# Chemerin Level as a Marker in Preeclampsia and its Relation to the Disease Severity and Neonatal Outcome

**Ali Mohammed Murad, Marwa Jaafar Sadac (M.B.Ch.B)2; Hanan Hazim Mohammed Noori (M.B.Ch.B, C.A.B.O.G, DGO)3**

*[1]Department of Obstetrics and Gynecology, College of Medicine, Mustansiriya University, Baghdad, Iraq, [2]Ministry of Health, Al-Yarmouk Teaching Hospital, Baghdad, Iraq, [3]Head of Department of Gynecology and Obstetrics, Al-Qaim Hospital, Al-Anbar Province, Iraq*

## Abstract

**Aim of study:** To detect serum chemerin level in patient with preeclampsia and evaluate the association between maternal serum chemerin, disease severity and neonatal outcome.

**Patients and Method:** A case control study included 100 pregnant women with singleton pregnancy, gestational age of 20 weeks or more, normal fetal morphology, and absence of concomitant diseases, who were collected from inpatient during delivery was conducted in the Department of Obstetrics and Gynecology at Al-Yarmouk Teaching Hospital during the period from 1st of June 2018 till end of May 2019. They were divided into three groups (control, mild preeclampsia, and severe preeclampsia). Patients with history of chronic hypertension, diabetes mellitus, cardiovascular disease, neurological disorder, renal impairment, or premature rapture of membrane were excluded from this study. blood sample was taken from all patients and sent for human chemerin assay. After delivery, birthweight of baby, APGAR scores at one and five mints, neonatal intensive care unit and adult intensive care unit admission, and hospitalization time were also noted.

**Results:** There were no statistically significant differences between the study groups in age, BMI level, and parity. Chemerin level was significantly elevated in patients with severe preeclampsia (435.06 ng/ml) and mild preeclampsia (227.49 ng/ml) than that in non-preeclamptic patients (202.6 ng/ml). It was negatively correlated with each of gestational age, birth weight, Apgar score at one and five minutes. While it was positively correlated with admission's duration. Serum chemerin > 228.5 ng/ml is predictive for diagnosis of preeclampsia and level > 380.9 ng/ml is indicator for severe preeclampsia.

**Conclusion:** Chemerin may play a role in the pathogenesis of preeclampsia as maternal serum chemerin level was significantly higher in patients with preeclampsia

***Keywords:*** *Preeclampsia, chemerin, APGAR score, birthweight, Iraq*

## Introduction

Preeclampsia (PE) is a syndrome that chiefly includes the new onset of hypertension and either proteinuria or signs of other end-organ dysfunction (e.g. hepatic abnormality, pulmonary edema, thrombocytopenia) [(1)]. PE affect between 3% and 5% of all pregnancies and account for more than 60,000 maternal and 500,000 fetal deaths per year worldwide [(2)]. It is one of the most important causes of maternal, perinatal, and fetal morbidity and mortality in the world [(3)]. Deficient spiral artery remodeling, placental ischemia, release of mediators into the maternal circulation, systemic endothelial dysfunction, inflammation, and consequent increased vascular constriction are biological mechanisms that contribute to preeclampsia [(4, 5)]. Additionally, abnormal placentation, imbalance of angiogenesis regulators, and maternal immune

**Corresponding Author:**
Hanan Hazim Mohammed Noori
E-mail: dr.ammar2013@gmail.com

maladaptation are other possible factors associated with preeclampsia [6]. Moreover, the future risk of vascular and metabolic disease is significantly increased after a preeclamptic pregnancy [7]. However, the pathogenesis of this life-threatening condition remains unclear [8]. The placenta is thought to be a major source of endogenous nitric oxide (NO) during pregnancy. Endothelial NO, which is synthesized by endothelial NO synthase (eNOS), is an important regulator of blood flow and vasomotor tone via its inhibition of smooth muscle contraction. Thus, it is hypothesized that NO–eNOS system abnormalities are associated with the onset of preeclampsia [9, 10]. Chemerin, named also as tazarotene-induced gene protein 2or retinoic acid receptor responder protein 2, is a novel adipocy-tokine that is mainly expressed in adipocytes, liver, placenta, and ovaries [11]. Evidence has been presented that chemerin is linked to facets of the metabolic syndrome in vitro and in vivo [12] hence this adipokine is correlated with insulin resistance and body fat accumulation [13]. Hypertension, coronary disease [14], diabetes mellitus [15], atherosclerosis [16], obesity and metabolic syndrome [17] are also associated with chemerin. Although its specific biological functions are controversial, chemerin may play a role in the pathogenesis in preeclampsia. The aim of this study is to determine whether serum chemerin concentrations are elevated in preeclamptic women and whether serum chemerin levels differ according to severity of preeclampsia and to evaluate the association between maternal serum chemerin and neonatal outcome.

## Patients and Method

**Study design, setting:** This is a case control study that was conducted in the Department of Obstetrics and Gynecology at Al-Yarmouk Teaching Hospital during the period from 1st of June 2018 till end of May 2019.

**Study Population and sample size:** The study included 100 pregnant women with singleton pregnancy, gestational age of 20 weeks or more, normal fetal morphology, and absence of concomitant diseases, who were collected from inpatient during delivery in labor room. They were divided into three groups:

- Severe Group: Included 33 pregnant women who had diagnosed with severe PE.
- Mild Group: Included 33 pregnant women who had diagnosed with mild PE.
- Control Group: Included 34 pregnant women with uncomplicated pregnancy who were selected after matching for age and gestational age of another one in the other two groups after proof that she was normotensive by history, examination and investigation.

Mild PE is diagnosed when hypertension with two readings (separated by 4-6 hrs. apart) of systolic blood pressure ≥ 140 mmHg and / or diastolic pressure ≥ 90 mmHg. Another characteristic feature of mild PE is the development of protein urea ≥ 300 mg / 24 hrs. [18]. Severe PE can be identified by presence of sustained elevation in blood pressure, systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg, proteinuria of > 2 gm in a 24-hrs urine specimen, serum creatinine of >1.2 mg/dl, platelets of < 100,000/dl, increased lactate dehydrogenase, elevated serum transaminase levels, persistent headache, and oliguria (urinary output<400 ml/ 24 hours). In addition, any patient with cerebral or visual impairment, persistent epigastric pain, pulmonary edema or cyanosis, impaired liver function, or thrombocytopenia (platelet count less than 100,000/ml) was diagnosed with severe PE [3]. Pregnant women with history of chronic hypertension, diabetes, cardiovascular disease, neurological disorders, renal impairment, or with premature rapture of membrane were excluded from this study.

**Data collection:** All patient told about the nature of the study and verbal consent was taken from them. Information about maternal age, gestational age, parity, gravidity, mode of delivery, previous history of preeclampsia, family history of any previous medical history. Then both group undergo to general examination, vital signs (systolic and diastolic blood pressure), abdominal and obstetric examination, laboratory investigation and sonographic examination. Then, from all study patients, we took 10 ml blood sample which was divided into two equal parts, the first one was sent to our hospital laboratories for CBC, blood group and Rh, blood sugar, b. urea, s. creatinine, SGOT, SGPT, coagulation profile and platelet count. In the other part, serum was separated by centrifugation at 2,500 rpm for 10 min and frozen at -70 °C. The serum chemerin levels were measured by enzyme linked immunosorbent assay according to the manufacturer's instructions. The lowest level of human chemerin that can be detected by this assay is 31.2 ng/ml.

After delivery, birthweight of baby, APGAR scores at one and five mints, neonatal intensive care unit

(NICU) and adult intensive care unit (AICU) admission, and hospitalization time were also noted.

## Statistical analysis

The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. They presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Analysis of Variance (ANOVA) (two tailed) was used to compare the continuous variables accordingly. Pearson's correlation test (r) was used to assess correlation between continuous variables accordingly. Receiver operating characteristic (ROC) curve analysis was used for prediction of chemerin level as diagnostic of preeclampsia. A level of P – value less than 0.05 was considered significant.

## Results

In this study, 100 pregnant women were enrolled. The age was ranging from 17 to 40 years with a mean of 25.9 ± 6.13 years. Regarding general characteristics, there were no statistical significant differences ($P \geq 0.05$) between the study groups in age, BMI, and parity. Concerning blood pressure, SBP and DBP were significantly higher in severe group than that in mild and control groups (169.34 versus 148.93 and 123.81 mmHg, P= 0.001; and 107.1 versus 95.9 and 75.53 mmHg, P= 0.001 respectively).

About investigation, AST, ALT, s. urea and chemerin level were significantly higher in severe group than that in mild and control groups (155.06 versus 45.48 and 30.37 U/l, P= 0.001; 126.0 versus 35.36 and 25.71 U/l, P= 0.001; 31.65 versus 25.0 and 25.78 mg/dl, P= 0.001; and 435.06 versus 227.49 and 202.6 ng/ml, P= 0.001 respectively). Mean of platelet count was significantly lower in severe group than that in mild and control groups (101.65 versus 149.21 and 198.09, P= 0.001)

No statistical significant differences ($P \geq 0.05$) between the study groups in WBC and s. creatinine as shown in table (1).

**Table 1: Comparison between study groups by general characteristics, blood pressure, and investigation**

| Variable | Severe Group Mean ± SD | Mild Group Mean ± SD | Control Group Mean ± SD | P - Value |
|---|---|---|---|---|
| General characteristics | | | | |
| Maternal age (Year) | 24.45 ± 6.3 | 25.0 ± 5.0 | 26.23 ± 6.5 | 0.564 |
| BMI (Kg/m2) | 28.43 ± 3.8 | 26.61 ± 3.8 | 29.35 ± 4.1 | 0.093 |
| Parity | 1.36 ± 1.7 | 1.37 ± 1.7 | 1.35 ± 1.7 | 0.279 |
| Blood pressure | | | | |
| SBP (mmHg) | 169.34 ± 17.3 | 148.93 ± 6.2 | 123.81 ± 10.1 | 0.001 |
| DBP (mmHg) | 107.1 ± 20.1 | 95.9 ± 5.3 | 75.53 ± 7.8 | 0.001 |
| Investigation | | | | |
| WBC (10 9/l) | 12.32 ± 2.8 | 11.17 ± 3.9 | 10.62 ± 3.4 | 0.127 |
| AST (U/l) | 155.06 ± 210.9 | 45.48 ± 7.4 | 30.37 ± 6.6 | 0.001 |
| ALT (U/l) | 126.0 ± 148.6 | 35.36 ± 7.5 | 25.71 ± 6.2 | 0.001 |
| Urea (mg/dl) | 31.65 ± 10.0 | 25.0 ± 4.2 | 25.78 ± 5.4 | 0.001 |
| Creatinine (mg/dl) | 0.71 ± 0.23 | 0.77 ± 0.16 | 0.81 ± 0.16 | 0.126 |
| PLT Count (10 9/l) | 101.65 ± 19.5 | 149.21 ± 26.6 | 198.09 ± 37.2 | 0.001 |
| Chemerin level (ng/ml) | 435.06 ± 55.4 | 227.49 ± 57.4 | 202.6 ± 21.1 | 0.001 |

Receiver operating characteristic (ROC) curve analysis was constructed for chemerin level as indicator of preeclampsia. As shown in figure (1) and table (2), the cut point of chemerin level was 228.5 ng/ml, so s. chemerin > 228.5 ng/ml is predictive for diagnosis of preeclampsia indicating significant association between higher level of chemerin and diagnosis of preeclampsia.

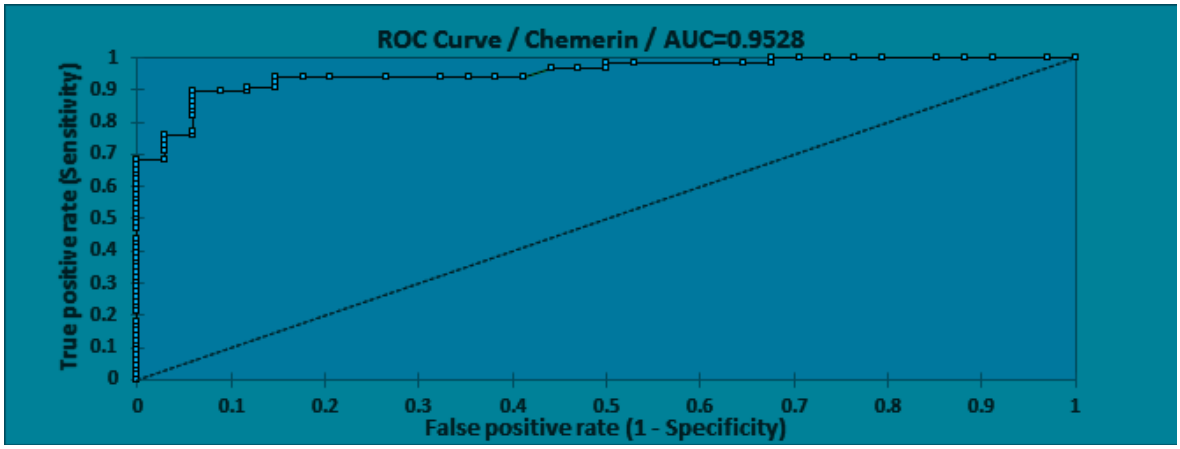


**Figure 1: ROC curve for chemerin as a marker of preeclampsia**

**Table 2: Diagnostic accuracy for test of preeclampsia**

| | **Cut-off value** | **Sensitivity** | **Specificity** | **PPV** | **NPV** | Accuracy |
|---|---|---|---|---|---|---|
| Chemerin level (ng/ml) | 228.5 | 89.3% | 94.1% | 96.7% | 82% | 91% |

ROC curve analysis was constructed again for chemerin level as diagnostic for severity of preeclampsia. As shown in figure (2) and table (3), the cut point of chemerin level was 380.9 ng/ml, so s. chemerin > 380.9 ng/ml is indicator for severe preeclampsia indicating significant association between higher level of chemerin and diagnosis of severe preeclampsia.

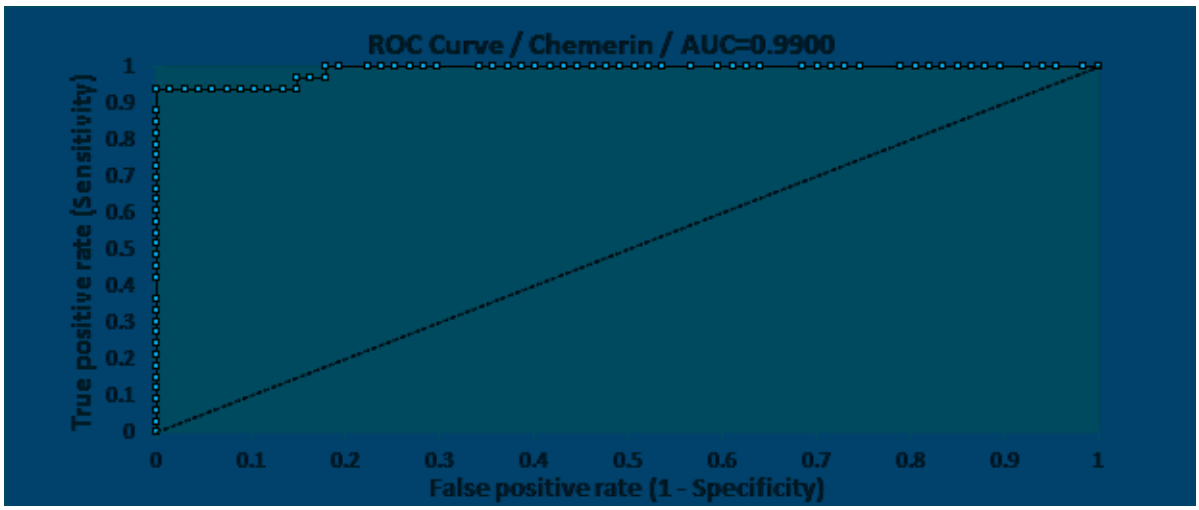


**Figure 2: ROC curve for chemerin level as a marker of severe preeclampsia**

**Table 3: Diagnostic accuracy for test of severe preeclampsia**

| | **Cut-off value** | **Sensitivity** | **Specificity** | **PPV** | **NPV** | **Accuracy** |
|---|---|---|---|---|---|---|
| Chemerin Level (ng/ml) | 380.9 | 93.9% | 100% | 100% | 97.1% | 98% |

Chemerin level was negatively correlated with each of gestational age, birth weight, Apgar score at one and five minutes. While it was positively correlated with admission's duration, and these correlations were demonstrated in table (4).

**Table 4: Correlation between level of chemerin and certain obstetric and neonatal outcomes of the study groups**

| Variable | Chemerin Level (ng/ml) | |
|---|---|---|
| | r | P - Value |
| Gestational age (Weeks) | - 0.711 | 0.001 |
| Birth Weight | - 0.714 | 0.001 |
| Apgar Score at 1 Mint | - 0.615 | 0.001 |
| Apgar Score at 5 Mint | **- 0.709** | **0.001** |
| Duration of Admission | **0.547** | **0.001** |

## Discussion

Recently, it has been reported that circulating chemerin concentrations were strongly correlated with the key markers of the metabolic syndrome, including insulin resistance, hyperlipidemia, and high blood pressure. In the current study, we found that maternal serum chemerin level was significantly higher in severe and mild preeclamptic patients compared to healthy pregnant women, and elevated serum chemerin level (>228.5 ng/ml) indicated preeclampsia with 89.3% sensitivity and 94.1% specificity and > 380.9 ng/ml indicated severe preeclampsia with 93.9% sensitivity and 100% specificity. These result was agreed with results conducted by Cetin et al study 2017 [3], Xu QL et al study 2014 [19], Wang L et al study 2015 [8], Duan DM et al study 2012 [20], and Stepan H et al study 2011 [21] when they all showed that serum chemerin was significantly higher in patients with preeclampsia than that of healthy pregnant women. These findings indicate that differential expressions of chemerin may be responsible for pathological changes in patients with preeclampsia. Chemerin was identified in maternal circulation during pregnancy. Placenta releases the major part of chemerin during the gestational period and also it plays a critical role in controlling /contributing to metabolic processes [22, 23]. The signaling pathway between high expression of chemerin and its receptor CMKLR1 is the common pathogenic factor of obesity, diabetes, hypertension and metabolic syndrome. Meanwhile, chemerin is also overexpressed in preeclampsia. It is a matter of further investigation to determine whether the chemerin/CMKLR1 signaling pathway is an internal factor between preeclampsia and obesity, diabetes, hypertension and metabolic syndrome [24]

In this study, chemerin level was negatively correlated with each of gestational age, birth weight, Apgar score at one and five minutes, while it was positively correlated with admission's duration. This is similar to studies conducted by Cetin et al 2017 [3], and by Duan DM et al 2012 [20] Additionally, preeclampsia can lead to higher frequency of induced labor, neonatal respiratory difficulties, and increased frequency admission to neonatal intensive care unit [25]. In conclusion, maternal serum chemerin level is significantly increased in preeclampsia, especially in severe preeclampsia. Larger studies and work are needed to better determine the mechanisms by which serum chemerin is increased in preeclampsia.

**Ethical Clearance:** The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

**Conflict of Interest**: The authors declare that they have no conflict of interest.

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