ORIGINAL RESEARCH

Expression and Clinical Significance of Irisin in Serum and Placenta Tissues of Pregnant Women with Severe Preeclampsia

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Objective: Preeclampsia (PE) is a serious pregnancy-specific disorder that poses significant risks to maternal and fetal health, with severe preeclampsia (SPE) being a particularly life-threatening complication. The objective of this study is to investigate the effects and clinical significance of irisin in pregnant women with severe preeclampsia (SPE). Irisin levels in the serum and placental tissues of healthy pregnant women and those with early- and late-onset SPE were measured and compared.

Methods: A total of 70 pregnant women treated at our hospital from January to November 2023 were selected for this study. The participants were divided into three groups: 20 women with early-onset severe preeclampsia (ES-PE group), 20 women with late-onset severe preeclampsia (LS-PE group), and 30 healthy pregnant women (control group). Fasting peripheral blood samples (5 mL) were collected from each participant, and placental tissues were obtained after delivery. Irisin levels in serum were measured using enzyme-linked immunosorbent assays (ELISA) with a commercial kit, and irisin expression in placental tissues was assessed by immunohistochemistry (IHC) with a rabbit anti-irisin antibody. The modes of delivery were also recorded.

Results: The concentrations of irisin in both serum and placental tissues were significantly higher among pregnant women in the control group compared to the ES-PE and LS-PE groups. There was a significant difference between the control group and the ES-PE and LS-PE groups in the mode of delivery. Additionally, a significant positive correlation was identified between the serum irisin concentration and its differential expression in placental tissues, while there was a significant negative correlation between irisin levels in both serum and placental tissue and systolic and/or diastolic blood pressure.

Conclusion: Reduced serum and placental irisin levels in pregnant women with SPE were associated with the onset and progression of SPE and may serve as a potential biological marker for SPE screening.

Keywords: irisin, placental tissue, pregnant women, serum, severe preeclampsia

Introduction

Hypertensive disorders of pregnancy (HDP) refer to conditions characterized by elevated blood pressure in pregnant women after 20 weeks of gestation.[1] Among these, preeclampsia (PE) is a pregnancy-specific syndrome closely linked to HDP.[2] Affecting approximately 2–8% of pregnant women worldwide, PE is more prevalent in developing countries than in developed countries. Due to its insidious onset and rapid progression, PE poses a significant risk for maternal and perinatal mortality.[3] In China, women with PE have a higher risk of stillbirth (4.6%) compared to the general population (1.1%).[4] According to data from the Centers for Disease Control and Prevention (CDC) of the United States, nearly 19% of all pregnancies and 11% of first-time pregnancies involve women aged 35 years and older.[5] The rising number of pregnancies in women of advanced maternal age is particularly concerning in light of the recent changes in the

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restructuring of China's reproductive policy, which may impose a significant strain on the nation's healthcare system.[6] This is a trend that is equally evident globally.[7,8]

PE is a multi-system disorder that results in endothelial cell dysfunction and can adversely affect maternal health.[9] The currently accepted pathogenesis of PE follows a "two-stage model."[10] In the first stage, local hypoxia and ischemia occur due to vascular malperfusion of the placenta and insufficient remodeling of the spiral arteries. The second stage involves oxidative stress (OS) and endothelial dysfunction, which contribute to clinical manifestations such as inflammatory responses and hypertension. It has been established that abnormal placental development is primarily driven by inadequate spiral artery remodeling in the myometrium—a condition that is especially evident when PE is complicated by severe fetal growth restriction (FGR).[11]

Risk factors for PE include maternal characteristics, poor obstetric history, and family history of PE.[12] Severe preeclampsia (SPE) is one of the major complications of PE and includes both early-onset PE (ES-PE) and late-onset PE (LS-PE) subtypes. ES-PE occurs before 34 weeks of gestation, and LS-PE occurs at 34 weeks or later. Genetic studies have shown that ES-PE is more strongly correlated with intraplacental factors, whereas LS-PE is more strongly correlated with maternal susceptibility factors.[13] The prevalence of LS-PE is approximately 10 times higher than that of ES-PE,[14] and is generally accompanied by a more adverse outcomes for both mother and fetus, including more severe hypertension, eclampsia, low birth weight, preterm labor, FGR, and increased maternal and fetal mortality. The prevalence of PE is generally lower in low- and middle-income countries—excluding sub-Saharan Africa—than in high-income countries.[15] In the United States, between 2014 and 2017, 6.6% of pregnancy-related deaths were attributed to maternal PE, compared to 26% in Latin America and the Caribbean, and 9% in Africa and Asia.[16,17] Previous research indicates that women with PE face an increased risk of long-term cardiovascular and metabolic disorders.[18] If left untreated, PE poses a serious threat to the health of both mothers and infants.[19] Despite ongoing research, the pathogenesis of PE remains unclear. Given the rising prevalence of PE and its significant impact on maternal and neonatal health, it is crucial to understand its underlying mechanisms in order to enhance survival rates.

Irisin, an exercise-induced myokine that was first identified by Boström et al in 2012,[20] typically exists as a -homodimer.[20,21] It plays a diverse role in regulating physiological processes, including energy expenditure, glucose homeostasis, and insulin sensitivity.[22] Irisin has been linked to various diseases, with lower circulating levels reported in patients with obesity and type 2 diabetes mellitus (T2DM).[23,24] In patients newly diagnosed with T2DM, circulating irisin levels were found to be positively correlated with endothelium-dependent vasodilation,[25] while reduced irisin levels were independently associated with endothelial dysfunction in patients with obesity.[26]

Irisin has been implicated in the pathogenesis of PE and placental abnormalities; however, the precise mechanisms remain unclear. Irisin may protect blood vessels by enhancing endothelial function, such as via activation of the AMPK-eNOS signaling pathway.[27] Its anti-inflammatory effects include the suppression of macrophage proliferation, selective activation of macrophage polarization, and inhibition of inflammasome formation.[22] Irisin also promotes angiogenesis by activating the ERK pathway, lowers blood pressure through the AMPK-Akt-eNOS-NO pathway, reduces insulin resistance, and regulates energy metabolism by acting on the p38-PGC-1α-irisin-β axis, which is involved in the renin pathway.[28]

PE often leads to ischemic injury, which exacerbates placental cell death. Irisin has been shown to exert an anti-apoptotic effect in the placentas of women with early PE by inhibiting apoptosis and enhancing cell survival via the Akt signaling pathway.[29] With China's social economy developing and adjustments made to its population planning policies, there has been a rise in the proportion of pregnant women of advanced maternal age. This trend has been accompanied by an increased risk of fetal chromosomal abnormalities and the incidence of congenital malformations in newborns with advancing gestational age.[30,31] Understanding the specific mechanisms underlying the relationship between irisin and PE is essential for reducing the adverse effects of PE on maternal and fetal health and for enhancing the safety and quality of life for affected individuals.

In this study, we aimed to investigate the effects and clinical significance of irisin in SPE by comparing the expression levels of irisin in the serum and placental tissues of pregnant women with SPE to those of women experiencing typical pregnancies.

Materials and Methods

Study Population

A total of 70 pregnant women were selected for this study between January 2023 and November 2023 at our hospital. This cohort included 20 women diagnosed with early-onset severe preeclampsia (the ES-PE group), 20 pregnant women with late-onset severe preeclampsia (the LS-PE group), and 30 healthy pregnant women with no pregnancy complications (the control group). Five mL of fasting peripheral blood was collected from each participant, and the expression level of irisin was measured using an enzyme-linked immunosorbent assay (ELISA). Placental tissue samples were collected from each participant, appropriately sectioned, fixed, and embedded in paraffin for further analysis. The inclusion criteria for the severe preeclampsia (SPE) group were as follows: (1) diagnosis of SPE according to the 9th edition of Obstetrics and Gynecology; (2) conception through natural pregnancy; (3) singleton pregnancy; and (4) regular antenatal care at our hospital with complete medical records. The exclusion criteria included: (1) presence of chronic diseases before pregnancy, such as hypertension, diabetes, cardiovascular diseases, or autoimmune diseases; (2) history of assisted reproductive technology; (3) multiple pregnancies (twins or more) conceived naturally; (4) other pregnancy complications; (5) history of recurrent miscarriages, fetal demise, placental abruption, or fetal growth restriction; (6) presence of psychiatric disorders; and (7) irregular antenatal care.

For the normal control group, the inclusion criteria were: (1) normal blood pressure during pregnancy; (2) conception through natural pregnancy; (3) singleton pregnancy; and (4) regular antenatal care at our hospital with complete medical records. The exclusion criteria were the same as those for the SPE group, ensuring that both groups were comparable in terms of baseline characteristics and potential confounding factors. All participants provided written informed consent prior to enrollment. Ethical approval was obtained from the Ethics Committee of the The First Affiliated Hospital of Dali University.

Experimental Equipment and Reagents

Experimental Equipment

Centrifuge (Shanghai Lichen Technology LC-LX-HRT 250E); −80°C low-temperature refrigerator (Konka BCD-307WEGY4S); Enzyme marker (LabSystems Multiskan MS 352); Dehydrator (Shanghai Leica Instrument Co., Ltd. ASP300); Embedding machine (Wuhan Junjie Electronics Co., Ltd. JB-L5); Pathological microtome (Shanghai Leica Instrument Co., Ltd. RM2016); Ice platform (JB-L5 of Wuhan Junjie Electronics Co., Ltd.); Tissue spreading machine (Wuhan Junjie Electronics Co., Ltd. JK-5); Oven (Shanghai Lichen Bangxi Instrument Technology Co., Ltd. 101-3BS); 37°C incubator (Shanghai Jinghong GNP-9080); Slide (Jiangsu Shitai Experimental Equipment Co., Ltd. 188105); Cover glass (Jiangsu Shitai Experimental Equipment Co., Ltd. 10212432C); Microwave oven (Galanz Microwave Electric Appliance Co., Ltd. M1-L213B); Decolorization shaker (Kylin-Bell TB-2); Vortex mixer (DLAB MX-F); Palm centrifuge (Beyofugetm E6686-1); Pipette gun (eppendorf 0.1–2.5/0.5–10/20–200/100–1000); Combination pen (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd. ZLI-9305); Microscope (CICXSP-C2042.4 Experimental Protocol).

Experimental Reagents

Human fibronectin type III domain packaging protein 5 (FNDC5, ELISA scientific research test kit, Jiangsu Su Enzyme Biotechnology Co., Ltd. MK4576A); Anhydrous ethanol (Sinopharm Chemical Reagent Co., Ltd. 100092683); Xylene I/I/II/III (Sinopharm Chemical Reagent Co., Ltd. 1002341922); EDTA (PH8.0) antigen repair solution (SolarBio C1033); EDTA (PH9.0) antigen repair solution (SolarBio C1038); Citric acid (PH6.0) antigen repair solution (SolarBio C1031); PBS buffer (Beyotime ST 1447); 3% hydrogen peroxide (Guangdong Hengjian Pharmaceutical Co., Ltd.); BSA (Beyotime ST025); Hematoxylin staining solution (Beyotime C0107); Ultrafast differentiation solution of hydrochloric acid and ethanol (Beyotime C0165m); Neutral gum (SolarBio G 8590); Primary antibody (rabbit antibody) (bs-8486R of Beijing boansen biotechnology co., ltd); Secondary antibody (HRP labeled goat against rabbit) (Xavier G1215); DAB staining solution (Aifang Bio- AFIHC004).

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Determination of Irisin Levels in Peripheral Serum

Standard and sample wells were prepared on the ELISA plate. Serum was extracted from the collected blood samples through centrifugation. A standard curve was established by preparing standard curve wells with dilutions of different concentrations of standards. Once all standards and samples to be tested were added to the respective wells, the membrane was sealed, and the plate was incubated at 37 °C for 60 minutes in a thermostat. The plate was then removed, washed, conjugated with the antibody, and incubated again for another 60 minutes. A color developer was added to the plate, and it was incubated again, shielded from light. Finally, a termination solution was added, and the absorbance of each well was measured at 450 nm using a microplate reader.

Determination of Irisin Levels in Placental Tissue

The placental tissues of the patients were removed from the fixative and embedded in paraffin wax to make wax blocks. After cooling, the wax blocks were sectioned at approximately 4 μm thickness, transferred onto glass slides, and dried to remove the wax. Antigen retrieval was performed using EDTA (pH 8.0). Endogenous catalase activity was inhibited by the addition of 3% hydrogen peroxide. The tissue sections were outlined and then incubated for 30 minutes. Primary and secondary antibodies were applied for binding, followed by color development using DAB reagent. Hematoxylin was used for restaining. Later, the sections were dehydrated with alcohol and sealed with neutral gum. Finally, images were captured using a microscope, and the results were recorded.

The scoring for the percentage of positive cells was as follows: < 5% of positive cells was scored 0 points, 5% to 25% was scored 1 point, 25% to 50% was scored 2 points, 50% to 75% was scored 3 points, and > 75% was scored 4 points.

The staining intensity of positive cells was scored as follows: negative was scored 0 points, weak positive (yellow) was scored 1 point, positive (brownish yellow) was scored 2 points, and strong positive (dark brownish yellow) was scored 3 points.

The final immunohistochemical score (IHS) was obtained by multiplying the percentage score by the staining intensity score.

Statistical Analysis

Excel and SPSS 25.0 were used for statistical data analysis. Normally distributed data were represented using the mean ± standard deviation ($\bar{X} \pm$ SD). If variance was homogeneous, the one-way ANOVA was conducted; if variance was not homogeneous, the corrected F-test (Welch's test) was employed. The least significant difference (LSD) method was used for post-hoc multiple comparisons. For non-normally distributed data, the non-parametric rank sum test was used, expressed as M (P25, P75), and the Kruskal–Wallis one-way ANOVA test was used for multiple comparisons, while the independent samples t-test was utilized for pairwise comparisons. Binary data were analyzed with the chi-square test. A P value of < 0.05 was considered statistically significant.

Results

Comparison of General Clinical Data of Patients in the Three Groups

Statistical analysis of age, body mass index (BMI), blood creatinine levels, transaminase levels, and platelet counts among the three groups—control group, ES-PE group, and LS-PE group—revealed that the differences in age, platelet counts, and transaminase levels were not statistically significant ($P > 0.05$). In contrast, there were statistically significant differences in BMI, blood creatinine, neonatal body weight, and the quantification of 24-hour urinary protein ($P < 0.05$), as shown in Table 1. Further analysis of potential confounding factors, including maternal age, BMI, and clinical indicators, revealed no significant differences in age, platelet counts, or transaminase levels across groups (P > 0.05). However, significant differences were observed in BMI, serum creatinine, neonatal birth weight, and 24-hour urinary protein excretion (P < 0.05), as detailed Supplementary Table 1.

Comparison of Irisin Levels in Peripheral Serum Among the Three Groups

Patients in the control group had significantly higher serum irisin concentrations compared to the ES-PE and LS-PE groups ($P < 0.01$). Additionally, the concentrations in the ES-PE group were lower than those in the LS-PE group ($P > 0.05$). Details are provided in Table 2, Figure 1A–F and Supplementary Figure 1.

Table 1 Comparison of General Clinical Data of Participants in Each Group ($\bar{X} \pm$ S), M (P25, P75)

Group	Control Group	ES-PE Group	LS-PE Group	F value or H value	P value
Number of cases	30	20	20		
Age (years)	29.47±0.813	31.35±1.312	30.30±1.069	0.859	0.428
	22.5673±0.42638	25.3025±0.96907	27.5965±1.2430	9.335*	0.001
Platelet (10^9/L)	189.43±8.696	195.40±11.874	220.90±15.210	2.022	0.140
Blood creatinine (μmol/L)	51.13±1.269	67.05±5.285	65.45±5.752	6.740*	0.004
Transaminase (U/L)	10.50 (7.00, 16.25)	13.00 (10.25, 25.50)	12.00 (9.00, 13.75)	5.588#	0.061
Birth weight (g)	3130.00 (2937.50, 3445.00)	1980.00 (1461.75, 2307.50)	3155.00 (2788.75, 3722.00)	25.068#	<0.001
24 h-urinary albumin excretion (mg/24h)	-	1083.00 (443.00, 3037.00)	261.50 (165.00, 549.25)	2.380**	0.023

Notes: *The variance was not homogeneous, and F-corrected test was chosen, F′; #The value is for skewed data, and H value was obtained by non-parametric rank sum test; **T-value obtained by two independent samples t-test for ES-PE and LS-PE.
Abbreviations: ES-PE group, Early-onset Severe Preeclampsia group; LS-PE group, Late-onset Severe Preeclampsia group.

Table 2 Comparison of Serum Irisin Levels Between Pregnant Women with PE and Healthy Pregnant Women

Group	Number of Cases	Serum Irisin Level	H value	P value
Control group	30	69.14 (50.54, 75.77)	24.898	p<0.001
ES-PE	20	35.67 (27.85, 53.69)		
LS-PE	20	49.54 (23.05, 56.96)		
				p<0.001
				P** <0.001
				P***=1.000

Notes: The data were in a skewed distribution, the non-parametric rank sum test was employed. A P value of < 0.05 was considered statistically significant. The Kruskal–Wallis one-way ANOVA test was used for multiple comparisons. P** denotes the comparison between the control group and the LS-PE group; P*** refers to the comparison between the ES-PE group and the LS-PE group.
Abbreviations: ES-PE, Early-onset Severe Preeclampsia; LS-PE, Late-onset Severe Preeclampsia.

Comparison of Irisin Protein Expression in Placental Tissues Among the Three Groups

The expression of irisin in placental tissues was significantly higher among patients in the control group compared to those in the ES-PE and LS-PE groups ($P < 0.01$). Irisin levels in placental tissues were higher in the LS-PE group compared to the ES-PE group ($P > 0.05$), as shown in Table 3.

Comparison of the Mode of Delivery Among the Three Groups

There was a significant difference in the mode of delivery between pregnant women in the control group and those in the ES-PE and LS-PE groups ($P < 0.01$). However, the differences in the mode of delivery between the ES-PE and LS-PE groups were not significant ($P > 0.05$). Details are shown in Table 4.

Correlation Analysis of Serum Irisin Concentration and Irisin Expression Level (IHS Value) in Placental Tissues

There was a significant positive correlation between the concentration of serum irisin and the expression level of irisin (IHS value) in placental tissues ($P < 0.01$). Additional details are provided in Table 5 and Supplementary Figure 2.
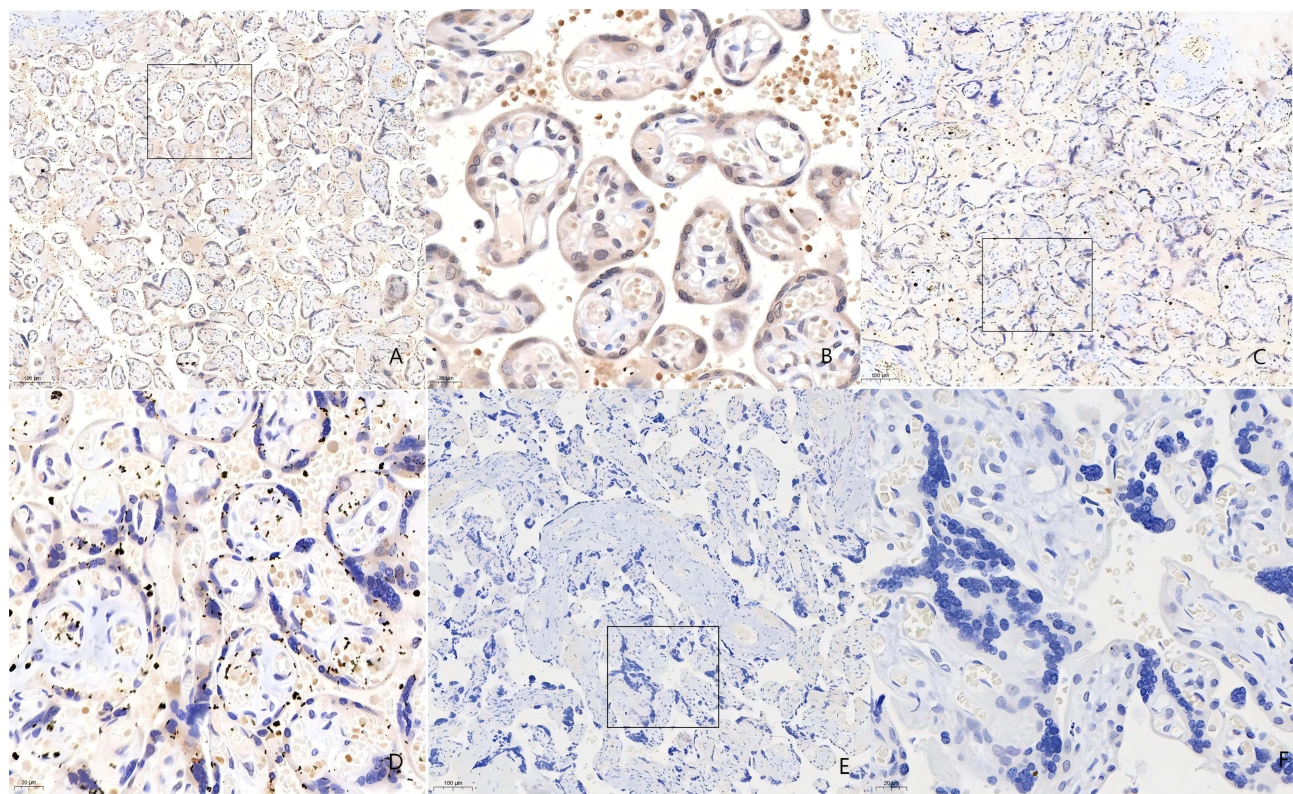
Figure 1 Expression of irisin in the placental tissues of the control, ES-PE, and LS-PE groups. (**A** and **B**) Placenta of the control group (100x) vs placenta of the control group (400x); (**C** and **D**) Placenta of the LS-PE group (100x) vs placenta of the LS-PE group (400x); (**E** and **F**) Placenta of the ES-PE group (100x) vs placenta of the ES-PE group (400x).
Abbreviations: IHS value, Intensity - Hue - Saturation value; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

Correlation Analysis Between Serum Irisin Concentration and Placental Irisin Expression Levels and Blood Pressure Among the Three Groups

The serum irisin concentrations in the control, ES-PE, and LS-PE groups were 69.14, 35.67, and 49.54 ng/mL, respectively. The corresponding placental irisin expression levels (IHS values) were 9, 4, and 1, respectively. Systolic blood pressure (SBP) readings were 113.60 ± 1.729, 155.55 ± 3.189, and 159.15 ± 3.065 mmHg, while diastolic blood pressure (DBP) readings were 76.43 ± 1.384, 102.4 ± 1.965, and 102.95 ± 3.020 mmHg, respectively. There was a significant negative correlation between serum irisin concentration and SBP and/or DBP ($P < 0.01$), as presented in

Table 3 Comparison of Expression Levels of Irisin (IHS Value) in Placental Tissue Among the Three Groups

Group	Number of Cases		*H* value	*P* value
Control group	30	9 (6, 12)	48.20	*p*<0.001
ES-PE	20	1 (0, 1)		
LS-PE	20	4 (1.25, 4.0)		
				p<0.001 *P*** <0.001 *P****=1.000

Notes: The data were skewed, the non-parametric rank sum test was employed. A *P* value of < 0.05 was considered statistically significant. The Kruskal–Wallis one-way ANOVA inspection was used for multiple comparisons. *P*** indicates the comparison between the control group and the LS-PE group; *P**** denotes the comparison between the ES-PE group and the LS-PE group.
Abbreviations: ES-PE, Early-onset Severe Preeclampsia; LS-PE, Late-onset Severe Preeclampsia.

Table 4 Comparison of the Mode of Delivery of Pregnant Women Among the Three Groups X^2

Group	Number of Cases	Mode of Delivery		X^2 value	P value
		Vaginal Birth	Cesarean Section		
Control group	30	25	5	29.200[a]	p<0.001
ES-PE	20	2	18		
LS-PE	20	6	14		
				*25.980[a]	p<0.001
				**14.488[a]	P** <0.001
				***1.406[b]	P***=0.236

Notes: The chi-square test was utilized for data analysis. [a]0 cells (0.0%) had an expected count < 5, using the Pearson chi-square test. [b]Calculations were performed only for the 2×2 table with 2 cells with expected counts < 5, using the continuity modified chi-square test. The Pearson chi-square test was employed. A P value of < 0.05 was considered statistically significant. *Represents the comparison between the control group and the ES-PE group; ** denotes the comparison between the control group and the LS-PE group; ***Indicates the comparison between the ES-PE group and the LS-PE group.
Abbreviations: ES-PE, Early-onset Severe Preeclampsia; LS-PE, Late-onset Severe Preeclampsia.

Table 5 Correlation of Serum Irisin Concentration and Irisin Expression Levels (IHS Value) in the Placental Tissue

Variable	Serum Irisin Level	Placental Irisin Expression Level (IHS value)
Serum irisin level (r)	1.000	0.434
P value	–	p<0.001

Note: Spearman rank correlation analysis was used.
Abbreviation: IHS value, Intensity - Hue - Saturation value.

Table 6 Correlation of Serum and Placental Irisin Concentrations with Maternal SBP and DBP

Variable	Serum Irisin Level		IHS value		SBP	DBP
	r	P	r	P	r	p
SBP	−0.386	0.001	−0.738	p<0.001	–	p<0.001
DBP	−0.378	0.001	−0.662	p<0.001	0.863	–

Supplementary Figure 3. Additionally, a significant negative correlation was observed between placental irisin expression level (IHS value) and SBP and/or DBP ($P < 0.01$), shown in Supplementary Figures 4, 5 and Table 6.

Discussion

The novelty of our study lies in several key aspects. Firstly, this is one of the few studies that comprehensively examines the expression and clinical significance of Irisin in both serum and placental tissues of pregnant women with severe preeclampsia, providing a more holistic understanding of its role in this condition compared to previous research that has primarily focused on either serum or tissue levels alone. Secondly, we have identified a significant correlation between serum Irisin levels and its expression in placental tissues, as well as a notable negative correlation with blood pressure parameters. These findings not only elucidate the potential mechanisms underlying Irisin's involvement in the pathogenesis of SPE but also highlight its potential as a biomarker for early detection and screening of the condition. Lastly, our study underscores the differential impact of early- and late-onset SPE on Irisin levels, suggesting distinct pathophysiological pathways that may warrant tailored clinical approaches. These innovative aspects collectively advance the field's understanding of Irisin's role in pregnancy complications and pave the way for future targeted interventions.

HDP are specific conditions occurring during pregnancy, affecting up to 8% of pregnancies and 15% of multiparous women.[18] PE, a serious complication associated with HDP, can lead to multiple adverse outcomes for pregnant women.[32] An estimated 2% to 8% of pregnancies worldwide are complicated by PE, with the associated risk of death being higher among African American women compared to other ethnic groups.[32,33]

Irisin is encoded by the gene for type III fibronectin structural domain-binding protein 5 and consists of 209 amino acids.[34,35] It is a novel myokine/adipokine that enhances glucose tolerance. Studies have shown that irisin improves glucose tolerance in individuals with gestational diabetes.[36] Irisin is expressed in various tissues, including the thyroid, ovaries, liver, lungs, and kidneys.[37] It is also present in the female reproductive system, including the ovaries, as well as in placental tissues and the serum in the umbilical cord of the newborn.[38,39] Factors such as physical activity, age, BMI, glucose levels, and various cytokines have been associated with serum irisin levels.[40]

Adipokines play a crucial role in regulating several essential metabolic processes in the body.[41] The role of adipokines is particularly significant in the physiology and pathophysiology of pregnancy. Specifically, adipokines are known to influence uterine contractility, pregnancy outcomes, and fetal growth.[42–47] In their IHC analysis of placental tissue, Garcés et al found that serum irisin levels were elevated throughout pregnancy when compared to nonpregnant women. Additionally, irisin levels were found to increase progressively, with higher levels observed during mid- and late pregnancy than in early pregnancy.[38] Decreased levels of irisin have been linked to common pregnancy complications, suggesting that irisin may play a role in the pathogenesis of PE.[48] Adenosine 5′-monophosphate activated protein kinase (AMPK) signaling plays a crucial role in trophoblast differentiation and placental pathology, with irisin shown to enhance differentiation in chorionic villus and extrachorionic trophoblast models through activation of the AMPK pathway. These findings suggest that irisin promotes the differentiation and function of trophoblasts in the human placenta—a process often compromised in abnormal placental development.[49]

The human placenta is a vital organ that supports fetal growth and development during pregnancy and consists of two distinct compartments. Placental chorionic villi are formed through a dynamic balance between proliferation and differentiation of mononuclear cytotrophoblasts (CTBs). Following mitosis, CTBs fuse to form multinucleated syncytio-trophoblasts, which create the chorionic villi responsible for nutrient and gas exchange. Simultaneously, invasive extrachorionic trophoblasts migrate and infiltrate the uterine wall and its vasculature, establishing the feto-maternal interface.[50] The proliferation and differentiation of trophoblasts operate synergistically to ensure proper human placental development.[18] Any significant disruption to this balance may impair trophoblast function, potentially leading to pregnancy complications.[51,52] Inadequate remodeling of spiral arteries by invading trophoblasts results in decreased blood perfusion to the uteroplacental region, leading to localized hypoxia at the placental implantation site. In response to this hypoxic environment, the placenta releases proteins into the maternal circulation, resulting in systemic maternal endothelial dysfunction, proteinuria, and hypertension, among other adverse consequences.[53]

The pathogenesis of PE is largely attributed to defective placental development, characterized by superficial invasion of the cytotrophoblast layer, inadequate remodeling of spiral arteries, and endothelial dysfunction. However, the exact mechanisms remain poorly understood. What has become increasingly evident is that pathological processes at the interface of fetal and maternal circulation lead to significant endothelial cell dysfunction.[54] Studies have demonstrated that irisin induces both endothelium-dependent and endothelium-independent relaxation of mesenteric arteries in mice.[26,55] Placental hypoxia-induced PE results from endothelium dysfunction, which irisin can modulate by inhibiting inflammation and oxidative stress while promoting cell proliferation.[56] Zhang et al[57] found that irisin could regulate the p38 MAPK/NF-κB pathway by inhibiting the production of reactive oxygen species (ROS) and the nuclear translocation of NF-κB in animal experiments. Irisin also inhibits PKC-β/NADPH oxidative enzymes, reducing the release of inflammatory factors and vascular endothelial inflammation.[57,58]

In addition, Zhang et al[59] found that irisin could enhance cell viability, promote cell migration, and stimulate capillary formation by upregulating microRNA-126-5p in the ERK signaling pathway. It functions as an anti-inflammatory agent in adipose tissue, helping to reduce inflammation by inhibiting macrophage polarization.[60,61] Additionally, it mitigates oxidative stress by decreasing the gene expression of inflammatory biomarkers such as NF-κB, cyclooxygenase-2 (COX2), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), as well as by downregulating ROS production in hepatocytes.[62,63] A recent study has demonstrated that exercise-induced irisin competitively inhibits the binding of

myeloid differentiation factor 2 (MD2) to Toll-like receptor 4 by forming a complex with MD2 in hepatocytes, thereby suppressing the inflammatory response.[64]

During pregnancy, women experience a phase of decreased insulin sensitivity during mid-pregnancy, which intensifies in late pregnancy. This results in a reduction of glucose uptake by maternal tissues and an increase in glucose production through gluconeogenesis.[65] However, in a significant proportion of pregnancies, insulin resistance (IR) is exacerbated, resulting in an adverse maternal metabolic profile and abnormal fetal growth.[61] Irisin influences subcutaneous adipose tissue by enhancing thermogenesis and energy expenditure, helping to prevent obesity and IR.[66] Additionally, functioning as an exercise-induced insulin sensitizer, irisin can regulate the metabolic processes in both muscle and adipocytes.

The results of our study indicated that serum irisin concentrations were significantly elevated in the control group compared to the ES-PE and LS-PE groups, with the LS-PE group showing higher concentrations than the ES-PE group. These results are consistent with prior research. For instance, Zhang et al[67] found no significant difference in serum irisin levels among 30 patients with SPE, 6 patients with mild PE, and 31 control participants. On the other hand, Foda et al[68] reported that serum irisin levels were significantly higher in typical pregnancies (early labor) than in cases of mild PE. Similarly, Ozel et al[69] conducted a study involving 54 women with PE (27 participants each with ES-PE and LS-PE). They found that the serum irisin levels in these women were significantly lower than those in the control group of 26 women with typical pregnancies. Furthermore, the mean maternal serum irisin level in the ES-PE group was significantly lower than those in the LS-PE group and the control group. The LS-PE group also had significantly lower irisin levels than the control group. These findings align closely with the results of our study.

In our study, serum irisin expression levels were significantly higher in the control group compared to the ES-PE and LS-PE groups, and the LS-PE had higher concentrations than the ES-PE group. ES-PE has been primarily attributed to placental factors, specifically the inadequate remodeling of maternal spiral arteries, which fails to supply sufficient nutrients to both the mother and the fetus. This deficiency may lead to intrauterine FGR and low birth weight. In contrast, LS-PE is predominantly associated with maternal factors, with little to no placental involvement. However, placental and maternal origins are not mutually exclusive, and their influences often overlap in PE pathogenesis.[13,70] In our study, irisin expression was found to be lowest in the placentas of pregnant women in the ES-PE group. This is consistent with the observation by Dadelszen that abnormal placental vascular development is a primary cause of ES-PE.[71] Thus, it can be inferred that irisin may be predominantly secreted by the placenta in pregnant women. The positive correlation between serum irisin concentration and placental irisin expression observed in our study further supports this hypothesis. Therefore, irisin may play a role in the onset and progression of PE.

We additionally found significant differences in the mode of delivery between the control group and the ES-PE group, as well as between the control group and the LS-PE group in the current study. There was no significant difference in the delivery mode between the ES-PE and LS-PE groups. This is consistent with findings of Saadat et al[72] that the frequency of cesarean sections was higher in pregnant women with PE compared to healthy pregnant women. Similarly, Al-Mulhim et al[73] reported that cesarean sections were more frequent among women with PE (14.9%) compared to the healthy group (9.6%).

With respect to serum irisin levels and blood pressure, our results showed a negative correlation between irisin levels and both SBP and DBP in pregnant women with PE. Zhang et al[67] also reported a similar negative correlation between the two factors in their study on women with PE. In their meta-analysis, Vivek et al[74] found that maternal serum irisin levels were significantly lower in patients with PE compared to pregnant women with normal blood pressure. These findings collectively suggest a negative correlation between serum irisin levels and blood pressure, which is consistent with the results of our study. Similar to these previous studies, our research also observed a significant negative correlation between serum Irisin levels and both systolic (SBP) and diastolic blood pressure (DBP) in pregnant women with preeclampsia (PE). However, our study uniquely extends these findings by demonstrating that this correlation is consistent across both early- and late-onset severe PE groups, highlighting the potential role of Irisin in different subtypes of PE. Additionally, we further explored the relationship between Irisin expression in placental tissues and blood pressure, providing a more comprehensive understanding of Irisin's involvement in the pathophysiology of PE.

In this study, the small sample size and the limited time frame are notable limitations, potentially affecting the reliability of the statistical analyses and overall results. Additionally, the exclusion of certain clinical indicators as well as the restricted methods for detecting relevant biomarkers may have introduced additional constraints on the findings.

Conclusion

In summary, in this study, we found that serum and placental irisin levels were negatively correlated with blood pressure in patients with PE, while the expression of irisin was significantly reduced in pregnant women with SPE. These findings suggest that irisin could serve as a potential biomarker for the early detection and screening of PE.

Abbreviations

HDP, Hypertensive disorders of pregnancy; PE, Preeclampsia.

Data Sharing Statement

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of The First Affiliated Hospital of Dali University. A written informed consent was obtained from all participants.

Consent for Publication

Consent for publication was obtained from every individual whose data are included in this manuscript.

Funding

Disclosure

None of the authors have any financial disclosure or conflict of interest to report for this work.

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