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Original Article

# Interleukin-1β-gene polymorphisms in preeclamptic Egyptian women

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ABSTRACT

*Aim of work:* To investigate the relationship between IL-1β -31C/T (rs 1143627) and -11T/C (rs 16944) gene polymorphisms and preeclampsia.
*Patients and methods:* Polymorphisms at -31C/T and -511T/C of IL-1β were genotyped using polymerase chain reaction restriction fragment length polymorphisms (PCR-RFLP).
*Results:* Concerning results of interleukin-1β -31C/T, there were no statistically significant differences between the 2 studied groups regarding CC, CT or TT genotypes. Concerning -511T/C gene polymorphisms, there was statistically significant difference between the 2 studied groups regarding TT genotype, but there were no statistically significant differences between the 2 studied groups regarding CC or CT genotypes.
*Conclusion:* To our knowledge, it is the first study to investigate the relationship between IL-1β gene polymorphisms and preeclampsia in Egyptian females.
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## 1. Introduction

Hypertensive disorders complicating pregnancy (HDCP) continues to be a leading cause of maternal and neonatal mortality and morbidity [1]. It complicates 2–5% of pregnancies worldwide and 10% of pregnancies in developing countries [2,3]. In recent years, important reports have been made in understanding of the pathogenesis and pathophysiology of preeclampsia, but most of the factors that contribute to the disease still remain unclear.

Preeclampsia is a pregnancy-specific multisystem disorder, which is characterized by new-onset hypertension, edema, and proteinuria that develop after 20 weeks of gestation in previously normotensive women [4,5].

Severe preeclampsia is a pregnancy-specific syndrome characterized by systolic blood pressure of ≥160 mmHg and diastolic blood pressure of ≥110 mmHg, with qualitative proteinuria of >+1 or 0.3 g/24 h. [6,7]. World Health Organization (WHO) in 2006, reported that almost 16% of 3201 mortality caused by pregnancy was contributed by gestational hypertension [8]. According to data from National Center for Health Statistics in USA, gestational hypertension occurs in 150,000 women or 3.7% of all pregnancy [6]. It has been hypothesized that the underlying mechanism of preeclampsia involve genetic factor, immunologic factor, vascular disease, and conditions in which excessive trophoblast was unable to invade spiral artery in the early phase of the first trimester [9–11].

Epidemiological research indicated that PE w as associated with family and genetic control and inheritance appeared to have a major function in the pathology of this disease [12]. Moreover, PE is a multiple gene disorder, affected by genetic and environmental factors, such as interaction between maternal and fetal genes, which were important determinant of maternal disease susceptibility [13] (Therefore, genetic factors cannot be ignored in the pathogenesis of preeclampsia).

During pregnancy, many cytokines are secreted by immune cells and lymphocytes at the interface of trophoblast and decidua, which mainly mediate and regulate immunity, inflammation and hematopoiesis.. Benyo et al. indicated that several cytokines had been found to be increased in pregnant women with PE. The serum level of inflammation cytokines, one kind of cytokines, such as IL-1β, IL-2, IL-6 and IFN-c, had been found to be higher in women with PE than in normotensive pregnant women [14–16], which lead to harmful Th1 immunity, threatening pregnancy by generating cytotoxic factors that injured maternal endothelium and affect other factors which were implicated in trophoblast invasion and maternal spiral artery remodeling [17,18]. The production of inflammatory cytokines is regulated by the cytokine gene, thus the cytokines gene polymorphism may play a key role in the development of PE.

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The aim of this work was to investigate the relationship between IL-1β -31C/T (rs 1143627) and -511T/C (rs 16944) gene polymorphisms and preeclampsia.

## 2. Patients and methods

A case control study was conducted at obstetrics and gynecology department of Kasr El Aini School of medicine, in the period between June 2015 and November 2015. The studied cases and control members were recruited from outpatient antenatal care clinic. They were all Egyptian women living in Cairo. Local institutional research board approval as well as informed consent was obtained from all participants prior to their participation in the study. Samples were selected from blood samples collected from pregnant women in their first trimester (between 10 and 14 weeks of gestation) as a part of first trimester screening program and they were followed throughout pregnancy till delivery. The 80 preeclamptic cases and the 80 members of the control group were selected to be matched as regard age and parity to eliminate the effect of these factors on our results.

The present study was enrolled on 80 preeclamptic pregnant women. Diagnosis of preeclampsia was established before 37 weeks of gestation by the following criteria:

1. Blood pressure of 140/90 mmHg (twice on separate occasions >6 h apart).
2. Protein urea >300 mg/l protein excreted; +/+ dipstick urine analysis.

The control group in the study included 80 pregnant women with no complications.

The fetal outcomes were assessed for intrauterine growth retardation (IUGR), intrauterine fetal death (IUFD), and prematurity. IUGR was diagnosed in neonates when their birth weight at delivery was below the 10 percentile value for the given gestational age.

All women with essential hypertension, diabetes, or autoimmune diseases were excluded from the research.

### *2.1. All studied cases and controls were subjected to the following investigations*

Complete blood picture, prothrombin time and concentration, kidney function test, and liver function test.

Venous blood samples were collected on EDTA vacutainers. IL-1β -31C/T (r s 1143627) and -511T/C (rs 16944) gene polymorphisms were identified by the PCR-restriction fragment length polymorphism method (PCR-RFLP).

### *2.2. Genotyping*

Genomic DNA was isolated from peripheral blood cells, and DNA was extracted from the whole blood using a DNA extraction kit, (QIAamp Blood Kit (Cat. No. 51106; Qiagen Inc., Valencia, CA)), following the manufacturer's instructions.

Interleuki n-1β -3 C/T an d -511T/ C gene po l y m o r p h i sm s were identified by the PCR-RFLP method.

The amplification primers that we used are as follows: IL-1β -31 locus: The forward primer: 5′AGAAGCTTCCACCAATACTC-3′ and reverse primer: 5′-ACCACCTAGTTGTAAGGAAG-3′. For IL-1β -511 promoter region, forward primer: 5′-GTTTAG GAAT CT TCCCACTT-3′ and reverse primer: 5′-TG GCATTGATCTGGTTCATC-3′. The PCR amplification was performed in 25μl reaction volume, containing 12.5μl 2×PCR Master Mix; 2 × PCR buffer, 3mM MgCl2, 0.5 units Taq DNA polyme rase/μl , 400μM of each dNTP, 1μl of each primer (10pmol), 2.5μl of genomic DNA, and 8μl sterilized nuclease free water. The reaction was performed in a Hybaid therm al cycler (Promeg). Corporation 2800 Woods Hollow Road Madison, WI1 53711 - 539 9 USA), programmed as follows: initial denaturation at 94°C for 3min , 3 5 cycle s of 30s denaturation at 94°C, 30s annealing at 54°C and 45s extension at 72° C, and a 10-min final extension at 72°C. The amplified products were detected in 1.5% agarose gel as a single band of 239 and 518bp for IL-1b -31 and IL-1β -511 respectively.

Digestion of the amplified products of interleukin 1 beta-31 and interleukin 1 beta-511 was done using 10 units restriction endonucleases Alu1 (New England Biolabs) and Ava1 (New England Biolabs) respectively and incubated at 37°C for 16h. The digested products were checked on 3% agarose gel. The expected results of IL-1β -31C/T were as follows: CC: 239b p, TT: 137bp, 102bp, CT: 239bp, 137b p, 102bp. And LL-1β -511T/C is digested into 3 expected results: TT showing one band with 518bp, CC showing two bands with 403bp and 115b p, TC showing three bands with 518bp, 403bp and 115bp.

### *2.3. Statistical analysis*

Statistical calculations were performed using Microsoft Excel version 7 (Microsoft Corp., Redmond, WA, USA) and SPSS for Windows version 16 (SPSS Inc., Chicago, IL, USA) software. Results were reported as mean ± standard deviation (±SD) or frequency (%) when appropriate. Comparison of categorical data was done using the chi-Squared test ($x^2$), while for the numerical data, independent *T*-test and ANOVA test were used. Odds ratio were used to assess the risk conferred by a particular allele and genotype. P value less than 0.05 was considered statistically significant and less than 0.01 was considered highly statistically significant.

## 3. Results

The clinical and laboratory data of the 2 studied groups are summarized in Table 1. The clinical characteristics of the three studied groups were not significantly different.

**Table 1**
Comparison of clinical and laboratory data of the 2 studied groups.

| | Severe preeclampsia (n = 80) | Controls (n = 80) | P value |
|---|---|---|---|
| Maternal age (years) | 26.3 ± 4.22 | 27.5 ± 5.3 | 0.87(NS) |
| Parity | 1.3 ± 1.1 | 1.5 ± 1.0 | 0.75(NS) |
| Gestational age (weeks) | 36.7 ± 2.5 | 38.1 ± 1.6 | 0.74(NS) |
| Blood pressure (third trimester) | | | |
| - Systolic blood pressure (mmHg) | 168.5 ± 11.5 | 115.3 ± 6.13 | <0.001(HS) |
| - Diastolic blood pressure (mmHg) | 120.3 ± 11.8 | 70.5 ± 5.48 | <0.001(HS) |
| - Haematocrite value (%) | 33.1 ± 5.5 | 34.8 ± 5.2 | 0.85(NS) |
| Platelets count ( × $10^3$/μL) | 197.3 ± 79.16 | 233.4 ± 55.25 | <0.001(HS) |
| Total bilirubin (mg/dL). | 1.44 ± 0.2 | 1.04 ± 0.15 | 0.86(NS) |
| AST(mg/dL) | 33.5 ± 11.5 | 19.2 ± 5.45 | <0.001(HS) |
| ALT(mg/dL) | 36.4 ± 10.2 | 23.2 ± 6.75 | <0.001(HS) |
| Creatinine (mg/dL) | 2.05 ± 0.25 | 0.75 ± 0.33 | <0.001(HS) |
| Urinary proteins (g/24 h urine) | 5.6 ± 1.7 | Nil | <0.001(HS) |

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