IL-10 -819C/T, -592A/C polymorphisms are associated with the susceptibility to PE. However, there were unknown significance referring the relationship between IL-10 -819C/T, -592A/C polymorphisms and PE susceptibility, it had a significant association with PE susceptibility in Asian and Caucasian.

2. Methods

2.1. Search strategy

The literature, whose publication date is up to June 2020, was searched from online databases, including Web of Science, PubMed, EMBASE, and Chinese databases (Chinese National Knowledge Infrastructure and Wan Fang). The searching terms were used as following: (“preeclampsia” OR “pre-eclampsia”) AND (“polymorphism” OR “single nucleotide polymorphism” OR “SNP” OR “variant”) AND (“interleukin-10” OR “IL-10”).

2.2. Inclusion and exclusion criteria

Overall, the inclusion criteria for eligible studies in this meta-analysis were:

1. case-control studies focused on associations between IL-10 -819C/T, -592A/C polymorphisms and risk of PE;
2. cases were strictly included and excluded;
3. the studies provided adequate original data in the case and control groups for various genotypes.

Except for English and Chinese, language constraint was applied in the selection of articles. The exclusion criteria were as follows:

1. prospective study;
2. meeting abstract;
3. editorial;
4. meta-analysis and review;
5. repeated publication.

2.3. Data extraction

The relevant data was carefully extracted from all the eligible publications by 2 independent researchers for this meta-analysis. Any divergences between the 2 reviewers were resolved by consensus. The information collected from each study was as follows: first author’s name, publication date, country, ethnicity, genotyping methods, case inclusion criteria, source of controls, total number of case and control group, the number of cases and controls of each studied polymorphism.

2.4. Ethical statement

Because this is a literature-based meta-analysis, ethical approval is not required.

2.5. Statistical analysis

Stata 10.0 software (Stata Corporation, USA) was carried out to perform statistical data analysis. The association between IL-10 -819C/T, -592A/C polymorphisms and PE susceptibility was evaluated by calculating odds ratios (OR) and 95% confidence interval. An allele contrast model, homozygote model, dominant and recessive model were used for evaluation of association between IL-10 -819C/T, -592A/C polymorphisms and PE susceptibility, respectively. When the heterogeneity test of P value is <.1 and the $I^2$ is >50%, the random effect model is applied, whereas the fixed effect model is used instead. The significance of the OR was determined by the Z-test, in which $P < .05$ was considered that there was statistically significant correlation between each SNP and PE susceptibility. Begg funnel plot was performed to evaluate potential publication bias.

3. Results

3.1. The baselines of studies included in the meta-analysis

The flow chart of study selection shown in Figure 1 exhibits the process, of which the studies were searched and screened. Totally, 122 studies were searched online from 5 databases. At and then 46 duplicate studies among databases were excluded. Fifty one irrelevant articles were removed by reviewing titles and abstracts. According to inclusion and exclusion criteria, 6 of them were prospective study, conference abstracts, reviews or meta-analysis, which were excluded. Ten records were deleted owing to duplicate publication, no data, referring to other loci polymorphism or language constraint. Finally, 9 case-control studies were included in this meta-analysis, of which 8 studies in IL-10 -819C/T polymorphism, 7 in IL10 -592A/C polymorphism. A total of 1423 cases and 2031 controls, which were from 3 Caucasians, 4 Asian populations, 2 African populations, and 1 Mulatto, mixed white and black ancestry, were included in this meta-analysis. Besides, the study by Haggerty included African population and Caucasian. However, because of the insufficient population of some ethnic groups, we selectively conducted ethnicity-specific meta-analysis of 2 SNPs. The general characteristics of 9 eligible studies with respect to associations between the IL-10 -819C/T, -592A/C polymorphisms and PE are summarized in Table 1.

3.2. Association between IL-10 -819C/T, -592A/C polymorphisms and PE

In this meta-analysis, we evaluated the association between IL-10 -819C/T, -592A/C polymorphisms and the susceptibility of PE (data shown in Table 2). Meta-analysis of IL-10 -819C/T polymorphism revealed that IL-10 -819C allele was not significantly associated with the risk of PE (OR=1.188, 95% CI: 0.958–1.472, $P=0.116$) (Table 2 and Fig. 2A). Stratification analysis by ethnicity showed that the association between IL-10 -819C allele and PE was significantly in Caucasians (OR=1.270, 95% CI: 1.024–1.576, $P=0.039$) and in Asians (OR=1.410, 95% CI: 1.054–1.886, $P=.021$) (Table 2). On the contrary, IL-10 -819C allele was found to be associated with the risk of PE in
Africans (OR = 0.791, 95% CI: 0.628–0.996, P = .046). The strong association between PE and the \textit{IL-10}-819C/T polymorphism was recorded using the recessive model (OR = 1.316, 95% CI: 1.002–1.728, P = .048) or a homozygote contrast in Asians (OR = 1.755, 95% CI: 1.236–2.492, P = .002), other than overall or in Caucasians and Africans (Table 2 and Fig. 2B and 2D). However, no association was found between \textit{IL-10}-819C/T polymorphism and PE under the dominant model analysis (Table 2 and Fig. 2C).

Besides, the meta-analysis indicated that no association was found between \textit{IL10}-592A/C polymorphism and the risk of PE in overall under an allele contrast (OR = 0.786, 95% CI: 0.617–1.001, P = .051) (Fig. 3A), the recessive model contrast (OR = 0.855, 95% CI: 0.537–1.361, P = .508) (Fig. 3B) or a homozygote contrast (OR = 0.784, 95% CI: 0.459–1.341, P = .374) (Fig. 3D). Analysis by a dominant model contrast showed a significant association between the \textit{IL10}-592A/C polymorphism and PE (OR = 0.716, 95% CI: 0.526–0.975, P = .034) (Table 2 and Fig. 3C). Stratification by ethnic divisions displayed \textit{IL}-10-592A/C polymorphism was significantly related to a risk of PE in Asians under an allele contrast (OR = 0.635, 95% CI: 0.530–0.762, P < .001) (Table 2), homozygote contrast (OR = 0.441, 95% CI: 0.308–0.633, P < .001) (Table 2), recessive (OR = 0.536, 95% CI: 0.408–0.704, P < .001) (Table 2), and dominant contrast models (OR = 0.609, 95% CI: 0.444–0.836, P = .002) (Table 2). Moreover, ethnic stratification analysis revealed a significant association between the \textit{IL}-10-592A/C polymorphism and PE in Caucasians under an allele contrast (OR = 0.725, 95% CI: 0.554–0.948, P = .019) and dominant contrast model (OR = 0.700, 95% CI: 0.404–0.836, P = .001), rather than recessive contrast model (OR = 1.170, 95% CI: 0.585–2.338, P = .658) or homozygous contrast (OR = 0.952, 95% CI: 0.463–1.959, P = .894) (Table 2).

### 3.3. Publication bias

Begg funnel plot was performed to assess potential publication bias of the included studies, which revealed no significant publication bias in 2 SNPs in the allele contrast (\textit{IL}-10-819C/T, P = .271; \textit{IL}-10-592A/C, P = .368) (Fig. 4A and 4B).

### 4. Discussion

PE is a pregnancy-specific complication with undefined etiology and pathogenesis. Increasing evidence indicates that the occurrence and development of PE were caused by multivariate
Table 1
General characteristics of 9 eligible studies contained in this meta-analysis.

| Study name          | Country          | Ethnicity          | Methods                  | Case selection                                                                 | Source of control                                                                 | Sample Size | Polymorphisms studied |
|---------------------|------------------|--------------------|--------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------|------------------------|
| Haggarty, 2005      | USA              | European           | TaqMan                   | 1. SBP/DBP > 140/90 mmHg 2. Proteinuria > 300 mg/24 h or protein/creatinine ratio > 0.3 3. Hyperuricemia | 1. Normotensive 2. No proteinuria or hyperuricemia during pregnancy               | 130/462     | IL-10 -819 C/T         |
| Kamali, 2006        | Iran             | Asian              | ASO-PCR/PCR-RFLP         | National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy National High Blood Pressure | 1. At least two successful deliveries 2. Without any history of PE               | 134/164     | IL-10 -819 C/T, L-10   |
| Mirahmadian, 2008   | Iran             | Asian              | PCR-SSP                 | National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy National High Blood Pressure | 1. Normal laboratory examination 2. No clinical signs and symptoms of PE          | 260/100     | IL-10 -819 C/T, L-10   |
| de Lima, 2009       | Brazil           | South American     | PCR-SSP                 | National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy National High Blood Pressure | 1. Normotensive in previous pregnancy 2. At least one successful pregnancy without any maternal or fetal disorder | 92/101      | IL-10 -819 C/T, L-10   |
| Soymya, 2014        | India            | South-Asian        | ARMS-PCR                | New onset of proteinuria > 2 + diastolic hypertension without any maternal or fetal disorder | More than 20 weeks pregnancy with normal blood pressure, fetal growth and physiological normalities | 120/120     | IL-10 -819 C/T, L-10   |
| Song, 2015          | China            | Asian              | PCR-RFLP                | 1. SBP/DBP ≥ 140/90 mm Hg 2. Proteinuria ≥ 300 mg/24 h or 2+ | 1. More than 20 wks pregnant women 2. No history of chronic hypertension, renal, autoimmune, metabolic or cardiovascular disease | 155/201     | IL-10 -819 C/T, L-10   |
| Liu, 2015           | China            | Asian              | PCR-RFLP                | Normal pregnant women in the same period | Normal pregnant women in the same period | 177/182     | IL-10 -819 C/T         |
| Fan, 2017           | China            | Asian              | PCR-RFLP                | 1. SBP/DBP ≥ 140/90 mm Hg 2. Proteinuria ≥ 300 mg/24 h | 1. More than 20 wks pregnant women 2. No history of chronic hypertension, cardiovascular disease, end-stage liver or renal diseases, or diabetes | 142/260     | IL-10 -592AC           |
| Raguema, 2018       | Tunisia          | African            | TaqMan                  | 1. SBP/DBP ≥ 140/90 mm Hg 2. Proteinuria ≥ 300 mg/24 h or 2+ | 1. Age-matched with cases and from the same region 2. No personal or family history of hypertension and PE | 345/500     | IL-10 -819 C/T, L-10   |

ARMS = amplification refractory mutation system, ASO = antisense oligonucleotide, DBP = diastolic blood pressure, IL = interleukin, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism, SBP = systolic blood pressure, SSP = sequence specific primer.

Table 2
Meta analysis of the association of IL-10 -819C/T, -592A/C polymorphisms and PE susceptibility.

| Polymorphism studied | Ethnicity | Number | Study of association | Heterogeneity of study design |
|----------------------|-----------|--------|----------------------|------------------------------|
|                      |           | Cases  | OR                   | 95% CI                       | Z (P value)                  |
| *IL-10 -819*         |           |        |                      |                              |                              |
| C vs T               | Overall   | 1281   | 1.188               | 0.958-1.472                 | 1.57 (116)                   |
|                      | African   | 356    | 0.701               | 0.628-0.969                 | 2.00 (48)                    |
|                      | Caucasian | 385    | 1.270               | 1.024-1.576                 | 2.17 (039)                   |
|                      | Asian     | 452    | 1.410               | 1.054-1.866                 | 2.31 (021)                   |
|                      | CC vs CT (recessive) | Overall | 1281 | 1.065 | 0.858-1.322 | 0.57 (569) |
|                      | African   | 356    | 0.862               | 0.391-1.121                 | 1.54 (125)                   |
|                      | Caucasian | 385    | 1.040               | 0.581-1.883                 | 0.15 (880)                   |
|                      | Asian     | 452    | 1.316               | 1.002-1.728                 | 1.98 (048)                   |
|                      | CC vs CT (dominant) | Overall | 1281 | 1.361 | 0.984-1.883 | 1.86 (063) |
|                      | African   | 356    | 0.774               | 0.576-1.041                 | 1.69 (031)                   |
|                      | Caucasian | 385    | 1.487               | 0.953-2.321                 | 1.75 (081)                   |
|                      | Asian     | 452    | 1.770               | 0.948-3.303                 | 1.79 (073)                   |
|                      | CC vs TT  | Overall | 1281 | 1.175 | 0.743-1.859 | 0.69 (491) |
|                      | African   | 356    | 0.600               | 0.347-1.037                 | 1.83 (067)                   |
|                      | Caucasian | 385    | 1.188               | 0.645-2.189                 | 0.55 (58)                    |
|                      | Asian     | 452    | 1.755               | 1.236-2.492                 | 3.14 (002)                   |
| *IL-10 -592*         |           |        |                      |                              |                              |
| A vs C               | Overall   | 1133   | 0.786               | 0.617-1.001                 | 1.95 (051)                   |
|                      | Caucasian | 288    | 0.725               | 0.554-0.948                 | 2.35 (018)                   |
|                      | Asian     | 417    | 0.635               | 0.530-0.762                 | 4.88 (<001)                  |
|                      | AA vs AC+CC (recessive) | Overall | 1133 | 0.855 | 0.537-1.361 | 0.66 (508) |
|                      | Caucasian | 288    | 1.170               | 0.585-2.338                 | 0.44 (658)                   |
|                      | Asian     | 417    | 0.536               | 0.408-0.703                 | 4.50 (<001)                  |
|                      | AA vs AC (dominant) | Overall | 1133 | 0.716 | 0.526-0.957 | 2.12 (034) |
|                      | Caucasian | 288    | 0.700               | 0.404-0.904                 | 3.21 (001)                   |
|                      | Asian     | 417    | 0.609               | 0.444-0.836                 | 3.07 (002)                   |
|                      | AA vs CC  | Overall | 1133 | 0.764 | 0.459-1.341 | 0.89 (374) |
|                      | Caucasian | 288    | 0.952               | 0.463-1.959                 | 0.13 (894)                   |
|                      | Asian     | 417    | 0.441               | 0.308-0.633                 | 4.45 (<001)                  |

CI = confidence interval, OR = odds ratios.
interaction including heredity, among which genetic polymorphisms have caught increasing attention.[30,31] Meanwhile, inflammation is also an accomplice in the development of PE, in which inflammatory factors make a crucial contribution.[19,32,33] Considering the importance of inflammation and genetic polymorphisms in the etiology and progression of PE, a growing number of studies have been performed to explore the associations between inflammatory gene polymorphisms and susceptibility to PE.[21–23,34–42] More and more meta-analysis have been conducted on the relationship between inflammatory factors IL-6,[43] TNF-α[44] and anti-inflammatory factors IL-10[45] gene polymorphism and PE, which further indicates that gene polymorphism is closely related to the susceptibility of PE. In the present study, we synthesized data from published studies to explore the relationship between the risk of PE and other commonly studied polymorphisms of the IL-10 -819C/T and -592A/C.

IL-10 gene, located on chromosome 13q13, encodes an anti-inflammatory cytokine IL-10. During PE, decreased IL-10 was present in the plasma and placenta.[46,47] It was found that IL-10 treatment in PE pregnant mice significantly increasing Treg cells and decreased hypertension.[48] Hence, the decrease of IL-10 contributes to the pathogenesis of PE. So more and more studies are now investigating the relationship between IL-10 gene polymorphisms and the risk of PE. It was reported that several polymorphisms in the IL-10 gene were associated with IL-10 production, including IL-10 -819C/T,[49] and -592A/C[50,51] polymorphisms. Increasing studies are involved in investigating the relationship between IL-10 -819C/T and -592A/C polymorphisms and PE susceptibility. Fan et al have revealed that IL-10 -592A/C polymorphism was associated with PE susceptibility.[28] Moreover, it was reported that IL-10 -819C/T are associated with PE in different populations.[25,29] On the contrary, some studies have demonstrated that there was no correlation between

Figure 2. Meta-analysis of the association between the IL10 -819 C/T polymorphism and PE. (A). allele control model; (B). recessive genotype model; (C). dominant genotype model; (D). homozygous genotype model.
Figure 3. Meta-analysis of the association between the IL10 -592 A/C polymorphism and PE. (A). allele control model; (B). recessive genotype model; (C). dominant genotype model; (D). homozygous genotype model.

Figure 4. Bigger funnel plot for publication bias among included studies. (A). IL10 -819 C/T polymorphism; (B). IL10 -592 A/C polymorphism.
**IL-10 -819C/T and -592A/C polymorphisms and PE risk.** Due to the limitation of sample size and the genetic characteristics of different ethnicity, the conclusion is contradictory. In order to attenuate the analytical bias of the results depended on sample size and ethnicity, we conducted a meta-analysis. In our meta-analysis, the IL-10 -819C/T and -592A/C polymorphisms had no correlation with the risk of PE overall under an allele contrast, but had a significantly strong relation with the risk of PE in Asian under an allele contrast, dominant contrast model, recessive contrast model or homozygous contrast. Besides, IL-10 -819 C allele and IL-10 -592 C allele were related to PE susceptibility in Caucasian. The possible reason for this discrepancy was difference in study population. Ethnicity with different genetic backgrounds has a significant heterogeneity. Therefore, our results are not consistent with the meta-analysis results of Yang et al, which showed that IL-10 -819C/T and -592A/C polymorphisms were associated with PE risk under the allelic model. Due to the small number of literatures and people included for data analysis, the ethnic group analysis was not carried out in their meta-analysis. In our meta-analysis, a total of 1281 cases and 1771 controls from 8 studies were included in IL-10 -819 C/T polymorphism, 1133 cases, and 1238 controls from 7 studies were included in IL10 -592 A/C polymorphism. Nevertheless, only 5 case-control studies with 631 cases and 1059 controls for IL-10 -819 C/T polymorphism and a total of 376 cases and 445 controls from 3 case-control studies were included in the 2014 meta-analysis. The inconsistent results may be that more studies containing a larger sample size and more populations, have been included in our meta-analysis, which attenuating statistical analysis results bias.

We must admit that there are some limitations in our meta-analysis. Although we updated the original meta-analysis and increased the number of included case-control studies, the number of subjects is still relatively small, which indicates that the final results may not be enough to study the real relationship statistically. It is necessary to follow up the research progress in order to update the results of system review and meta-analysis in time. Secondly, the source of control was inconsistent in each case-control study, which may lead to bias in the results. In the future investigation, the source of the control group should be unified as far as possible. Finally, our meta-analysis results showed that there was no significant association between IL-10 -819 C/T, -592 A/C polymorphisms and PE susceptibility overall, but the different genotypes and alleles of IL-10 -819 C/T, -592 A/C polymorphisms had different effects on PE susceptibility in different ethnic groups. Therefore, according to the different genotypes and alleles, different regular follow-up are adopted for pregnant women of different ethnic groups. For example, an Asian pregnant woman with a CC genotype in the IL-10 -819 C/T polymorphism should pay more attention to the monitoring of blood pressure during pregnancy, whether she has symptoms related to gestational hypertension.

## 5. Conclusion

Our meta-analysis suggested that IL-10 -819 C/T and -592 A/C polymorphisms had no correlation with the risk of PE overall, but had a significant association with PE susceptibility in Asian and Caucasian.**

**Acknowledgments**

The authors would like to thank the Department of Science and Technology of Sichuan Province project (no. 2020YS0100), and the Office of Science and Technology of Chengdu (no. 2019-YF05-01178-SN).

**Author contributions**

**Conceptualization:** Li Chang, Yongmei Jiang.

**Data curation:** Li Chang, Yongmei Jiang.

**Formal analysis:** Guanglu Che.

**Software:** Yongmei Jiang.

**Writing – original draft:** Guanglu Che.

**Writing – review & editing:** Guanglu Che, Fang Liu.
[21] Hagerty CL, Ferrell RE, Hubel CA, Markovic N, Harger G, Ness RB. Association between allelic variants in cytokine genes and preeclampsia. Am J Obstet Gynecol 2005;193:209–15.

[22] Kamali-Sarvestani E, Kiany S, Gharesi-Fard B, Robati M. Association study of IL-10 and IFN-gamma gene polymorphisms in Iranian women with preeclampsia. J Reprod Immunol 2006;72:118–26.

[23] Mirahmadian M, Kalantar F, Heidari G, Saldaran L, Mansouri R, Amirzargar AA. Association of tumor necrosis factor-alpha and interleukin-10 gene polymorphisms in Iranian patients with preeclampsia. Am J Reproductive Immunol 2008;60:179–85.

[24] de Lima TH, Sass N, Mattar R, et al. Cytokine gene polymorphisms in preeclampsia and eclampsia. Hypertens Res 2009;32:565–9.

[25] Sowmya S, Sri Manjri K, Ramaiah A, et al. Interleukin 10 gene promoter polymorphisms in women with early-onset pre-eclampsia. Clin Exp Immunol 2014;178:334–41.

[26] Song L, Zhong M. Association between Interleukin-10 gene polymorphisms in Iranian patients with pre-eclampsia and eclampsia. Hypertens Res 2009;32:565–9.

[27] Liu QY, Gao FY, Liu XR, et al. Investigations into the association of tumor necrosis factor-alpha gene haplotype is associated with pre-eclampsia in pregnant women. Mol Hum Reprod 2005;11:437–40.

[28] Daher S, Sass N, Oliveira LG, Mattar R. Cytokine genotyping in preeclampsia. Am J Reproductive Immunol 2006;55:130–5.

[29] Saarela T, Hiltunen M, Helsalmi S, Heinonen S, Laakso M. Polymorphisms of interleukin-6, hepatic lipase and calpain-10 genes, and preeclampsia. Eur J Obstet Gynecol Reprod Biol 2006;128:175–9.

[30] Thakoordeen S, Moodley J, Naicker T. Candidate gene, genome-wide association and bioinformatic studies in pre-eclampsia: a review. Curr Hypertens Rep 2018;20:90:91.

[31] Benveniste EN, Peakman M, Kimpton PW, et al. IL-10 and IL-6 polymorphisms modulate cytokine production in response to Toll-like receptor (TLR) 9 and TLR9-DNA complexes in human primary monocytes. J Immunol 2015;195:440–56.

[32] Valenzuela FJ, Perez-Sepulveda A, Torres MJ, Correa P, Repetto GM. Polymorphisms of interleukin-6, hepatic lipase and calpain-10 genes, and preeclampsia. Eur J Obstet Gynecol Reprod Biol 2006;128:175–9.

[33] Fleischer DM, Wang Y, Liu XL, Zhang A, Xu Q. Polymorphisms in interleukin-10 gene are associated with pre-eclampsia. J Reproductive Immunol 2018;80:e13055.

[34] Hennessy A, Pilmoro HL, Simmons LA, Painter DM. A deficiency of placental IL-10 in preeclampsia. J Immunol 1999;163:3491–5.

[35] Arriaga-Pizano L, Jimenez-Zamudio L, Vadillo-Ortega F, Martinez-Flores A, Herreras-Canedo T, Hernandez-Guerrero C. The predominant TH1 cytokine profile in maternal plasma of preeclamptic women is not reflected in the chorionicdecidual and fetal compartments. J Soci Gynecologic Investigation 2005;12:335–42.

[36] Harmon A, Cornelius D, Aamaral L, et al. IL-10 supplementation increases Tregs and decreases hypervitosis in the RUPP rat model of preeclampsia. Hypertens Pregnancy 2015;34:291–306.

[37] Chenjiao Y, Zili F, HaiLin C, et al. IL-10 promoter polymorphisms affect IL-10 production and associate with susceptibility to acute myeloid leukemia. Die Pharmazie 2013;68:201–6.

[38] Zhao N, Chen HL, Chen ZZ, Li J, Chen ZB. IL-10-592 polymorphism is associated with IL-10 expression and severity of enterovirus 71 infection in Chinese children. J Clin Virol 2017;95:42–6.

[39] Berti FCB, Perreira APL, Truglio KP, et al. IL-10 gene polymorphism c.-592C>A increases HPV infection susceptibility and influences IL-10 levels in HPV infected women. Infection, Genetics Evolution 2017;53:128–34.

[40] Yang W, Zhu Z, Wang J, Ye W, Ding Y. Evaluation of association of maternal IL-10 polymorphisms with risk of preeclampsia by a meta-analysis. J Cellular Mol Med 2014;18:2466–77.