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Original Article

Correlation of Kisspeptin-10 level and fetal well-being in preeclamptic patients

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ABSTRACT

Objective: This study aims to evaluate the role of kisspeptin-10 in preeclampsia and check for possible relationship between its severity and fetal growth well-being. Kisspeptin-10 may participate in implantation of the embryo, placenta formation, and maintenance of pregnancy.
Materials and Methods: One hundred women who completed 20 weeks of gestation with singleton pregnancies were divided into 60 peeclamptic and 40 normotensive control women. Kisspeptin-10 level estimation, and ultrasound and Doppler ultrasound studies for umbilical artery were performed during their second and third trimesters of pregnancy.
Results: Plasma kisspeptin-10 level was lower in preeclamptic groups and inversely correlated with the severity of the disease. Its level directly correlated with estimated fetal weight *in utero* during both trimesters in patients with severe preeclampsia and with fetal birth weight in patients with mild preeclampsia, whereas an inverse correlation was observed in those with severe preeclampsia during their second trimester. Kisspeptin-10 level was directly related to the resistance index in the second trimester in patients with severe preeclampsia, while it inversely correlated with the systolic/diastolic ratio and resistance index in the third trimester in patients with mild preeclampsia.
Conclusion: Kisspeptin-10 level is useful in assessing the severity of preeclampsia and can be a novel marker downregulated in pregnant women with preeclampsia, especially in those who also developed impaired uteroplacental perfusion or intrauterine growth restriction.

Introduction

The placenta mediates rapid implantation, trophoblast invasion, proliferation and differentiation, and the processes of vasculogenesis and angiogenesis via its endocrine and immunomodulatory properties [1,2]; in addition, the placenta produces hormones that alter maternal physiology during pregnancy and forms a barrier against the maternal immune system [3].

Impaired implantation, anomalous placental development, and placental malfunction pose high risk for pregnancy complications such as miscarriage, preeclampsia (PE), gestational diabetes, fetal growth restriction, or preterm birth [4].

PE as a maternal syndrome develops in about 10% of pregnancies, and is a leading cause of perinatal morbidity and mortality, i.e., growth restriction and chronic hypoxia of the fetus [5]. The invasion of trophoblast cells of the placenta into the maternal decidua during the first trimester of pregnancy is a key process for successful reproduction and embryonic development, and dysregulation of trophoblast invasion and shallow invasion have been implicated in a wide spectrum of abnormal pregnancies [6].

Several hypotheses have been proposed to clarify the abnormal trophoblastic invasion early in pregnancy associated with PE, many of them suggesting that it might be activated by distorted maternal immune response, faulty development of maternal tolerance to the semiallogeneic fetus, or dysregulation of the invasive process of endometrial mesenchymal stem cells [7–10]. The extravillous trophoblast invasion into uterine tissue is a key process of successful embryogenesis and placentation. The important role in

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placentation processes is assigned to the so-called kisspeptins (KPs) and their receptors [11].

KPs are peptide products of the *KISS-1* gene, which act through binding with the G-protein coupled receptor 54 (GPR54), also known as the *KISS-1* receptor. The initial protein product of the *KISS-1* gene is a 145-amino-acid peptide, which is cleaved into shorter, biologically active peptides known as KP-54, KP-14, KP-13, and KP-10, where each number relates to the number of amino acids, with KP-10 representing the common C-terminal decapeptide sequence shared by all [12,13].

The KP/GPR54 system has an important physiologic role in neuroendocrine regulation of reproduction via its regulation of the hypothalamic–pituitary–gonadal axis; it plays a critical role in the onset of puberty and acts as a regulator of seasonal reproduction [14]. In addition, it affects pregnancy and implantation, and regulates nutrition and fertility [15], stress [16], and variable effects at different stages of the menstrual cycle [14]. Members of the KP family (KP-10, KP-13 and KP-54) also possess vasoactive activity [17,18], and KP-54, known as metastin, was found to inhibit metastasis of malignant melanoma cells [19].

Altered KP levels are associated with different conditions, such as reduced KP levels in pregnancies with gestational diabetes, hypertension, PE, placental dysfunction, and intrauterine growth retardation [20]. Severely decreased KP levels, in these patients, during early pregnancy may be associated with an increased risk of spontaneous abortion [21]. Furthermore, circulating concentrations of KP were found to be lower at early stages of pregnancy in women who had miscarriage, preterm delivery, small-for-gestational-age neonates, or intrauterine growth retardation [21–27]; therefore, KP was proposed to have a pivotal role in successful placental and fetal development.

Both *KISS-1* and *KISS-1R* mRNA are expressed centrally in the brain, spinal cord, and hypothalamus, and peripherally in the placenta, pituitary, testes, pancreas, liver, small intestine, skeletal muscle, kidney, and cardiovascular system [28,29].

Evidence suggests that KP acts as a regulator of trophoblast invasion [12,30]. Specifically KP-10, produced by first-trimester trophoblast cells, has been shown to inhibit migration [30]. This ability to inhibit the migration of cells was further confirmed when the movement of primary trophoblasts, crucial for placental development during pregnancy, was halted by KP-10 treatment [30].

KISS-1 is present at the fetomaternal interface with abundant expression in the syncytiotrophoblast cells [30]. Interestingly, mRNA and protein expressions of both *KISS-1* and *KISS-1R* have been shown to be higher in first-trimester placental trophoblast cells than in term gestation, contrasting with the increasing circulating *KISS-1* levels during pregnancy [30,31]. This finding coincides with the time of maximal extravillous cytotrophoblast invasion and has therefore been suggested to represent a crucial control mechanism regulating placental development [30]. It is, therefore, suggested that altered placental expression of *KISS-1* and/or *KISS-1R* may be associated with poor placentation and the associated disorder of PE. Further support for this comes from the observation of lower circulating *KISS-1* concentrations in early-second-trimester serum samples from women who subsequently develop PE and intrauterine growth restriction [25].

Placental origin for the peptide has been suggested due to the observation that circulating *KISS-1* levels fall 5 days postdelivery compared with nonpregnant concentrations [32]. *KISS-1* is dramatically increased throughout pregnancy when the invasive potential of the placenta is maximal, and when regulation and limitation of trophoblast invasion take place [31,33]. Its dysregulation may contribute to improper trophoblast invasion and subsequently cause pathological pregnancy [6,31]. Increased expression of *KISS* and its receptor GPR54 in the placental terminal villi in early-onset PE reflects limited trophoblast invasion processes [11].

It has been shown that trophoblasts from women with PE have significantly higher *Kiss-1* mRNA and KP-54 peptide levels than trophoblasts during normal pregnancies [34]. By comparison, contrasting data have also been published, suggesting that serum from women with PE contain less KP-10 than serum from control individuals [25].

The objective of our study is to evaluate the role of KP-10 levels in the pathophysiology of PE and to determine whether there is a relationship between the severity of the disease and fetal growth well-being parameters.

Materials and methods

This is a prospective case–control study of 100 pregnant women who attends the Primary Health Care Centers/Antenatal Care and the Department of Obstetrics & Gynecology/Al-Imamian Al-Kadhimyian Medical City. The local medical ethics committee approved the study, and informed consent was obtained from all study participants.

One hundred pregnant women completed 20 weeks of gestation with singleton pregnancies were enrolled in the study. They were divided into two groups:

Group 1: comprised 60 preeclamptic pregnant women aged 17–44 years (mean ± standard deviation = 30.90 ± 6.56 years) with blood pressure (BP) of ≥140/90 mmHg associated with proteinuria with 1+ dipstick in women who were previously normotensive. The patients were observed 6 hours apart on at least two occasions.

Preeclamptic pregnant women with no comorbidities were studied, while those with metabolic, vascular, and systemic diseases; hypertension and proteinuria or urinary tract infection during early pregnancy; multiple gestation; previous bad obstetric history (i.e., incompetent cervix) or obstetric complications of the current pregnancy (i.e., placenta previa); and fetal anomaly were excluded. The preeclamptic women were subdivided into 39 with mild PE (BP ≥ 140/90 mmHg to <160/110 mmHg with proteinuria ≥300 mg/24 hours or ≥1+ dipstick), and 21 with severe PE (BP ≥ 160/110 mmHg with proteinuria 2.0 g/24 hours or ≥2+ dipsticks in the absence of urinary tract infection).

Group 2: comprised 40 normotensive nonsmoker pregnant women, considered as a control group aged 17–44 years (mean ± standard deviation = 30.58 ± 6.13).

Once PE was diagnosed, hematological and biochemical evaluations were performed. Clinical follow-up of the pregnant women was also carried out till delivery, and the mode of delivery and fetal birth weight (FBW) were registered. The frequency and timing of patients' visits were assessed twice throughout the periods of gestation: the first appointment during the second trimester (20–27 weeks of gestation) and the second appointment during the third trimester (28–40 weeks of gestation). The time interval between the first and second appointments for clinical follow-up visit was 4 weeks. Gestational age was estimated depending on the last menstrual period and early ultrasound examination as a baseline examination, i.e., during the first trimester.

Two milliliters of aspirated venous blood obtained by venipuncture were put in an EDTA tube and centrifuged (centrifuge; Andreas Hettich GmbH & Co.KG, Tuttlingen, Germany). The plasma was then separated using a micropipette (Dragon Laboratory Instruments Limited, Beijing, China) and utilized for plasma KP-10 level estimation. The samples were kept in plastic sterile specimen containers (Citotest, Nanjing, China) and stored in a freezer at −20 ± 6°C in upright position until the day of KP-10 hormone analysis. KP-10 level was estimated using Kiss1 (112–121) amide/KP10/metastin (45–54) amide (Human) EIA KIT (Phoenix

Pharmaceuticals, Inc., Burlingame, CA, USA; catalog no. EK-048-56 and lot no. 603626). The enzyme immunoassay kit is designed to detect a specific peptide and its related peptides based on the principle of competitive enzyme immunoassay using an enzyme-linked immunosorbent assay system (BioTek, Winooski, VT, USA).

Ultrasound examination was performed using Siemens Diagnostic Ultrasound System (Tokyo, Japan). An abdominal probe (5.0C5) was used transabdominally, with the mother in the semi-recumbent position. The parameters measured and assessed were placenta thickness, fetal gestational age, fetal biometry (biparietal diameter and femur length), estimated fetal weight (EFW), amniotic fluid index, and FBW.

Doppler velocimetry measurements of the umbilical artery were made and demonstrated by the same physician using the Color and Pulsed wave Doppler imaging system (Siemens Diagnostic Ultrasound System) and an abdominal probe (5.0C5). The mother was in the semirecumbent position. The indices studied were the systolic/diastolic ratio (S/D) ratio or A/B ratio, pulsatility index (PI), and resistance index (RI).

Statically analysis

Analysis of data was carried out using the available statistical package of SPSS-20 (Statistical Packages for Social Sciences-version 20). The significance of difference of different means (quantitative data) was tested using independent Student *t* test for the difference between two independent means at 0.05 level, while paired *t* test for the difference between two dependent means at 0.05 level. Different percentages (qualitative data) were tested using chi-square test (χ^2 test) with application of Yet's correction or Fisher exact test whenever applicable. Pearson correlation was calculated for the correlation between two quantitative variables with its *t* test for testing the significance of correlation. The correlation coefficient value (r) was either positive (direct correlation) or negative (inverse correlation), with values <0.3 representing no correlation, 0.3–<0.5 weak correlation, 0.5–<0.7 moderate strength, and >0.7 strong correlation. Statistical significance was considered for $p \leq 0.05$.

Results

With regard to maternal age, no significant difference was noticed between the PE and control groups (30.90 ± 6.56 years vs. 30.58 ± 6.31 years). Likewise, the parity was not different between the two groups (3.23 ± 2.13 vs. 2.70 ± 2.19). Moreover, in terms of gestational age, no significant difference was noticed between the PE and control groups, whereas a statistically significant difference ($p < 0.05$) in body mass index, systolic and diastolic BP, and FBW was observed between the two groups (Table 1).

Table 1
Demographic and clinical features of preeclampsia patients and control individuals.

Feature	Trimester	PE patients ($N = 60$)	Normotensive women ($N = 40$)
BMI (kg/m^2)	Second	32.79 ± 6.49	28.27 ± 3.50*
	Third	34.02 ± 6.53	29.28 ± 3.84*
Systolic BP (mmHg)	Second	146.17 ± 10.27	118.25 ± 5.01*
	Third	141.58 ± 12.06	118.38 ± 3.47*
Diastolic BP (mmHg)	Second	99.83 ± 7.19	77.50 ± 5.43*
	Third	95.25 ± 9.63	75.00 ± 5.99*
FBW (g)		2891.67 ± 620.52	3362 ± 285.72*

BMI = body mass index; BP = blood pressure; FBW = fetal birth weight; PE = preeclampsia [mild ($N = 39$) and severe ($N = 21$)]; SD = standard deviation.
* Student *t* test for difference between two independent means at 0.05 level, values are expressed as mean ± SD.

Plasma KP-10 levels were significantly lower in the PE groups as compared with the normotensive pregnant women ($p < 0.05$); moreover, it was significantly lower in severe preeclamptic women compared with mild preeclamptic women (Table 2).

Table 3 shows the correlation between maternal plasma KP-10 hormone and parameters of fetal growth well-being, i.e., EFW *in utero*, FBW, and umbilical artery Doppler ultrasound velocimetry examination including S/D ratio, and PI and RI indices.

A significant direct correlation was noticed between plasma KP-10 level and EFW in those patients with severe PE during the second and third trimesters ($r = 0.760$, $p = 0.001$, and $r = 0.920$, $p = 0.0001$, respectively) as shown in Figure 1. Furthermore, a significant direct correlation ($r = 0.395$, $p = 0.012$) was found in pregnant normotensive women.

During their second trimester, patients with mild PE showed direct correlation ($r = 0.358$, $p = 0.016$) between plasma KP-10 level and FBW; however, a significant inverse correlation ($r = -0.952$, $p = 0.0001$) was observed in patients with severe PE (Figure 2). While there was no correlation between plasma KP-10 levels and FBW during the third trimester of patients with PE, a significant inverse correlation ($r = -0.410$, $p = 0.009$) was found in normotensive women.

During the second trimester of patients with severe PE, neither the S/D ratio nor the PI correlated with plasma KP-10 level, whereas the RI was in a direct relationship ($r = 0.865$, $p = 0.0001$) with KP-10 level (Figure 3).

Plasma KP-10 level inversely correlated with the S/D ratio and RI ($r = -0.326$, $p = 0.029$, and $r = -0.294$, $p = 0.050$, respectively) but not with the PI during the third trimester of patients with mild PE (Figure 4).

Discussion

The collected demographic, obstetric, and clinical data of PE patients and normotensive women were homogenous to a very high extent with regard to maternal age, parity, and gestational age; however, it is worthy to state here that, although there was no statistical significance in gestational age between PE patients and controls, it is lower in the former group than in the latter group. The exceptions of these data where variations are present are as follows: first, the body mass index, which is greater in the PE group due to the fact that an elevated maternal body mass index is a predisposing risk factor of PE disorder, which is in harmony with the findings of others [35–37]. The second exception is the raised BP in the PE group since it is considered one of the hypertensive disorders of pregnancy, which is characterized by BP ≥ 140/90 mmHg; similar findings were reported by other researchers [38,39].

The third exception is the lower FBW in the PE group, which could be explained on the basis that PE is a pregnancy-specific heterogenous systemic disorder, affecting both the mother and the fetus. Maternal syndrome affects fetal well-being, i.e., growth restriction and chronic hypoxia of the fetus. In addition, PE might be associated with premature delivery or abruptio placentae, and is a leading cause of perinatal morbidity and mortality [5]. Moreover, PE is associated with reduced uteroplacental perfusion as a result of abnormal cytotrophoblast invasion. Thus, pathological uteroplacental perfusion predicts a high risk for fetal growth restriction originating from deterioration of placental function [38].

Maternal levels of plasma KP-10 were markedly lower in PE patients when compared with normotensive controls. This finding is consistent with that reported by Adali et al [38] and Ćetković et al [20]. KP-10 and its receptor have been identified in both villous and invasive extravillous human cytotrophoblasts, and it has a prime location at the fetomaternal interface [30,40]. Thus, because KP-10

Table 2
Plasma KP-10 concentrations during the second and third trimesters of pregnancy in patients with preeclampsia versus normotensive pregnant women.

Trimester	KP-10 level (ng/mL)			*p*		
	Normotensive women	Mild PE	Severe PE	Mild versus severe	Mild versus control	Severe versus control
Second	2.30 ± 0.51 (1.22–3.32)	2.18 ± 0.76 (1.10–3.50)	1.59 ± 0.26 (1.14–1.82)	0.004*	0.402	0.0001*
Third	2.95 ± 1.82 (1.31–9.09)	2.16 ± 0.48 (1.52–3.04)	2.39 ± 0.57 (1.57–2.96)	0.137	0.006*	0.243
p	0.016#	0.841	0.0001#			

KP-10 = kisspeptin-10; PE = preeclampsia; SEM = standard error of the mean.
* Significant using Student *t* -test for difference between two independent means at 0.05 level.
# Significant using paired *t* test for difference between two dependent means (2nd and 3rd trimesters) at 0.05 level, values are expressed as mean ± SEM.

Table 3
Correlation between maternal plasma KP-10, and parameters of fetal growth well-being and umbilical artery Doppler velocimetry measurements.

Parameter	Trimester	KP-10 level (ng/mL)		
		Control women	PE patients	
			Mild	Severe
EFW (g)	Second	−0.167	0.146	0.760
FBW(g)		0.058	0.358*	−0.952
S/D ratio		−0.171	−0.123	−0.022
PI		−0.226	−0.020	0.128
RI		−0.264	−0.016	0.865
EFW (g)	Third	0.395	0.165	0.920
FBW(g)		−0.410	0.192	−0.365
S/D ratio		−0.054	−0.326	0.149
PI		−0.037	−0.289	0.175
RI		0.031	−0.294	0.160

* Equals to 0.016. EFW = estimated fetal weight; FBW = fetal birth weight; KP-10 = kisspeptin-10; PE = preeclampsia; PI = pulsatility index; RI = resistance index; S/D ratio = systolic/diastolic ratio.

plays a key role in the regulation of placental invasion, this indicates its importance in the pathophysiology of PE [38].

It was shown that the key role of KP-10 in the regulation of placental invasion is corroborated by elevated levels of placental KiSS-1 mRNA and KP in PE, which is characterized by reduced trophoblast invasion [6,34]. Similarly, Smets et al [24] and Armstrong et al [25] suggested that KP level was significantly lower in maternal plasma during the second trimester in pregnancies that end with subsequent PE as a result of poor placentation characterized by insufficient placental invasion. These findings appear to refute the role of KP-10 in inhibiting invasion. However, this result disagrees with that of Nijher et al [41] who did not find any difference in circulating KP levels between patients with hypertensive diseases of pregnancy and trimester-matched normotensive controls.

It was hypothesized that *in vivo* KP-10 is involved in fine-tuning of placental invasion, in which a high invasive capacity would be

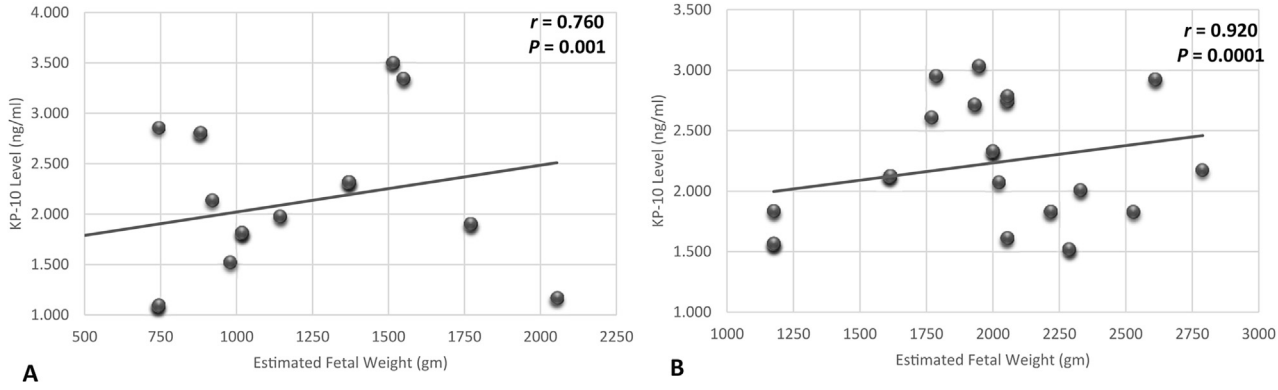

Figure 1. Correlation between plasma KP-10 levels and EFW *in utero* during the (A) second and (B) third trimesters in patients with severe preeclampsia (KP-10 level directly correlated with EFW in the second and third trimesters). EFW = estimated fetal weight; KP = kisspeptin.

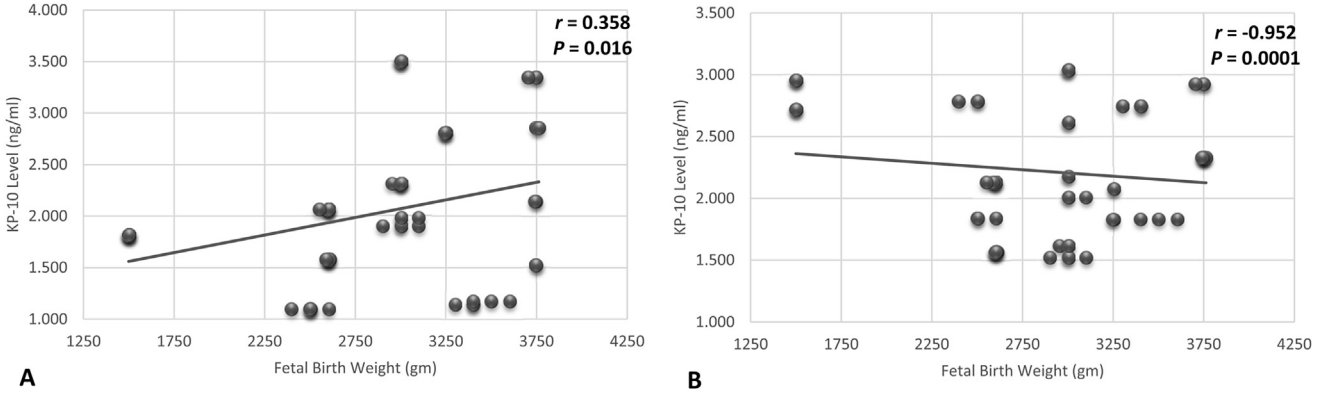

Figure 2. Correlation between plasma KP-10 levels and fetal birth weight during (A) second and (B) third trimesters in patients with preeclampsia (KP-10 level directly correlated with FBW in mild PE and inversely in severe PE during the second trimester). EFW = estimated fetal weight; KP = kisspeptin.

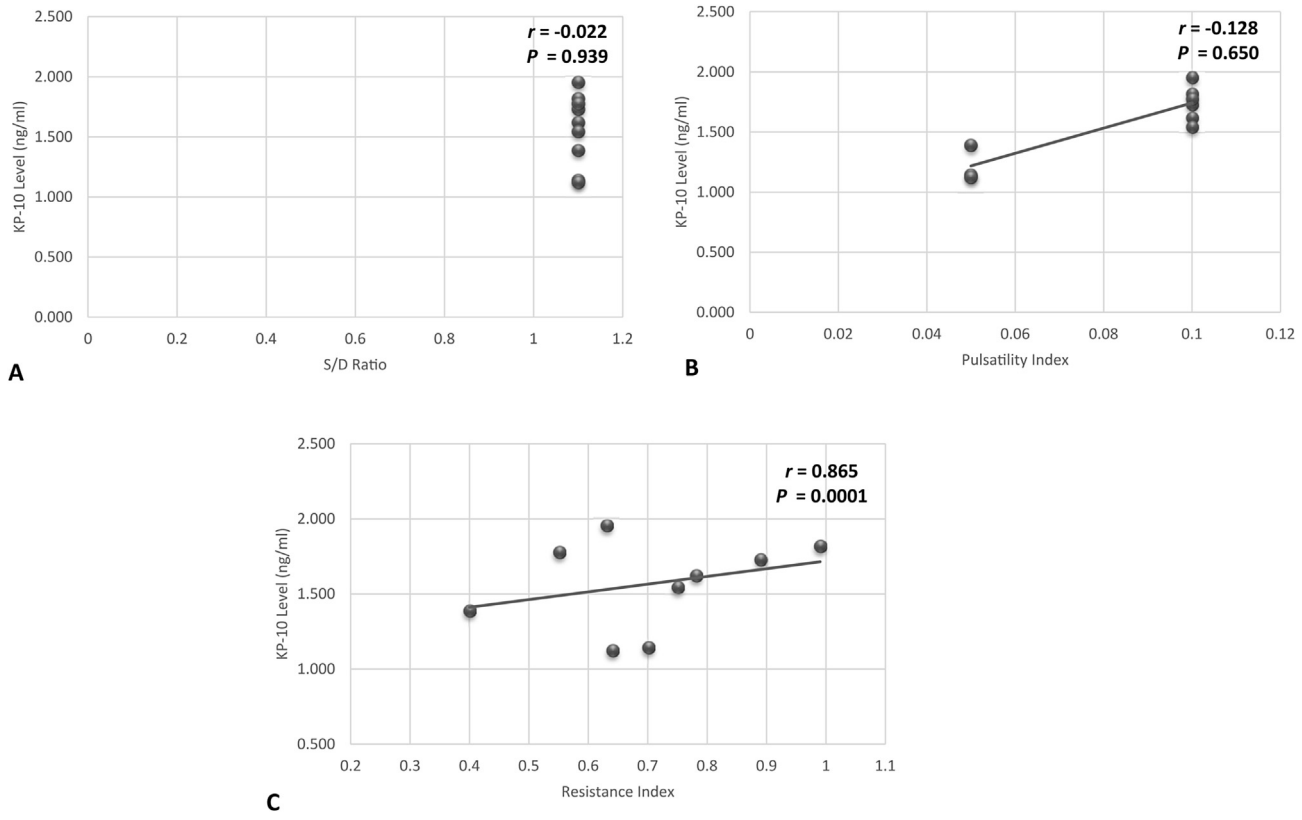

Figure 3. Correlation between plasma KP-10 levels and umbilical artery Doppler study indices, i.e., (A) S/D ratio, (B) PI, and (C) RI, during the second trimester (KP-10 level directly correlated with RI but not with S/D ratio or PI in severe PE). KP = kisspeptin; PE = preeclampsia; PI = pulsatility index; RI = resistance index; S/D = systolic/diastolic.

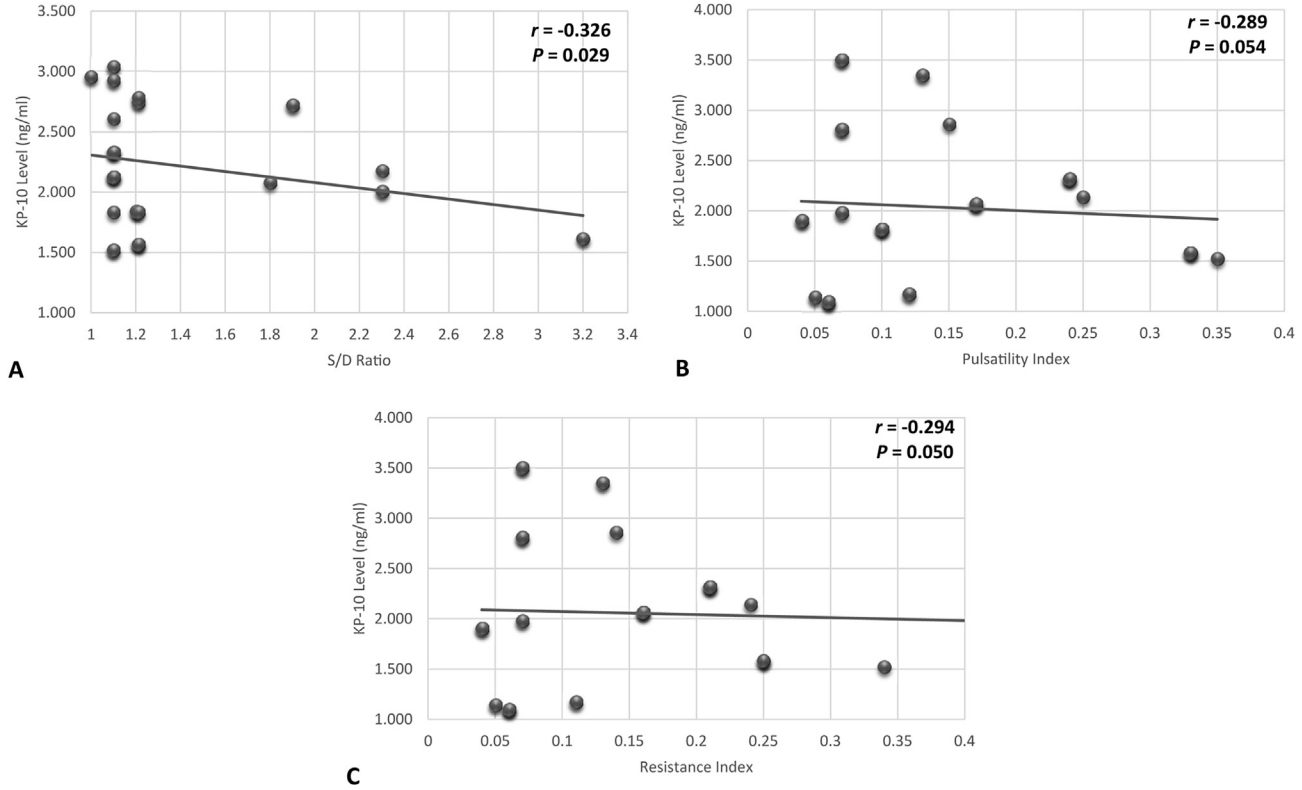

Figure 4. Correlation between plasma KP-10 levels and umbilical artery Doppler study indices, i.e., (A) S/D ratio, (B) pulsatility index, and (C) RI, during the third trimester (KP-10 level inversely correlated with S/D ratio and RI in mild PE). KP = kisspeptin; PE = preeclampsia; RI = resistance index; S/D = systolic/diastolic.

counteracted by the inhibitory effect of high levels of KP-10 and a low expression of KP-10 would signal low invasive capacity [24]. Alternatively, development of smaller, less invasive placentas occurs first, and these produce less KP-10 [42].

C KP-10 concentrations directly correlated with EFW *in utero* during the second and third trimesters in patients with severe form of PE and in normotensive women during the third trimester. These results were consistent with the observations of Ćetković et al [20] and Kavvasoglu et al [22], who found a significant association between reduced KP-10 levels and parameters of placental dysfunction, and pregnancy outcome in pregnancies with PE, i.e., low KP-10 levels correlated with a higher incidence of adverse outcomes and disturbances in fetoplacental circulation, and fetal and placental weights were significantly lower in PE patients.

On the contrary, Lunghi et al [43] and Rampello et al [44] found high KP-10 levels to be associated with low fetal weight (events commonly seen in PE). This is due to deficient uterus/placental blood perfusion that reduces the supply of nutrients from the mother to the growing fetus.

In patients with mild PE and during the second trimester, maternal plasma KP-10 level directly correlated with FBW, a finding that was also reported by Kavvasoglu et al [22]. On the contrary, KP-10 level inversely correlated with FBW in patients with severe PE, which was also noticed by Vazquez-Alaniz et al [45]. Among all KPs, KP-10 has the strongest invasion inhibiting effects, which suggests its major role in regulating trophoblast invasion. This may explain the relationship between its elevated level seen in PE patients and its role in low weight of newborns.

Concerning the umbilical artery Doppler velocimetry study, neither the S/D ratio nor the PI correlated with plasma KP-10 levels in patients with severe PE, whereas the RI had a direct relationship during the second trimester. This finding appears to be recognized in accordance with the results of Zahumensky [5] and Vazquez-Alaniz et al [45], who noticed abnormal parameters of fetoplacental imaging for umbilical artery, reflecting an insufficient flow between the placenta and fetus.

In women with mild PE and during their third trimester of gestation, plasma KP-10 level inversely correlated with the S/D ratio and RI, but not with the PI. This result appears to be in contrast to the activity of KP-10 in inhibiting trophoblast invasion through its action as a vasoconstrictor (a crucial phase in angiogenesis), suggesting a role in the vascular system. A potential angiostatic effect of KP may also explain, at least in part, the antimetastatic potential of this peptide, given that angiogenesis is intimately involved in this process. Angiogenesis is a common feature of implantation and is of vital importance in establishing the placenta [18], which suggests its role in the pathophysiologic changes of PE disorder.

Potentially, KP-10 may act as a local paracrine regulator of vascular tone at the endothelial level. Dysfunctional endothelial cells produce altered quantities of vasoactive mediators, tipping the balance toward vasoconstriction [46]. Thus, an increase in local perivascular production of KP-10 and a decrease in its release from the endothelial cells due to endothelial dysfunction may underlie the compromised vascular reactivity in hypertensive disorders, including PE. It is, therefore, possible that different pathways determine the relationship between KP-10 and physiological processes involving peripheral vascularity [38].

With regard to umbilical artery Doppler velocimetry examination that evaluates intrauterine fetal well-being in high-risk pregnancies, Cartwright and Williams [32] and O'Neill et al [47] reported that with advancing gestational age, the end-diastolic velocity increases secondary to the decrease in placental resistance, which is reflected as a decrease in the S/D ratio or PI. Moreover, Adali et al [38] reported that KP plasma levels in preeclamptic patients with abnormal Doppler velocimetry findings were significantly lower than those in such patients with normal Doppler velocimetry findings. This result suggests that maternal plasma KP-10 level might be a novel marker downregulated in pregnant women with PE, especially in those who had also developed impaired uteroplacental perfusion or intrauterine growth retardation.

In conclusion, the data of this study show that decreased KP-10 levels in women with PE may reflect the severity of the disease and may be a potential marker of pathological uteroplacental perfusion predicting a high risk for fetal growth restriction. However, whether altered KP-10 levels are a cause or a consequence of the disease cannot be determined. Further studies are needed to obtain more information on this topic.

Conflicts of interest

The authors have no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

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