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Original Article

Correlation between serum selenium level and maternal-fetal complications following premature rupture of membranes

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Abstract: Objective: To explore the correlation between serum selenium levels and adverse pregnancy outcomes in pregnant women with premature rupture of membranes (PROM). Methods: A total of 169 parturients were enrolled and divided into the PROM group (n=57) and the normal group (n=112) according to the presence or absence of PROM. We compared serum trace element levels and the incidence of adverse pregnancy events between the two groups. Spearman's rank correlation analysis was used to analyze the correlations between indicators, and multivariate regression analysis was performed to screen the influencing factors of adverse pregnancy outcomes. Compared with the normal group, the PROM group had significantly shorter gestational age, lower serum calcium and magnesium levels, and higher serum phosphorus, interleukin-6 (IL-6), and matrix metalloproteinase-9 (MMP-9) levels (all P<0.05). The incidence of adverse pregnancy outcomes was 21.05% in the PROM group and 14.29% (16/112) in the normal group, with no significant difference between the two groups (P>0.05). Serum magnesium and selenium levels were positively correlated with serum iron levels (r=0.208, r=0.340, both P<0.01), while both elements were negatively correlated with serum phosphorus levels (r=-0.196, r=-0.226, both P<0.05). Serum calcium level was negatively correlated with the onset of PROM (r=-0.177, P<0.05). Subgroup analysis showed that the PROM incidence in the low selenium subgroup (<35.0 μg/L) was significantly higher than that in the normal selenium subgroup (48.39% vs. 29.84%, P<0.05). After adjusting for confounding factors, low serum selenium level was an independent risk factor for PROM (odds ratio [OR]=2.31, P=0.037). Conclusion: Serum magnesium, calcium, phosphorus, iron and selenium levels are closely related to the maintenance of maternal pregnancy health, and low selenium level is significantly associated with increased PROM risk.

Keywords: Trace elements, premature rupture of membranes, adverse pregnancy outcomes, selenium, calcium

Introduction

Premature rupture of membranes (PROM) refers to the rupture of fetal membranes before the onset of labor during pregnancy, which leads to continuous loss of amniotic fluid [1]. PROM occurs in 2% to 4% of singleton pregnancies worldwide, and approximately 30% of preterm deliveries are caused by PROM [2]. Amniotic fluid loss after PROM disrupts the intrauterine environment stability, induces uterine contractions and cervical dilation, and ultimately results in preterm birth [3]. Meanwhile, reduced amniotic fluid causes abnormal pressure on the fetus, hinders fetal growth and nutrient supply, and easily triggers intrauterine fetal distress. Preterm infants born due to PROM are also prone to multiple complications, including respiratory disorders, digestive dysfunction and neurodevelopmental abnormalities [4, 5]. In addition, PROM increases the risk of ascending cervical bacterial infection, which can cause intrauterine infection. Severe intrauterine infection may lead to fetal growth restriction, fetal distress, preterm birth or even fetal death, greatly increasing the risk of adverse pregnancy outcomes [6, 7]. Early monitoring, timely intervention and infection preven-

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tion can effectively improve pregnancy outcomes and neonatal survival rate.

Trace elements are essential nutrients for maintaining human physiological functions, which directly affect maternal physical condition and fetal development throughout pregnancy [8-10]. Abnormal levels of serum trace elements (deficiency or excess) are closely associated with PROM and various adverse pregnancy outcomes, including gestational diabetes mellitus, hypertensive disorders of pregnancy and preterm birth. Gestational deficiency of iron, copper, zinc and other trace elements can cause maternal anemia, further leading to fetal intrauterine growth restriction, low birth weight, preterm birth and stillbirth [11]. Calcium and vitamin D insufficiency during pregnancy increases the risk of maternal gestational hypertension and gestational diabetes, and impairs fetal bone development [12].

Selenium is an indispensable rare trace element for human health. It exerts antioxidant effects to reduce free radical damage, delay cell aging, repair damaged cells, improve erythrocyte oxygen-carrying capacity, enhance immune function and promote detoxification [13]. Existing studies have confirmed that low gestational serum selenium levels are correlated with elevated risks of gestational hypertension and gestational diabetes mellitus [14, 15]. However, few studies have focused on the relationship between serum selenium level and PROM as well as subsequent adverse pregnancy outcomes.

Therefore, this retrospective study enrolled pregnant women with PROM and healthy pregnant women as research subjects. We compared serum trace element levels and adverse pregnancy outcome incidence between the two groups, analyzed the correlation between trace element profiles and PROM-related adverse pregnancy outcomes, and explored the potential pathogenesis. The research results aim to provide evidence for clinical prenatal care and maternal health management.

Materials and methods

Study subjects and PROM diagnostic criteria

A total of 169 pregnant women who delivered in Minda Hospital of Hubei Minzu University from January 2023 to September 2025 were enrolled in this retrospective observational study. The study was approved by the Institutional Ethics Committee of Minda Hospital of Hubei Minzu University, and all procedures complied with the Declaration of Helsinki. The ethics committee waived the requirement for informed consent due to the retrospective study design based on clinical medical records.

All subjects were divided into two groups according to clinical PROM diagnostic criteria: the PROM group (57 cases) and the normal group (112 cases, no PROM).

PROM diagnostic criteria: Spontaneous massive vaginal fluid outflow; vaginal secretion pH>7 detected by acid-base test strips; microscopic examination of dried vaginal fluid smears showing sheep-tooth crystals; microscopic examination of vaginal fluid sediments showing fetal vellus hairs. PROM was diagnosed if any one of the above conditions was met.

Inclusion criteria: singleton pregnancy; Normal thyroid function. Exclusion criteria: History of special selenium exposure; severe systemic infection; immune system diseases, endocrine diseases or reproductive tract malformations; adverse pregnancy outcomes caused by genetic factors; pre-pregnancy liver and renal dysfunction.

Detection method and reference range of serum trace elements

After PROM onset, 5 mL of venous blood from the elbow was collected from each subject, centrifuged immediately, and the separated serum was sealed and stored at 4°C for subsequent detection. Disposable heparin anticoagulant vacuum blood collection tubes, BS series trace element analyzer and supporting kits (Guiyang Caiyue Technology Co., LTD.) were used for detection. Serum levels of zinc, iron, calcium, phosphorus, magnesium and selenium were measured by the BS series trace element analyzer. The normal reference ranges were set as follows: zinc 76.5-150.0 μmol/L, iron 6.63-11.82 μmol/L, calcium 2.25-2.75 mmol/L, phosphorus 0.90-1.32 mmol/L, magnesium 0.65-1.05 mmol/L, selenium 35.0-110.0 μg/L.

Detection of serum interleukin-6 and matrix metalloproteinase-9 levels

Serum levels of interleukin-6 (IL-6) and matrix metalloproteinase-9 (MMP-9) in all subjects were detected by enzyme-linked immunosor-

bent assay (ELISA). ELISA kits were purchased from Beyotime Biotechnology Co., Ltd., and all experimental operations were strictly implemented in accordance with the kit instructions.

Definition of adverse pregnancy outcomes and observation indicators

Adverse pregnancy outcomes included macrosomia, threatened preterm labor, fetal growth restriction, fetal distress, very low birth weight infant, preeclampsia, spontaneous miscarriage and intrauterine fetal death. All diagnostic criteria were in line with national clinical standards:

Macrosomia was defined as neonatal birth weight ≥4.0 kg. Threatened preterm labor was diagnosed at 28-37 weeks of gestation, characterized by regular uterine contractions (4 times/20 min or 8 times/60 min) without cervical dilation or cervical canal length <20 mm. Fetal growth restriction was confirmed by ultrasound measurements (biparietal diameter, head circumference, abdominal circumference, femur length) and Doppler blood flow detection. Fetal distress was defined as fetal heart rate >160 beats/min or <110 beats/min, accompanied by meconium-stained amniotic fluid, decreased or irregular fetal movement, or fetal scalp blood pH <7.25. Very low birth weight was defined as neonatal birth weight <1.0 kg.

Preeclampsia was diagnosed as gestational hypertension (blood pressure ≥140/90 mmHg after 20 weeks of gestation) combined with 24-hour urinary protein excretion ≥0.3 g/L or systemic organ damage (hepatic dysfunction, renal dysfunction, thrombocytopenia, etc.).

Statistical analysis

SPSS 25.0 software was used for statistical analysis. Quantitative data were expressed as mean ± standard deviation ($\bar{x}$ ± sd), and independent samples t-test was used for inter-group comparison. Count data were expressed as cases and percentages, and Chi-square (χ^2) test was used for inter-group comparison. Spearman's rank correlation analysis was used to analyze the correlations between serum trace elements, inflammatory markers, PROM occurrence and adverse pregnancy outcomes.

Multivariate binary logistic regression analysis was performed with PROM occurrence as the dependent variable to screen independent influencing factors and adjust confounding factors. $P<0.05$ was considered statistically significant.

Results

Comparison of baseline characteristics

There were no significant differences in maternal age, gravidity, and parity between the groups (all P>0.05). Compared with the normal group, the PROM group had shorter gestational age, lower pre-pregnancy body mass index (BMI) and shorter cervical length, and higher proportions of previous PROM/preterm birth history, reproductive tract infection and smoking history (all $P<0.05$; **Table 1**).

Comparison of serum trace element levels

There were no significant differences in serum zinc and iron levels between the groups (all $P>0.05$). The PROM group had significantly lower serum calcium and magnesium levels, and significantly higher serum phosphorus levels than the normal group (all $P<0.05$) (**Figure 1**).

Comparison of serum inflammatory factor levels

Serum inflammatory factor levels (IL-6 and MMP-9) in the PROM group were significantly higher than those in the normal group (both P<0.01, **Figure 2**).

Comparison of adverse pregnancy outcome incidence

In the PROM group, adverse pregnancy outcomes included 4 cases (7.02%) of fetal distress, 5 cases (8.77%) of preterm birth, 2 cases (3.51%) of macrosomia, 1 case (1.75%) of fetal growth restriction, 1 case (1.75%) of spontaneous miscarriage and 1 case (1.75%) of very low birth weight infant, with no stillbirth cases. The total incidence of adverse pregnancy outcomes was 21.05% (12/57).

In the normal group, there were 5 cases of fetal distress (4.46%), 3 cases of preterm birth (2.68%), 7 cases of macrosomia (6.25%), 1 case of fetal growth restriction (0.89%) and 1 case of stillbirth (0.89%), with no miscarriage or very low birth weight cases. The total incidence of adverse pregnancy outcomes was 14.29% (16/112). Although the adverse pregnancy out-

Table 1. Contrast of baseline characteristics of all subjects

Information	PROM group	Normal group	t or χ^2	*P*
n	57	112		
Age (years)	28.72±5.01	28.63±4.85	-0.107	0.915
Gestational age	38.17±2.43	39.20±1.00	3.874	0.000
Number of pregnancies	2.21±1.28	2.29±1.18	0.427	0.670
Parity	1.49±0.60	1.53±0.55	0.384	0.702
Previous PROM/history of preterm birth [n (%)]	11 (19.30)	5 (4.46)	4.632	0.031
Reproductive tract infection [n (%)]	14 (24.56)	12 (10.71)	5.682	0.017
Smoking history [n (%)]	7 (12.28)	5 (4.46)	4.051	0.044
Pre-pregnancy BMI (kg/m^2)	21.34 ± 2.67	22.85 ± 2.91	3.347	0.001
Cervical length (mm)	31.62 ± 5.18	35.47 ± 4.92	4.721	0.000

Note: BMI: body mass index; PROM: premature rupture of membranes.

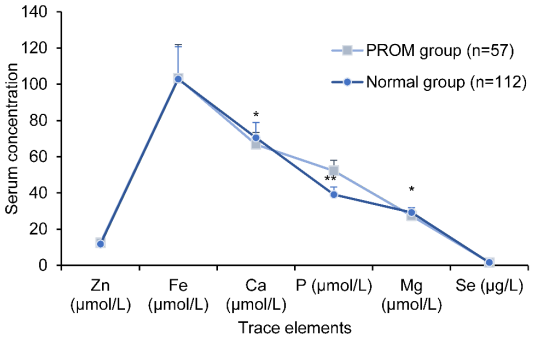


Figure 1. Comparison of serum trace element levels. Compared with the PROM group, *P<0.05, **P<0.01, PROM: premature rupture of membranes; Zn: zinc; Fe: iron; Ca: calcium; P: phosphorus; Mg: magnesium; Se: selenium.

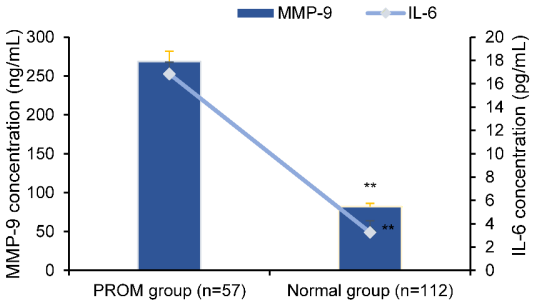


Figure 2. Comparison of serum inflammatory factor levels. Compared with the PROM group, **P<0.01, PROM: premature rupture of membranes; IL-6: Interleukin 6; MMP-9: matrix metalloproteinase 9.

come incidence was higher in the PROM group, the difference was not statistically significant (χ^2=1.251, *P*=0.263) (**Figure 3**).

Correlation between serum indicators and PROM/adverse pregnancy outcomes

Spearman correlation analysis showed that serum magnesium and selenium levels were positively correlated with serum iron levels (r=0.208, r=0.340, all *P*<0.01), and negatively correlated with serum phosphorus levels (r=-0.196, r=-0.226, both *P*<0.05). Serum calcium level was negatively correlated with PROM occurrence (r=-0.177, *P*<0.05). Serum IL-6 level was positively correlated with MMP-9 level (r=0.521, *P*<0.01). Both IL-6 and MMP-9 levels were positively correlated with PROM occurrence (r=0.437, r=0.396, both *P*<0.01). However, IL-6 and MMP-9 levels had no significant correlation with adverse pregnancy outcomes (both *P*>0.05). Furthermore, serum selenium level was not correlated with IL-6 and MMP-9 levels (both *P*>0.05) (**Figure 4**).

PROM and adverse pregnancy outcomes in different selenium subgroups

According to serum selenium reference levels, all subjects were divided into three subgroups: low selenium group (<35.0 μg/L, n=31), normal selenium group (35.0-110.0 μg/L, n=124) and high selenium group (>110.0 μg/L, n=14).

The PROM incidence of the three subgroups was 48.39% (15/31), 29.84% (37/124) and 35.71% (5/14), respectively, with significant inter-group differences (χ^2=6.172, *P*=0.046). The adverse pregnancy outcome incidence was 32.26% (10/31) in the low selenium group, 16.94% (21/124) in the normal selenium group and 14.29% (2/14) in the high selenium group. Although the low selenium group had the highest incidence, the inter-group difference was not statistically significant (χ^2=4.018, P=0.134) (**Table 2**).

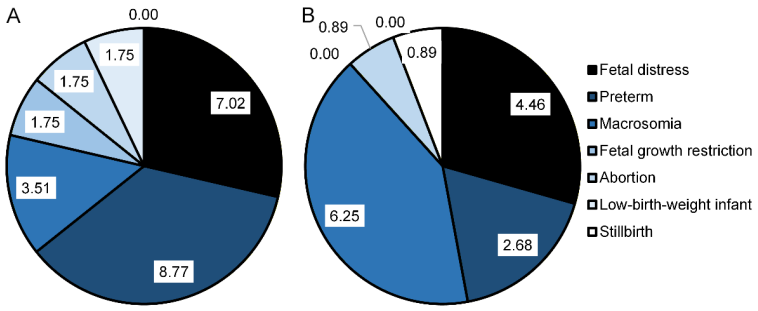


Figure 3. Comparison of adverse pregnancy outcome incidence. A. PROM group; B. Normal group. PROM: premature rupture of membranes.

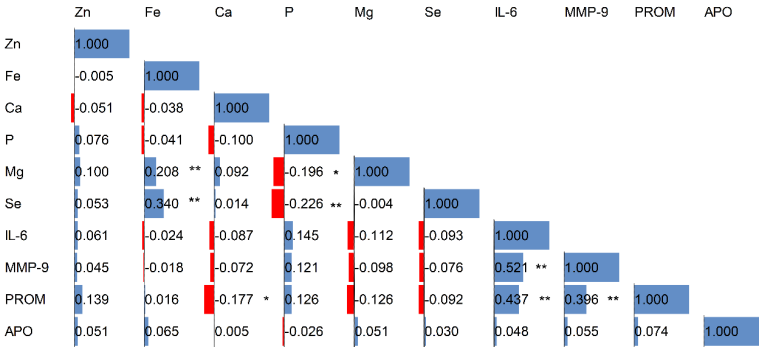


Figure 4. Correlation between serum indicators and PROM/adverse pregnancy outcomes. Blue indicates positive correlation, and red indicates negative correlation. *P<0.05, **P<0.01, APO: adverse pregnancy outcome; PROM: premature rupture of membranes; IL-6: Interleukin 6; MMP-9: matrix metalloproteinase 9; Zn: zinc; Fe: iron; Ca: calcium; P: phosphorus; Mg: magnesium; Se: selenium.

Multivariate logistic regression analysis of PROM risk factors

Multivariate logistic regression analysis was performed with PROM as the dependent variable (occurrence = 1, non-occurrence = 0). Independent variables included selenium grouping, gestational age, previous PROM/preterm birth history, reproductive tract infection, smoking history, pre-pregnancy BMI and cervical length.

After adjusting for all confounding factors, low serum selenium level was an independent risk factor for PROM (OR=2.31, 95% CI: 1.05-5.08, *P*=0.037). No significant correlation was found between high selenium level and PROM risk (odds ratio [OR]=1.30, 95% CI: 0.41-4.12, *P*=0.658).

In addition, previous PROM/preterm birth history (OR=3.50, *P*=0.003) and reproductive tract infection (OR=2.78, *P*=0.009) were independent risk factors for PROM, while longer gestational age (OR=0.58, *P*<0.001) and longer cervical length (OR=0.84, *P*=0.007) were protective factors against PROM. Pre-pregnancy BMI and smoking history had no significant correlation with PROM (both *P*>0.05) (**Table 3**).

Receiver operating characteristic curve analysis of serum selenium for PROM prediction

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the predictive value of serum selenium for PROM. The area under the curve (AUC) of serum selenium was 0.557 (95% CI: 0.465-0.649, *P*>0.05), with the optimal cut-off value of 36.2 μg/L, corresponding to a sensitivity of 54.4% and a specificity of 56.3%. The results indicated that serum selenium alone had limited predictive value for PROM (**Figure 5**).

A typical case of 34-week gestation with serum selenium of 28.6 μg/L (low selenium level) was selected for ultrasonic imaging observation. The patient had severe oligohydramnios with amniotic fluid index of 3.2 cm, and fetal limbs closely adhered to the uterine wall (clinging sign). The cervical length was 3.1 cm with closed internal os, which directly reflected the amniotic fluid loss after PROM (**Figure 6**).

Discussion

PROM is a common high-risk pregnancy complication with increasing clinical incidence in recent years, which seriously endangers maternal and fetal safety [16, 17]. Gestational serum trace element levels can objectively reflect the nutritional status of mothers and fetuses [18, 19], and abnormal trace element metabolism is closely related to various adverse pregnancy outcomes [20]. This study systematically analyzed the correlation between common serum trace elements and PROM, and further clarified the predictive value of selenium for PROM risk.

Table 2. PROM and adverse pregnancy outcomes in different selenium subgroups

Selenium level	Countdown	Number of exceptions for premature membranes (%)	Number of adverse pregnancy outcomes (%)
Low selenium group	31	15 (48.39%)	10 (32.26%)
Normal selenium group	124	37 (29.84%)	21 (16.94%)
High selenium group	14	5 (35.71%)	2 (14.29%)
χ^2		6.172	4.018
P-value		0.046	0.134

Table 3. Multivariate logistic regression analysis of PROM risk factors

Variable	B	S.E.	Wald χ^2	*P*-value	OR (Exp(B))	95% CI
Reference: Normal selenium group						
Low selenium group	0.837	0.402	4.335	0.037	2.31	1.05-5.08
High selenium group	0.247	0.579	0.182	0.670	1.28	0.41-3.99
gestational week	-0.512	0.143	12.823	<0.001	0.60	0.45-0.79
Previous PROM/history of preterm birth (yes vs. no)	1.252	0.421	8.844	0.003	3.50	1.53-8.00
Reproductive tract infection (yes vs. no)	1.021	0.392	6.786	0.009	2.78	1.29-5.98
Smoking (Yes vs. No)	0.621	0.523	1.410	0.235	1.86	0.67-5.18
Pre pregnancy body mass index (kg/m^2)	-0.018	0.059	0.093	0.760	0.98	0.87-1.11
Cervical length (mm)	-0.172	0.064	7.225	0.007	0.84	0.74-0.95
constant	23.108	6.247	13.689	<0.001	-	-

Note: Model fitting information: -2Log Likelihood = 186.42, Nagelkerke R^2=0.187, Hosmer-Lemeshow test P=0.423, BMI: body mass index, PROM: premature rupture of membranes, S.E.: standard error, OR: odds ratio, CI: confidence interval.

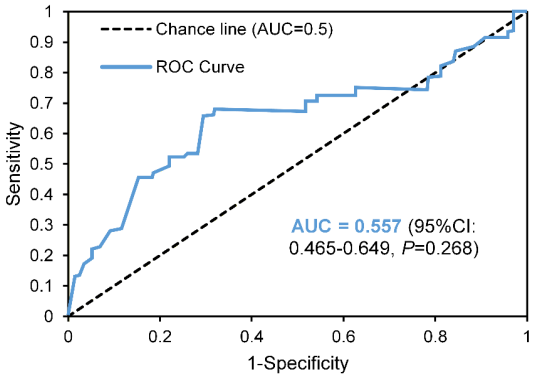


Figure 5. ROC curve analysis of serum selenium for PROM prediction. ROC: Receiver Operating Characteristic; AUC: area under the curve.

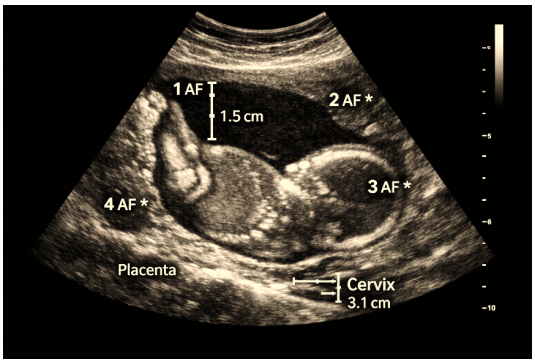


Figure 6. Ultrasound image of a patient with PROM (at 34 weeks of gestation). 1 AF: maximum vertical depth of amniotic fluid in the first quadrant (AF, amniotic fluid, PROM: premature rupture of membranes).

This study found that PROM patients had lower serum calcium and magnesium levels and higher serum phosphorus levels than healthy pregnant women. Calcium maintains cell junction stability and extracellular matrix integrity, and serves as a key cofactor for collagen cross-linking. Hypocalcemia can cause abnormal cross-linking and arrangement of fetal membrane collagen fibers, reduce fetal membrane tensile strength, and damage fetal membrane biomechanical stability, thereby inducing PROM [21]. In addition, hypocalcemia can upregulate the activities of phospholipase A2 and matrix metalloproteinases (including MMP-9), which are core enzymes for fetal membrane collagen degradation [22]. As a typical pro-inflammatory factor, IL-6 can activate the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling pathway to promote MMP-9 expression. Consistent with previous

studies, this study confirmed that PROM patients had significantly elevated serum IL-6 and MMP-9 levels, and the two indicators were positively correlated. The "hypocalcemia-inflammation-MMP-9" axis jointly promotes fetal membrane matrix degradation and participates in PROM pathogenesis.

Magnesium can relax uterine smooth muscle and reduce uterine excitability. Low serum magnesium levels increase uterine hypersensitivity, which is closely related to preterm labor and fetal membrane rupture [23, 24]. Elevated serum phosphorus in PROM patients may be related to gestational renal metabolism and bone metabolism abnormalities, and its specific causal mechanism needs further verification [25].

Stratified analysis confirmed that low serum selenium level was significantly associated with increased PROM risk. After adjusting for multiple confounding factors, low selenium remained an independent risk factor for PROM, which is consistent with previous research conclusions [26]. Selenium exerts biological functions through selenoproteins. Selenium deficiency reduces glutathione peroxidase 4 activity, induces ferroptosis of amniotic epithelial cells, activates the nuclear factor kappa-B (NF-κB) pathway to upregulate MMP-9 expression and degrade type IV collagen, and inhibits selenoprotein S (SelS) expression to aggravate endoplasmic reticulum stress and local inflammation [27-29]. The above three mechanisms jointly destroy fetal membrane integrity and trigger PROM.

Notably, ROC analysis showed that the single indicator of serum selenium had limited predictive value for PROM. This result does not contradict the significant correlation between low selenium and PROM. Statistical correlation reflects the association between indicators and diseases, while AUC reflects the independent diagnostic and predictive ability of a single indicator. PROM is a multifactorial disease affected by multiple nutritional, inflammatory and clinical factors. The overlapping distribution of selenium levels between case and control groups, as well as the U-shaped biological effect of selenium and individual genetic differences, lead to the low independent predictive value of serum selenium. Nevertheless, selenium deficiency is still a definite independent risk factor for PROM.

This study showed that the PROM group had a higher incidence of adverse pregnancy outcomes than the normal group, mainly manifested as increased fetal distress and preterm birth cases. Amniotic fluid loss after PROM disrupts intrauterine environmental stability, induces uterine contractions and cervical dilation, and causes preterm birth [30, 31]. Reduced amniotic fluid volume also increases fetal mechanical compression, impairs placental oxygen and nutrient transport, and leads to fetal distress and fetal growth retardation [32].

Correlation analysis showed that serum magnesium and selenium levels were positively correlated with iron levels and negatively correlated with phosphorus levels. This indicates that the metabolic utilization of magnesium and selenium is synergistic with iron metabolism. Iron deficiency anemia is a confirmed risk factor for PROM, which can reduce placental blood supply and amniotic fluid volume, and damage fetal development [33-35]. As an important antioxidant trace element, selenium can resist gestational oxidative stress and protect maternal and fetal cells. Selenium deficiency weakens maternal antioxidant defense and immune function, increases susceptibility to reproductive tract infection and inflammatory response, and further increases the risk of PROM and adverse pregnancy outcomes [36-39]. In addition, serum calcium deficiency can cause cervical relaxation, which is another potential mechanism for PROM occurrence [40].

Gestational serum trace element levels are affected by diet, individual physical differences and environmental factors. Different trace element types and deficiency degrees exert different effects on pregnancy outcomes. Targeted monitoring and supplementation of trace elements during pregnancy are of great significance for reducing PROM and adverse pregnancy risks.

Conclusion

Gestational serum selenium, calcium, magnesium, phosphorus and iron levels are closely related to PROM occurrence and adverse pregnancy outcomes. Low serum selenium level is an independent risk factor for PROM, and abnormal calcium, magnesium and phosphorus metabolism combined with inflammatory activation jointly promotes PROM pathogenesis.

This study has certain limitations. All blood samples were collected after PROM onset, so the causal relationship between selenium deficiency and PROM cannot be fully confirmed. In addition, this study only analyzed the cross-sectional correlation between single trace element levels and pregnancy outcomes, without dynamic monitoring of trace element fluctuations during pregnancy.

In the future, large-sample prospective cohort studies and dynamic gestational monitoring will be carried out to further clarify the causal mechanism of trace elements in PROM and adverse pregnancy outcomes, and provide more accurate guidance for clinical prenatal nutritional intervention.

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Disclosure of conflict of interest

None.

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