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Maternal serum apelin-13 levels in early- and late-onset preeclampsia

Erken ve geç başlangıçlı preeklampside maternal serum apelin-13 düzeyleri

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Abstract

Objective: To assess whether alterations in maternal serum apelin-13 levels differ between early-onset preeclampsia (EO-PE) and late-onset preeclampsia (LO-PE).

Materials and Methods: A prospective case-control study included 90 preeclamptic cases and 90 normotensive healthy pregnant women as controls. Preeclampsia cases were subclassified as EO-PE and LO-PE. Blood samples were collected, centrifuged, and the separated serum was stored at -80°C for further testing. Ethylenediamine tetraacetic acid blood was used for complete blood count. Serum sample was used for analysis of biochemical parameters. Maternal serum apelin-13 concentrations were measured using ELISA. Demographic details and fetal outcomes were recorded.

Results: Results indicated significantly lower gestational age at sampling and delivery in preeclampsia cases. Blood pressure (systolic, diastolic, and mean arterial pressure) was elevated in preeclampsia. Maternal serum apelin-13 levels (261.7±110.6 pg/mL) were significantly reduced in preeclamptic cases compared to controls (575.3±164.7 pg/mL). Adverse fetal outcomes were more prevalent in preeclampsia. Regarding EO-PE and LO-PE, gestational age at sampling and delivery was lower in EO-PE compared to LO-PE. Maternal serum apelin-13 levels (371.3±116.0 pg/mL) were higher in EO-PE. A 40.9% reduction in apelin-13 levels was observed in LO-PE compared to EO-PE, indicating a gradual reduction in apelin-13 levels in preeclampsia. Adverse fetal outcomes, such as birth weight (1.8±0.5 kg), were lower, and other adverse outcomes were higher in EO-PE compared to LO-PE.

Conclusion: Circulating serum apelin-13 concentration was reduced in preeclampsia and was higher in EO-PE than in LO-PE. Apelin-13 serves as a potential indicator for discriminating early-onset preeclampsia.

Keywords: Apelin-13, adverse fetal outcomes, early-onset preeclampsia, late-onset preeclampsia, vasoconstriction

Öz

Amaç: Erken başlangıçlı preeklampsi (EO-PE) ve geç başlangıçlı preeklampsi (LO-PE) arasında maternal serum apelin-13 düzeylerindeki değişikliklerin farklılık gösterip göstermediğini araştırmak planlanmıştır.

Gereç ve Yöntemler: Bu çalışmaya 90 preeklamptik olgu ve 90 normotansif sağlıklı gebe kontrol olarak dahil edildi. Preeklampsi olguları EO-PE ve LO-PE olarak alt sınıflara ayrıldı. Maternal kan örnekleri toplandı, santrifüj edildi ve serum örnekleri daha ileri testler için -80°C'de saklandı. Tam kan sayımı için etilendiamin tetraasetik asitli kan örnekleri kullanıldı. Serum örneği biyokimyasal parametrelerin analizi için kullanıldı. Maternal serum apelin-13 düzeyleri ELISA yöntemi ile ölçüldü. Demografik bilgiler ve fetal sonuçlar kaydedildi.

Bulgular: Preeklampside örnekleme ve doğum sırasında anlamlı olarak daha düşük gebelik yaşı tespit edildi. Kan basıncı (sistolik, diyastolik ve ortalama arter basıncı) preeklampside anlamlı olarak yüksekti. Maternal serum apelin-13 (261,7±110,6 pg/mL) düzeyleri preeklamptik olgularda anlamlı olarak düşüktü (575,3±164,7 pg/mL). Olumsuz fetal sonuçlar preeklampside daha fazlaydı. EO-PE ve LO-PE ile ilgili olarak, örnekleme ve doğum anındaki

PRECIS: Circulating maternal serum apelin-13 concentrations were low in preeclampsia. The levels of early-onset preeclampsia were higher, indicating that apelin-13 serves as an indicator for discriminating early-onset preeclampsia.

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gebelik yaşı EO-PE'de LO-PE'den anlamlı olarak düşüktü. Maternal serum apelin-13 (371,3±116,0 pg/mL) düzeyleri EO-PE'de LO-PE'den anlamlı olarak yüksekti. Başka bir deyişle, LO-PE'de EO-PE'ye göre apelin-13 düzeylerinde %40,9 azalma gözlendi, bu da preeklampside apelin-13 düzeylerinin kademeli olarak azaldığını göstermektedir. Doğum ağırlığı (1,8±0,5 kg) EO-PE'de LO-PE'den düşüktü, diğer olumsuz fetal sonuçlar ise EO-PE'de LO-PE'den fazlaydı.

Sonuç: Dolaşımdaki maternal serum apelin-13 düzeyleri preeklampside düşüktü. Düzeyler EO-PE'de LO-PE'den anlamlı olarak daha yüksekti. Apelin-13'ün erken başlangıçlı preeklampsinin ayrımında belirteç görevi gördüğü kanıtlanmıştır.

Anahtar Kelimeler: Apelin-13, olumsuz fetal sonuçlar, erken başlangıçlı preeklampsi, geç başlangıçlı preeklampsi, vazokonstriksiyon

Introduction

Preeclampsia (PE) is a pregnancy-specific complication associated with the onset of hypertension and proteinuria after 20 weeks of gestational age[1]. The prevalence of PE is around 2-8% globally and 10.3% in India[2].

Based on the time of onset or delivery, PE has been sub-classified into early-onset PE (EO-PE), which requires delivery ≤34 weeks of gestational age, and late-onset PE (LO-PE), with delivery ≥34 weeks of gestational age. The EO-PE and LO-PE have different etiopathogenesis and outcomes. Hence, PE can be treated in two different forms. However, there are some uncertainties regarding pregnancy outcomes. EO-PE is mainly linked to improper placentation and abnormal remodeling of spiral arteries, which usually occurs during the first half of pregnancy. Placental dysfunction results in increased secretion of inflammatory and antiangiogenic factors into the circulation, causing PE. Whereas in fetuses, this will result in utero-placental circulatory issues, intrauterine fetal growth restriction (IUGR), or intrauterine death (IUD), posing increased risk to mother and fetus, whereas LO-PE may be due to predisposing maternal factors[1,3]. It was reported that EO-PE is linked to adverse maternal/perinatal outcomes, whereas LO-PE is usually not as severe. The incidence of abnormal placentation, overall mortality, and IUGR has been shown to be associated with PE severity and its duration[4,5]. This novel concept provides better knowledge of the PE etiopathogenesis mechanism. Understanding this concept will increase awareness of disease severity and facilitate better maternal and fetal outcomes.

Despite the considerable maternal and fetal complications, the exact mechanism of PE remains unclear. However, PE is a multisystem disorder with possible underlying pathophysiological mechanisms like abnormal placentation, shallow remodeling of spiral arteries, systemic inflammation, endothelial dysfunction, and hemodynamic alterations during pregnancy[3,5].

Studies have reported that Apelin is an angiogenic molecule essential for blood vessel growth and endothelial cell proliferation[6,7]. In humans, the *APLN* gene, located on chromosome Xq25-26.1, contains 3 exons and 1 intron, and it produces short fragments of apelin peptides. In the biosynthesis of apelin, the precursor preproapelin is sequentially cleaved to generate short peptides such as apelin-36, apelin-17, apelin-13, and (Pyr1) apelin-13. All of these short peptides show agonistic activity on the apelin receptor (APJ/APLNR receptor). Among these, apelin-13 is biologically more active and causes vasodilation[8].

Apelinergic system role in cardiovascular diseases is reported [9]. Whereas, apelinrole in PE has not been explored much. Expression of apelin and APJ/APLNR are expressed in human tissues, with increased concentrations observed in placenta[10,11]. In addition, the apelinergic system is associated with the regulation of vascular bore size and integrity[7]. Apelin induces nitric oxide (NO)-dependent vasodilation, apoptosis, and decreases vascular inflammation[7,12].

A few studies have reported that apelin and the APJ/APLNR receptor are targeted for the treatment of cardiovascular diseases and increased blood pressure[13,14]. In addition, studies have reported an association between apelin and pregnancy diseases like PE, gestational diabetes and IUGR[15-17].

Abnormal placentation is a key pathophysiological mechanism in PE development, especially EO-PE. Therefore, there is a need to establish markers for the early detection of PE. To our knowledge, this is the first report to assess maternal serum apelin-13 (a biologically active peptide) concentration in EO-PE and LO-PE in PE patients in Southern India. We aimed to investigate whether changes in maternal serum apelin-13 levels differ between EO-PE and LO-PE.

Materials and Methods

This prospective case-control study was conducted at the biochemistry department in association with the obstetrics and gynecology department of RL Jalappa Hospital and Research Center, Sri Devaraj Urs Medical College, a constituent institute of Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India. The sample size was calculated with 80% power and a 95% confidence interval. A total of 180 participants were recruited after obtaining ethics committee approval Sri Devaraj Urs Academy of Higher Education and Research Central Ethics Comnittee (decision no: SDUAHER/KLR/CEC/34/2018-2019, date: 14.05.2018) and informed consent. The study subjects were divided into 90 preeclamptic cases and 90 healthy (normotensive) pregnant controls. Furthermore, the PE cases were sub-classified into EO-PE (n=45), requiring delivery ≤34 weeks of gestation, and LO-PE (n=45), with delivery ≥34 weeks of gestation. PE was diagnosed based on ACOG guidelines[18].

Results

Table 1 presents demographic, hematological, and biochemical parameters. The results showed a lower gestational age at sampling (34.1±2.2 weeks) and at delivery (35.2±2.1 weeks) in PE compared to normotensive healthy pregnant

Table 1. Demographic details, haematological and biochemical parameters of preeclampsia and normotensive healthy pregnant women

Parameters	Preeclampsia (n=90) (mean ± SD)	Normotensive healthy pregnant women (n=90) (mean ± SD)	p
Demographic details			
Age (years)	23.0±3.5	23.4±3.2	0.290
Primigravida (n, %)	70 (77.7%)	66 (73.3 %)	-
Multigravida (n, %)	20 (22.2%)	24 (26.6%)	-
Gestational age at sampling (weeks)	34.1±2.2	38.1±1.2	0.000*
Gestational age at delivery (weeks)	35.2±2.1	38.2±1.1	0.000*
SBP (mmHg)	159.1±16.6	116.4±7.8	0.000*
DBP (mmHg)	102.4±11.5	74.7±6.3	0.000*
MAP (mmHg)	120.9±11.7	88.5±6.2	0.000*
Presence of proteinuria (n, %)	90 (100%)	-	-
Haematological parameters			
Hb (g%)	11.1±2.0	11.3±1.4	0.784
WBC (10^3/L)	12.7±3.3	13.4±4.2	0.503
Platelet count x (10^9/L)	221.2±75.5	242.8±60.2	0.147
Biochemical parameters			
RBS (mg/dL)	84.1±21.2	83.6±16.9	0.549
Serum urea (mg/dL)	17.1±10.4	14.5±4.6	0.185
Serum creatinine (mg/dL)	0.57±0.22	0.47±0.11	0.000*
Serum uric acid (mg/dL)	5.9±1.8	4.7±1.4	0.000*
Serum AST (IU/L)	27.9±17.7	20.5±7.9	0.000*
Serum ALT (IU/L)	20.1±12.2	13.7±6.8	0.000*
Maternal serum apelin-13 (pg/mL)	261.7±110.6	575.3±164.7	0.000*

*: Statistically significant, SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, Hb: Haemoglobin, WBC: White blood cells, RBS: Random blood sugar, AST: Aspartate transaminase, ALT: Alanine transaminase

women. Systolic blood pressure (SBP) (159.1±16.6 mmHg), diastolic blood pressure (102.4±11.5 mmHg), mean arterial pressure (120.9±11.7 mmHg), serum creatinine (0.57±0.22 mg/dL), serum uric acid (5.9±1.8 mg/dL), serum aspartate aminotransferase (27.9±17.7 IU/L), and serum alanine aminotransferase (20.1±12.2 IU/L) levels were significantly elevated in PE compared to healthy pregnant women. Proteinuria was observed in all preeclamptic subjects. Serum apelin-13 (261.7±110.6 pg/mL) levels were significantly lower in PE cases than in healthy pregnant women.

Table 2 depicts the adverse fetal outcomes, which were higher in babies born to preeclamptic mothers, including low birth weight (2.2±0.6 kg), babies requiring neonatal intensive care unit (NICU) admission (42, 46.6%), respiratory distress syndrome (RDS) (29, 32.2%), low birth weight (LBW) (19, 21.1%), and IUD (11, 12.2%).

Table 3 describes the demographic details, hematological, and biochemical parameters of EO-PE and LO-PE. Maternal age was significantly higher in EO-PE (23.9±3.5 years) compared to LO-PE. Gestational age at sampling (31.5±1.7 weeks) and at delivery (32.6±1.2 weeks) was significantly lower in EO-PE (31.0±3.0 weeks) compared to LO-PE. Serum urea (19.8±12.9 mg/dL), serum creatinine (0.62±0.25 mg/dL), and serum uric acid (6.2±1.8 mg/dL) levels were higher in early-onset PE than in late-onset PE. In the subgroup analysis, serum apelin-13 (371.3±116.0 pg/mL) levels were higher in EO-PE than in LO-PE. A 40.9% reduction in apelin-13 levels was observed in LO-PE compared to EO-PE, indicating a gradual reduction in apelin-13 concentration in PE.

Table 4 presents the adverse fetal outcomes in babies born to mothers with EO-PE and LO-PE. Birth weight (1.8±0.5 kg) was lower in early-onset PE than in late-onset PE. Other adverse outcomes, such as babies requiring NICU admission (32, 71.1%), RDS (20, 44.4%), LBW (18, 40%), and IUD (8, 17.7%), were more common in EO-PE.

Table 2. Comparison of birth weight and adverse foetal outcomes in babies born to mother with preeclampsia and normotensive healthy pregnant women

Parameters (n, %)	Preeclampsia (n=90)	Normotensive healthy pregnant women (n=90)
Birth weight (kg)	2.2±0.6	2.8±0.4a*
Respiratory distress syndrome	29 (32.2%)	6 (6.6%)
Low birth weight	19 (21.1%)	5 (5.5%)
New borns requiring NICU Admission	42 (46.6%)	16 (17.7%)
Intrauterine death	11 (12.2%)	-

[a]: Mean±SD ($p<0.05$), *: Statistically significant, NICU: Neonatal intensive care unit

Table 3. Demographic details, haematological and biochemical parameters of EO-PE and LO-PE

Parameters	EO-PE (n=45), mean ± SD	LO-PE (n=45), mean ± SD	p
Demographic details			
Age (years)	23.9±3.5	22.1±3.3	0.003*
Primigravida (n, %)	31 (68.8%)	39 (86.6%)	-
Multigravida (n, %)	14 (31.1%)	6 (13.3%)	-
Gestational age at sampling (weeks)	31.5±1.7	36.0±1.3	0.000*
Gestational age at delivery (weeks)	32.6±1.2	36.2±1.1	0.000*
SBP (mmHg)	162.0±16.8	156.2±15.9	0.094
DBP (mmHg)	103.3±12.0	101.5±11.0	0.520
MAP (mmHg)	122.0±11.8	119.9±11.6	0.292
Presence of proteinuria (n, %)	45 (100%)	45 (100%)	-
Pulse rate (bpm)	88.4±6.0	88.1±6.1	0.549
Haematological parameters			
Hb (g%)	10.9±2.0	11.2±1.9	0.675
WBC (10^3/L)	12.1±3.5	13.4±3.0	0.030*
Platelet count x (10^9/L)	205.1±88.1	237.2±56.8	0.125
Biochemical parameters			
RBS (mg/dL)	86.2±25.6	82.0±15.6	0.732
Serum urea (mg/dL)	19.8±12.9	14.4±6.2	0.024*
Serum creatinine (mg/dL)	0.62±0.25	0.51±0.18	0.006*
Serum uric acid (mg/dL)	6.2±1.8	5.6±1.8	0.045*
Serum AST (IU/L)	30.0±15.8	25.8±19.4	0.065
Serum ALT (IU/L)	21.2±13.6	19.0±10.7	0.523
Maternal serum apelin-13 (pg/mL)	371.3±116.0	152.2±47.9	0.000*

*: Statistically significant, SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, Hb: Haemoglobin, WBC: White blood cells, RBS: Random blood sugar, AST: Aspartate transaminase, ALT: Alanine transaminase, EO-PE: Early-onset preeclampsia, LO-PE: Late-onset preeclampsia

Table 4. Comparison of birth weight and adverse foetal outcomes in babies born to mother with EO-PE and LO-PE

Parameters (n, %)	EO-PE (n=45)	LO-PE (n=45)
Birth weight (kg)	1.8±0.5	2.6±0.5[a*]
Respiratory distress syndrome	20 (44.4%)	9 (20%)
Low birth weight	18 (40%)	1 (2.2%)
Newborns requiring NICU admission	32 (71.1%)	10 (22.2%)
Intrauterine death	8 (17.7%)	3 (6.6%)

[a]: Mean ± SD, ($p<0.05$), *:Statistically significant, NICU: Neonatal intensive care unit EO-PE: Early-onset preeclampsia, LO-PE: Late-onset preeclampsia

Discussion

PE is a pregnancy-specific and life-threatening disorder. The placenta plays a crucial role in the pathophysiology of such diseases and is regarded as the source of inflammation. It secretes vasoconstrictor molecules into the maternal circulation, initiating endothelial cell dysfunction and vasospasm[19].

In this study, serum apelin-13 concentration was measured to evaluate its usefulness as a discriminative biomarker to differentiate between early-onset PE (EO-PE) and late-onset PE (LO-PE). The results indicated reduced apelin-13 levels in PE compared to healthy pregnant women. In the subgroup analysis, apelin-13 concentrations were higher in EO-PE than in LO-PE. In other words, a 40.9% reduction in apelin-13 levels was observed in LO-PE compared to EO-PE, suggesting a gradual reduction in serum apelin-13 levels from EO-PE to LO- PE. In line with our previous studies, we reported significantly lower serum apelin-13 levels in PE compared to healthy pregnant women[15,19].

Similar to our findings, a study by Deniz et al.[20] demonstrated that apelin and NO levels were lower in PE compared to healthy pregnant women. Another study by Sattar Taha et al.[21] reported decreased apelin levels in PE compared to healthy pregnant women. Inzukua[22] found reduced mRNA expression of apelin in the placenta of preeclamptic women and decreased immune-histochemical signals for the apelin/APJ receptor.

Regarding EO-PE and LO-PE. Kucur et al.[3] reported increased circulating levels of apelin in EO-PE compared with LO-PE. However, the authors reported total apelin concentration rather than bioactive short peptides/fragments[23]. In this study, we observed significantly elevated serum apelin-13 (biologically active peptide) levels in EO-PE compared with LO-PE. Therefore, this reduced bioactive apelin-13 concentration may affect the trophoblast invasion of spiral arteries. These abnormalities in the remodeling of spiral arteries cause high-resistance utero-placental circulation, as seen in PE[24].

Although apelin peptides in PE have been recently studied, the possible discriminative role of apelin-13 in EO-PE and LO-PE has not yet been established. The human placenta is a tissue where angiogenesis, blood pressure, and flow are essential for promoting embryonic development and fetal growth. It has been reported that, in normal pregnancy, placental expression of apelin is higher, indicating its role in placentation[25]. Apelin favors angiogenesis, stimulates blood vessel growth and differentiation, and regulates blood pressure and flow[5].

Based on the current study findings, maternal serum apelin-13 may serve as a discriminative marker between EO-PE and LO-PE. EO-PE is usually linked with improper placentation and subsequent hypoxic placenta, which causes the activation of a cascade of events, such as an imbalance between angiogenic and anti-angiogenic factors, increased oxidative stress, dysfunctional endothelium, and immunological dysregulation, ultimately leading to the clinical manifestation and complications of PE[26-29]. LO-PE is linked with normal placentation and utero-placental perfusion, resulting in better perinatal outcomes[27].

In this study, adverse fetal outcomes were higher in EO-PE compared to LO-PE, including decreased birth weight, babies requiring NICU admission, RDS, and low birth weight. In accordance with our findings, Akbar et al.[27] reported that EO-PE is associated with poor maternal and perinatal outcomes.

It is well known that an imbalance between angiogenic and anti-angiogenic markers is associated with PE complications[30-32]. Numerous pro-angiogenic and anti-angiogenic markers play significant roles in the development of the placental vascular bed, especially vascular endothelial growth factor (VEGF). The levels of VEGF have been shown to be reduced in EO-PE[33,34]. It has been reported that the apelinergic system promotes the expression of VEGF. Therefore, the reduced apelin-13 concentration in PE may result in reduced VEGF levels, playing a significant role in the development of abnormal placentation associated with EO-PE[23].

Study Limitations

The main limitation of this study was the sample size, screening for placental expression of apelin and other confounding factors, such as lifestyle parameters and genetic and epigenetic factors.

Conclusion

The current study may conclude that circulating maternal serum apelin-13 concentrations were lower in PE than in normotensive pregnant women. The levels were higher in EO-PE than in LO-PE, indicating the role of apelin in discriminating EO-PE. Further studies with larger sample sizes are recommended to investigate its precise role in EO-PE and LO-PE, treatment strategies for PE management.

Ethics

Ethics Committee Approval: The study was approved by the Sri Devaraj Urs Academy of Higher Education and Research Central Ethics Committee (decision no: SDUAHER/KLR/CEC/34/2018-2019, date: 14.05.2018)

Informed Consent: All participants provided informed consent before entering the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S.R, Concept R.G., D.C.D., S.S.R, Design R.G., D.C.D., S.S.R, Data Collection or Processing: R.G., D.C.D., S.S.R, Analysis or Interpretation R.G., D.C.D., S.S.R, Literature Search: R.G., D.C.D., S.S.R, Writing: R.G., D.C.D., S.S.R.

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