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RESEARCH ARTICLE

Placental levels of essential and non-essential trace element in relation to neonatal weight in Northwestern Spain: application of generalized additive models

Esther Álvarez-Silvares[1] · Tania Fernández-Cruz[2] · Mónica Bermudez-González[1] · Paula Rubio-Cid[1] · Agostinho Almeida[3] · Edgar Pinto[3,4] · Teresa Seoane-Pillado[5] · Elena Martínez-Carballo[2]

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Abstract

Adequate gestational progression depends to a great extent on placental development, which can modify maternal and neonatal outcomes. Any environmental toxicant, including metals, with the capacity to affect the placenta can alter the development of the pregnancy and its outcome. The objective of this study was to correlate the placenta levels of 14 essential and non-essential elements with neonatal weight. We examined relationships between placental concentrations of arsenic, cadmium, cobalt, copper, mercury, lithium, manganese, molybdenum, nickel, lead, rubidium, selenium, strontium, and zinc from 79 low obstetric risk pregnant women in Ourense (Northwestern Spain, 42°20′12.1″N 7°51.844′O) with neonatal weight. We tested associations between placental metal concentrations and neonatal weight by conducting multivariable linear regressions using generalized linear models (GLM) and generalized additive models (GAM). While placental Co ($p=0.03$) and Sr ($p=0.048$) concentrations were associated with higher neonatal weight, concentrations of Li ($p=0.027$), Mo ($p=0.049$), and Se ($p=0.02$) in the placenta were associated with lower newborn weight. Our findings suggest that the concentration of some metals in the placenta may affect fetal growth.

Keywords Metals · Placenta · Birth weight · Newborn weight

Introduction

The placenta has a number of essential functions for maintaining pregnancy. It allows the transfer of gases and nutrients as well as acting as a selective barrier to adverse environmental factors. Similarly, it presents a great plasticity, adapting structurally and functionally to various noxae that may alter fetal normal development. If placental function is altered or its capacity for adaptation is exceeded, placental development will be compromised. It may cause a deficiency of protective elements or an excess of harmful elements in the fetus. Therefore, an oxidative stress response, epigenetic changes, or abnormal apoptosis affecting cell differentiation and development will be occurred. As a result, abnormalities in fetal development and later life can be induced (Burton et al. 2016; Al-Enazy et al. 2017; Iyengar and Rapp 2001; Iyengar and Rapp 2001).

Exposure to harmful toxic elements in the preconception period or in the first trimester of gestation could produce a structural alteration when organogenesis is affected.

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Highlights
- Increased concentrations of some metals in the placenta are associated with lower newborn birth weights: lithium, molybdenum, and selenium.
- Increased concentrations of some metals in the placenta are related to higher newborn weights: cobalt and strontium.

✉ Esther Álvarez-Silvares
lacuentadealvarez@gmail.com

[1] Obstetrics and Gynaecology Department, Complexo Hospitalario Universitario de Ourense, C/ Ramón Puga 54, 32005 Ourense, Spain

[2] Food and Health Omics, Analytical and Food Chemistry Department, Campus da Auga, Faculty of Sciences, University of Vigo, 32004 Ourense, Spain

[3] LAQV/REQUIMTE, Department of Chemical Sciences, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal

[4] Department of Environmental Health, School of Health, P. Porto, 4200-072 Porto, Portugal

[5] Statistical Studies, Official College of Physicians, 32003 Ourense, Spain

Exposure in more advanced stages of pregnancy will affect fetal growth and maturation (Stasenko et al. 2010).

It has been seen that fetuses with growth disturbances compared to fetuses that develop properly have higher rates of morbidity and mortality and a higher incidence of chronic diseases in adulthood (Barker 2004; Crump et al. 2011). To this end, the appearance of different chronic disorders has been related to events that occurred during the intrauterine phase. Fetal exposure to environmental heavy metals has been mainly linked to intrauterine growth restriction and neonatal death.

There is controversy over which chemical compounds should be categorized as toxic, beneficial, or essential (Maret 2016). Metals such as Na, K, Mg, Ca, Fe, Mn, Co, Cu, Zn, and Mo are essential for life in adequate amounts, while others, such as V, Ni, and Sn, are conjectured as essential for humans, though with less evidence. Recent studies have excluded Cr as essential in our species (Vincent 2017; Di Bona et al. 2011). Non-essential elements are a set of metals and metalloids widespread in the environment that are obtained from natural and anthropogenic sources. Our body also accumulates non-essential beneficial metals such as Li, Rb, Sr, Pb, Au, and some others (Zoroddu el al. 2019). Alteration in these compound levels could adversely impact human health. In addition, some of these non-essential metals can be toxic regardless of their concentration and are included as environmental pollutants (Cortés-Eslava et al. 2018). They accumulate in the tissues and cross the placenta giving rise to morphological and functional alterations (Omeljaniuk et al. 2018; Taylor et al. 2018).

In the last years, several studies have focused on the determination of essential and non-essential elements in different biological matrices such as maternal and cord blood (Murcia et al. 2016; Dack et al. 2021), maternal hair and urine (Wang et al. 2019; Osorio-Yáñez et al. 2018; Zhao et al. 2020; Lozano et al. 2022), or placenta (Freire et al. 2019; Gómez-Roig et al 2021; Punshon et al. 2021; Al-Saleh et al. 2014). They have investigated the impact of metal exposure in human health although with conflicting data (Murcia et al. 2016; Dack et al. 2021; Wang et al. 2019; Osorio-Yáñez et al. 2018; Zhao et al. 2020; Lozano et al. 2022; Lozano et al. 2019; Gómez-Roig et al. 2021; Punshon et al. 2019; Al-Saleh et al. 2014). Moreover, the effect that these metals produce on fetal growth has not yet been clarified.

Based on these theoretical approaches and taking into account that several authors expose that ensuring optimal placentation offers a new approach for the prevention of different chronic pathologies (Burton et al. 2016), the aim of the present work is to determine how the concentrations of 14 metals in placental tissues can be associated with neonatal weight.

Methods

Study design

A study cohort was established in Ourense by the staff of the University of Vigo and University Hospital of Ourense (Northwestern Spain; 42°20′12.1″ N 7°51.844′ O). A total of 79 low obstetric risk pregnant women were randomly recruited between October and December 2017. The mothers had signed informed consent and answered a questionnaire related to their diet, lifestyle, and personal habits.

The study was approved by Pontevedra-Vigo-Ourense Research Ethics Committee with registry code 2014/410. The Declaration of Helsinki on biomedical research was applied at all times. After being contacted during their antenatal visit, pregnant women received a thorough explanation of the study and, before being included in it, were invited to sign an informed consent.

Exclusion criteria are as follows: pregnant women under 18 years of age, twin gestations, pregnant women diagnosed with chronic diseases prior to gestation, premature labor (amenorrhea < 37 weeks), women with exclusive follow-up in other centers, women with follow-up in our center and birth outside the Ourense healthcare area, and patients who did not agree to participate in the study after reading the informed consent form.

Placenta samples were collected at the time of delivery, and once in the laboratory, placenta samples, including maternal and fetal sides and central and peripheral parts (umbilical cord was kept separate), were placed in a mincer for homogenization. Once homogenized, aliquots were placed into 250-mL amber glass vials and frozen at – 20 °C until analysis.

Determination of targeted metals and trace elements

The set of essential and non-essential trace elements are listed in Table S1 in the supplementary material. Placenta samples were processed following analytical procedures based on an optimized one by our research team (Fernández-Cruz 2019) (Fig Suppl 1). Briefly, about 0.300 g of dried sample was weighed directly in the microwave oven digestion vessels, and 3.0 mL of high-purity HNO_3 ($\geq 69\%$ w/w, TraceSELECT®, Fluka, France) and 1.0 mL of H_2O_2 (30–32% w/w, Primar™, for Trace Metal Analysis, Fisher Chemical, Loughborough, UK) were added. Digestion was carried out in a MLS-1200 Mega microwave oven (Milestone, Sorisole, Italy) equipped with an HPR-1000/10S rotor, using the following power (W)/time (min) program: 250/1, 0/2, 250/5, 400/5, and 650/5. After cooling, the digests were made up to 10 mL with ultrapure water (> 18.2 MΩ.cm at 25 °C), obtained with an Arium® pro system (Sartorius, Göttingen, Germany), in decontaminated plastic volumetric flasks and stored in closed propylene tubes at 4.0 °C until analysis. Sample blanks were prepared in the same way. All samples were prepared in triplicate. The determination of selected trace elements was performed by inductively coupled plasma-mass spectrometry (ICP-MS) using an iCAP™ Q (Thermo Fisher Scientific, Bremen, Germany) instrument equipped with a MEINHARD™ TQ$^+$ Quartz Nebulizer (Golden, CO, USA), a Peltier-cooled baffled cyclonic spray chamber, a standard quartz torch, and a two-cone (sample and skimmer Ni cones) interface design. High-purity (99.9997%) argon (Gasin II, Leça da Palmeira, Portugal) was used as nebulizer and plasma gas. The following elemental isotopes (m/z ratios) were monitored for analytical determinations: ^{7}Li, ^{55}Mn, ^{59}Co, ^{65}Cu, ^{66}Zn, ^{75}As, ^{82}Se, ^{85}Rb, ^{88}Sr, ^{98}Mo, ^{111}Cd, ^{137}Ba, ^{202}Hg, ^{205}Tl, and ^{208}Pb. The elemental isotopes ^{45}Sc, ^{89}Y, ^{115}In, and ^{159} Tb were monitored as internal standard (Fernández-Cruz 2019).

Analytical quality control

Since human placenta is not available as certified reference material (CRM) for trace elements determination, fish protein (DORM-3), dogfish liver (DOLT-4), and fish muscle (ERM-BB422) were used for analytical quality control purposes. Procedural (sample) blanks were used to assess potential contamination. The recoveries obtained in the analysis of the CRMs are presented in Table S2 (supplementary material).

Calibration curves were obtained with eleven standard solutions with concentrations ranging from 0.010 to 100 μg/L (0.010 to 5.0 μg/L for Hg). The calibration standard solutions were prepared by adequate dilution of a 10 mg/L multi-element commercial standard solution (PlasmaCAL SCP-33-MS, SCP Science, Baie-d'Urfé, Quebec, Canada) and a 1000 mg/L standard solution of Hg (TraceCERT®, Sigma-Aldrich, St. Louis, MO, USA) in 2% HNO_3, 0.5% HCl, and 400 ppb of Au. Ten sample blanks were analyzed to calculate the limit of detection (LOD; calculated as the concentration corresponding to three times the standard deviation of these sample blanks) and the limit of quantification (LOQ; corresponding to ten times the standard deviation) of the analytical procedure. Results are shown in the Table S3, expressed as the correspondent content (μg/g) in the placenta samples.

Statistical analyses

A descriptive analysis of all the variables included in the study was performed. Quantitative variables were expressed as mean and standard deviation. Qualitative variables were reported with absolute and relative frequency (percentage). For statistical calculations, results below the LOD were imputed as the LOD divided by the square root of 2, a commonly used procedure for data imputation.

Multivariate linear regressions were used using generalized linear models (GLM) that adapt to the variables with arbitrary distributions, to check the effect of the metals studied on the weight of the newborns (NB). For the analysis, the linearity relationship between the predictor variable (trace elements) and the weight mean was previously verified.

For cases in which the linearity assumption is not met, generalized additive models (GAM) were implemented, using smoothing splines, because, unlike GLMs, in GAM models, it is not necessary to assume a parametric relationship between the variables. GAMs have the potential to increase statistical (Hastie and Tibshirani 1995) power and allow better elucidation of the more nuanced and nonlinear associations between placental metal concentration and birth weight. In these, the weight of the neonates is estimated assuming that the effect of trace elements is unknown, thus obtaining a flexible estimate.

Models were adjusted for maternal age at the beginning of pregnancy (continuous), parity (ordinal), BMI at the beginning of pregnancy (continuous), amenorrhea at the time of delivery, and maternal exposure to smoking (ordinal).

For the statistical calculations, the IBM SPSS Statistics software for Windows, Version 22.0 was used, Armonk, NY: IBM Corp and software R version 4.0.4 (2021–02-15). The significance level was set at $p < 0.050$.

Results

Characterization of the study participants

The concentration of metals was analyzed in a total of 79 placentas; those corresponding to gestations with premature deliveries (amenorrhea less than 37 weeks) were discarded in order to homogenize and avoid a confounding factor in relation to the weight of the newborn.

The clinical characteristics of the cohort are summarized in Table 1. The study enrolled healthy Caucasian women; all pregnant women with medical pathology prior to pregnancy, such as high blood pressure, diabetes mellitus, and rheumatoid diseases, were discarded. Maternal age ranged from 19 to 42 years (mean: 32.87 ± 4.98), with a body mass index (BMI) between 17.6 and 38.95 kg/m^2 at the onset of gestation with a mean of 24.7 ± 4.53 kg/m^2 and 36.71% ($n = 29$) reported to be steady smokers. Amenorrhea at delivery averaged 39.72 ± 1.58 weeks (38.38–41.61). Birth weight ranged from 1700 to 4340 g (media 3051.7 ± 599 g).

Table 1 Clinical characteristics of the cohort

	Age (years)	BMI (kg/m^2)	Amenorrhea at birth (weeks)	Newborn weight (g)
N	79	79	79	79
Mean	32.87	24.7	39.72	3051.71
DS	4.98	4.53	1.58	599.87
Median	33	23.4	39.89	3120
Minimum	19	17.6	38.38	1700
Maximum	42	38.95	41.61	4340

Trace element concentrations

Mean, standard deviation, and maximum and minimum levels (µg/g) of the determined trace elements in placenta samples ($n=79$) are summarized in Table 2.

Most of the trace elements were detected in the biological samples with the following decreasing order of content: Zn (50.25 ± 8.470) > Cu (4.66 ± 0.890) > Se (0.969 ± 0.109) > Mn (0.3831 ± 0.1148) > Mo (0.0259 ± 0.0244) > Co (0.0205 ± 0.0077) for essential trace elements and Rb (14.85 ± 3.380) > Sr (0.9501 ± 0.1230) > Hg (0.0355 ± 0.0240) > Cd (0.0276 ± 0.0152) > Pb (0.036 ± 0.035) > Li (0.0189 ± 0.0240) for non-essential trace elements.

Using GLM or GAM models, no significant association was established between the weight of the newborn and the concentrations in the placenta of the following elements: Cd ($p=0.604$; Fig S2), Cu ($p=0.914$, Fig S3), Hg ($p=0.500$, Fig S4), Mn ($p=0.530$, Fig S5), Pb ($p=0.505$; Fig S6), Rb ($p=0.746$, Fig S7), and Zn ($p=0.165$, Fig S8). Nevertheless, linear models using GAM showed an increase in mercury levels in placenta determined lower birth weight, but did not reach statistical significance.

An association between increased concentrations of metals in the placenta and lower newborn weight with statistical significance was demonstrated in the following elements: Li ($p=0.027$) (Fig. 1); Mo ($p=0.049$) (Fig. 2); and Se ($p=0.020$) (Fig. 3).

We found a positive relationship between placental concentrations and neonatal weight (i.e., higher concentration, higher birth weight) in the following elements: Co ($p=0.030$) (Fig. 4) and Sr ($p=0.048$) (Fig. 5).

The result of the study of placental concentrations in relation to newborn weight can be observed in Table 3.

Discussion

The levels found were generally in close agreement with those reported in previous studies (Freire et al; 2019; Gómez-Roig et al. 2021; Punshon et al. 2019; Al-Saleh et al. 2014). As commented before, some authors have evaluated the concentration of metals in placenta samples. Most of them have detected limited trace elements, and just a few small studies have been focused in its effects on perinatal outcomes. Table 4 summarizes the published manuscripts about the determination of essential and non-essential trace elements detected in placenta samples with the related health effects (Freire et al; 2019; Gómez-Roig et al. 2021; Punshon et al. 2019; Al-Saleh et al. 2014; Jin et al. 2013; Kozikowska et al. 2013; Laine et al. 2015; Roverso et al. 2015; Xu et al. 2015; Bedir Findik et al. 2016; Ricketts et al. 2017; Freire et al. 2018; Kosik-Bogacka et al. 2018; Pi et al. 2018; Omeljaniuk et al. 2018; Wang et al. 2018; Irwinda et al. 2019; Mikelson et al. 2019; Yin et al. 2020; McKeating et al. 2021; Lee et al. 2021).

Table 2 Statistical values for placental trace element concentrations (µg/g dw)

Placental metal concentrations (µg/g dw)	Cd	Co	Cu	Hg	Li	Mn	Mo	Pb	Rb	Se	Sr	Zn
Mean	0.02761	0.0205	4.66	0.0355	0.0189	0.3831	0.0259	0.0361	14.85	0.969	0.9501	50.25
D.S	0.0152	0.0077	0.89	0.024	0.0244	0.1148	0.0054	0.035	3.38	0.109	0.123	8.47
Median	0.0237	0.0190	4.738	0.031	0.009	0.365	0.026	0.027	14.251	0.958	0.456	49.91
Minimum	0.007	0.009	2.879	0.006	0.002	0.205	0.015	0.009	7.834	0.744	0.149	34.11
Maximum	0.085	0.044	7.080	0.031	0.123	0.957	0.043	0.247	23.134	1.202	7.925	76.82

As arsenic, *Cd* cadmium, *Co* cobalt, *Cu* copper, *Hg* mercury, *Li* lithium, *Mn* manganese, *Mo* molybdenum, *Ni* nickel, *Pb* lead, *Rb* rubidium, *Se* selenium, *Sr* strontium, *Zn* zinc, *LOD* limits of detection, *LOQ* limits of quantification

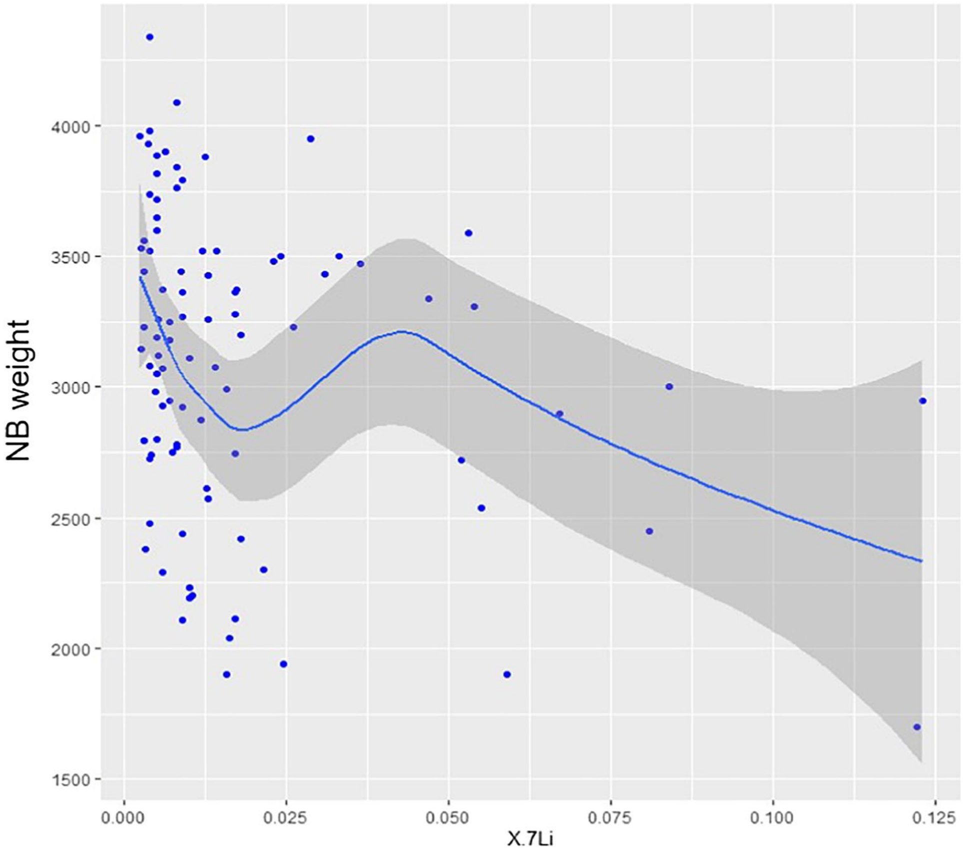


Fig. 1 GAM models for Li ($p = 0.027$)

In our study, placenta samples from women of a geographical area of low environmental pollution were analyzed and related with birth weight. Therefore, the birth weight estimation was the main objective of using GAM models, assuming that the effect of metals on placenta is unknown. A flexible birth weight estimate was obtained. Other authors used these statistical study models to demonstrate the association between placenta metal concentrations and birth weight (Punshon et al. 2019) and between placenta metal concentrations and placental weight and efficiency.

Higher placental metal levels associated with higher birth weight (Co and Sr)

To the best of our knowledge, few studies linked placental Co and Sr levels with birth weight. Mikelson et al. [40] obtained similar results showing that 1.0% increase in placental Co concentration determined an increase of 0.84 g at birth ($p = 0.0060$). Recently, Gómez-Roig et al. (2021) also described similar placenta Co concentrations in a cohort study from Barcelona Center (Spain). They found no relationship between placental concentration and small fetuses (SGA) as compared with normally grown fetuses (AGA).

At trace levels, Co is ubiquitous in the environment. Drinking water and diet (cereals, dairy products, fish, leafy greens, or meat) are the main source of Co. Moreover, Co is a relatively rare metal in the Earth's crust although it is an essential element in several species, including humans, since it forms the nucleus of vitamin B12 (cobalamin) (Liang et al. 2018). Co is also required for the production of red blood cell, in the formation of DNA, the synthesis of fatty acids, and in energy metabolism (O'Leary and Samman 2010). In addition, Co is key in erythropoiesis since it detects oxygen deficit in cells by stimulating the production of erythropoietin (Saxena et al. 2012).

Co appears to have a transplacental transfer. A cross-sectional study involving 62 pairs of women and their newborns found that Co concentrations in maternal blood are positively correlated with those in placenta and umbilical cord blood. These data suggest that placental Co concentration may reflect the level of exposure of the fetus (Rudge et al. 2009).

With regard to Sr, only Herrera Giménez (2015) detected Sr levels in maternal blood and found positive correlation ($rs = 0.226$, $p < 0.05$) with birth weight. Osada et al. (2002) showed similar Sr levels in umbilical cord venous, arterial blood, and also in maternal venous. Nevertheless, higher Sr levels were detected in placental than in maternal serum. Kot et al. (2021) also detected similar

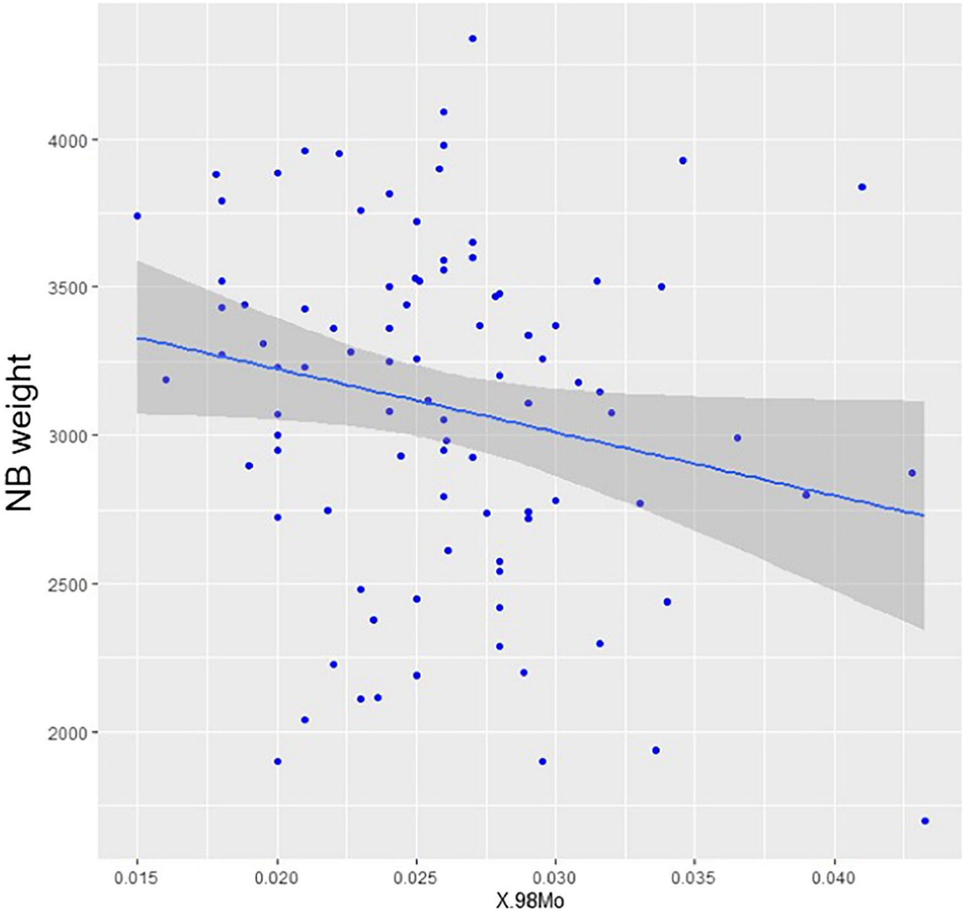


Fig. 2 GAM models for Mo ($p = 0.049$)

Sr levels in maternal blood and umbilical cord, but no correlations with neonatal weight was found.

Strontium is a mineral found in rocks, soil, and water. Animal foods, wheat bran, and root vegetables are the main source of Sr.

Higher placental metal levels associated with lower fetal weight (Mo, Se, and Li)

In the present study, placental Mo, Se, and Li concentrations presented an inverse correlation with newborn weight.

Mo is a necessary component of sulfite oxidase, xanthine oxidase, aldehyde oxidase, and the mitochondrial amidoxime-reducing component in the human body (Yin et al. 2020). The main route of Mo exposure is diet, especially the intake of cereals and dairy products (Lozano et al. 2022). The positive relationships between Mo concentrations and rice and seafood intake have also been reported (Wang et al. 2019).

Fagerstedt et al. (2015) with a cohort of Swedish women find placental Mo concentrations similar to ours and report that these concentrations increase with gestational age. In contrast, other authors report a decrease in placental Mo concentration with advancing gestation (Pi et al. 2019).

Gómez-Roig et al. (2021) fail to find relationships between Mo concentrations and small fetuses for gestational age.

The few studies related with placenta Se levels and birth weight agreed that a higher placenta Se concentration is a greater risk of fetal weight alterations (Gómez-Roig et al. 2021; Osada et al. 2002; Zadrozna et al. 2009). The physiological mechanisms of the placenta that mediate the association between placenta Se levels and lower birth weight remains poorly understood (Wang et al. 2021). High placenta Se levels could decrease the activity of the cytochrome C oxidase enzyme leading to hypoxia of placental cells and eventually alter fetal (Zadrozna et al. 2009; Matsubara et al. 1997). Placenta Se concentrations and fetal weight were mainly studied in maternal blood and serum, with a discrepancy between the results. While Lewandowska et al. (2019) and Mistry and Williams (2011) related positive correlation between Se levels and fetal weight, Wilson et al. (2018) founded negative correlations in a cohort of 1065 nulliparous women. Discrepancy between results could be explained by gestational age due to maternal Se blood decreases with increasing gestational age (up to 12%). Plasma volume expansion and Se transfer to fetus mediated by selenoprotein P (SEP1)

Fig. 3 GAM models for Se ($p=0.049$)

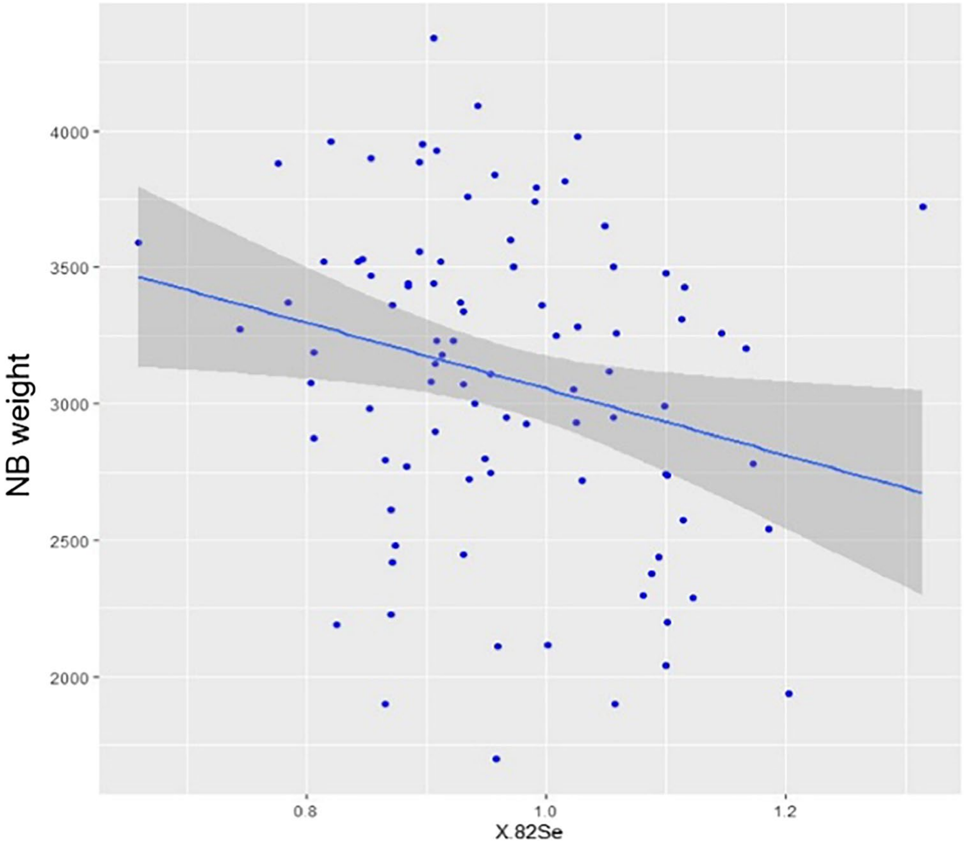
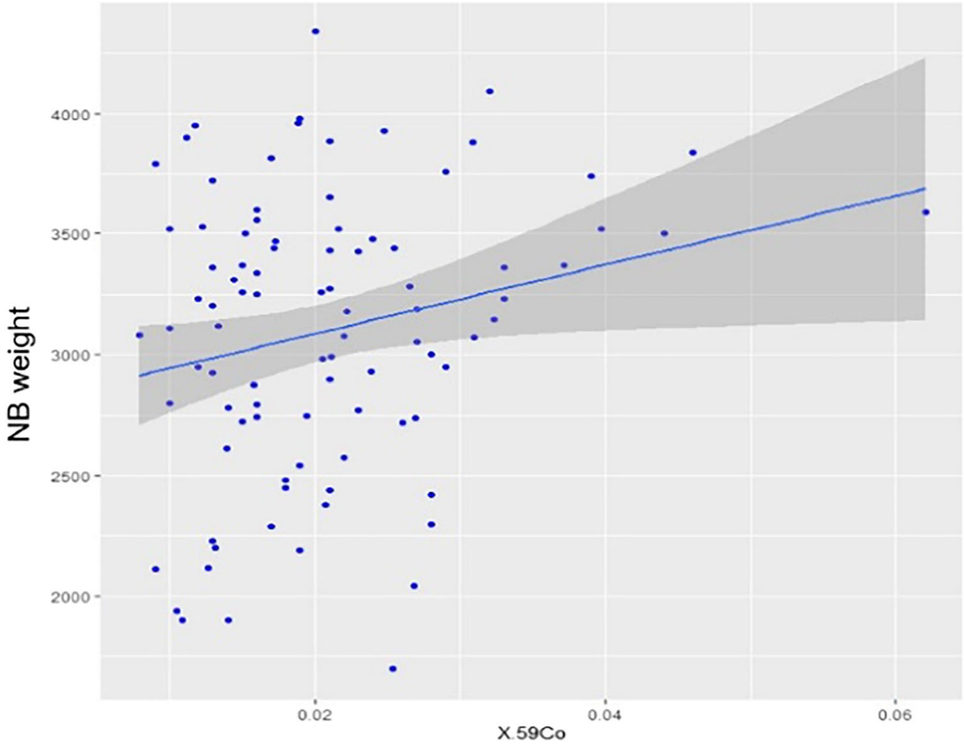


Fig. 4 GLM models for Co ($p=0.03$)



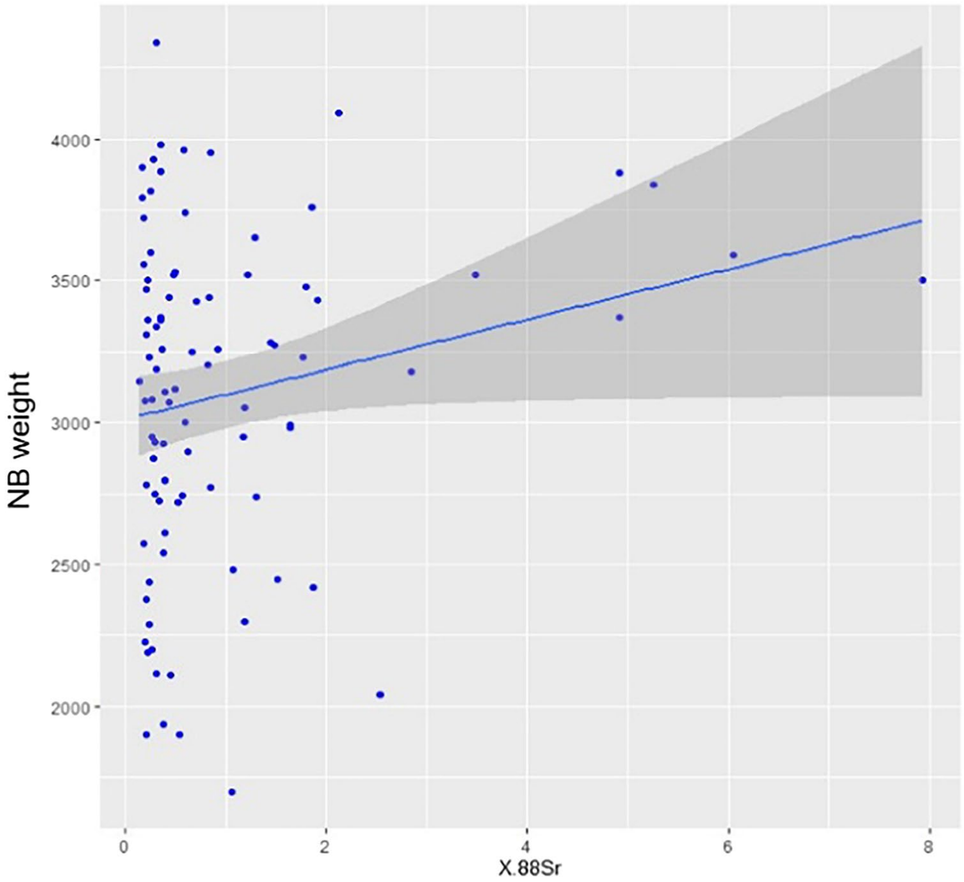


Fig. 5 GAM models for Sr ($p = 0.048$)

Table 3 Statistical values for placental trace element concentrations (µg/g dw)

Placental metal (µng/g dw)	Placenta detection rate	Relationship with neonatal weight	Type	p (value)
Cd	79/79	No	——-	0.604
Co	79/79	Yes	> Co → > birth weight	0.030
Cu	79/79	No	——-	0.914
Hg	79/79	Yes	> Hg → < birth weight	0.50
Li	79/79	Yes	> Li → < birth weight	0.027
Mn	79/79	No	——-	0.530
Mo	79/79	Yes	> Mo → < birth weight	0.049
Pb	79/79	No	——	0.505
Rb	79/79	No	——	0.746
Se	79/79	Yes	> Se → < birth weight	0.020
Sr	79/79	Yes	> Sr → > birth weight	0.048
Zn	79/79	No	——	0.165

could be the two main factors (Jariwala et al. 2014; Kieliszek 2000).

Selenium is a cofactor of enzymes that have an important function as an antioxidant, including glutathione peroxidases, deiodinases, and oxidized lipoproteins (Rayman 2000). Se also releases active thyroid hormone cells. Deiodinases, by regulating the conversion of thyroxine (T4) to triiodothyronine (T3) and reversing triiodothyronine (rT3) and thyroidonamines, control thyroid hormone turnover. Se-dependent antioxidant enzymes have also been identified in placental tissue, and they protect trophoblast cells during the trophoblastic invasion process of the spiral arteries (Lewandowska et al. 2019; Mendes et al. 2019; Li et al. 2017).

Some authors have reported correlations between Li levels in maternal and fetal blood (Newport et al. 2005; Harari et al. 2015a, b). To the best of our knowledge, no studies

Table 4 Summary of published manuscripts about determination of essential and non-essential trace elements detected in placenta samples with the related health effects

Element	Health effects	Region	Reference
Pb	Birth outcomes	Birmingham	Wibberley (1977)
Pb	Birth outcomes	Australia	Baghurst (1991)
Cd	Neonatal anthropometry	New York (USA)	Loiacono (1991)
Cd	Neonatal anthropometry	Villejuif (France)	Fréry (1993)
Mg, Mn, Fe, Cu, Zn, Se, Rb, Sr, Cd, Cs	Birth outcomes	Chiba (Japan)	Osada (2002)
Pb	Preterm delivery	Murcia (Spain)	Falcón (2003)
Cd	Birth outcomes	Hubei (China)	Zhang (2004)
Cd, Cu, Zn, Pb	Neonatal anthropometry	Santiago (Chile)	Ronco (2005)
Pb, Se, Cd	Fetal growth restriction	Osijek (Croatia)	Klapec (2008)
Cd, Ar, Pb	Fetal growth restriction	Santiago (Chile)	Llanos (2009)
Zn, Se, Cu	Birth outcomes	Kraków (Poland)	Zadrozna (2009)
Pb	Preterm delivery	Lucknow (India)	Ahamed (2009)
Pb, Cd, Cr, Ni	Birth outcomes	Guiyu (China)	Guo (2010)
As, Cd, Hg, Pb	Neural tube defects (NTDs)	Sanxi (China)	Jin (2013)
Hg	Birth outcomes	Bytom, Upper Silesia (Poland)	Kozikowska (2013)
Cd, Pb	Birth outcomes	Kraków (Poland)	Suprewicz (2013)
Cd, Hg, Pb	Birth outcomes	Al-Kharj (Saudi Arabia)	Al-Saleh (2014)
Cd, Se, Zn	Preeclampsia risk	North Carolina (USA)	Laine (2015)
As, Cd, Co, Cr, Cu, Hg, Mn, Mo, Ni, Pb, Rb, Se, Sr	Gestational diabetes mellitus	Padua (Italy)	Roverso (2015)
Cd	Birth outcomes	Guiyu and Haojiang (China)	Xu (2015)
Hg	Birth outcomes	Ankara (Turkey)	Bedir Findik (2016)
As	Birth outcomes	New Hampshire (UAS)	Gilbert-Diamond (2016)
Hg	Neonatal anthropometry	Kingston (Jamaica)	Ricketts (2017)
Cd, Hg, Pb, As, Zn	Neonatal anthropometry	Barcelona (Spain)	Sabra (2017)
As, Cd, Cr, Hg, Mn, Pb	Neurodevelopment disorders	Asturias, Gipuzkoa, Granada, Sabadell, Valencia (Spain)	Freire (2018)
Hg, Se	Birth outcomes	Central, Northwestern Poland	Kosik-Bogacka (2018)
Ba	Congenital heart defect	China	Zhang (2018)
As, Cd, Hg, Pb	Neonatal orofacial clefts (OFCs)	Sanxi (China)	Pi (2018)
Mg, Zn, Cu, Cd, Pb	Preterm delivery	Konya (Turkey)	Kucukaydin (2018)
Cd, Pb, Se	Miscarry	Central, Northwestern Poland	Omeljaniuk (2018)
Cd	Birth outcomes and preeclampsia	Zhejiang (China)	Wang (2018)
As, Cd, Cr, Hg, Mn, Pb	Birth outcomes	Asturias, Gipuzkoa, Granada, Sabadell, Valencia (Spain)	Freire (2019)
Cu, Hg, Mn, Pb, Se, Zn	Birth outcomes	Jakarta (Indonesia)	Irwinda (2019)
As, Cd, Co, Cu, Mn, Ni, Pb, Se, Tl, Zn	Birth outcomes (birth length and weight, gestational age, placental weight, and head circumference)	Chattanooga (USA)	Mikelson (2019)
As	Birth weight	New Hampshire (USA)	Punshon (2019)
Al, B, Ba, Ca, Cd, Cr, Cu, Fe, K, Li, Mg, Mn, Mo, Na, Ni, Pb, Sr, V, Zn	Birth outcomes	Sevilla (Spain)	Cerrillos (2019)
Co, Fe, Mn, Mo, Se, Zn	Neural tube defects (NTDs)	China	Yin (2020)
Co	Birth weight	Wroclaw (Poland)	Mazurek (2020
Cd	Congenital heart defect	China	Zhang (2020)
CA, P, K, Mg, Fe, Cu, Cd	Birth weight	Rhode Island (USA)	Hussey (2020)
Al, Be, Bi, Ca, Cd, Co, Cr, Cu, Mg, Mn, Mo, Ni, P, Pb, Rb, S, Sr, Ti, Tl, Sb, Se, Zn	Birth outcomes Preeclampsia	Barcelona (Spain)	Gómez-Roig (2021)

Table 4 (continued)

Element	Health effects	Region	Reference
Na, Mg, P, K, Ca, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Se, Rb, Sr, Mo, Ag, Sb, I, Cs, Ba, Hg, Tl, Pb, U	Neurodevelopment disorders Neurodevelopment disorders	Victoria (Australia)	McKeating (2021)
Se	Neurodevelopment disorders	Boston (USA)	Lee (2021)
Cd, Mn; Pb	Neurodevelopment disorders	Rhode Island (USA)	Tung (2022)
Ti	Congenital heart defects	Lanzhou (China)	Sun (2022)

NTDs neural tube defects

have previously reported correlations between placental Li levels and neonatal weight without chronic Li treatment. Only Harari et al. (2015a, b) studied Li exposure through drinking water. They found negative associations between Li levels in maternal blood and urine samples and birth weight.

Li is found in rocks, soil, and water. Cereals and vegetables are their main sources. On the other hand, Li has long been used in the treatment of bipolar disease. Li therapy during pregnancy has been associated with increased fetal heart malformations (Patorno et al. 2017). This metal crosses the placenta freely and alters the thyroid system increasing thyrotropin (TSH) and decreasing free thyroxine (Broberg et al. 2011; Harari et al. 2015a, 2015b).

Limitations and strong points

Our study is not without limits. In the first place, this work focused on determining the concentrations of the different metals in the placenta without analyzing other morphological or functional placental parameters, so we cannot establish the mechanism by which these metals lead to fetal growth. Thus, the exchange of metals can be compromised by the placental accumulation of certain elements. The results found in our study could be explained by this process. Second, it is known that the placental concentrations of these metals can be influenced by various modifiable variables, such as diet and gestational nutritional supplements, and non-modifiable, such as genetics. In our work, the impact of these factors on the levels of placental metals has not been analyzed. Lastly, this is a cohort study with a limited sample size, which could lead to unreliable effect estimates.

Study strengths include the use of a non-invasive matrix to the assessment of cumulative gestational exposure of a large set of essential and non-essential trace elements. There are few studies on placental metal levels, but limited reports detected a large set of metals and examined their association with fetal weight.

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Author contribution All authors contributed to the study conception and design.

Esther Álvarez-Silvares, Mónica Bermudez-González, Paula Rubio-Cid: methodology, supervision, investigation, formal analysis, writing—review and editing.

Elena Martínez Carballo: methodology, supervision, formal analysis, writing—review and editing.

Tania Fernández-Cruz: data curation, methodology, formal analysis.

Agostinho Almeida, Edgar Pinto: data curation, methodology, formal analysis.

Teresa Seoane-Pillado: methodology, statistical analysis.

Data availability Data from this study are available but anonymized.

Declarations

Ethics approval and consent to participate The study was approved by Pontevedra-Vigo-Ourense Research Ethics Committee with registry code 2014/410. The Declaration of Helsinki on biomedical research was applied at all times. After being contacted during their antenatal visit, pregnant women received a thorough explanation of the study and, before being included in it, were invited to sign an informed consent.

Consent for publication All authors read and approved the final manuscript and give their consent for the publication of the study.

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