Environmental Health

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Association between light rare earth elements in maternal plasma and the risk of spontaneous preterm birth: a nested case-control study from the Beijing birth cohort study

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Abstract

Background Parental exposure to rare earth elements (REEs) could increase the risk of premature rupture of membranes, a major cause of spontaneous preterm birth (SPB). In addition, different subtypes of SPB, such as spontaneous preterm labor (SPL) and preterm premature rupture of membranes (PPROM), may have different susceptibility to environmental exposure. Therefore, we investigated the potential associations between REE exposure in different trimesters and SPB and its subtypes.

Methods A nested case-control study was performed. We included 244 women with SPB as cases and 244 women with full-term delivery as controls. The plasma concentrations of light REEs were measured in the first and third trimesters. Logistic regression was used to analyze the associations between single REE levels and SPB, and Bayesian kernel machine regression (BKMR) was used to analyze the mixed-exposure effect.

Results Exposure to light REEs was associated with SPB and its subtypes only in the third trimester. Specifically, the intermediate- and highest-tertile concentration groups of La and the highest-tertile concentration group of Sm were associated with an increased risk of SPL, with adjusted odds ratios (AORs) of 2.00 (95% CIs: 1.07–3.75), 1.87 (95% CIs: 1.01–3.44), and 1.82 (95% CIs: 1.00–3.30), respectively. The highest-tertile concentration group of Pr was associated with an increased risk of PPROM, with an AOR of 1.69 (95% CIs: 1.00–2.85). Similar results were also found in BKMR models.

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Conclusions La and Sm levels in plasma may be associated with the risk of SPL, and Pr levels in plasma may be associated with the risk of PPROM.

Keywords Rare earth elements, Spontaneous preterm birth, Nested case-control study, Preterm premature rupture of membranes, Spontaneous preterm labor

Introduction

Preterm birth, which is widely defined as all births at < 37 gestational weeks, is the leading cause of death in children aged under 5 years worldwide and may increase the risk of long-term morbidities [1, 2]. Approximately 5–7% of neonates, or one million neonates per year, are affected by preterm birth in China [1–3]. Preterm birth can be classified as spontaneous preterm labor (SPL), preterm premature rupture of membranes (PPROM), and provider-initiated preterm birth (induced labor or elective cesarean delivery for maternal and fetal indications) [4, 5]. SPL and PPROM are both designated spontaneous preterm birth (SPB) [4]. The causes of SPB are unclear, although some risk factors have been reported, including infection, poor nutritional status, and maternal age [4]. Some studies have found that exposure to certain trace elements, such as copper, manganese, mercury, and lead, may be related to SPB [6–9]. Liu et al. found that parental exposure to rare earth elements (REEs) could increase the risk of premature rupture of membranes, a major cause of SPB [10]. However, to the best of our knowledge, there is no evidence of associations between REE exposure and SPB.

REEs include scandium, yttrium, and 15 lanthanides: lanthanum (La), cerium (Ce), praseodymium (Pr), neodymium (Nd), promethium (Pm), samarium (Sm), europium (Eu), gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium and lutecium [11]. They are generally classified as light REEs(La, Ce, Pr, Nd, Pm, Sm, and Eu) and heavy REEs(other elements except for scandium) [11, 12]. REEs are widely used in electronics, manufacturing, medicine, and agriculture [13]. People can be exposed to them through water, food, the atmosphere, and through some medical tests [13, 14]. China has the largest reserves of REEs and contributes more than 90% of the global supply [12, 13]. Mining in China has resulted in higher REE concentrations in environmental components (i.e., soil, water, and atmosphere) than in other countries [15, 16]; this may be worsened by nearby coal burning and traffic emissions [16]. It has also been found that REE concentrations in food are higher in China than in other countries [17, 18]. Thus, the levels of environmental exposure to and the health risks of REEs in China are likely high.

Previous studies have found that environmental REE exposure can lead to excess health risks in pregnancy. With the exception of a premature rupture of membranes, Liu et al. also found that parental REE exposure may be associated with neonatal thyroid-stimulating hormone levels [10, 19]. Two case-control studies conducted in Shanxi Province, China, found that REE exposure increased the risk of birth defects, including orofacial clefts and neural tube defects [20, 21]. Li et al. found that high La exposure may increase the failure risk of in vitro fertilization-embryo transfer [22]. Previous in vivo and in vitro experiments have demonstrated that high REE exposure can cause increased oxidative stress levels, inflammatory cytokine expression, cytogenetic toxicity, neurotoxicity, and liver toxicity [23–25]. Oxidative stress and inflammation are usually thought to be detrimental factors in preterm birth pathology [26, 27].

We hypothesized that high REE exposure could increase the risk of SPB. In addition, previous studies have suggested that SPL and PPROM may be caused by different pathways and could have different susceptivity to environmental exposure [28, 29]. Hence, we further explored the associations between REE exposure and SPL and PPROM. Only light REEs were analyzed due to the low detection rate of heavy REEs.

Methods

Study design and participants

This nested case-control study was based on the Beijing Birth Cohort Study (registered on the Chinese Clinical Trial Registry: ChiCTR2200058395) at Beijing Obstetrics and Gynecology Hospital. Pregnant women were recruited into the cohort if they consented, and the following inclusion criteria were met: 18–44 years old, planned to accept routine prenatal examinations and delivery at Beijing Obstetrics and Gynecology Hospital, first parental examination was at < 14 gestational weeks, and provided signed informed consent. From July 2018 to October 2020, 32,496 pregnant women were recruited. Maternal sociodemographic data were collected by questionnaires when recruiting. This study was approved by the Ethics Committee of the Beijing Obstetrics and Gynecology Hospital (approval number: 2018-KY-009-01), and all participants provided signed informed consent. Pregnant women were excluded if they were lost to follow-up (n = 946), had a stillbirth (n = 46), had a baby with birth defects (n = 968), had multiple births (n = 1030), or had cervical insufficiency (n = 203) (Fig. 1). Gestational weeks were estimated counting from the women's last menstrual period and were verified by ultrasonography in the first trimester. A live birth at ≥ 28 and < 37 gestational weeks was diagnosed as preterm birth according to

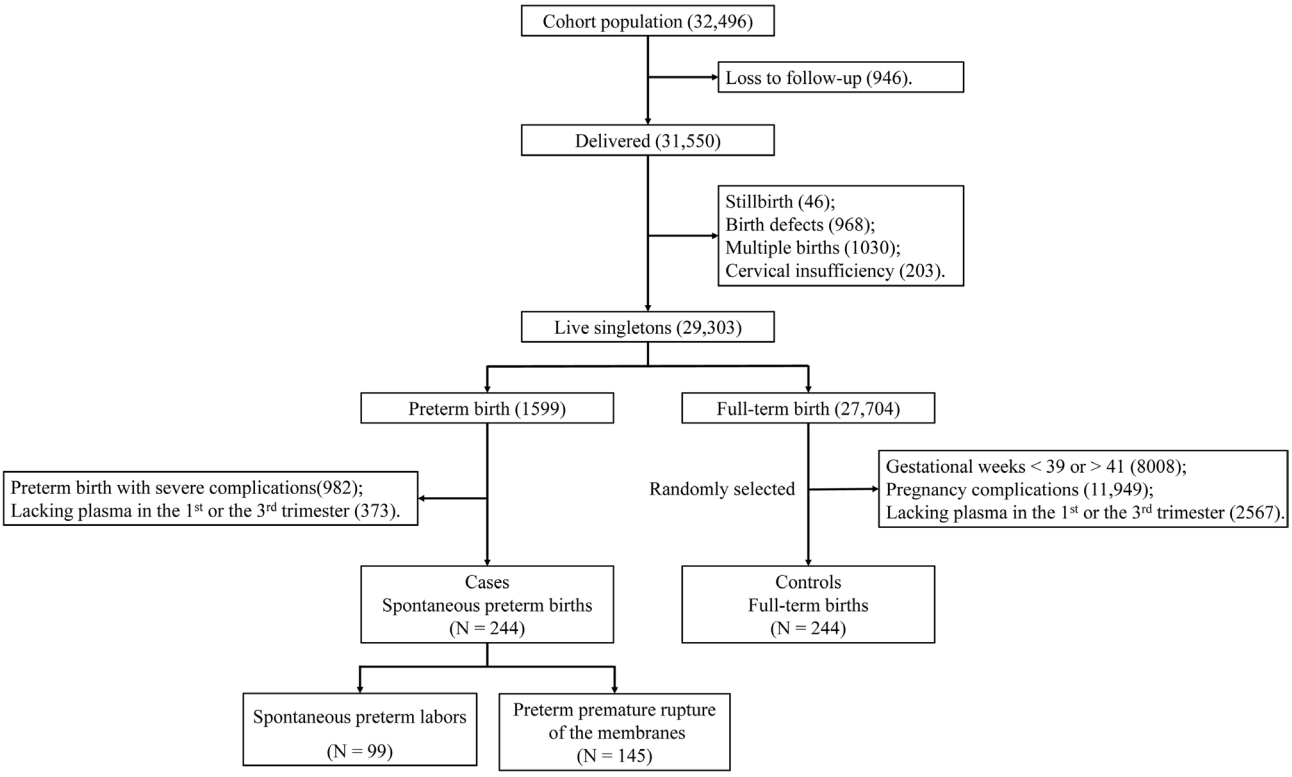

Fig. 1 Selection of cases and controls from the cohort

the guideline for preterm birth in China [30]. A total of 29,303 women remained, including 1599 preterm births and 27,704 full-term births.

Of all preterm births, 982 were induced labor or elective cesarean delivery for severe complications (i.e., severe preeclampsia, eclampsia, HELLP syndrome, cholestasis, fetal distress, placental abruption, placenta previa and acute appendicitis) and 373 women lacked plasma samples in the first or the third trimester; these two groups were further excluded. The subtypes of SPB were defined based on the characteristics of the initiation of labor [5, 31, 32]. SPL was initiated by spontaneous contractions and cervical dilation, without premature rupture of membranes. PPROM was initiated by premature rupture of membranes. Of all full-term births, 22,524 women were further excluded due to their gestational weeks being <39 or >41, have being diagnosed with pregnancy complications (gestational hypertension, gestational diabetes mellitus, fetal growth restriction, and others), or lacking plasma samples in the first or the third trimester. Then, 244 full-term births (controls) were randomly selected at a ratio of 1:1. Thus, 244 cases (i.e., SPB) and 244 controls were included in our study. Among these, 99 women had SPL and 145 had PPROM.

Laboratory analyses

In the first and third trimester, maternal blood was collected by healthcare workers into vacuum blood collection tubes lined with ethylenediaminetetraacetic acid (EDTA). After collection, the samples were centrifuged at 1680 g for 10 min within 1 h, and plasma was extracted from the supernatant, stored at −80 ℃, and thawed before analysis. The plasma concentrations of REEs were measured via inductively coupled plasma-mass spectrometry (ICP-MS, ELAN DRC II; PerkinElmer, USA). Pm values were not analyzed in the lab due to its radioactivity. Quantitative analyses were conducted at the Central Laboratory of Biological Elements in Peking University Health Science Center, and experiments were performed following the China Metrology Accreditation protocols. The specific methods used are described in previous studies, and some instrument conditions are shown in Text S1 [22, 33]. Briefly, 0.1 mL plasma was spiked with 0.1 mL internal standard (rhenium, Re) and 1.8 mL 1% nitric acid, and then the mixture was analyzed via ICP-MS. Standard materials (National Standard Material Center in China, standard materials of rare earth elements in human hair, GBW09101a) were used to assess accuracy, and the measured values fit the reference values (Table S1). The method detection limits (MDLs) and method quantification limits are shown in Table S1. The detection rates of most light REEs were greater than

85%, except for Eu (Table S2). In the third trimester, only 243 controls were included because one plasma sample was not adequate for laboratory analyses.

Statistical analysis

The characteristics of pregnant women in different groups were compared using the t-test, ANOVA test, and Pearson chi-square test. The concentrations of REEs below MDLs were replaced by $1/\sqrt{2}$ of MDLs for the statistical analysis, except for correlation analysis. Due to the nonnormal distribution of the data, the concentrations of REEs were log(e)-transformed. The median, the lower quartile, and the upper quartile were used to describe the distribution of REEs. The Mann-Whitney U test and the Kruskal-Wallis test were used to compare concentrations among different groups. Spearman's correlation coefficient was determined to assess correlations between REEs.

Then, the concentrations of REEs were classified into high, intermediate, and low exposure groups based on their tertiles. Eu was classified into low (<MDL) and high (≥MDL) groups because of its low detection rate. Binary logistic regression was used to obtain the odds ratio (OR) and the corresponding 95% confidence intervals (CIs) of SPB. Multinomial logistic regression was used to obtain the ORs and 95% CIs of different subtypes of SPB (i.e., SPL and PPROM). Ethnicity, education level, age, prepregnancy BMI, parity, and family income were considered potential confounders based on previous studies [4, 34]. These were treated as categorical variables (the specific classification is shown in Table 1) and adjusted in logistic models to obtain the adjusted OR (AOR). We combined two age groups (20–24 and 25–29) into one (20–29), and two BMI groups (24–28 and ≥28) into one (≥24), considering that only one woman in the case group was <25 years old and only three women in the control group were ≥28 kg/m^2. Each element was modeled separately in logistic regression models. Statistical significance was defined as a two-tailed $P<0.05$. Due to the high correlations between REEs and mixed exposure in general observations, Bayesian kernel machine regression (BKMR) was applied to verify the association between REE exposure and the risk of SPB and its subtypes [35]. Posterior inclusion probability (PIP) was used to assess the relative importance of each REE in BKMR. Due to the low detection rate of Eu, we excluded it from the BKMR to test the robustness of the results. Sensitivity analysis was performed in pregnant women without group B Streptococcus (GBS) infection, considering that this was an important risk factor for preterm birth [36, 37]. All statistical analyses were performed using R software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

Table 1 The characteristics of pregnant women in cases and controls

Characteristics [a]	Case (n = 244)	Control (n = 244)	*P*[b]
Age (year)			
Mean ± SD	31.9 ± 4.0	31.1 ± 3.8	0.018
20–29	76 (31.1)	85 (34.8)	0.128
30–34	101 (41.4)	111 (45.5)	
≥ 35	67 (27.5)	48 (19.7)	
BMI (kg/m^2)			
Mean (SD)	22.1 ± 3.2	21.2 ± 2.4	< 0.001
Slim (BMI < 18.5)	29 (11.9)	29 (11.9)	0.003
Normal (18.5 ≤ BMI < 24)	154 (63.1)	183 (75.0)	
Overweight (BMI ≥ 24)	61 (25.0)	32 (13.1)	
Ethnicity			
Han	223 (91.4)	226 (92.6)	0.738
Others	21 (8.6)	18 (7.4)	
Education level			
Junior college and below	66 (27.0)	49 (20.1)	0.164
Undergraduate	123 (50.4)	140 (57.4)	
Postgraduate and above	55 (22.5)	55 (22.5)	
Family income (yuan/month)			
< 10,000	61 (25.0)	50 (20.5)	0.336
10,000–19,999	96 (39.3)	93 (38.1)	
≥ 20,000	87 (35.7)	101 (41.4)	
Parity			
Primiparous (= 1)	157 (64.3)	186 (76.2)	0.006
Multiparous (≥ 2)	87 (35.7)	58 (23.8)	
GBS infection			
Yes	9 (3.7)	15 (6.1)	0.295
No	235 (96.3)	229 (93.9)	
Smoke			
No	244 (100)	244 (100)	/
Infant sex			
Male	136 (55.7)	125 (51.2)	0.364
Female	108 (44.3)	119 (48.8)	
Sampling times (gestational weeks)			
First trimester	8.3 ± 1.6	8.3 ± 1.7	0.892
Third trimester	33.8 ± 0.9	33.8 ± 1.1	0.824

[a]: Data are presented as "mean ± SD" or "number (percentage)"

[b]: Statistical test by Pearson chi-square test when variables were categorized and t-test when variables were continuous

Result

The characteristics of the pregnant women who were included in the final analysis are presented in Table 1. The mean age of all included women was 31.5 ± 3.9 years old. The ranges of gestational weeks were 33–36 in the case group and 39–41 in the control group. No women were smokers. Ethnicity, education level, family income, and GBS infection status were comparable between the case and control groups. However, age and BMI were higher in the case group. Larger proportions of multiparous and/or overweight women were found in the case group. The sampling time of plasma was comparable between

the groups both in the first and third trimester. Similar results were also found in the SPL, PPROM, and control groups (Table S3).

La was the most common REE in plasma in our population. The median (quartiles) concentrations of La in our population were 0.071 (0.054–0.088) ng/mL in the first trimester and 0.073 (0.059–0.096) ng/mL in the third. Most REEs were positively related to each other in both the first and third trimesters, except for Eu (Fig. 2). La and Ce were most positively related, with correlation coefficients ranging from 0.7 to 0.8. In different trimesters, while negative correlations were found among REEs, their correlation coefficients were relatively small. The concentrations of REEs in different groups are shown in Table 2. Unlike what we anticipated, the differences in REE concentrations were not statistically significant between the case and control groups. Similar results were also found among the SPL, PPROM, and control groups (Table S4).

Table 3 and S5 show the associations between REE exposure levels and the risk of SPB in the first and third trimesters. Overall, no significant association was found in the first trimester with or without adjustment for confounders (Table S5). For the third trimester, La and Pr were associated with SPB risk (Table 3). The intermediate exposure level for La significantly increased the risk of SPB, with an AOR of 1.70 (95% CIs: 1.07–2.68, $P=0.024$). However, no significant association was found between the high La exposure level and the risk of SPB ($P=0.281$). Compared to the low Pr exposure level, the high exposure level significantly increased the risk of SPB, with an AOR of 1.65 (95% CIs: 1.05–2.59, $P=0.031$). After classifying SPB into SPL and PPROM, similar results were found in the first trimester; however, using multinomial logistic models, different results were found in the third trimester (Fig. 3 and Table S6). An increased risk of SPL was found for pregnant women with intermediate La exposure levels (AOR=2.00, 95% CIs: 1.07–3.75, $P=0.030$), high La exposure levels (AOR=1.87, 95% CIs: 1.01–3.44, $P=0.045$), and high Sm exposure levels (AOR=1.82, 95% CIs: 1.00–3.30, $P=0.049$) relative to the low exposure. We still found that La and Sm had a dose-response relationship with the risk of SPL (Table S6). Relative to the low exposure level, the AORs of the intermediate and high exposure levels were 2.16 and 2.00 for La, and 1.48 and 1.82 for Sm, respectively. For PPROM, an

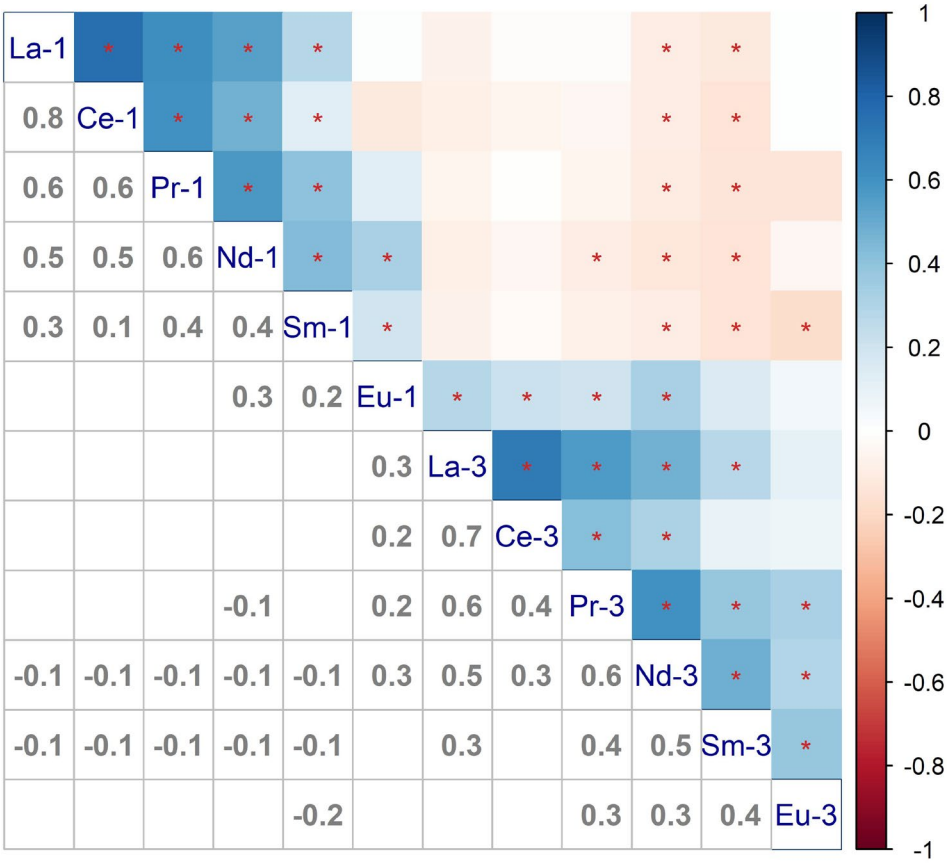

Fig. 2 Correlations among different elements during different trimesters. -1: first trimester; -3: third trimester; *: $P<0.05$; the lower-left part showed the correlation coefficients

Table 2 Comparison of median concentrations of rare earth elements between cases and controls

Trimester	Elements	Case (n = 244)	Control (n = 244 [a])	*P*[b]
First	La	0.073 (0.059, 0.093) [c]	0.073 (0.058, 0.099)	0.708
	Ce	0.118 (0.085, 0.159)	0.126 (0.091, 0.165)	0.347
	Pr	0.031 (0.023, 0.040)	0.030 (0.024, 0.038)	0.674
	Nd	0.163 (0.113, 0.220)	0.161 (0.115, 0.231)	0.882
	Sm	0.047 (0.021, 0.080)	0.048 (0.024, 0.076)	0.718
	Eu	0.014 (0.014, 0.016)	0.014 (0.014, 0.014)	0.527
Third	La	0.072 (0.055, 0.090)	0.070 (0.052, 0.088)	0.217
	Ce	0.103 (0.073, 0.143)	0.102 (0.071, 0.134)	0.234
	Pr	0.031 (0.024, 0.040)	0.030 (0.021, 0.037)	0.111
	Nd	0.179 (0.115, 0.245)	0.173 (0.118, 0.234)	0.453
	Sm	0.055 (0.029, 0.096)	0.049 (0.022, 0.091)	0.355
	Eu	0.014 (0.014, 0.026)	0.014 (0.014, 0.023)	0.485

[a]: In the third trimester, only 243 controls were included because one plasma sample was not adequate for laboratory analyses

[b]: Statistical test by the Mann-Whitney U test

[c]: Units: ng/mL; Data are presented as "median (lower quartile, upper quartile)"

Table 3 Association between rare earth elements and SPB in the third trimester

Elements	Case	Control	OR	AOR
La				
low	74 (30.3)	89 (36.6)	1.00	1.00
intermediate	90 (36.9)	72 (29.6)	1.50 (0.97–2.33)	1.70 (1.07–2.68) *
high	80 (32.8)	82 (33.7)	1.17 (0.76–1.81)	1.28 (0.81–2.02)
*P*_trend			0.471	0.289
Ce				
low	79 (32.4)	84 (34.6)	1.00	1.00
intermediate	79 (32.4)	83 (34.2)	1.01 (0.66–1.56)	1.05 (0.67–1.64)
high	86 (35.2)	76 (31.3)	1.20 (0.78–1.86)	1.25 (0.80–1.96)
*P*_trend			0.405	0.327
Pr				
low	77 (31.6)	86 (35.4)	1.00	1.00
intermediate	70 (28.7)	92 (37.9)	0.85 (0.55–1.32)	0.88 (0.56–1.37)
high	97 (39.8)	65 (26.7)	1.67 (1.07–2.59) *	1.65 (1.05–2.59) *
*P*_trend			0.023*	0.033*
Nd				
low	81 (33.2)	82 (33.7)	1.00	1.00
intermediate	79 (32.4)	83 (34.2)	0.96 (0.62–1.49)	1.04 (0.66–1.62)
high	84 (34.4)	78 (32.1)	1.09 (0.71–1.68)	1.12 (0.71–1.75)
*P*_trend			0.698	0.626
Sm				
low	74 (30.3)	89 (36.6)	1.00	1.00
intermediate	89 (36.5)	73 (30.0)	1.47 (0.95–2.27)	1.43 (0.91–2.24)
high	81 (33.2)	81 (33.3)	1.20 (0.78–1.86)	1.23 (0.78–1.92)
P_trend			0.405	0.365
Eu				
low	147 (60.2)	151 (62.1)	1.00	1.00
high	97 (39.8)	92 (37.9)	1.08 (0.75–1.56)	1.11 (0.76–1.62)

[a]: Adjusted for ethnicity (Han & others), education level (Junior college and below, Undergraduate & Postgraduate and above), age (20–29, 30–34 & ≥35), BMI (slim, normal & overweight), parity (Primiparous & Multiparous), and family income (< 10,000, 10,000–19,999 & ≥20,000)

*: $P < 0.05$

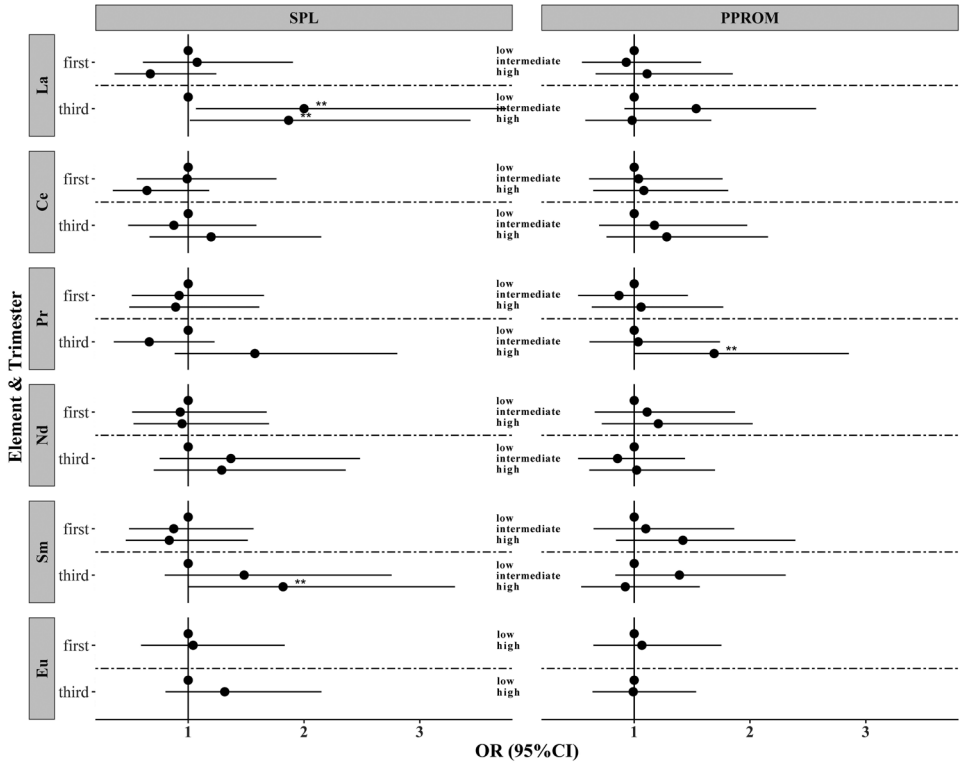

Fig. 3 Association between levels of rare earth elements in different trimesters and SPL and PPROM. Adjusted for ethnicity, education level, age, BMI, parity, and family income; **: $P<0.05$

increased risk was found for pregnant women only with high Pr exposure levels (AOR=1.69, 95% CIs: 1.00–2.85, P=0.049). No dose-relationship of REE exposure levels with PPROM was found in adjusted multinomial models. After excluding pregnant women with a GBS infection, an increased risk of SPL was still found in high La exposure levels and high Sm exposure levels, and an increased risk of PPROM was still found in high Pr exposure levels (Table S7).

Taking into account that the associations between REEs and SPL and PPROM were different and that no obvious association was found in the first trimester in former analyses, we used BKMR models only for SPL and PPROM in the third trimester. Figure 4 shows the exposure-response relationships between REEs and risks of SPL and PPROM in the third trimester. When other REEs were fixed at their median concentrations, and the models were adjusted for potential confounders, we found that La and Sm were positively associated with the risk of SPL, and Pr was positively associated with the risk of PPROM. Unlike the results in the multinomial models, Pr was negatively associated with the risk of SPL. Among all REEs, La (PIP=0.72) and Pr (PIP=0.34) contributed the most to SPL and PPROM, respectively (Table 4). When taking into account joint exposure effects, the increased risks of SPL and PPROM were associated with increased mixed REE exposure (Fig. 5). Considering the low detection rates of Eu, we excluded Eu in BKMR models to test the robustness of the results and the results did not change significantly (Figs. S1 and S2, Table S8). After excluding pregnant women with GBS infections, the results remained similar to the results obtained for all pregnant women (Figs. S3 and S4, Table S9).

Discussion

Our study explored the associations between light REE exposure in different trimesters and SPB and its subtypes. We found that the associations between La, Pr, and Sm and SPB existed only in the third trimester. Different associations between light REE exposure and SPL and PPROM were found. In the third trimester, high La and Sm exposure levels were associated with elevated risk of SPL, and a high level of Pr exposure was associated with an elevated risk of PPROM, both including and excluding pregnant women with GBS infection.

REE exposure levels were highly correlated with local concentrations of REEs in environmental components [15]. However, the concentrations of REEs in our study were much lower than those in people who live around REE mines (Table S10) [38]. REE exposure levels vary among people living in non-mining areas and differ by region, age, and sex [19, 39]. A previous study found that all light REEs existed in 11 major food categories and the major REEs consumed from foods were La and Ce [40].

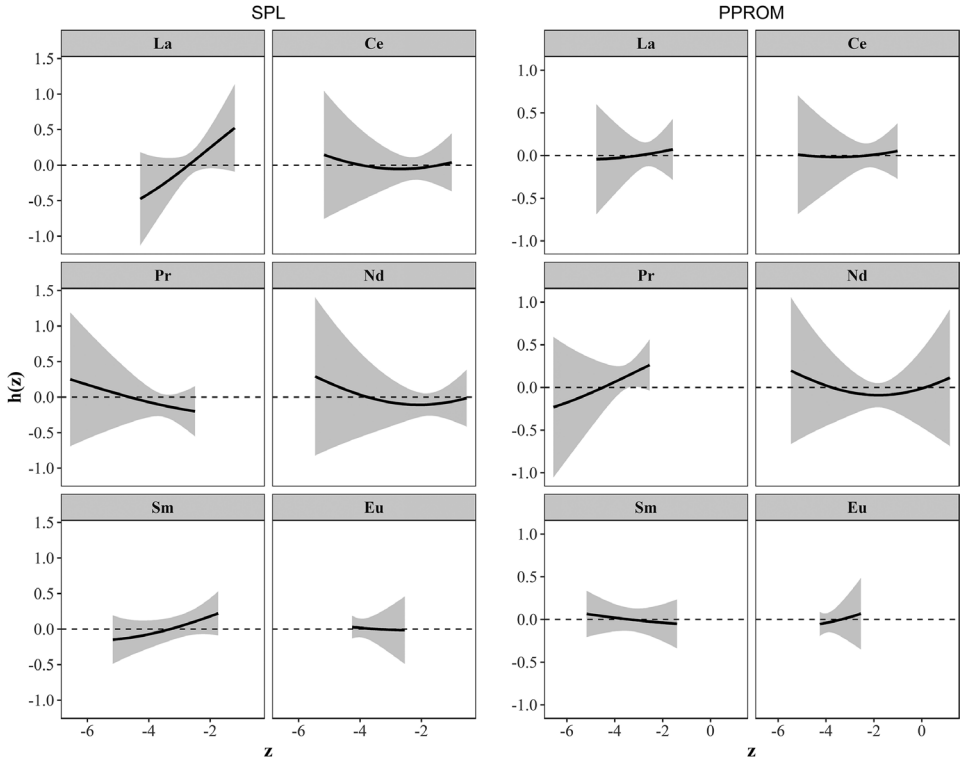

Fig. 4 Association between single rare earth element in the third trimester and SPL and PPROM. Adjusted for ethnicity, education level, age, BMI, parity, and family income

Table 4 PIP of rare earth element exposure in the third trimester

REE	SPL	PPROM
La	0.72	0.29
Ce	0.45	0.29
Pr	0.39	0.34
Nd	0.47	0.26
Sm	0.48	0.17
Eu	0.39	0.31

Another study suggested that traffic emissions could increase the concentrations of REEs in environmental components [16]. Different food habits and different family locations might lead to different REE exposure levels. A few previous studies have reported concentrations of REEs in pregnant women and newborns (Table S10). However, it is difficult to evaluate the relative exposure level between our study and other studies due to differences in sample types and populations. Only four studies

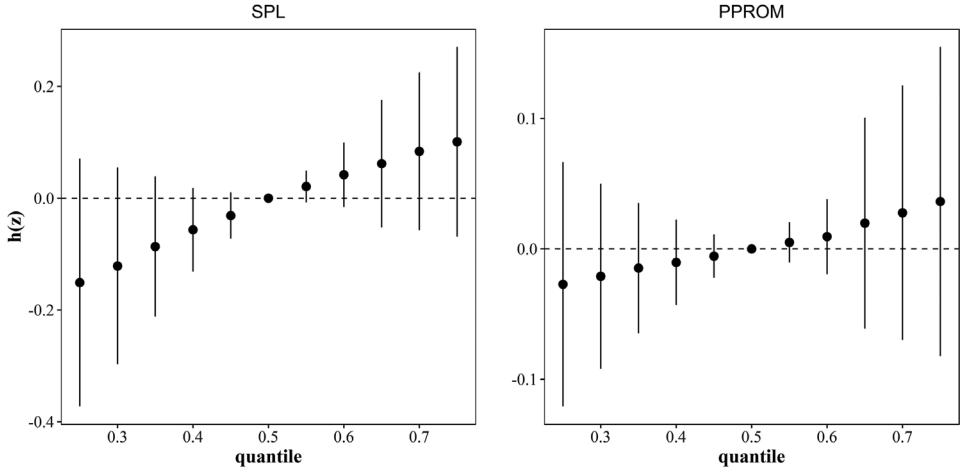

Fig. 5 Associations between mixed rare earth element exposures in the third trimester and SPL and PPROM. Adjusted for ethnicity, education level, age, BMI, parity, and family income

have reported concentrations of REEs in serum or plasma samples of pregnant women. The concentrations of most REEs in our study were higher than those in pregnant women in Shanxi, China [21, 41]. With the exception of Sm and Eu, levels of REE exposure in our study are comparable to those in other pregnant women in Beijing, China [39]. However, our concentrations were lower than those in pregnant women in Serbia [42]. The types of REEs that are most abundant in any given area, and their translocation patterns, may differ by regions, which could explain these differences between studies. More studies are necessary to investigate REE exposure levels of pregnant women in China, considering that China has the greatest reserves of REEs and the wild range of REE applications in the world.

No previous studies have reported the potential associations between REE exposure and SPB. Liu et al. explored the potential associations between REEs in urine before delivery with premature rupture of membranes and PPROM [10]. Unlike other studies of preterm birth, they focused on the premature rupture of membranes, and the control group did not exclude women with preterm births. They found that high concentrations of REEs in urine (i.e., La, Ce, Pr, Nd, Eu, and some other heavy REEs) before delivery might be a risk factor for PPROM. Another study, which focused on preterm birth, found that Sm in cord blood was associated with the risk of preterm birth in the elastic net model but was not associated with gestational age or preterm birth in further analysis [43]. Taking into account the different causes of SPB and provider-initiated preterm birth, the results for preterm birth have limited interpretations for SPB. In addition, sample type, sampling trimester, and participants' regions were also different between our study and the other two studies. These major differences could explain the different results among studies.

We found that La, Sm, and Pr exposure in the third trimester might increase the risk of SPL or PPROM. A previous study found that La exposure increased the risk of cessation of pregnancy and decreased litter sizes in mice [44]. REE exposure is usually associated with oxidative stress, inflammation, and cytogenetic effects [23, 45]. In previous animal experiments, exposure to La, Ce, and Nd increased the levels of malondialdehyde, reactive oxygen species, lipid peroxidation, and other biochemical indicators of oxidative stress [23, 46, 47]. This may have been, in part, a response to oxidative stress and inflammation, considering that these are detrimental factors in preterm birth pathology [26, 27]. Previous studies have also reported that SPL and PPROM were differ in terms of redox and other molecular processes [28, 48, 49]. This could potential explain the different effects of REE exposure on the different subtypes of SPB. However, in our study, relevant biomarkers were not measured, and further exploration could not be performed. Omics technology could be used to explore the differences in the effects of environmental exposure on SPL and PPROM in the future. Previous studies have also reported that REE exposure might increase the risk of neural tube defects, orofacial clefts, and failure of in vitro fertilization-embryo transfer [20–22]. More efforts are needed to monitor REE exposure levels and evaluate the health effects of REEs in pregnant women, particularly around REE mining areas in China.

To the best of our knowledge, this was the first study to explore the associations between REE exposure in the first and third trimesters and SPB and its subtypes. Previous studies have reported that any associations between elements and SPB might only exist in a specific trimester [6, 50]. Multiple measures of light REE exposure could be helpful to determine in which trimester light REE exposure might increase the risk of SPB. In addition, we explored associations between light REE exposure and subtypes of SPB, which may have different pathogeneses and susceptivity to environmental exposure [28, 29]. Further, 244 mothers who experienced SPB and who had plasma samples in the first and third trimesters were included in our study, a larger number than in previous studies on trace elements and SPB. Furthermore, excluding pregnant women with GBS infection could decrease the potential confounding effects of GBS infections on preterm birth. However, some limitations must be considered. First, although previous studies have shown that concentrations of REEs in plasma could reflect REE exposure levels, they generally reflect short-term rather than long-term exposure [51, 52]. Second, the gestational weeks of the control group were limited to between 39 and 41, which is not comparable to other studies of preterm birth. Births occurring between 37 and 0 days and 38 weeks 6 days were further subclassified as early term. Maternal and neonatal adverse outcome rates are higher for early-term births than for those occurring after 39 weeks [53, 54]. Thus, we only included births occurring between 39 and 41 weeks as our control groups. Third, it may not be possible to extrapolate our results to other populations because our study only included pregnant women living in Beijing, China. More studies in other places are needed to confirm our results.

Conclusion

Different levels of REE exposure may be associated with different subtypes of SPB. Specifically, levels of La and Sm in plasma may be associated with SPL, and levels of Pr may be associated with PPROM. Multicenter and high-quality prospective studies are required to confirm our findings, particularly near areas of REE mining.

List of abbreviations

SPB	spontaneous preterm birth
SPL	spontaneous preterm labor
PPROM	preterm premature rupture of membranes
REEs	rare earth elements
La	lanthanum
Ce	cerium
Pr	praseodymium
Nd	neodymium
Pm	promethium
Sm	samarium
Eu	europium
ICP-MS	inductively coupled plasma-mass spectrometry
MDLs	method detection limits
OR	odds ratio
AOR	adjusted odds ratio
CIs	confidence intervals
BKMR	Bayesian kernel machine regression
PIP	Posterior inclusion probability
GBS	group B Streptococcus

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-023-01027-1.

Supplementary Material 1

Authors' contributions

JXC and ALW contributed equally to this work. JCX and ALW analyzed the data and drafted the manuscript. ZWL and GHL designed this study. WZ and LLY acquired and cleaned the data. All authors contributed to interpretation of data and in editing the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by Beijing Hospitals Authority' Ascent Plan (No: DFL20191402), National Natural Science Foundation of China (No: 82171671), Scientific Research Common Program of Beijing Municipal Commission of Education (No: KM202110025007), the National Key Research and Development Program of China (No: 2016YFC1000304), and Beijing Natural Science Foundation (No:7222248).

Data Availability

The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All the procedures of this study were reviewed and approved by the Ethics Committee of the Beijing Obstetrics and Gynecology Hospital (approval number: 2018-KY-009-01).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 19 June 2023 / Accepted: 14 October 2023
Published online: 23 October 2023

References

1. Chawanpaiboon S, Vogel JP, Moller A-B, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. The Lancet Global Health. 2019;7(1):e37–e46.
2. Deng K, Liang J, Mu Y, Liu Z, Wang Y, Li M, et al. Preterm births in China between 2012 and 2018: an observational study of more than 9 million women. The Lancet Global Health. 2021;9(9):e1226–e41.
3. Song Q, Chen J, Zhou Y, Li Z, Li H, Liu J. Preterm delivery rate in China: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2022;22(1):383.
4. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. The Lancet. 2008;371(9606):75–84.
5. Villar J, Abalos E, Carroli G, Giordano D, Wojdyla D, Piaggio G, et al. Heterogeneity of perinatal outcomes in the preterm delivery syndrome. Obstet Gynecol. 2004;104(1):78–87.
6. Hao Y, Pang Y, Yan H, Zhang Y, Liu J, Jin L, et al. Association of maternal serum copper during early pregnancy with the risk of spontaneous preterm birth: a nested case-control study in China. Environ Int. 2019;122:237–43.
7. Ren M, Zhao J, Wang B, An H, Li Y, Jia X, et al. Associations between hair levels of trace elements and the risk of preterm birth among pregnant women: a prospective nested case-control study in Beijing Birth Cohort (BBC), China. Environ Int. 2022;158:106965.
8. Hao Y, Yan L, Pang Y, Yan H, Zhang L, Liu J, et al. Maternal serum level of manganese, single nucleotide polymorphisms, and risk of spontaneous preterm birth: a nested case-control study in China. Environ Pollut. 2020;262:114187.
9. Kim SS, Meeker JD, Carroll R, Zhao S, Mourgas MJ, Richards MJ, et al. Urinary trace metals individually and in mixtures in association with preterm birth. Environ Int. 2018;121(Pt 1):582–90.
10. Liu Y, Wu M, Song L, Bi J, Wang L, Chen K, et al. Association between prenatal rare earth elements exposure and premature rupture of membranes: results from a birth cohort study. Environ Res. 2021;193:110534.
11. Hoshino M, Sanematsu K, Watanabe Y. Chapter 279 - REE mineralogy and resources. In: Jean-Claude B, Vitalij KP, editors. Handbook on the Physics and Chemistry of Rare Earths. Volume 49. Elsevier; 2016. pp. 129–291.
12. Dushyantha N, Batapola N, Ilankoon IMSK, Rohitha S, Premasiri R, Abeysinghe B et al. The story of rare earth elements (REEs): occurrences, global distribution, genesis, geology, mineralogy and global production. Ore Geol Rev. 2020;122.
13. Balaram V. Rare earth elements: a review of applications, occurrence, exploration, analysis, recycling, and environmental impact. Geosci Front. 2019;10(4):1285–303.
14. Gwenzi W, Makuvara Z, Marumure J. Rare earth elements: Human exposure, risk factors, and health risks. Emerging Contaminants in the Terrestrial-Aquatic-Atmosphere Continuum:2022. p. 273 – 90.
15. Liang T, Li K, Wang L. State of rare earth elements in different environmental components in mining areas of China. Environ Monit Assess. 2014;186(3):1499–513.
16. Shajib MTI, Hansen HCB, Liang T, Holm PE. Rare earth elements in surface specific urban runoff in Northern Beijing. Sci Total Environ. 2020;717:136969.
17. Dai Y, Sun S, Li Y, Yang J, Zhang C, Cao R, et al. Residual levels and health risk assessment of rare earth elements in Chinese resident diet: a market-based investigation. Sci Total Environ. 2022;828:154119.
18. Squadrone S, Brizio P, Stella C, Mantia M, Battuello M, Nurra N, et al. Rare earth elements in marine and terrestrial matrices of Northwestern Italy: implications for food safety and human health. Sci Total Environ. 2019;660:1383–91.
19. Liu Y, Wu M, Zhang L, Bi J, Song L, Wang L, et al. Prenatal exposure of rare earth elements cerium and ytterbium and neonatal thyroid stimulating hormone levels: findings from a birth cohort study. Environ Int. 2019;133(Pt B):105222.
20. Liu L, Wang L, Ni W, Pan Y, Chen Y, Xie Q, et al. Rare earth elements in umbilical cord and risk for orofacial clefts. Ecotoxicol Environ Saf. 2021;207:111284.

21. Wei J, Wang C, Yin S, Pi X, Jin L, Li Z, et al. Concentrations of rare earth elements in maternal serum during pregnancy and risk for fetal neural tube defects. Environ Int. 2020;137:105542.
22. Li M, Zhuang L, Zhang G, Lan C, Yan L, Liang R, et al. Association between exposure of light rare earth elements and outcomes of in vitro fertilization-embryo transfer in North China. Sci Total Environ. 2021;762:143106.
23. Pagano G, Guida M, Tommasi F, Oral R. Health effects and toxicity mechanisms of rare earth elements-knowledge gaps and research prospects. Ecotoxicol Environ Saf. 2015;115:40–8.
24. Pagano G, Thomas PJ, Di Nunzio A, Trifuoggi M. Human exposures to rare earth elements: present knowledge and research prospects. Environ Res. 2019;171:493–500.
25. Weng W, Biesiekierski A, Li Y, Dargusch M, Wen C. A review of the physiological impact of rare earth elements and their uses in biomedical mg alloys. Acta Biomater. 2021;130:80–97.
26. Menon R. Oxidative stress damage as a detrimental factor in preterm birth pathology. Front Immunol. 2014;5:567.
27. Stefanovic V, Andersson S, Vento M. Oxidative stress - related spontaneous preterm delivery challenges in causality determination, prevention and novel strategies in reduction of the sequelae. Free Radic Biol Med. 2019;142:52–60.
28. Dutta EH, Behnia F, Boldogh I, Saade GR, Taylor BD, Kacerovsky M, et al. Oxidative stress damage-associated molecular signaling pathways differentiate spontaneous preterm birth and preterm premature rupture of the membranes. Mol Hum Reprod. 2016;22(2):143–57.
29. Gat R, Kachko E, Kloog I, Erez O, Yitshak-Sade M, Novack V, et al. Differences in environmental factors contributing to preterm labor and PPROM - Population based study. Environ Res. 2021;196:110894.
30. Obstetrics Division of Obstetrics and Gynecology, Branch CMA. Guidelines for clinical diagnosis and treatment of preterm delivery. Chin J Perinat Med. 2015;18(4):241–5.
31. Liao JB, Buhimschi CS, Norwitz ER. Normal labor: mechanism and duration. Obstet Gynecol Clin N Am. 2005;32(2):145–64.
32. Hutchison J, Mahdy H, Hutchison J. Stages of labor. StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
33. Pang Y, Yan L, Ren M, Jia X, Liu T, Du W, et al. Environmental complex exposure and the risk of influenza-like Illness among housewives: a case study in Shanxi Province, China. Ecotoxicol Environ Saf. 2020;194:110405.
34. World Health Organization. Born too soon: decade of action on preterm birth. Geneva2023.
35. Bobb JF, Claus Henn B, Valeri L, Coull BA. Statistical software for analyzing the health effects of multiple concurrent exposures via bayesian kernel machine regression. Environ Health. 2018;17(1):67.
36. Vornhagen J, Quach P, Boldenow E, Merillat S, Whidbey C, Ngo LY et al. Bacterial hyaluronidase promotes ascending GBS Infection and Preterm Birth. mBio 2016;7(3).
37. Gonçalves BP, Procter SR, Paul P, Chandna J, Lewin A, Seedat F, et al. Group B streptococcus Infection during pregnancy and infancy: estimates of regional and global burden. Lancet Glob Health. 2022;10(6):e807–e19.
38. Bao TM, Tian Y, Wang LX, Wu T, Lu LN, Ma HY, et al. An investigation of lanthanum and other metals levels in blood, urine and hair among residents in the rare earth mining area of a city in China. Chin J Industrial Hygiene Occup Dis. 2018;36(2):99–101.
39. Xu X, Wang Y, Han N, Yang X, Ji Y, Liu J, et al. Early pregnancy exposure to Rare Earth elements and risk of gestational Diabetes Mellitus: a nested case-control study. Front Endocrinol (Lausanne). 2021;12:774142.
40. Yang D, Sui H, Mao W, Wang Y, Yang D, Zhang L et al. Dietary exposure Assessment of Rare Earth elements in the Chinese Population. Int J Environ Res Public Health. 2022;19(23).
41. Zhang. YHYL, Zhang. L, Pang. Y, Hao. Y. The association between serum light rare earth elements in pregnant women and small for gestational age birth [in Chinese]. Chin J Reproductive Health. 2020;31(06):501–5.
42. Stojsavljević A, Rovčanin M, Miković Ž, Perović M, Jeremić A, Zečević N, et al. Analysis of essential, toxic, rare earth, and noble elements in maternal and umbilical cord blood. Environ Sci Pollut Res Int. 2022;29(25):37375–83.
43. Huang H, Wei L, Chen X, Zhang R, Su L, Rahman M, et al. Cord serum elementomics profiling of 56 elements depicts risk of preterm birth: evidence from a prospective birth cohort in rural Bangladesh. Environ Int. 2021;156:106731.
44. Abramczuk JW. The effects of lanthanum chloride on pregnancy in mice and on preimplantation mouse embryos in vitro. Toxicology. 1985;34(4):315–20.
45. Hong J, Yu X, Pan X, Zhao X, Sheng L, Sang X, et al. Pulmonary toxicity in mice following exposure to cerium chloride. Biol Trace Elem Res. 2014;159(1–3):269–77.
46. Huang P, Li J, Zhang S, Chen C, Han Y, Liu N, et al. Effects of lanthanum, cerium, and neodymium on the nuclei and mitochondria of hepatocytes: accumulation and oxidative damage. Environ Toxicol Pharmacol. 2011;31(1):25–32.
47. Adeel M, Lee JY, Zain M, Rizwan M, Nawab A, Ahmad MA, et al. Cryptic footprints of rare earth elements on natural resources and living organisms. Environ Int. 2019;127:785–800.
48. Gupta JK, Care A, Goodfellow L, Alfirevic Z, Muller-Myhsok B, Alfirevic A. Genome and transcriptome profiling of spontaneous preterm birth phenotypes. Sci Rep. 2022;12(1):1003.
49. Capece A, Vasieva O, Meher S, Alfirevic Z, Alfirevic A. Pathway analysis of genetic factors associated with spontaneous preterm birth and pre-labor preterm rupture of membranes. PLoS ONE. 2014;9(9):e108578.
50. An H, Wang B, Li Z, Jin Y, Ren M, Yu Y, et al. Distribution of mercury in serum and blood cells and risk of spontaneous preterm birth: a nested case-control study in China. Ecotoxicol Environ Saf. 2021;217:112228.
51. Brouziotis AA, Giarra A, Libralato G, Pagano G, Guida M, Trifuoggi M. Toxicity of rare earth elements: an overview on human health impact. Front Environ Sci. 2022;10.
52. Li X-f, Chen Z-b, Chen Z-q. Distribution and fractionation of rare earth elements in soil–water system and human blood and hair from a mining area in southwest Fujian Province, China. Environ Earth Sci. 2014;72(9):3599–608.
53. Spong CY. Defining term pregnancy: recommendations from the defining term pregnancy workgroup. JAMA. 2013;309(23):2445–6.
54. ACOG. Committee Opinion No 579. Definition of term pregnancy. Obstet Gynecol. 2013;122(5):1139–40.

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