Original Article

Evaluation of Maternal Serum Sestrin2 Levels in Preeclampsia and their Relationship with the Disease Severity

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Abstract

Background: Preeclampsia (PE) is considered one of the major causes of both maternal and fetal mortality and morbidity. Advances have been made on understanding the pathophysiology of this pregnancy-specific disorder. Sestrin2 (SESN2) is a metabolic regulator protein, whose expression is induced in response to exposure to different adverse effects such as hypoxia, DNA damage, or oxidative stress, thus acting as cytoprotective. **Objective:** The objective of the study was to investigate the levels of maternal serum SESN2 in preeclamptic and uncomplicated pregnancies and their association with the disease severity. **Patients and Methods:** This was a case–control study conducted at the Department of Obstetrics and Gynecology at Al-Yarmouk Teaching Hospital in Iraq – Baghdad city from the first of March till the end of November 2019. The study included a total of 92 pregnant women, 27 with a healthy pregnancy, 33 with nonsevere PE, and another 32 having severe PE. From all participants, blood samples were collected for the evaluation of serum SESN2 levels using enzyme-linked immunosorbent assay. **Results:** The mean readings of SESN2 for normal pregnancies were 5.22 ± 1.71 ng/ml which was significantly lower than that for the nonsevere PE group (8.41 ± 1.42 ng/ml), while SESN2 levels were the highest among those with severe PE (16.92 ± 5.15 ng/ml). A negative correlation was found between each of GA at delivery, birth interval, and birth weight and the SESN2 level ($P = 0.001$); while mean arterial pressure positively correlated with SESN2 levels ($P = 0.001$), the cutoff value for the diagnosis of severe PE was 9.95 ng/ml (sensitivity of 93.8% and specificity of 98.8%). **Conclusion:** Maternal serum SESN2 levels are significantly higher in pregnancies complicated by severe PE than nonsevere PE and control groups. It could be a useful biomarker that can help in diagnosing severe PE.

Keywords: Oxidative stress, preeclampsia, pregnancy, sestrin2

Introduction

Preeclampsia (PE) is a multisystemic disorder and a leading complication of pregnancy with a significant contribution to maternal and fetal morbidity and mortality and the long-term predisposition to cardiovascular disease in the mother.[1-3] Globally, it affects 2%–8% of all pregnancies.[4] Concerning the pathogenesis of PE, it involves abnormal placentation with placental ischemia-reperfusion injury development that results in placental oxidative stress, with exaggerated systemic inflammatory response and the development of the maternal syndrome.[1,3,5] The occurrence of abnormal placentation, oxidative stress, systemic inflammatory response, an imbalance between pro-angiogenic and anti-angiogenic factors, renin–angiotensin–aldosterone system, all can contribute to endothelial dysfunction which will initiate disease manifestations.[6]

Sestrin2 (SESN2) is a member of the family of stress-inducible proteins called sestrins. SESN2 can protect against the endothelial toxicity induced by angiotensin II (ANG II) through its antioxidant activity, besides its potential role as protective in inflammatory responses.[7-9] Studies have confirmed that SESN2 levels are elevated in patients with various diseases including pregnancy-specific hypertensive disease and that SESN2 levels correlate with their severity.[10-13] In their study,

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Yi *et al*. found that ANG II induces SESN2 expression in endothelial cells of human umbilical vein in a dose- and time-dependent manner.[7] SESN2 can modulate many cell activities, thereby providing a pivotal and protecting role that can make it a possible biomarker and therapeutic target for different diseases.[11]

This study aimed to evaluate SESN2 levels in preeclamptic patients and whether they correlate with PE severity.

Patients and Methods

This was a case-control study that was conducted at the Department of Obstetrics and Gynecology at Al-Yarmouk Teaching Hospital in Baghdad during the period from the first of March till the end of November 2019. The study protocol was approved by the Ethics Committee of the Iraqi Board for Medical Specializations (Scientific Council of Obstetrics and Gynecology). The study included 92 pregnant women attending the outpatient clinic of Obstetrics and Gynecology Department and those who were admitted to the obstetrical ward. They were informed about the study's nature and informed verbal consent was obtained from them before enrolling them in the study.

Patients were assigned to the PE groups in accordance with the American College of Obstetricians and Gynecologists criteria for the diagnosis of PE. PE was diagnosed if the pregnant woman had blood pressure (Bp) ≥140/90 mmHg measured on two occasions 6 h apart beyond 20 weeks of gestation and was previously normotensive with proteinuria >300 mg/day or reading of ≥1+ by dipstick. PE was considered nonsevere when the patient had PE without severe features. The diagnosis of severe PE was established in the presence of any of the following findings: a Bp of ≥160/110 mmHg, thrombocytopenia (platelet count lower than 100,000/μl), progressive renal insufficiency, liver function impairment as indicated by an abnormal increase in blood concentrations of liver transaminases to twofold the normal levels, new-onset visual or cerebral symptoms, and the occurrence of pulmonary edema.[14] Three groups were defined: the control group included 27 healthy pregnant women free of hypertension and proteinuria, the nonsevere PE group included 33 pregnant women with PE without severe features, and the severe PE group included other 32 pregnant women with severe PE. For the three groups, the maternal age, parity, gravidity, gestational age (GA) at blood sampling, and body mass index (BMI) were matched. The inclusion criteria for the present study were as follows: viable singleton pregnancy, any parity status, and maternal age and GA for more than 20 weeks. Patients with multiple gestations, active labor, premature rupture of membranes, chorioamnionitis, congenital anomalies, chronic hypertension, overt or gestational diabetes, any systemic disease such as severe liver disease, chronic kidney disease, or autoimmune diseases were excluded from the present study.

GA was calculated by the reliable date of the last menstrual period or early dependable ultrasound. Bp was measured by a properly calibrated mercury sphygmomanometer while the patient is sitting and using the patient's right arm at the level of the heart. The mean arterial pressure (MAP) was estimated as advocated by Page using the formula: (systolic Bp + [2 × diastolic blood pressure])/3.[15]

The weight and height were measured at the time of sample collection and the BMI was calculated by dividing the patient's weight in kilogram (kg) on height in square meter (m^2) using the following equation: BMI = weight in kg/height in m^2. A transabdominal ultrasound examination was done to all women using the Voluson E6 device with a 3.0–5.0 MHz convex transducer to assess for signs of placental insufficiency and intrauterine growth retardation.

Maternal blood samples were collected from all participants and sent for full investigations including full blood count, random blood sugar, liver and renal function tests, and coagulation profile. Mid-stream urine samples were collected from each participant for urinary protein measurement by dipstick.

Venous blood samples of 5 ml were collected from the pregnant women in the three groups in a plain tube and before administering any medication, the samples were allowed to clot at room temperature for 10–20 min then centrifuged at 2000–3000 rpm for 20 min, and the supernatant (serum) was collected and stored in a deep freeze at −20°C till the day of analysis.

Serum SESN2 level was measured by a kit using enzyme-linked immunosorbent assay, Catalog Number: MBS760249, MyBioSource/USA. The detection range was 0.156–25 ng/ml.

All pregnant women were followed until the time of delivery to determine the GA at delivery and record the birth interval which is the time in weeks from blood sampling till delivery. Maternal and fetal complications were also recorded including HELLP syndrome, imminent eclampsia, eclampsia, placental abruption, and fetal growth restriction. The newborn babies were examined by the pediatrician for assessment of birth weight which was recorded in grams.

Statistical analysis

The collected data were introduced into Microsoft sheet EXCEL 2016 and loaded into Statistical Package for the Social Sciences (SPSS) version 24. The descriptive statistics were presented using tables and graphs; while one-way ANOVA was used to find out the significance of differences between means of scale data after testing the normality of distribution using the Shapiro–Wilk's test and Levene's test was used to test homogeneity of variance, *post hoc* test was used to find out the significance of the difference between peer wise data. If the scale data were found to be not normally distributed, the Kruskal–Wallis test was used to find out the significance of differences between medians of related data. A Chi-square test was used to find out the significance of the association between categorical data. Spearman correlation (r) was used to find out the significance of correlations between SESN2 and other studied variables. The receiver operator characteristic (ROC)

curve was used to find out the discrimination cutoff point for SESN2 to differentiate between severe and nonsevere PE and to find sensitivity and specificity. $P < 0.05$ was considered as a discrimination point of significance.

Results

The total number of studied pregnant ladies was 92 distributed among three groups. Twenty-seven (29%) were ladies of normal pregnancy and considered as the control group, 33 (36%) ladies were diagnosed as nonsevere PE, while 32 (35%) ladies were proved to have severe PE.

As shown in Table 1, nonsignificant statistical differences were noticed between the means of the age of the three studied groups ($P > 0.05$). GA at delivery was significantly lower in those who got severe PE than those with nonsevere PE which, in turn, was found to be lower than those of normal pregnancy ($P = 0.001$). The birth interval was also found to be significantly shorter among those who got severe PE than those with nonsevere PE which, in turn, was found to be shorter than those of normal pregnancy ($P = 0.001$). MAP for patients with severe PE was significantly higher than the MAP for those with nonsevere PE, while normal pregnancy showed significantly lower MAP than the other two groups ($P = 0.001$). Regarding birth weight for newborn babies, it was significantly lower in the group with severe PE than those with nonsevere PE group and controls and that birth weight for those with normal pregnancy was significantly higher than the other groups with a $P = 0.001$. The mean readings of SESN2 for ladies with normal pregnancy were found to be significantly lower than that found among pregnant ladies with nonsevere PE, while SESN2 levels were found to be the highest among those with severe PE [$P = 0.001$, Table 1 and Figure 1]. In Table 2, the Kruskal–Wallis test failed to prove any statistically significant differences between BMI, the GA at the time of blood sampling, the number of gravida, or parity readings between different groups in this study ($P > 0.05$).

In this study and on the follow-up of studied women till delivery, maternal and fetal complications were recorded. HELLP syndrome occurred in eight patients, imminent eclampsia in ten patients, eclampsia in five patients, and placental abruption occurred in four patients, all were in the severe PE group, while fetal growth restriction was seen in 30 patients, 20 of them in severe PE group and the remaining 10 were in nonsevere PE group.

Table 3 summarizes the correlation between the serum SESN2 and the women's clinical parameters. No significant correlation was detected between the levels of SESN2 and the maternal age, BMI, and GA at blood sampling, but a significant and moderate negative correlation was noticed between serum SESN2 and GA at the time of delivery (r =-0.650; $P = 0.001$), birth interval ($r = -0.646$; $P = 0.001$), and birth weight ($r = -0.698$; $P = 0.001$) and that a strong positive and significant correlation was noticed between the levels of SESN2 and the MAP ($r = -0.707$ and $P = 0.001$).

Figure 2 shows the ROC curve for the concentrations of SESN2 in severe PE, the area under the curve was 0.985 (95% confidence interval: 0.997–1) with an optimal cutoff value of 9.95 ng/ml. The ratio that is above this value had a sensitivity of 93.8% and a specificity of 98.8%, $P = 0.001$.

Discussion

In this study, maternal serum SESN2 levels were evaluated in patients with PE and whether its levels have any association

Table 1: Differences between means of normally distributed scale variables according to preeclampsia

	Control ($n=27$)	Nonsevere PE ($n=33$)	Severe PE ($n=32$)	*P*
Age (years)	27.07±6.16	29.15±7.25	29.25±8.45	0.459
GA at delivery (weeks)	38.77±1.21	35.81±1.37$^{\alpha}$	32.18±2.32$^{\alpha,*}$	0.001
Birth interval (weeks)	6.48±3.06	3.30±1.84$^{\alpha}$	0.09±0.02$^{\alpha,*}$	0.001
MAP	80.66±6.86	108.06±6.27$^{\alpha}$	124.84±8.24$^{\alpha,*}$	0.001
Birth weight (g)	3327.77±249.74	2283.33±281.36$^{\alpha}$	1667.50±283.52$^{\alpha,*}$	0.001
Sestrin2 (ng/ml)	5.22±1.71	8.41±1.42$^{\alpha}$	16.92±5.15$^{\alpha,*}$	0.001

Data are expressed as the mean±SD, the ANOVA followed by the Tukey–Kramer *post hoc* test were used for the two-group pairwise comparisons. *$P<0.05$ versus nonsevere PE, $^{\alpha}P<0.05$ versus controls. PE: Preeclampsia, MAP: Mean arterial pressure, GA: Gestational age, SD: Standard deviation, Sestrin2: Sestrin2

Table 2: Distribution of studied cases according to Kruskal–Wallis test of not normally distributed scale data

	Median (IQR)			*P*
	Control ($n=27$)	Nonsevere PE ($n=33$)	Severe PE ($n=32$)	
BMI (kg/m^2)	30 (11)	32 (5)	29.5 (4.5)	0.263
GA at blood sampling (weeks)	33 (4)	33 (3.5)	32 (4)	0.776
Gravida	3 (2)	3 (2)	3 (2)	0.638
Parity	1 (3)	2 (2.5)	2 (3.75)	0.812

Data are expressed as the median (interquartile), The Kruskal–Wallis test. IQR: Interquartile range, PE: Preeclampsia, BMI: Body mass index, GA: Gestational age

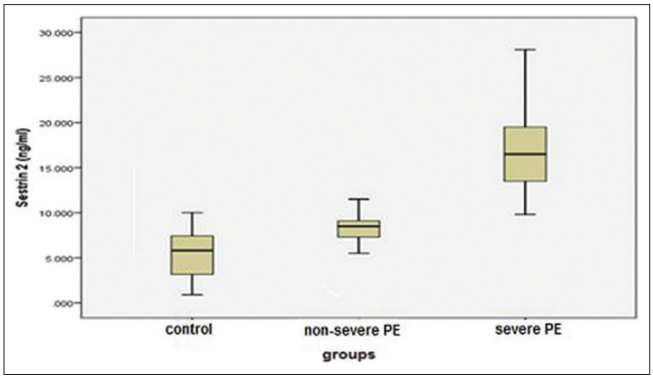

Figure 1: Boxplot graph of serum sestrin2 levels in the three study groups

Table 3: Correlation analyses of the maternal serum sestrin2 and the clinical parameters

Variables		SESN2	
		r	*P*
Age (years)	Pearson correlation	0.122	0.246
BMI (kg/m^2)	Pearson correlation	0.000	0.998
MAP	Pearson correlation	0.707**	0.001
GA at blood sampling (weeks)	Pearson correlation	0.009	0.930
GA at delivery (weeks)	Pearson correlation	−0.650**	0.001
Birth interval (weeks)	Pearson correlation	−0.646**	0.001
Birth weight (g)	Pearson correlation	−0.698**	0.001

BMI: Body mass index, MAP: Mean arterial pressure, GA: Gestational age, *r*: Spearman's rank correlation, Sestrin2: Sestrin2

with the disease severity. In the literature, only a few data are found about this topic. SESN2 is a metabolic protein that is stress induced, it has a protective effect via regulating oxidative stress, endoplasmic reticulum stress (ER), and inflammation and that oxidative stress can induce the expression of SESN2.[8,16,17] SESN2 is known to suppress reactive oxygen species (ROS) under conditions of genotoxic and oxidative stress, hypoxia, and ER stress, thus providing cytoprotection against different harmful stimuli ultimately reducing the cellular levels of ROS.[18] It has also been demonstrated that as SESN2 plays an important function in regulating ER stress, this role turns to have a vital place in the pathophysiology of PE.[19] Defective trophoblast invasion and the release of placental factors as a consequence of augmented inflammatory and oxidative stresses are involved in the pathogenesis of PE. The presence of phosphorylated adenosine monophosphate-activated protein kinase (AMPK) has been confirmed in the placental tissues of rats and human beings. Its levels are raised in hypoxic conditions such as PE and that AMPK also enables the preservation of uterine artery blood flow.[20] SESN2 and AMPK are stress-inducible proteins, they suppress the production of ROS, thus protect against oxidative stress. SESN2 activates AMPK, thus improves endothelial function, decreases oxidative stress, and ameliorates hypertension secondary to placental ischemia.[21-24]

In the literatures, several biomarkers were investigated and their association with PE has been studied.[12,25-27] SESN2

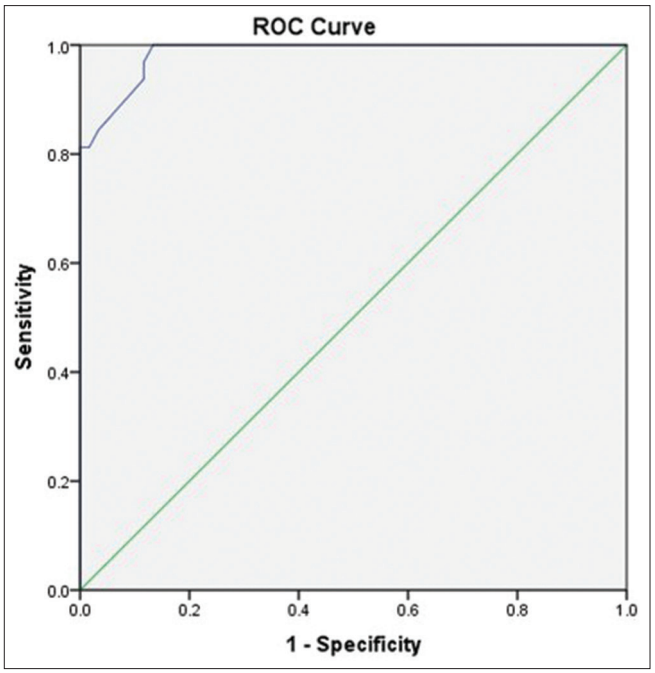

Figure 2: Receiver operating characteristic curve for the sestrin2 concentration in severe preeclampsia

was one of these markers; an activation of its placental synthesis and increased expression was reported under the harmful effects of hypoxia, oxidative stress, and various pro-inflammatory substances. Furthermore, SESN2 was found to induce its regulatory function in the cardiovascular system and kidneys, thus protecting the endothelial cells exposed to the stress induced by ANG-II.[7,9,28]

In the current study, the maternal age, gravidity, parity, BMI, and GA at blood sampling were matched between study groups to avoid bias.

In the current study, significantly higher SESN2 levels were detected in the nonsevere preeclamptic pregnancies than the controls, but its levels were the highest among pregnancies with severe PE with a statistically significant difference ($P = 0.001$), this was in partial agreement with a recent study conducted by Tayyar *et al*.[12] in 2018 which was the first and the only study investigating the link between SESN2 and pregnancies complicated by PE and its association with the disease severity; this study enrolled 80 pregnant women, 26 of them with nonsevere PE, other 24 were severe preeclamptic patients, and 30 healthy controls. They reported that serum SESN2 concentrations were significantly higher in the severe PE group in comparison with the control and the nonsevere PE groups ($P = 0.004$).On the other hand, no statistically significant difference was found between the nonsevere PE and the control groups. Regarding the correlation between serum SESN2 levels and the clinical parameters, serum SESN2 levels positively correlate with MAP and negatively correlate with GA at delivery, birth interval, and birth weight, while in the study by Tayyar *et al*.,[12] a significant negative correlation was only detected between birth interval and serum SESN2 levels.

These differences can be explained by the smaller number of patients in their study. The maternal and fetal complications seen in the current study necessitate earlier delivery and this can explain the shorter birth interval and the lower birth weight in pregnancies complicated with severe PE than nonsevere PE and controls.

In the present study, the best cutoff value for the serum SESN2 levels in the identification of severe PE was 9.95 ng/ml with a sensitivity of 93.8% and a specificity of 98.8%, $P = 0.001$, while in the study by Tayyar *et al*.[12] and for the identification of severe PE, the reported sensitivity and specificity of the serum SESN2 concentration at the optimal cutoff value of 1.637 ng/ml were 54.2% and 96.4%, respectively. Such discrepancies observed among the above-mentioned results might have been attributed to the sample size of each study. This study was the first one in Iraq in its subject. The fact that the significantly highest serum SESN2 concentrations detected in pregnancies with severe PE supports the allegation that oxidative stress and the antioxidant defense systems play important roles in PE and could open new fascinating therapeutic scenarios.

Conclusion

Maternal serum SESN2 levels are significantly higher in pregnancies complicated by severe PE, with a sensitivity of 93.8%, a specificity of 98.8%, and a cutoff value of 9.95 ng/ml for the diagnosis of severe PE. It seems that SESN2 can be a valuable biomarker that can help in the diagnosis of severe PE.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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