International Journal of Women's Health

Dovepress
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ORIGINAL RESEARCH

Study on the Effects of Cadmium Exposure on Zinc Metabolism and FOXO3a Expression in the Preeclampsia Maternal-Fetal System

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Purpose: To detect the levels of cadmium (Cd) and zinc (Zn) in maternal blood, umbilical blood, and placenta of preeclampsia (PE) patients, elucidating their relationship with FOXO3a transcription factors and oxidative stress.

Patients and Methods: A total of 100 pregnant women admitted for childbirth at the obstetrics department of the First People's Hospital of Yunnan Province from September 2023 to September 2024 were included (normal group: 40 cases, PE group: 60 cases). Inductively coupled plasma mass spectrometry (ICP-MS) was used to measure Cd and Zn levels in maternal blood, umbilical cord blood, and placental tissues. Enzyme-linked immunosorbent assay (ELISA) was applied to detect Forkhead box O3a (FOXO3a) levels. Statistical analysis was performed using SPSS 27.0 software and RStudio to compare differences and correlations among groups. Perform post hoc statistical efficacy analysis on sample size using G*Power software.

Results: Compared with the normal group, placental Cd levels were significantly higher in the PE group ($P<0.05$) and the maternal blood and placental Zn levels were significantly lower in the PE group ($P<0.05$). In the PE group, the levels of Zn and Cd in maternal blood and placenta were positively correlated ($r=0.50$, $P<0.001$; $r=0.567$, $P<0.001$). Placental FOXO3a levels were significantly elevated in the PE group ($P<0.001$), while maternal and umbilical cord blood FOXO3a levels were reduced ($P<0.001$). The levels of FOXO3a in the placenta were negatively correlated with the levels of Zn ($r=-0.277$, $P<0.05$), and the levels of FOXO3a in umbilical cord blood were negatively correlated with the levels of Cd ($r=-0.326$, $P<0.05$).

Conclusion: The exposure and accumulation of Cd in the maternal-fetal system can affect the transport and metabolism of Zn in placenta, leading to increased expression of FOXO3a under oxidative stress, causing the occurrence and development of PE.

Keywords: preeclampsia, cadmium, zinc, FOXO3a, oxidative stress

Introduction

Preeclampsia (PE) is a pregnancy-specific disorder affecting 2–8% of pregnancies globally and is a leading cause of maternal and perinatal mortality.[1,2] Pathologically, PE is closely associated with placental dysfunction, where oxidative stress is a core mechanism.[3,4] In PE, placental ischemia-hypoxia increases reactive oxygen species (ROS) production while reducing antioxidant capacity, exacerbating endothelial damage and placental dysfunction.[5] Cadmium (Cd), an environmental pollutant, accumulates in the body through food chains and smoking, aggravating placental oxidative stress and injury.[6,7] Zinc (Zn), an essential antioxidant trace element, plays a protective role against Cd toxicity and placental impairment.[8,9] However, the interaction mechanisms of Cd and Zn in PE remain unclear.

Forkhead box O (FOXO) transcription factor family plays a central role in integrating cellular responses to a variety of stressors.[10] And Forkhead box O3a (FOXO3a) plays an important role in oxidative stress by regulating antioxidant

Received: 15 April 2025
Accepted: 31 July 2025
Published: 15 August 2025

enzymes.[11] Studies have found that the increased expression of FOXO3a in placenta can inhibit the proliferation and invasion of trophoblasts,[12] leading to incomplete remodeling of uterine spiral artery, and then affect the blood supply of placenta. At the same time, under hypoxic environment, FOXO3a can increase the apoptosis rate of trophoblast by inducing the expression of apoptosis-related genes (such as FasL),[13] thus affecting the structure and function of placenta and promoting the occurrence and development of PE. Previous studies have shown that FOXO3a is highly expressed in placental tissue of patients with PE.[14]

In conclusion, we believe that the metabolic disorder of environmental heavy metals Cd and element Zn in the maternal-fetal system may lead to the increase of FOXO3a expression under oxidative stress and induce the occurrence and development of PE. Therefore, this study aims to compare the concentrations of Cd and Zn and the expression of FOXO3a in maternal blood, placenta and umbilical cord blood of normal and PE pregnant women, evaluate the relationship between Cd and Zn levels and FOXO3a expression, and explore the role of Cd and Zn in PE and their potential relationship with oxidative stress, so as to provide an experimental basis for further understanding and analyzing the pathogenesis of PE.

Materials and Methods

Study Participants and Data Collection

This cross-sectional case-control study enrolled 100 pregnant women, including PE patients and normal pregnant women, who delivered at the Department of Obstetrics, First People's Hospital of Yunnan Province, from September 2023 to September 2024. Participants were categorized into a normal group (40 cases) and a PE group (60 cases). And the study used a study design and baseline maternal demographic, clinical characteristics, and neonatal outcome data were collected from electronic medical records and standardized questionnaires. Inclusion Criteria: ① Resided in the study area for ≥2 years; ② Singleton pregnancy with vaginal delivery or cesarean section; ③ No family history of genetic diseases; ④ For the disease group: Diagnosis of PE per the 9th edition of Obstetrics and Gynecology (People's Education Press): Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after 20 weeks of gestation, accompanied by random urine protein (+) or 24-hour urinary protein ≥0.3 g/24h, without severe clinical manifestations; ⑤ Normal group: No gestational or chronic diseases. Exclusion Criteria: ① History of occupational exposure to specific or heavy metals; ② Unhealthy habits (eg, smoking, alcohol consumption); ③ Neonatal death, congenital anomalies, stillbirth, or multiple pregnancies; ④ Local residency <6 months; ⑤ Missing clinical data; ⑥ Pre-pregnancy chronic conditions (eg, hypertension, diabetes); ⑦ Pre-pregnancy autoimmune diseases (eg, systemic lupus erythematosus); ⑧ Illiteracy; ⑨ Inability to provide informed consent.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the First People's Hospital of Yunnan Province. All participants and their families provided written informed consent.

Research Methods

Sample Collection and Preprocessing

Immediately after delivery, maternal venous blood (3 mL) from the antecubital vein and neonatal umbilical cord blood (3 mL) were collected under aseptic conditions into sterile vacuum blood collection tubes. Placental tissues (5 g) were preserved in sealed bags labeled with maternal information. A 1 mL aliquot of maternal blood and umbilical cord blood was centrifuged to obtain plasma. All samples were stored in a −80°C ultra-low temperature freezer, and relevant maternal and neonatal information was recorded.

Cadmium and Zinc Levels Detection

Prior to analysis, samples were thawed at 4°C. For digestion, 0.5 g of maternal/umbilical cord blood was mixed with 3 mL nitric acid (HNO_3) and 1 mL hydrogen peroxide (H_2O_2) in digestion tubes. 1 g Placental tissue was mixed with 5 mL HNO_3 and 2 mL H_2O_2. Samples were digested at high temperature using a microwave digestion system for 30 minutes. After cooling, the digested solution was diluted to 25 mL with 1% HNO_3. Two blank controls were included to minimize experimental error. Cadmium and zinc levels were quantified using inductively coupled plasma mass spectrometry (ICP-MS). Calibration curves were generated and validated using multi-element standard solutions.

FOXO3a Levels Detection

The placental samples were thawed at 4 °C, rinsed with 1 × phosphate buffered saline (1 × PBS) to remove the residual blood on the tissues, 0.1 g wet weight placental tissue was weighed with an electronic balance and put into EP tubes, and 1 × PBS was added according to 1:9 For grinding. The homogenate of placental tissue was centrifuged to take the supernatant (4°C, 5000 × g, 8 min). The supernatant of maternal blood and umbilical cord blood was also obtained by centrifugation (4°C, 3000 × g, 10 min). Enzyme linked immunosorbent assay (ELISA) kit was used to detect the above samples. Finally, a microplate reader was used to detect the absorbance (OD value) at 450nm, and the actual concentration of FOXO3a in maternal blood, placenta and umbilical cord blood was calculated by linear regression equation.

Statistical Analysis

Data analysis was performed using SPSS 27.0 software. Continuous variables are expressed as mean ± standard deviation ($\bar{x} \pm s$). Differences in Cd, Zn, and FOXO3a levels among maternal blood, placental tissue, and umbilical cord blood were analyzed using independent samples t-tests. A two-tailed P-value < 0.05 was considered statistically significant for all analyses. In addition, RStudio was used to evaluate the correlation between Cd, Zn, and FOXO3a. Pearson correlation coefficient was expressed as r, with $|r| \geq 0.8$: strong correlation; $0.5 \leq |r| < 0.8$: moderate strength correlation; $0.2 \leq |r| < 0.5$: weak correlation; $|r| < 0.2$: almost no linear correlation. And the result is statistically significant with $P<0.05$.

Post-Hoc Power Analysis

In order to determine the significant difference in the test results of the existing sample size of 100 cases (40 cases in the normal group and 60 cases in the PE group), this study used G*Power (v3.1) for post hoc power analysis. Based on the differences of Cd and Zn contents in placenta between the normal group and the PE group, the actual statistical power of this study was 0.96 when the two-sided test and the significance level was 0.05, which showed that this study had 96% confidence to detect the observed differences, suggesting that the selection of sample size in this study is sufficient for the result analysis.

Results

Comparison of General Information Between the Normal Group and the PE Group

The statistical analysis of general information of pregnant women in the normal group and the PE group (Table 1) shows that there are significant differences in age, parity, body mass index (BMI), systolic blood pressure, and diastolic blood pressure between the PE group and the normal group ($P<0.05$). In addition, the gestational age and newborn birth weight of the PE group were significantly lower than those of the normal group ($P<0.001$).

Table 1 Comparison of General Information Between the Normal Group and the PE Group ($\bar{x} \pm s$)

Variable (unit)	Normal Group (n=40)	PE Group (n=60)	P-Value
Age at delivery (years)	30.6±4.38	33.35±5.15	<0.05
Gravida (times)	1.98±1.10	2.72±1.80	<0.05
Parity (times)	1.43±0.64	1.58±0.79	0.291
Weight gain during pregnancy (kg)	13.96±3.88	14.65±5.35	0.489
Pre-pregnancy body mass index (kg/m2)	21.37±3.05	23.55±3.50	<0.05
Systolic pressure (mmHg)	115.18±10.20	144.12±15.76	<0.001
Diastolic pressure (mmHg)	75.18±7.89	96.85±11.48	<0.001
Gestational age (weeks)	38.65±0.95	37.35±2.43	<0.001
Birth weight (g)	3251.88±327.44	2850.58±670.28	<0.001

Notes: Data are presented as mean ± standard deviation (SD) ($\bar{x} \pm s$) based on data distribution. P-values were determined by Student's *t*-test. $P < 0.05$ was considered statistically significant, $P \geq 0.05$ was not considered statistically significant.
Abbreviation: PE, preeclampsia.

Table 2 Comparison of Cd, Zn, and FOXO3a Content Between the Normal Group and the PE Group ($\bar{x} \pm s$)

Indicator	Sample	Normal Group (n=40)	PE Group (n=60)	P-Value
Cd (μg/kg)	Maternal blood	0.09±0.03	0.10±0.03	0.169
	Placenta	0.25±0.11	0.43±0.35	<0.001
	Umbilical cord blood	0.08±0.03	0.08±0.03	0.92
Zn (μg/kg)	Maternal blood	150.86±41.00	128.39±37.97	<0.05
	Placenta	249.88±82.03	208.89±75.27	<0.05
	Umbilical cord blood	65.82±39.72	56.57±18.16	0.118
FOXO3a (ng/mL)	Maternal blood	2.36±0.36	1.76±0.36	<0.001
	Placenta	1.75±0.31	2.74±0.55	<0.001
	Umbilical cord blood	3.40±0.87	2.61±0.58	<0.001

Notes: Data are presented as mean ± standard deviation (SD) ($\bar{x} \pm s$) based on data distribution. P-values were determined by Student's *t*-test. P < 0.05 was considered statistically significant, P≥0.05 was not considered statistically significant.

Abbreviations: PE, preeclampsia; Cd, cadmium; Zn, zinc; FOXO3a, Forkhead box O3a.

Comparison of Cd, Zn, and FOXO3a Content Between the Normal Group and the PE Group

The Cd content in the placenta of the PE group was significantly higher than that of the normal group (P<0.05), and the Zn content in the maternal blood and placenta of the PE group was significantly lower than that of the normal group (P<0.05). In addition, we also found that the FOXO3a content in maternal and umbilical cord blood of the PE group was lower than that of the normal group (P<0.001), while the FOXO3a content in the placenta of the PE group was higher than that of the normal group (P<0.001). The specific numerical information is shown in Table 2.

Correlation Analysis of Cd and Zn in Normal and PE Maternal-Fetal Systems

In the normal group (Figure 1A), umbilical cord blood Cd levels were positively correlated with maternal blood Cd levels (r=0.99, P<0.001), and placenta Cd levels were positively correlated with maternal blood Cd levels (r=0.39, P<0.05). In the PE group (Figure 1B), there was a positive correlation between umbilical cord blood Cd levels and maternal blood Cd levels (r=0.66, P<0.001), and a positive correlation between placenta Cd levels and maternal blood Cd levels (r=0.31, P<0.05). The research results suggest that the placenta plays an important barrier role in reducing intrauterine exposure to heavy metal Cd. In addition, there was a positive correlation between maternal blood Zn levels and umbilical blood Zn levels in the normal group (r=0.60, P<0.001) (Figure 1A), but there was no significant correlation between umbilical blood Zn levels and maternal blood Zn levels in the PE group (Figure 1B). The levels of Zn in maternal blood and placenta were positively correlated with Cd levels in the PE group (r=0.50, P<0.001; r=0.567, P<0.001) (Figure 2), indicating that Cd exposure is related to the transport and metabolic disorders of Zn in the PE maternal-fetal system.

The Relationship Between FOXO3a, Cd, and Zn in Normal and PE Maternal-Fetal Systems

In the PE group, there was a negative correlation between placenta FOXO3a levels and Zn levels (r=−0.277, P<0.05), and a negative correlation between umbilical cord blood FOXO3a levels and Cd levels (r=−0.326, P<0.05) (Figure 2). No significant correlation was observed in the normal group (Figure 2). Indicating that in normal pregnancy, the levels of Zn and FOXO3a are maintained in a relatively balanced state. However, in the PE group, Cd exposure may damage the placental barrier function, leading to an imbalance between Zn metabolism and FOXO3a expression levels in the maternal-fetal system.

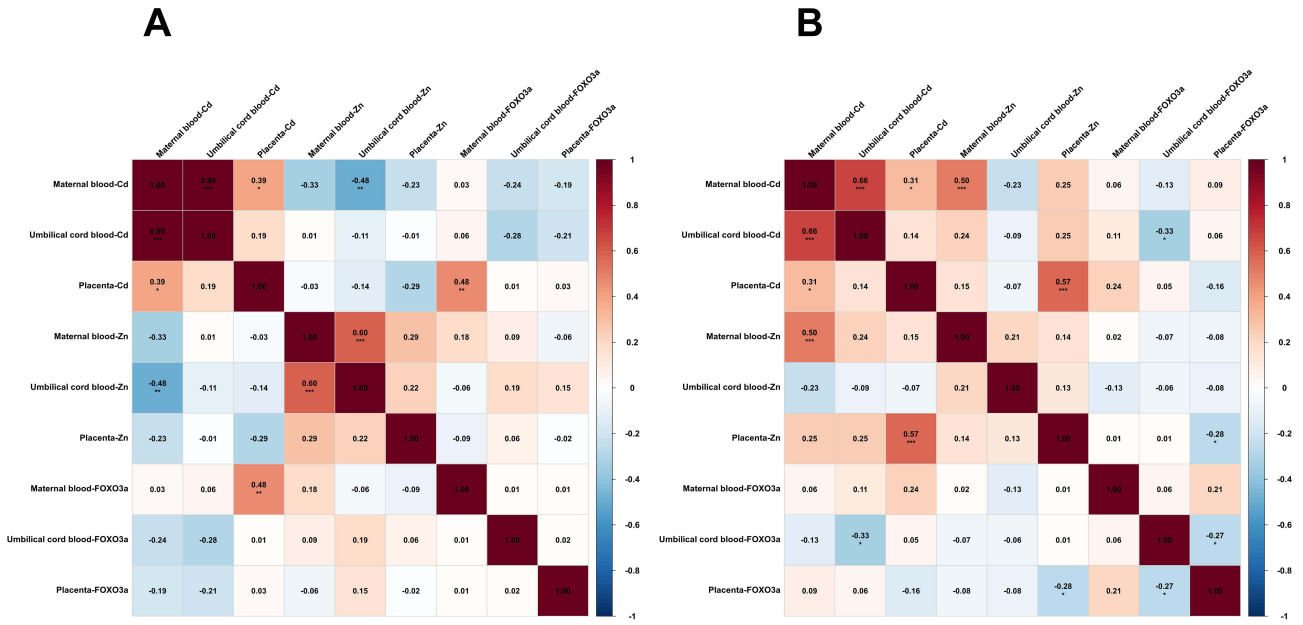

Figure 1 Heatmap of Correlation Analysis between Cd, Zn and FOXO3a. The heatmap displays Spearman's rank correlation coefficients (ρ) between Cd, Zn, and FOXO3a levels in maternal blood, placenta, and umbilical cord blood. The color scale indicates the strength and direction of the correlations, with red representing positive correlations and blue representing negative correlations. The numerical value of the correlation coefficient is provided in each cell. This analysis reveals the interrelationships between different biomarkers across the maternal-fetal system. (**A**) Heatmap of correlation analysis between Cd, Zn and FOXO3a across the normal group; (**B**) Heatmap of correlation analysis between Cd, Zn and FOXO3a across the PE group. Pearson correlation coefficient was expressed as r, with | r | ≥ 0.8: strong correlation; 0.5 ≤ | r |<0.8: moderate strength correlation; 0.2 ≤ | r |<0.5: weak correlation; | r |<0.2: almost no linear correlation. *: P < 0.05; **: P < 0.01; ***: P < 0.001; P < 0.05 was considered statistically significant, P ≥ 0.05 was not considered statistically significant.
Abbreviations: PE, preeclampsia; Cd, cadmium; Zn, zinc; FOXO3a, Forkhead box O3a.

Discussion

This study investigated the distribution characteristics of Cd, Zn, and FOXO3a in the maternal-fetal system of normal pregnancies and PE, as well as their potential associations with the pathogenesis of PE. Through comparative analysis, this study found that the accumulation of toxic heavy metal Cd in placenta of the PE group was significantly increased compared with that of the normal group, while the content of Zn was significantly decreased. The accumulation of placenta Cd leads to the impairment of barrier function, affects the transport and metabolism of Zn, and increases the expression of stress response transcription factor FOXO3a, thus causing the pathology of PE.

As a non-essential toxic heavy metal, Cd accumulation in the placenta is closely linked to PE development. The placenta, a critical interface between mother and fetus, not only facilitates material exchange but also serves as the primary site for maternal Cd accumulation.[15] This study found that the Cd content in the placenta of the PE group was significantly higher than that of the normal group (Table 2). This aligns with findings from a study in Wuhan, China, where gestational Cd exposure was associated with altered Cd concentrations and increased risk of hypertensive disorders of pregnancy.[16] The pathogenic role of Cd in PE may stem from its impairment of placental angiogenesis and trophoblast function. During a physiological pregnancy, spiral remodeling modifies arteries from low-flow/high-resistance to high-flow/low-resistance vessels,[17] and PE may change this process and the functioning of the placenta. Previous literature has reported that placental dysfunction leads to changes in placental perfusion and an imbalance of angiogenic factors. At the same time, imbalances in related vascular factors have also been detected in PE patients, indirectly revealing the pathophysiological mechanisms associated with PE and placental disorders.[18] And this study found that compared with the normal group, the correlation between placenta and umbilical cord blood Cd levels and maternal blood Cd levels in the PE group decreased, and the correlation between umbilical cord blood Zn levels and maternal blood Zn levels in the PE group changed from a significant correlation to no significant correlation (Figure 1). This result further showed that Cd significantly damaged the barrier function of the placenta in the PE group, and at the same time, led to the interference of Zn transport and metabolism.[19]

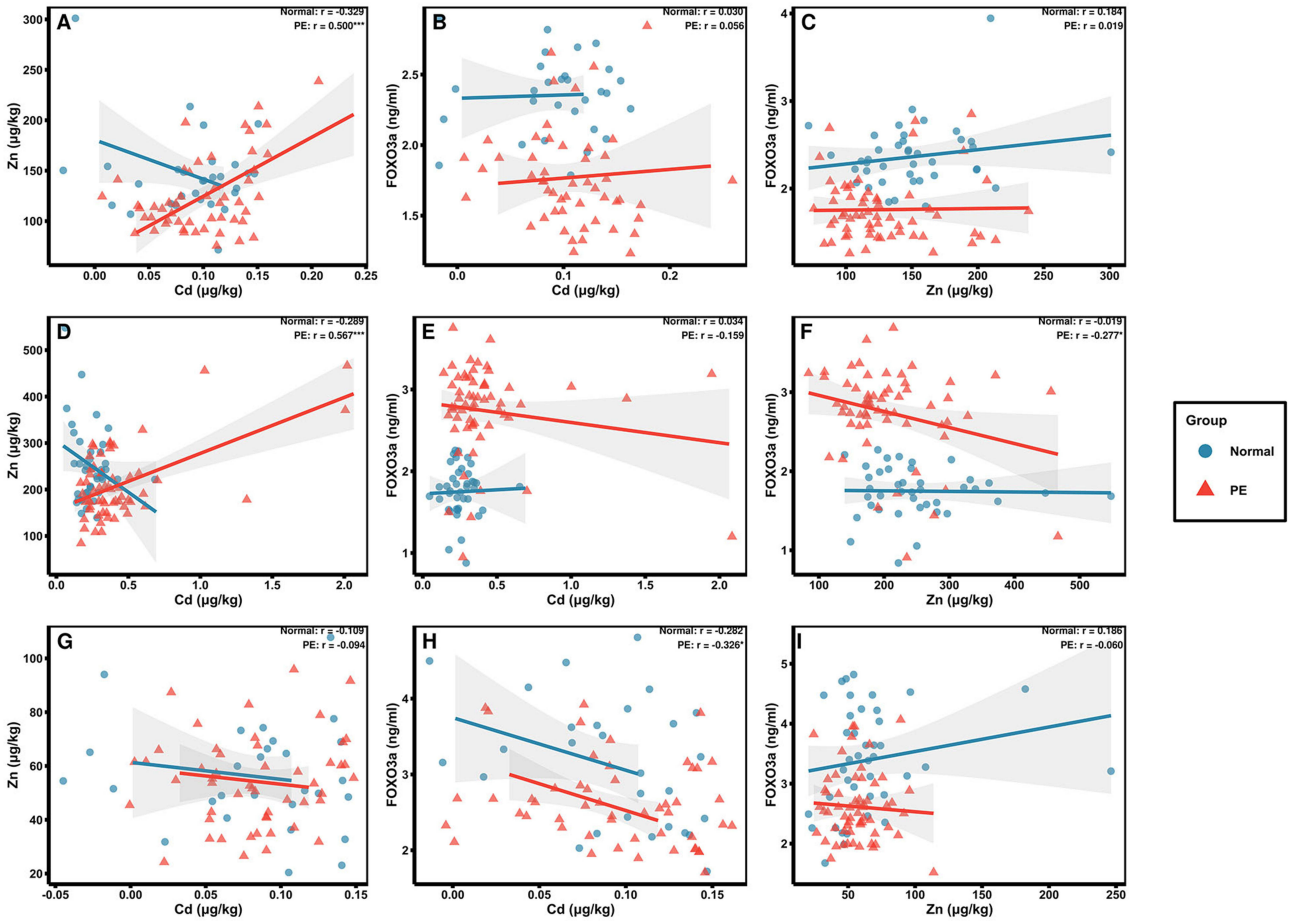

Figure 2 Scatter Plot of Correlation Analysis between Cd, Zn and FOXO3a. The comprehensive scatter plot matrix illustrates the pairwise correlations among three measured biomarkers in maternal blood, placenta, and umbilical cord blood between the normal group and the PE group. (**A**–**C**) Scatter plot of correlation analysis between Cd, Zn and FOXO3a in maternal blood; (**D**–**F**) Scatter plot of correlation analysis between Cd, Zn and FOXO3a in placenta; (**G**–**I**) Scatter plot of correlation analysis between Cd, Zn and FOXO3a in Umbilical cord blood. Pearson correlation coefficient was expressed as r, with | r | ≥ 0.8: strong correlation; 0.5 ≤ | r |<0.8: moderate strength correlation; 0.2 ≤ | r |<0.5: weak correlation; | r |<0.2: almost no linear correlation.*: P < 0.05; **: P < 0.01; ***: P < 0.001; P < 0.05 was considered statistically significant, P ≥ 0.05 was not considered statistically significant.
Abbreviations: PE: preeclampsia; Cd: cadmium; Zn: zinc; FOXO3a: Forkhead box O3a.

In contrast to Cd accumulation, Zn exhibited an opposing trend. As an essential trace element, Zn plays pivotal roles in immune function, cell division, and DNA synthesis, which are vital for maternal and fetal development. Our results demonstrated significantly lower Zn levels in maternal blood and placenta of the PE group compared to the normal group (Table 2), which indicates that Cd exposure will affect placental Zn transport and metabolism, reduce the Zn content of mother and fetus system, and increase the risk of PE. This aligns with existing evidence of reduced Zn levels in PE patients.[20] The synchronous decline in maternal blood and placental Zn levels in the PE group implies systemic Zn deficiency affecting both mother and fetus. Studies have confirmed that the toxic effect of Cd can affect the transport of Zn by displacing Zn in zinc metallothionein (MT) complex to form cadmium metallothionein complex.[21] The placenta Cd accumulation in PE patients may interfere with the normal transport of Zn, which is consistent with the results of this study, which shows that the correlation between umbilical cord blood Zn and maternal blood Zn in the PE group changed from a significant positive correlation in the normal group to no correlation (Figure 1). At the same time, Zn and Cd in the maternal blood and placenta of the PE group were positively correlated (Figure 2), which may be due to environmental Cd exposure, caused more Cd accumulated in the maternal-fetal system of the PE group. Although the mother can detoxify by synthesizing MT, this process may also lead to the "release" or redistribution of Zn. MT will release displaced Zn while chelating Cd, resulting in the increase of Zn levels in maternal blood and placenta. It is worth noting that although the previous results showed that the content of Zn in maternal blood and placenta of the PE group was

lower than that of the normal group, there may be a redistribution mechanism due to the continuous accumulation of Cd exposure, resulting in a positive correlation between Zn and Cd in maternal blood and placenta of PE. Zn is integral to antioxidant systems, as it forms the active center of numerous antioxidant enzymes.[22] Zn deficiency likely weakens antioxidant capacity, aggravates oxidative stress, and impairs placental and maternal vascular function. Prior studies also suggest that deficiencies in essential elements like Zn enhance Cd absorption and toxicity.[23]

On the one hand, Cd exposure interferes with Zn transport and metabolism through displacement. On the other hand, it can also damage placental function through oxidative stress, affecting Zn transport, which has a positive feedback enhancing effect on placental oxidative stress. Under oxidative stress, the expression of FOXO3a increases to enhance the antioxidant capacity of cells. Meanwhile, placental dysfunction may also lead to enhanced expression of FOXO3a and compensatory response to oxidative stress and cell function damage.[9] FOXO3a regulates diverse biological processes, including apoptosis, cell cycle control, and oxidative stress responses.[24] In a severely stressed cellular environment, such as the placenta of PE, long-term or excessive FOXO3a activation will instead trigger pro- apoptotic and cell cycle inhibition.[14] In addition, FOXO3a overexpression may inhibit trophoblast activity, impair spiral artery remodeling, and induce placental ischemia-hypoxia,[25] contributing to PE development. Cd can stimulate the production of excessive ROS in cells, increase oxidative stress, and lead to cell damage and dysfunction,[26] and oxidative stress is a key factor in the pathogenesis of PE. This is consistent with the results of this study, which found that the content of FOXO3a in placenta of the PE group was significantly higher than that of the normal group (Table 2), and the Cd levels in umbilical cord blood of the PE group was negatively correlated with the levels of FOXO3a (Figure 2), suggesting that Cd exposure in the maternal-fetal system and the accumulation effect of placental Cd damaged the placental barrier function, caused the increase of FOXO3a expression, aggravated the oxidative stress in vivo, and led to PE. In addition, hypoxia can also exacerbate oxidative stress,[27] further activating FOXO3a, forming a vicious cycle. Therefore, the high expression of FOXO3a in placenta of the PE group in this study reflects the adaptive response of placenta under hypoxia and oxidative stress.

In addition, our study also found a positive correlation between placenta Zn levels and FOXO3a levels in the PE group (Figure 2), suggesting that Zn may participate in the regulation of FOXO3a oxidative stress response in the pathological mechanism of PE. However, the exposure of environmental heavy metal Cd not only stimulated the oxidative stress response of the body, but also negatively affected the transport of Zn in the maternal-fetal system. At the same time, Zn deficiency likely weakens antioxidant capacity, aggravates oxidative stress, and impairs placental and maternal vascular function. Therefore, we guess that after Zn supplementation, Zn's antioxidant properties may counteract Cd-induced oxidative stress, protecting placental function and maternal vascular health to mitigate PE risk. However, whether FOXO3a directly mediates Cd-induced oxidative stress or Zn exerts protective effects via FOXO3a regulation requires further experimental validation.

Conclusion

This study demonstrates significant placental Cd accumulation, Zn deficiency, and FOXO3a upregulation in PE patients. These factors may affect the onset of PE by disrupting placental function and amplifying oxidative stress. Our findings highlight the risks of environmental heavy metal exposure in PE and underscore the importance of Zn homeostasis. Future studies should explore Cd-Zn-FOXO3a interactions, such as in vitro validation of Cd's direct activation of FOXO3a and Zn's role in mitigating Cd toxicity via FOXO3a inhibition to evaluate the predictive value of Cd, Zn, and FOXO3a as PE biomarkers. Such investigations will deepen our understanding of PE mechanisms and inform novel prevention and treatment strategies.

Abbreviations

Cd, cadmium; Zn, zinc; PE, preeclampsia; ROS, reactive oxygen species; FOXO3a, Forkhead box O3a; ICP-MS, inductively coupled plasma mass spectrometry; ELISA, enzyme-linked immunosorbent assay; PBS, phosphate-buffered saline; MT, metallothionein.

Data Sharing Statement

The dataset generated and analysed during the current study is available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Review Committee of the First People's Hospital of Yunnan Province (Approval number: KHLL2022-KY085). The data was collected with written permission from the facility director.

Funding

This research was supported by the National Natural Science Foundation of China (grant number: 42167060), Key research and development plan of Yunnan Province (grant number: 202403AC100002), and Yunnan Province Key Clinical Specialty of Obstetrical Department (open subject number: 2024CKKFKT-01).

Disclosure

The authors report no conflicts of interest in this work.

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