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Environmental exposure to lithium during pregnancy and fetal size: A longitudinal study in the Argentinean Andes ☆

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ABSTRACT

Background: Lithium, used for treating bipolar disease, crosses freely the placenta and is classified as teratogenic. It is unclear to what extent environmental lithium exposure may affect fetal growth and development.
Objectives: To elucidate potential effects of lithium exposure through drinking water during pregnancy on fetal size.
Methods: We developed a prospective population-based mother–child cohort (N = 194) in an area with highly varying drinking water lithium concentrations (5-1600 μg/L) in northern Argentinean Andes. Blood and urinary lithium concentrations (sampled repeatedly during pregnancy) were measured using inductively coupled plasma mass spectrometry. We measured fetal size by ultrasound in second and third trimesters, and weight, length and head circumference at birth. Multivariable models were used to examine associations between lithium exposure (continuous and in tertiles) and fetal size measures.
Results: Lithium in maternal blood (median 25; range 1.9–145 μg/L) and urine (1645; 105–4600 μg/L) was inversely associated (apparently linearly) with all fetal measures (body, head and femur) in the second trimester, and with birth length (β −0.53 cm per 25 μg/L increase in blood lithium, 95%CI −1.0; −0.052). An increase of 100 μg/L in blood was associated with 2 cm shorter newborns (about one standard deviation).
Conclusions: Lithium exposure through drinking water was associated with impaired fetal size and this seemed to be initiated in early gestation. Further studies are warranted to confirm causality and to understand the mechanisms. If confirmed, these findings have public health relevance and emphasize the need for more data on lithium concentrations in drinking water, including bottled water.

1. Introduction

Lithium has long been used in the treatment of bipolar disease (Grandjean and Aubry, 2009b). It is classified as teratogenic (category D) by the U.S. Food and Drug Administration. Besides fetal cardiac and other malformations, lithium seems to increase the risk of miscarriages and prematurity, as well as fetal goiter and hypothyroidism (Cohen et al., 1994; Diav-Citrin et al., 2014; Gentile, 2012; Grandjean and Aubry, 2009c; Oyebode et al., 2012).

A source of more general exposure to lithium is drinking water, although data on concentrations are scarce. Lithium concentrations between <1 and 170 μg/L have been reported for drinking water in Texas, Japan and England (Bluml et al., 2013; Kabacs et al., 2011; Sugawara et al., 2013), while concentrations exceeding 1000 μg/L have been reported for certain areas in Austria (Kapusta et al., 2011) and northern Chile (Zaldivar, 1980). High concentrations have also been reported for certain bottled water, e.g. with almost 10 mg/L in a product from Slovakia (Reimann and Birke, 2010). Elevated lithium concentrations in drinking water (~1000 μg/L) and human urine (~4500 μg/L) were detected in the Andean part of northern Argentina (Concha et al., 2010).

We recently reported that lithium from drinking water easily passes the placenta to the fetus (Harari et al., 2012). As it is unclear to what extent lithium, even from medication, may affect fetal growth and development (Diav-Citrin et al., 2014; Jacobson et al., 1992; Kallen and Tandberg, 1983; Mroczka et al., 1983), we initiated a population-

Abbreviations: LMP, last menstrual period; ICP-MS, inductively coupled plasma mass spectrometry; LOD, limit of detection; iAs, inorganic arsenic; MMA, methylarsonic acid; DMA, dimethylarsinic acid; HPLC, high-performance liquid chromatography; HG, hydride generation; SD, standard deviation; BPD, biparietal diameter; OFD, occipitofrontal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length; BMI, body mass index.

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based mother–child cohort study aiming at elucidating such potential effects from maternal exposure to drinking water lithium during pregnancy.

2. Material and methods

2.1. Study population

All pregnant women living in the Andean part of the Salta province (Departamento Los Andes and part of Departamento La Poma and Rosario de Lerma), northern Argentina (altitude 3180–4070 m above sea level), with estimated delivery date between October 2012 and December 2013, were invited to participate in this longitudinal mother–child cohort, designed to evaluate potential health effects of early-life exposure to lithium and other water pollutants. The study area (totally 8135 inhabitants) included the main village San Antonio de los Cobres (5893 inhabitants; mean water lithium 640 μg/L) and the surrounding villages Santa Rosa de los Pastos Grandes (110 μg/L), Tolar Grande (8 μg/L), Salar de Pocitos (100 μg/L), Olacapato (23 μg/L), Cobres (135 μg/L), Las Cuevas (98 μg/L), El Toro (65 μg/L), El Palomar (13 μg/L) and Esquina de Guardia (140 μg/L). The presence of elevated concentrations of arsenic in the drinking water, particularly in San Antonio de los Cobres, has been known since long (Vahter et al., 1995), while the presence of lithium, boron and cesium was recently detected (Concha et al., 2010).

All pregnant women were invited to the study with the assistance of the primary health care personnel at the hospital in San Antonio de los Cobres and surrounding villages. The 23 trained community health care workers visit the 20 different administrative areas (San Antonio de los Cobres comprising 11 areas, and 9 surrounding villages) on a regular basis, about every 3 months to update demographic information, including health status and pregnancies. Between October 2012 and December 2013, 221 women were pregnant, out of whom 194 became enrolled (participation rate: 88%). Reasons for not participating included deliveries before recruitment (n = 11), twin pregnancy (n = 1), fetal loss before recruitment (n = 5), refusal or not located (n = 6), and migration (n = 4). In addition, two women had spontaneous abortions and 12 lacked prenatal exposure data, giving a final sample of 180 pregnant women (see Supplementary material, Fig. S1). We formally invited the women to the main hospital in San Antonio de los Cobres or the local primary health care clinics in surrounding villages for the investigation of exposures and pregnancy-related conditions. In case a woman was not able to attend at the scheduled date, she was asked to come any day before or after. In this manner, all women were given maximum opportunity to participate in the examinations. The study was designed to see the pregnant women at least once during pregnancy; preferably 2–3 times in order to obtain repeated measures of exposure and fetal size.

The study was approved by the regional ethical committee at Karolinska Institutet, Stockholm, Sweden, and by the Ministry of Health, Salta, Argentina. Prior to recruitment we obtained written informed consent from all women after oral and written explanation of study details. For women below 18 years of age, informed consent was also obtained from the closest caregiver. We regularly reported to and discussed measured water contaminant concentrations with the hospital and the Health Ministry in Salta.

2.2. Data and sample collection

All women were interviewed about age, last menstrual period (LMP), pre-pregnancy weight, parity, time and place of residence, tap water sources and type of water (tap/bottled water), dietary habits, family income, living conditions, smoking, passive smoking, alcohol consumption, coca chewing and personal and familial history of diseases. We measured the women's weight (HCG-210QM, GA.MA® professional, Italy; accurate to 100 g) and height in a standardized way at each visit. Hemoglobin levels were measured in whole blood by HemoCue® 201 + (HemoCue AB, Ängelholm, Sweden). Gestational age was calculated based on the date of LMP which was checked against the estimation based on ultrasound. If LMP was not available or clearly wrong, we used the data based on ultrasound.

All women were asked to donate blood and spot-urine samples at baseline and at each follow-up visit. Whole blood samples were collected in Trace Elements Sodium Heparin tubes (Vacuette®; Greiner bio-one, Kremsmünster, Austria) with butterfly needles (BD Safety-Lok™, Vacutainer®, Becton, Dickinson and Company, Franklin Lakes, USA; tested negative for trace element contamination). One tube was centrifuged for 10 min at 3000 rpm, 15 min after blood withdrawal, for plasma extraction. Spot-urine samples were collected at the hospital or at the local health clinics using disposable trace element free plastic cups and transferred to 20 mL polyethylene bottles. Instructions on wet wipe cleaning and appropriate mid-stream urine sample collection were given in order to avoid contamination. We repeatedly collected water samples (20 mL polyethylene bottles). Blood, urine and water samples were kept at −20 °C until transported to Karolinska Institutet, Sweden, where they were stored at −80 °C until analysis.

2.3. Exposure assessment

To assess lithium exposure, we measured the concentrations in blood, urine, and drinking water. We also measured arsenic, boron and cesium in the same media to control for potential confounding, as they are also present in the drinking water in the study area. All elements were determined using inductively coupled plasma mass spectrometry (ICP-MS, Agilent 7700× ORS ICP-MS, Agilent Technologies, Tokyo, Japan), with the collision/reaction cell in no gas mode (lithium, boron and cesium) or helium mode (arsenic). Before analysis, urine and water samples were diluted 1:10 with 1% nitric acid (65% w/w, ppb-trace analysis grade, Scharlau, Scharlab S.L., Sentmenat, Spain) (Concha et al., 2010). Aliquots (0.2 mL) of blood samples were diluted 1:25 with an alkali solution consisting of 1-butanol 2% (w/v), EDTA 0.05% (w/v), triton X-100 0.05% (w/v), NH_4OH 1% (w/v) and internal standards (20 μg/L) (Lu et al., 2015). The mixture was sonicated for 5 min and centrifuged at 2000 rpm for 5 min (MSE centrifuge, Super Minor, MSE (UK) Ltd., London, England) before ICP-MS analysis. This method was found to provide more reliable results for blood lithium than acid digestion (Lu et al., 2014). For urine, acid and alkaline dilution gave essentially the same results ($r_s = 0.98$; n = 285). Results for commercially available reference materials and limits of detection are presented in Supplemental material, Table S1.

Concentrations of inorganic arsenic (iAs) and its methylated metabolites methylarsonic acid (MMA) and dimethylarsinic acid (DMA) in urine were determined using high-performance liquid chromatography (HPLC) coupled with hydride generation (HG) and ICP-MS as previously described (Harari et al., 2013). The sum of the metabolite concentrations in urine (iAs + MMA + DMA) was used as exposure marker for inorganic arsenic. For quality control, see Harari et al. (2013). The correlation between concentrations of sum of arsenic metabolites and total arsenic, measured in multi-element analyses, was 0.97 ($p < 0.001$), supporting reliable analytical data, and also that the women were exclusively exposed to inorganic arsenic (Vahter, 2002).

To compensate for variations in the dilution of urine, the measured element concentrations were adjusted to the mean urinary osmolality (694 mOsm/kg; range 141–1174), measured by a digital cryoscopic osmometer (OSMOMAT® 030, Gonotec Gesellschaft für Meß- und Regeltechnik mbH, Berlin, Germany). Osmolality was chosen since creatinine adjustment is markedly affected by muscle mass, age and meat intake (Suwazono et al., 2005) and specific gravity by urinary protein and glucose (Parikh et al., 2002). Microalbuminuria (urinary albumin 30–299 mg/L) was detected in 14% of all women and macroalbuminuria (>300 mg/L) in 6%, using HemoCue Albumin 201 (HemoCue AB,