Relationship of Serum Nesfatin-1 and Insulin-Like Growth Factor-1 Levels with Adverse Pregnancy Outcomes in Patients with Polycystic Ovary Syndrome

Yanyan Wang[1], Rui Li[1], Binzhou Sun[1], Weifu Song[1], Xin Zhao[2] and Yanqiong Hu[1]

[1]*Department of General Gynaecology, Maternity & Child Care Center of Qinhuangdao, Hebei, China*
[2]*Department of Women's Tumour, Maternity & Child Care Center of Qinhuangdao, Hebei, China*

ABSTRACT

Objective: To investigate the relationship between serum nesfatin-1 and insulin-like growth factor-1 (IGF-1) levels and adverse pregnancy outcomes (APOs) in patients with polycystic ovary syndrome (PCOS).

Study Design: Observational study.

Place and Duration of the Study: The study was performed from June 2021 to 2023 in the General Gynaecology section at the Maternity & Child Care Center of Qinhuangdao, Hebei, China.

Methodology: A total of 120 pregnant women with PCOS were divided into the control and study groups. The control group consisted of 70 pregnant women who successfully delivered healthy newborns, whereas the study group included 50 pregnant women who experienced APOs. The serum nesfatin-1 and IGF-1 levels in both groups were measured upon admission. The potential influencing factors of APOs in pregnant women with PCOS and the predictive value of serum nesfatin-1 and IGF-1 for APOs were analysed.

Results: Serum nesfatin-1 and IGF-1 levels were significantly higher in the study group than in the control group ($p < 0.05$). Multivariate analysis revealed that testosterone ≥45 μg/L, body mass index ≥25 kg/m², waist-hip ratio ≥0.80, gestational diabetes mellitus, nesfatin-1, and IGF-1 were independent risk factors of APOs in patients with PCOS. The AUC for IGF-1 plus nesfatin-1 in predicting APOs in pregnant women with PCOS was 0.900 (95% CI: 0.845, 0.955).

Conclusion: Elevated serum nesfatin-1 and IGF-1 levels are associated with pregnancy outcomes of patients with PCOS.

Key Words: *Polycystic ovary syndrome, Nesfatin-1, Insulin-like growth factor-1, Adverse pregnancy outcome.*

How to cite this article: Wang Y, Li R, Sun B, Song W, Zhao X, Hu Y. Relationship of Serum Nesfatin-1 and Insulin-Like Growth Factor-1 Levels with Adverse Pregnancy Outcomes in Patients with Polycystic Ovary Syndrome. *J Coll Physicians Surg Pak* 2024; **34(10)**:1425-1429.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common complex endocrine disorder among women characterised by reproductive dysfunction and abnormal glucose metabolism.[1] Notably, insulin resistance is detected in over 50% of PCOS cases. The pathogenesis of PCOS remains unclear. Existing literature revealed associations between insulin resistance, hypothalamic-pituitary dysfunction, environmental factors, and psychological factors.[2] PCOS affects reproductive function and predisposes individuals to diabetes, dyslipidaemia, and hyperlipidaemia, thereby increasing the risk of cardiovascular diseases and gynaecological tumours.[3]

Correspondence to: Dr. Yanyan Wang, Department of General Gynaecology, Maternity & Child Care Center of Qinhuangdao, Hebei, China
E-mail: 15076088397@163.com

Received: April 30, 2024; Revised: September 03, 2024; Accepted: September 20, 2024
DOI: https://doi.org/10.29271/jcpsp.2024.10.1425

The effect of PCOS on reproductive function may lead to adverse pregnancy outcomes, such as miscarriage, stillbirth, premature delivery, low-birth-weight infants, macrosomia infants, congenital abnormalities, intrauterine growth retardation, neonatal asphyxia, and neonatal death.[4] Nesfatin-1, an emerging adipokine, has been shown to stimulate adenosine monophosphate-activated protein kinase phosphorylation and thus inhibit hepatic gluconeogenesis and modulate insulin resistance levels.[5] Studies have demonstrated alterations in insulin-like growth factor-1 (IGF-1) expression levels in patients with PCOS.[6] IGF-1, a critical regulator of cell proliferation and differentiation, plays a crucial role in individual growth and development. This study's objective was to assess the nesfatin-1 and IGF-1 levels of pregnant women with PCOS, determine the expression levels of clinical parameters in patients with different pregnancy outcomes, and the relationship between adverse pregnancy outcomes (APOs) with nesfatin-1, IGF-1 and other parameters, aiming to investigate the relationship between serum nesfatin-1 and IGF-1 levels and APOs in patients with PCOS.

METHODOLOGY

This study was performed on 120 pregnant women diagnosed with PCOS who visited the Obstetrics and Gynaecology Depart-

ment of the Maternity & Child Care Center of Qinhuangdao, Hebei, China, between June 2021 and 2023. Specifically, 70 pregnant women who successfully delivered healthy newborns were classified as the control group and 50 pregnant women who experienced APOs as the study group. In this study, the women were considered to have an adverse pregnancy outcome if they had either miscarriage, stillbirth, premature delivery, low-birth-weight infants, macrosomia infants, congenital malformation, intrauterine growth retardation, neonatal asphyxia, or neonatal death. The study was approved by the Ethics Committee of the Maternity & Child Care Center of Qinhuangdao, Hebei, China (Approval No. 20210512; Dated: 12 May 2021). Written informed consent was obtained from all participants.

The criteria for inclusion in this study were diagnosis according to the diagnostic criteria for PCOS established at the Rotterdam Conference in 2003;[7] presence of typical symptoms such as hirsutism, hyperandrogenism, and oligo-ovulation or anovulation; age between 22 and 35 years; successful pregnancy following relevant treatments at the study centre; and full understanding of the study and provision of a signed informed consent form. Women with concurrent systemic infectious diseases, concurrent benign or malignant gynaecological tumours, severe liver or kidney dysfunction, and other factors leading to infertility and / or comorbid psychiatric disorders were excluded.

The study examined age, testosterone (T) levels, use of gonadotropins, luteinizing hormone (LH) levels, waist-hip ratio (WHR), body mass index (BMI), comorbid gestational diabetes mellitus (GDM), comorbid gestational hypertension (GH), and the duration of infertility. Patient data were obtained by dedicated personnel through the hospital medical record system.

All pregnant women had 8 ml of venous blood drawn before delivery and 8 ml of umbilical venous blood immediately after delivery. The samples were centrifuged for 10 minutes at 3000 rpm using a Hitachi low-speed centrifuge with a centrifugation radius of 6 cm. The supernatant was harvested and stored in a freezer. An enzyme-linked immunosorbent assay was conducted using a fully automated biochemical analyser (Mindray Bio-Medical Electronics, China) and assay kits (JonIn Biotechnology, China) to determine the serum nesfatin-1 and IGF-1 levels in both groups.

Data analysis was performed using the statistical software SPSS 22.0. Categorical data were expressed as n (%) and analysed using the Chi-square test. Measurement data conforming to a normal distribution were represented by mean ± standard deviation ($\bar{x} \pm s$), and comparisons between groups were examined using the student's t-test. Pearson's correlation analysis was performed to analyse the correlation between serum nesfatin-1 and IGF-1 levels and APOs in pregnant women with PCOS. The following parameters were subjected to multivariate logistic regression analysis to identify the influencing factors of pregnancy outcomes in pregnant women with PCOS: Age, duration of infertility, total amount of gonadotropin use, LH level, T level, BMI, WHR, GH, GDM, and serum nesfatin-1 and serum IGF-1 levels. Receiver operating characteristic (ROC) curves were plotted, and the area under the curve (AUC) was obtained to analyse the predictive value of serum nesfatin-1 and IGF-1 levels for APOs. A value of $p < 0.05$ indicated statistical significance.

RESULTS

Pregnant women in the study group, including 52 primiparas and 18 multiparas, were aged 22-35 years (average age: 27.86 ± 2.37 years). Pregnant women in the control group, including 42 primiparas and 8 multiparas, were aged 22-34 years (average age: 27.45 ± 2.42 years). No significant differences were noted in age or parity between the two groups ($p > 0.05$), indicating high comparability.

Significant differences were found in LH, T, WHR, BMI, and GDM between the study and control groups ($p < 0.05$, Table I).

The serum nesfatin-1 and IGF-1 levels in the study group were significantly higher than those in the control group ($p < 0.05$, Table II). The Pearson's analysis results showed a correlation between nesfatin-1 and IGF-1 levels and APOs, with correlation coefficients of 0.439 and 0.623, respectively ($p < 0.05$).

Multivariate analysis revealed that T ≥45 μg/L, BMI ≥25 kg/m², WHR ≥0.80, GDM, nesfatin-1, and IGF-1 were independent risk factors for APOs in patients with PCOS (Table III).

Using SPSS 24.00, ROC curves for nesfatin-1 and IGF-1 were constructed to predict APOs in pregnant women with PCOS. The results showed that the AUC for nesfatin-1 in predicting APOs was 0.773 (95% CI: 0.683, 0.8863). The optimal cut-off for prediction was 2.29 μg/L, with a maximum Youden's index of 0.654, sensitivity of 0.840, and specificity of 0.814. The AUC for IGF-1 in predicting APOs was 0.847 (95% CI: 0.774, 0.920). The optimal cut-off for prediction was 245.20 μg/L, with a maximum Youden's index of 0.614, sensitivity of 0.700, and specificity of 0.914. The AUC for IGF-1 plus nesfatin-1 in predicting APOs was 0.900 (95% CI: 0.845, 0.955), with a maximum Youden's index of 0.677, sensitivity of 0.920, and specificity of 0.757 (Figure 1).

DISCUSSION

PCOS is a common gynaecological and endocrine disorder characterised by menstrual irregularities, amenorrhoea and infertility. Patients with PCOS typically present with oligo-ovulation, hyperandrogenism, and hirsutism.[8] The definite pathogenesis of PCOS remains unclear; however, many studies have confirmed insulin resistance as a significant contributor to PCOS development. Insulin resistance is associated with hyperandrogenism in patients with PCOS, leading to ovarian dysfunction, metabolic disturbances, and an increased forward risk of cardiovascular diseases and fatty liver.[9] Although pregnant women with PCOS can achieve successful conception, the incidence of pregnancy complications (e.g. GDM and GH) and APOs (e.g. premature birth and neonatal emergencies) is significantly higher compared to normal pregnancies.[10] As supported by various studies, it is believed that PCOS is strongly associated with APOs.

Table I: Comparison of clinical parameters between the two groups (n).

Item		Control group (n = 70)	Study group (n = 50)	χ^2	p*
Age (years)	<30	53 (75.71)	37 (74.00)	0.05	0.83
	≥30	17 (24.29)	13 (26.00)		
T (μg/L)	<45	65 (92.86)	30 (60.00)	19.09	<0.01
	≥45	5 (7.14)	20 (40.00)		
Use of gonadotropin (ml/vial)	<25	10 (14.29)	11 (22.00)	1.20	0.27
	≥25	60 (85.71)	39 (78.00)		
LH (μg/L)	<5	33 (47.14)	7 (14.00)	14.42	<0.01
	≥5	37 (52.86)	43 (86.00)		
WHR	<0.80	60 (85.71)	17 (34.00)	33.92	<0.01
	≥8.0	10 (14.29)	33 (66.00)		
BMI (kg/m²)	<25	55 (78.57)	20 (40.00)	18.51	<0.01
	≥25	15 (21.43)	30 (60.00)		
GDM	Yes	5 (7.14)	20 (40.00)	19.09	<0.01
	No	65 (92.86)	30 (60.00)		
GH	Yes	15 (21.43)	7 (14.00)	1.08	0.30
	No	55 (78.57)	43 (86.00)		
Duration of infertility	<5	60 (85.71)	40 (80.00)	0.69	0.41
	≥5	10 (14.29)	10 (20.00)		

** χ^2 test.*

Table II: Comparison of serum nesfatin-1 and IGF-1 levels between the two groups ($\bar{x}\pm s$).

Group	Nesfatin-1 (μg/L)	IGF-1 (μg/L)
Control group (n = 70)	2.03 ± 0.42	219.21 ± 24.64
Study group (n = 50)	2.41 ± 0.33	268.10 ± 37.26
t	-5.31	-8.65
p△	<0.01	<0.01

Independent-sample t-test.

Table III: Factors influencing pregnancy outcomes in women with PCOS.

Factor	B	S.E.	Wald χ^2	p-value	OR	95% CI
T	2.727	0.926	8.673	0.003	15.292	2.490 - 93.921
LH	1.325	0.824	2.583	0.108	3.762	0.748 - 18.935
WHR	2.519	0.898	7.866	0.005	12.413	2.135 - 72.162
BMI	1.393	0.679	4.203	0.040	4.025	1.063 - 15.237
GDM	2.617	1.117	5.489	0.019	0.073	0.008 - 0.652
Nesfatin-1	2.087	0.941	4.922	0.027	8.058	1.275 - 50.920
IGF-1	2.179	0.785	7.708	0.005	8.838	1.898 - 41.153

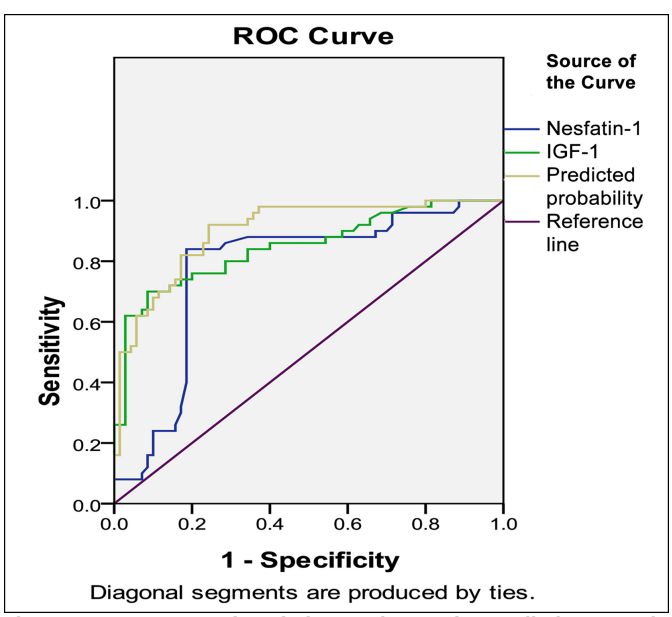

Figure 1: ROC curves of nesfatin-1 and IGF-1 for predicting APOs in pregnant women with PCOS.

In healthy women, physiological insulin resistance may occur during a normal pregnancy, reducing the utilisation of glucose in the metabolic process and increasing fat breakdown and gluconeogenesis, thus shifting the body's basic energy metabolism from glucose to fatty acids. This facilitates glucose transfer into the foetus and maintains normal blood sugar levels. Current studies indicate that in patients with PCOS, increased secretion of hormones, namely oestrogen, prolactin, and human placental lactogen, leads to disrupted glucose metabolism, resulting in hyperinsulinaemia and insulin resistance.[11] Peripheral tissues become less sensitive to insulin, leading to compensatory hyperinsulinaemia. Studies have shown that elevated insulin levels can stimulate cytochrome P45017α hydroxylase activation in ovarian cells, promoting the conversion of pregnenolone to T and androstenedione.[12] Notably, high insulin levels can increase the sensitivity of pituitary cells to gonadotropins, elevate androgen secretion levels, and inhibit the hepatic synthesis of sex hormone-binding globulin, resulting in difficulty in lowering free androgen levels in the blood and various adverse outcomes in PCOS.[13]

In patients with PCOS, menstrual irregularities and infertility are caused by ovulatory dysfunction. Previous studies on patients with PCOS mainly focused on hormones such as follicle-stimulating hormone(FSH), LH, and T. These hormones can function normally under the regulation of the hypothalamic-pituitary-gonadal axis.[14] Further research on PCOS found that LH secretion in pituitary cells increases in patients with PCOS. In cases of ovulatory dysfunction in patients with PCOS, dominant follicles fail to form in the ovaries, which induces feedback stimulation of LH secretion and inhibits FSH secretion, causing elevated LH and reduced FSH levels. IGF-1, a member of the insulin-like growth factor family, is a single-chain protein composed of 70 amino acid residues. Besides its involvement in the signal transduction mediated by insulin receptors, studies have shown that IGF-1 is crucial in diverse biological processes in the body.[15] For example, IGF-1 plays a regulatory role in cell differentiation and proliferation and participates in the synthesis of lipids, proteins, and glycogens. Additionally, at physiological concentrations, IGF-1 regulates follicular development. Related studies have reported elevated IGF-1 expression in patients with insulin resistance, manifested by amplification of the IGF-1 signalling pathway, while the insulin-stimulated glucose metabolism pathway is blocked.[6] Some studies have confirmed the accuracy of serum IGF-1 levels in predicting APOs in patients with severe preeclampsia, revealing that abnormal IGF-1 expression level is associated with APOs.[16] In the present study, IGF-1 expression was higher in the study group than in the control group, which is consistent with the conclusion of previous studies. This indicates that the potential mechanism of APOs is associated with insulin resistance and hyperinsulinaemia. Individuals with insulin resistance and hyperinsulinaemia have higher blood glucose levels and abnormal glucose metabolism. Glucose can be transported through the placental barrier to the foetus, leading to elevated foetal blood glucose levels. Insulin cannot pass through the placental barrier; hence, prolonged high-level blood glucose can promote the proliferation of foetal islets, causing increased insulin secretion, amino acid transfer system activation, significantly increased lipid and protein synthesis and reduced lipid and protein metabolism, and breakdown. This eventually results in increased deposition of glycogen, protein and fat in foetal tissues, increased oxygen consumption, and an elevated risk of APOs.

Nesfatin-1 is a physiological modulator of food intake composed of 82 amino acids. Some studies have revealed a close relationship between nesfatin-1 and insulin resistance.[17] Nesfatin-1 increases the body's sensitivity to insulin and reduces insulin resistance by upregulating the expression levels of insulin receptors through different pathways. Moreover, some studies have demonstrated that insulin resistance is an independent influencing factor of nesfatin-1 levels and showed a positive correlation between insulin resistance and nesfatin-1.[18] Further, studies have found that reducing nesfatin-1 in pregnant women with gestational diabetes can reduce the incidence of APOs.[19] The results of the present study indicate that the nesfatin-1 levels were higher in the study group than in the control group, which can be supported by previous research conclusions. This may be explained by higher degrees of insulin resistance and blood glucose levels in the presence of elevated nesfatin-1 levels, leading to APOs in patients with PCOS due to high-level blood glucose passing through the placental barrier. Analysis of factors influencing pregnancy outcomes in pregnant women with PCOS revealed that LH, BMI, WHR, GDM, IGF-1, and nesfatin-1 are associated with APOs in PCOS. Current studies indicated that abnormal LH levels and GDM can induce metabolic abnormalities in pregnant women, leading to endocrine dysfunction and APOs.[20] Pregnant women with higher BMI and WHR are at higher risk of developing placental inflammatory reactions, which can cause placental dysfunction and subsequently affect pregnancy outcomes. The results of this study, as indicated by the ROC curves, demonstrate that IGF-1 and nesfatin-1 have predictive value for APOs in patients with PCOS, indicating that IGF-1 and nesfatin-1 measurement is beneficial for the clinical assessment of the pregnancy status of patients with PCOS.

This study had some limitations, such as a small sample size, therefore, future studies should include more samples to further validate the findings of this study.

CONCLUSION

Elevated serum nesfatin-1 and IGF-1 levels are associated with the pregnancy outcomes of patients with PCOS and simultaneous detection of these markers can help in predicting APOs.

ETHICAL APPROVAL:

The study was approved by the Ethics Committee of the Maternity & Child Care Center of Qinhuangdao, Hebei, China (Approval No. 20210512; Dated: 12 May 2021).

PATIENTS' CONSENT:

Written informed consent was obtained from all participants.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

YW, RL: Designed the study and prepared the manuscript.
BS, WS: Collected and analysed the clinical data.
XZ, YH: Participated in the acquisition, analysis, and interpretation of data and drafted the manuscript.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Rababa'h AM, Matani BR, Yehya A. An update of polycystic ovary syndrome: Causes and therapeutics options. *Heliyon* 2022; **8(10)**:e11010. doi:10.1016/j.heliyon.2022.e11010.

2. Sadeghi HM, Adeli I, Calina D, Docea AO, Mousavi T, Daniali M, *et al*. Polycystic ovary syndrome: A comprehensive review of pathogenesis, management, and drug repurposing. *Int J Mol Sci* 2022; **23(2)**:583. doi:10.3390/ijms23020583
3. Wen J, Li X. Effect of magnesium sulfate combined with phentolamine and nifedipine for gestational hypertension and serum levels of LIF and Apelin. *J Coll Physicians Surg Pak* 2019; **29(3)**:231-4. doi:10.29271/jcpsp.2019.03.231.
4. Drummond RF, Seif KE, Reece EA. Glucagon-like peptide-1 receptor agonist use in pregnancy: A review. *Am J Obstet Gynecol* 2024; **22**:S0002-9378(24)00864-0. doi: 10.1016/j.ajog.2024.08.024.
5. Sobhan Bahreiny S, Ahangarpour A, Asghar Hemmati A, Kazemzadeh R, Bastani MN, Reza Dabbagh M, *et al*. Circulating nesfatin-1 levels in women with polycystic ovary syndrome: A systematic review and meta-analysis. *Int J Reprod Biomed* 2023; **21(10**):777-88. doi:10.18502/ijrm.v21i10.14533.
6. Huffman AM, Rezq S, Basnet J, Romero DG. Biomarkers in polycystic ovary syndrome. *Curr Opin Physiol* 2023; **36**:100717. doi:10.1016/j.cophys.2023.100717.
7. Joham AE, Norman RJ, Stener-Victorin E, Legro RS, Franks S, Moran LJ, *et al*. Polycystic ovary syndrome. *Lancet Diabetes Endocrinol* 2022; **10(9)**:668-80. doi:10.1016/S2213-8587(22)00163-2.
8. Ma C, Xiang Q, Song G, Wang X. Quercetin and polycystic ovary syndrome. *Front Pharmacol* 2022; **13**:1006678. doi:10.3389/fphar.2022.1006678.
9. Blum MR, Popat RA, Nagy A, Cataldo NA, McLaughlin TL. Using metabolic markers to identify insulin resistance in premenopausal women with and without polycystic ovary syndrome. *J Endocrinol Invest* 2021; **44(10)**:2123-30. doi:10.1007/s40618-020-01430-2.
10. Mills G, Badeghiesh A, Suarthana E, Baghlaf H, Dahan MH. Associations between polycystic ovary syndrome and adverse obstetric and neonatal outcomes: A population study of 9.1 million births. *Hum Reprod* 2020; **35(8)**:1914-21. doi:10.1093/humrep/deaa144.
11. Zhang H, Wang W, Zhao J, Jiao P, Zeng L, Zhang H, *et al.* Relationship between body composition, insulin resistance, and hormonal profiles in women with polycystic ovary syndrome. *Front Endocrinol (Lausanne)* 2023; **13**:1085656. doi:10.3389/fendo.2022.1085656.
12. Shahin L, Hyassat D, Batieha A, Khader Y, El-Khateeb M, Ajlouni K. Insulin Sensitivity Indices in Patients with Polycystic Ovary Syndrome with Different Body Mass Index Categories. *Curr Diabetes Rev* 2020; **16(5)**:483-9. doi:10.2174/1573399815666190823151222.
13. Greff D, Juhasz AE, Vancsa S, Varadi A, Sipos Z, Szinte J, *et al.* Inositol is an effective and safe treatment in polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials. *Reprod Biol Endocrinol* 2023; **21(1)**:10. doi:10.1186/s12958-023-01055-z.
14. Iervolino M, Lepore E, Forte G, Lagana AS, Buzzaccarini G, Unfer V. Natural molecules in the management of polycystic ovary syndrome (PCOS): An analytical review. *Nutrients* 2021; **13(5)**:1677. doi:10.3390/nu13051677.
15. Chang CW, Sung YW, Hsueh YW, Chen YY, Ho M, Hsu HC, *et al*. Growth hormone in fertility and infertility: Mechanisms of action and clinical applications. *Front Endocrinol (Lausanne)* 2022; **13**:1040503. doi:10.3389/fendo.2022.1040503.
16. Sun Y, Meng C, Yu L. Correlation of serum IGF-1 and sFlt-1 levels with adverse pregnancy outcomes in patients with severe preeclampsia. *Altern Ther Health Med* 2023; **29(5)**:364-9.
17. Demir Caltekin M, Caniklioglu A, Eris Yalcin S, Aydogan Kirmizi D, Baser E, Yalvac ES. DLK1 and Nesfatin-1 levels and the relationship with metabolic parameters in polycystic ovary syndrome: Prospective, controlled study. *Turk J Obstet Gynecol* 2021; **18(2)**:124-30. doi:10.4274/tjod.galenos.2021.39024.
18. Akbaba E, Sezgin B, Edgunlu T. The role of adropin, salusin-α, netrin-1, and nesfatin-1 in endometriosis and their association with insulin resistance. *Turk J Obstet Gynecol* 2021; **18(3)**:175-80. doi:10.4274/tjod.galenos.2021.12080.
19. Yang N, Guo R, Guo Y, Wei Y, An N. Effects of dietary intervention combined with insulin aspart on serum nesfatin-1 and CTRP12 levels and pregnancy outcomes in pregnant women with gestational diabetes mellitus. *Med (Baltimore)* 2023; **102(42)**:e35498. doi:10.1097/MD.0000000000035498.
20. Yang M, Shen X, Lu D, Peng J, Zhou S, Xu L, *et al.* Effects of vitamin D supplementation on ovulation and pregnancy in women with polycystic ovary syndrome: A systematic review and meta-analysis. *Front Endocrinol (Lausanne)* 2023; **14**:1148556. doi:10.3389/fendo.2023.1148556.