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Boron exposure through drinking water during pregnancy and birth size

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ABSTRACT

Background: Boron is a metalloid found at highly varying concentrations in soil and water. Experimental data indicate that boron is a developmental toxicant, but the few human toxicity data available concern mostly male reproduction.

Objectives: To evaluate potential effects of boron exposure through drinking water on pregnancy outcomes.

Methods: In a mother-child cohort in northern Argentina ($n = 194$), 1–3 samples of serum, whole blood and urine were collected per woman during pregnancy and analyzed for boron and other elements to which exposure occurred, using inductively coupled plasma mass spectrometry. Infant weight, length and head circumference were measured at birth.

Results: Drinking water boron ranged 377–10,929 μg/L. The serum boron concentrations during pregnancy ranged 0.73–605 μg/L (median 133 μg/L) and correlated strongly with whole-blood and urinary boron, and, to a lesser extent, with water boron. In multivariable-adjusted linear spline regression analysis (non-linear association), we found that serum boron concentrations above 80 μg/L were inversely associated with birth length (B − 0.69 cm, 95% CI −1.4; −0.024, $p = 0.043$, per 100 μg/L increase in serum boron). The impact of boron appeared stronger when we restricted the exposure to the third trimester, when the serum boron concentrations were the highest (0.73–447 μg/L). An increase in serum boron of 100 μg/L in the third trimester corresponded to 0.9 cm shorter and 120 g lighter newborns ($p = 0.001$ and 0.021, respectively).

Conclusions: Considering that elevated boron concentrations in drinking water are common in many areas of the world, although more screening is warranted, our novel findings warrant additional research on early-life exposure in other populations.

1. Introduction

Boron (B) is a metalloid found in the bedrock bound to oxygen as boric acid and borax, and it is mined for industrial applications such as borosilicate glass manufacturing (WHO, 2009). Boron in the ground may dissolve in the surrounding water, and may therefore appear in drinking water sources. Boron concentrations in drinking water up to 1 mg/L have been observed in northern France (Yazbeck et al., 2005), 1.4 mg/L in Public Water Systems in the U.S. (EPA, 2008), 3 mg/L in southern Sweden (SSI, 2008), 6 mg/L in the Argentinean Andes (Concha et al., 2010), 11 mg/L in Muenster, Germany (Queste et al., 2001) and Arica, Chile (Cortes et al., 2011), and 29 mg/L in Balikesir province, Turkey (Sayli et al., 1998). Also, bottled water may contain elevated boron concentrations; one brand from Slovakia as much as 120 mg/L (Reimann and Birke, 2010). The World Health Organization (WHO) health-based guideline value for drinking water boron is 2.4 mg/L (WHO, 2011). Food items rich in boron include nuts, legumes, fruit and vegetables (Rainey et al., 1999), but data on the typical daily intake of boron through food and drinking water are scarce. One U.S. study estimated the mean intake to about 1 mg/day (Rainey et al., 1999).

Boron is easily absorbed in the gastrointestinal tract and fairly rapidly excreted, mainly in urine (Moore, 1997). The toxicology of boron is largely unknown. Experimental studies on rats indicate that boron causes male reproductive toxicity, especially low sperm count (Weir and Fisher, 1972), and developmental toxicity (fetal skeletal malformations and impaired fetal growth) (Price et al., 1996). Only a few epidemiological studies are available, mainly concerning male reproduction, and these showed no convincing evidence of impaired semen quality (Başaran et al., 2012; Robbins et al., 2010). Boron passes through the placenta (Harari et al., 2012), and because the fetus may be particularly sensitive to boron toxicity (Huel et al., 2004), this study aimed at evaluating potential effects of boron on birth outcomes in a mother-child cohort in northern Argentina exposed to varying boron concentrations in the drinking water.

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2. Materials and methods

2.1. Study population

This study is based on a mother-child cohort study in the arid, high-altitude Andean part of the Province of Salta in northern Argentina. Details of the study area and recruitment have been described elsewhere (Harari et al., 2015). Briefly, we recruited pregnant women in the main village San Antonio de los Cobres and nine surrounding villages (in total about 8000 inhabitants), where we previously had discovered varying concentrations of boron (range 335–5956 μg/L), arsenic (3.5–322 μg/L), cesium (0.03–322 μg/L), and lithium (8.0–1005 μg/L) in the drinking water (Concha et al., 2010). Concentrations of other elements in the drinking water in this region are mostly low (Supplementary Table S1). Also, this remote rural area has no major industries besides lithium and boron mining, and the traffic is very low. The diet is primarily based on meat and vegetables, with essentially no fish, dairy products or rice. Taken together, this would indicate limited exposure to other toxic elements such as methylmercury, lead and cadmium.

All women being pregnant between October 2012 and December 2013 were invited to participate in the project with the assistance of the health care personnel at the hospital in San Antonio de los Cobres and the small health care centers in the surrounding villages. In total, 194 women were recruited (response rate = 88%; see Fig. S1). Reasons for not participating included twin pregnancy (one case identified by ultrasound), deliveries before recruitment (11), fetal loss (5), refusal or not located (6), and migration (4). Out of the 194 women enrolled in the project, 182 were interviewed and provided samples before delivery and out of these, two had a miscarriage. At enrollment, the women were interviewed regarding family characteristics, including known diseases, preferred diet, last menstrual period (LMP), and pre-pregnancy weight. The study was designed to see the pregnant women at least once during pregnancy; preferably 2–3 times (once per trimester) in order to obtain repeated measures of exposure. Blood and spot-urine samples were collected at each visit, at which time the women were also interviewed about encountered health problems.

The study was approved by the regional ethical committee at Karolinska Institutet, Stockholm, Sweden, and by the Ministry of Health, Salta, Argentina. After detailed explanation of the study, we obtained oral and written informed consent from all women before recruitment. Informed consent was also obtained from the closest caregiver if the women were younger than 18 years of age. We regularly report the findings to the medical personnel at the study area and to the Health Ministry in Salta.

2.2. Exposure assessment

Because it is the serum fraction of nutrients and potentially other substances that may reach the fetus through the placenta, we assessed the exposure to boron by the concentrations in serum. However, as a biomarker of boron exposure is not well established, we also measured boron concentrations in whole blood, urine and drinking water for validation. The boron concentration in serum was highly correlated with that in whole blood ($r_s = 0.87$, $p < 0.001$) and urine ($r_s = 0.71$, $p < 0.001$) and to a much lesser extent with the boron concentration in water ($r_s = 0.28$, $p < 0.001$). The correlation between urinary and water boron was $r_s = 0.37$ ($p < 0.001$). Urinary boron has been used as a biomarker for ongoing boron exposure, especially among occupationally exposed people (Sutherland et al., 1999). However, it represents the excreted boron (with short half-life) (Sutherland et al., 1999), and not the fetal exposure to the same extent as serum boron.

Serum samples were fractionated from whole blood samples collected in Trace Elements Serum Clot Activator tubes (Vacuette®, Greiner bio-one, Kremsmünster, Austria) by centrifugation at 3000 rpm for 10 min, exactly 15 min after blood drawing. Another sample of whole blood was collected in sodium heparin tubes (Vacuette®, NH Trace Elements; Greiner bio-one, Kremsmünster, Austria) for measurements of multiple exposures. Spot urine samples were collected in disposable trace element-free plastic cups and transferred to 20-mL polyethylene bottles (Zinsser Analytic GMBH, Frankfurt, Germany). Water samples were repeatedly collected during the study period using 20-mL polyethylene bottles (Concha et al., 2010).

Boron concentrations were measured using inductively coupled plasma mass spectrometry (ICP-MS, Agilent 7700×, Agilent Technologies, Tokyo, Japan), as described elsewhere (Harari et al., 2015; Lu et al., 2015). Serum and whole blood samples were diluted 1:25 in acid-washed polypropylene tubes with an alkali solution containing 2% 1-butanol, 0.05% EDTA, 0.05% triton X-100, and 1% NH_4OH (Lu et al., 2015). Urine and water samples were diluted 1:10 with 1% nitric acid (Suprapur; Merck, Darmstadt, Germany) before analysis. For comparison, we measured all urine samples, as well as other urine samples from the study site, after alkali dilution also, and acid and alkali dilution gave very similar results for urinary boron ($r_s = 0.98$, p-value < 0.001; $n = 667$). The limit of detection (LOD) for boron was 1.0 μg/L in serum, 0.23 μg/L in whole blood, 6.2 μg/L in urine and 6.4 μg/L in water. Only three serum samples had boron concentrations below the LOD value and those were replaced by LOD/√2.

Reference materials were prepared in an identical manner as the samples and were analyzed after about every 20 samples. As there are no certified standard reference materials (SRM) available for the determination of boron concentrations in serum, whole blood and urine, we used Seronorm™ reference samples (SERO AS, Billingstad, Norway). For water samples, we used certified SRM 1643e Trace Elements in Water (National Institute of Standards and Technology (NIST), Gaithersburg, USA). The results of boron in the reference materials used are shown in Table S2.

Because arsenic, cesium and lithium were also present at elevated concentrations in the drinking water (Supplemental Table S1 and Concha et al., 2010), and these elements may also impair fetal growth (Harari et al., 2015; Rahman et al., 2009), the exposure to these was considered. We additionally measures lead, cadmium and selenium to test for confounding. Cesium and lithium were measured in whole blood and urine, lead and cadmium in whole blood and selenium in serum, all by ICP-MS. Exposure to arsenic was assessed by the sum concentrations of inorganic arsenic (iAs) and its mono- and dimethylated metabolites (MMA and DMA) in urine, measured using HPLC-HG-ICPMS. The analytical details have been described elsewhere (Concha et al., 2010; Fängström et al., 2009; Harari et al., 2015; Lu et al., 2015).

To compensate for the variability in urine dilution, the metal concentrations were adjusted to the average urinary osmolality according to the equation: urinary concentration ∗ [(average osmolality of all women (694 mOsm/kg)) / (individual's osmolality)]. The boron concentrations in urine adjusted for specific gravity were highly correlated with those adjusted for osmolality ($r_s = 0.96$, $p < 0.0001$).

2.3. Outcomes and covariates

The pregnancy outcomes considered in this study were birth weight (g), length (cm) and head circumference (cm), measured by the health care personnel immediately after birth (for most women) or after a few hours for seven women (3.9%) who delivered at home. Birth weight was measured with a baby scale (Seca 725 Mechanical Beam Baby Scale, Brooklyn, NY, U.S.A.), birth length was measured to the nearest 5 mm using a portable wood infantometer with the child in supine position, and head circumference was measured with a soft, non-stretchable plastic tape line with mm indications.

Gestational age at birth was calculated by subtracting the last menstrual period (LMP) date from the date of birth. In a few cases where the date for LMP was not available, we used the ultrasound estimation. The season of birth was noted as winter during the months April–September, and summer October–March. We collected information about maternal age, parity (number of born children), parental monthly