Reproductive Toxicology 53 (2015) 68–74

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Manganese exposure through drinking water during pregnancy and size at birth: A prospective cohort study

Syed Moshfiqur Rahman[a,b], Maria Kippler[a], Sultan Ahmed[a,b], Brita Palm[a], Shams El Arifeen[b], Marie Vahter[a,*]

[a] Institute of Environmental Medicine, Karolinska Institutet, Box 210, SE-171 77 Stockholm, Sweden
[b] International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), GPO Box 128, Dhaka 1000, Bangladesh

ARTICLE INFO

Article history:
Received 19 September 2014
Received in revised form 6 February 2015
Accepted 20 March 2015
Available online 28 March 2015

Keywords:
Manganese toxicity
Drinking water
Pregnancy
Birth weight
Birth length

ABSTRACT

The essential element manganese (Mn) might be toxic at excess exposure. We assessed the impact of elevated Mn exposure through drinking water during pregnancy on birth size in a population-based cohort(n = 1695) in rural Bangladesh. Concentrations of water Mn (median = 236 μg/L, range = 7.1–6336; n = 1177) and erythrocyte Mn (median = 30 μg/kg, range = 6.3–114; n = 758) were measured using ICP-MS. In regression analyses, newborns of women in the highest tertile of water Mn (median = 1495 μg/L) were 0.49 cm (0.20 SD) shorter (B = −0.42; 95% CI: −0.77, −0.08) than those in the lowest tertile (56 μg/L). The inverse association was significant in girls and also in boys of mothers with lowest hemoglobin values, likely due to higher absorption of Mn. Manganese concentrations in water and erythrocytes did not correlate, and the associations of the latter with birth size were less obvious. This study suggests that consumption of water with highly elevated Mn levels during pregnancy may impair fetal growth.

1. Introduction

The essential micronutrient manganese (Mn) functions as a cofactor in the metabolism of carbohydrates and proteins and in antioxidants such as superoxide dismutase, all of which are important during development [1–3]. While Mn deficiency is rare in humans and a varied diet provides the required 2–3 mg/day during pregnancy [4], toxicity due to excess Mn exposure is more common [3,5]. In particular, several studies have shown associations between drinking water Mn concentrations and impaired child development [6–8]. Excess intake of Mn may be of particular concern during pregnancy, when the intestinal divalent metal transporter (DMT1) is up-regulated, causing increased absorption of both iron and Mn [2,9]. Still, we found only one study evaluating fetal growth (n = 16408) in relation to Mn in drinking water, and that indicated impairment of fetal growth at elevated water concentrations of both Mn (mean = 375 μg/L) and iron (mean = 835 μg/L) in Lithuania [10]. However, a few studies from China, Korea and USA have reported inverse associations between elevated maternal or cord blood Mn concentrations, mainly above 30 μg/L in maternal blood, and birth weight or length [11–14], while lower blood concentrations showed positive associations [11–13,15]. Therefore, we aimed to prospectively assess the impact of elevated Mn exposure through drinking water on birth weight and length. In the studied population, residing in rural Bangladesh, we have previously observed that elevated water Mn seemed to decrease the risk of spontaneous abortions [16].

2. Materials and methods

2.1. Study area and design

This prospective cohort study was carried out in Matlab, a rural area of Bangladesh, where the International Centre for Diarrhoeal Disease Research in Bangladesh (icddr,b) has an ongoing well-established Health and Demographic Surveillance System (HDSS) and provides health services to the residents [17]. The study was nested into a randomized food and micronutrient supplementation trial (MINIMat; no manganese), which enrolled 4436 pregnant women from November 2001 through October 2003 and evaluated

Abbreviations: AsMat, arsenic study at Matlab; BMI, body mass index; DMT1, divalent metal transporter 1; Ery-Mn, erythrocyte manganese; GW, gestational week; HDSS, Health and Demographic Surveillance System; Hb, hemoglobin; icddr,b, International Centre for Diarrhoeal Disease Research in Bangladesh; ICP-MS, inductively coupled plasma mass spectrometry; LOD, limit of detection; MINIMat, Maternal and Infant Nutrition Interventions in Matlab; SES, socioeconomic status; SD, standard deviation; 95% CI, 95% Confidence Intervals; W-Mn, water manganese.

* Corresponding author. Tel.: +46 8 524 875 40; fax: +46 8 336981.
E-mail address: marie.vahter@ki.se (M. Vahter).

http://dx.doi.org/10.1016/j.reprotox.2015.03.008
0890-6238/

size at birth [18]. It was discovered early on that well water, which is the main source of drinking water in this area, often contained elevated arsenic concentrations. All the wells in Matlab were screened for arsenic (AsMat study) [19] and research to evaluate the potential health effects of arsenic exposure in early-life was nested in the MINIMat trial [20,21]. The most efficient mitigation method seems to be construction of deep wells [22], but those wells were found often to contain elevated Mn concentrations [16]. Thus, we initiated studies also on potential Mn-related health effect.

The present study is based on the pregnant women who were enrolled in the MINIMat trial during one calendar year, from 1 February 2002 through January 2003, and had a singleton birth with anthropometric measurements at birth (n = 1695; Fig. 1). For 1361 of these women (81%) we had samples of the drinking water used during pregnancy. Reasons for missing water samples (n = 334) included unknown water sources as pregnancy was identified after completion of the household water survey or discarded water samples after the initial analysis of arsenic. The study was approved by the ethical review committees of icddr,b, Bangladesh and Karolinska Institutet, Sweden. Written consent was obtained from all the women prior to enrollment. The subjects were free to leave the study at any time.

2.2. Manganese in water and maternal blood (erythrocytes)

There is no optimal biomarker for Mn exposure [23]. We measured the concentrations in drinking water (W-Mn) and maternal blood (erythrocyte fraction; Ery-Mn), both of which have been associated with fetal growth and child development. Based on the obtained information on lifetime drinking water sources in the AsMat study [19], we identified the drinking water used by the women during pregnancy. In total, 1177 pregnancies had reliable water data (Fig. 1), as evaluated based on the agreement between the concentrations of arsenic in the water and arsenic metabolites in the urine, the latter being a useful biomarker of ongoing exposure [20]. The water samples were analyzed for Mn, iron, and arsenic using inductively coupled plasma mass spectrometry (ICP-MS; Agilent 7500ce, Agilent Technologies, Tokyo, Japan) [24]. No samples were below the limit of detection (0.01, 0.02, and 0.01 μg/L, respectively). Good analytical performance was ascertained by analysis of a certified reference water sample (NIST 1643e, Trace Elements in Water, National Institute of Standards and Technology, Gaithersburg, MD, USA).

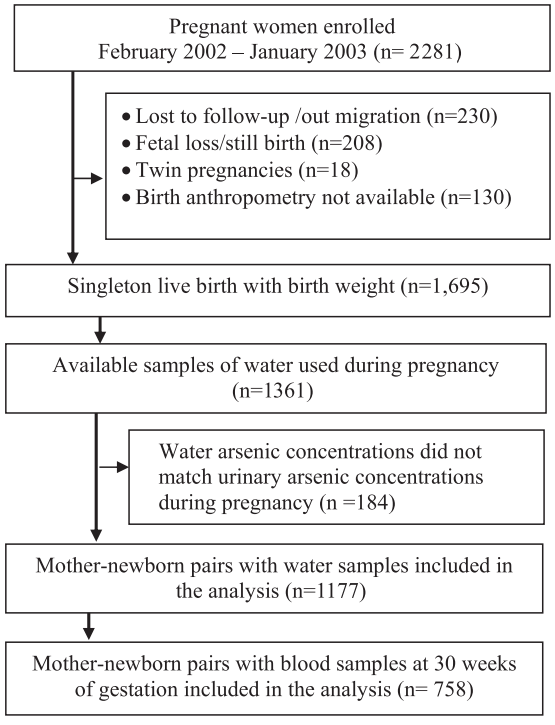

Fig. 1. Flow chart depicting the pregnancy cohort recruited February 2002 to January 2003.

Out of the 1177 women with outcome data and water samples, blood samples [gestational week (GW) 30] for Mn analysis were available for 758 (64%) women. Reasons for missing blood samples (n= 419) included refusal (n = 118) or samples used for other purposes (n = 301). Venous blood samples were collected at GW 30 in 5.5 mL Li-Heparin tubes (SARSTEDT, Nümbrecht, Germany), which provided <0.1 μg Mn/L upon prior testing with 0.03 M nitric acid. Blood sampling was performed at the health clinics (4 icddr,b subcenters, each serving around 28,000 people and run by paramedical staff), and the samples were kept in cold boxes until they were transported to the hospital laboratory (the same day) for separation of the plasma and erythrocytes, which were stored at −70 and −20 °C, respectively. The erythrocyte fractions were transported frozen to Karolinska Institutet, Sweden, for analysis. All the materials used during sample collection were tested for trace element contamination. Manganese in erythrocytes was measured using inductively coupled plasma mass spectrometry (ICPMS; Agilent 7700x, Agilent Technologies, Tokyo, Japan) after acid digestion [9]. No samples were below the limit of detection for Ery-Mn (0.16 μg/kg). The results of two commercial control values were in good agreement with the recommended values [25].

2.3. Outcome assessment

The weight and length of the babies delivered at health clinics (40%) were measured by the attending nurse [18]. For women who delivered at home, a birth notification system was established to enable the measurements of birth anthropometry by trained health workers, typically within 72 hours of birth (87%). The birth weight and length measured during the first 24 hours were used without adjustments. Measurements taken more than 24 hours after birth were adjusted using a standard deviation (SD) score transformation, assuming that infants tend to remain in the same relative position in the anthropometric distribution during the first 24 hours as described elsewhere [18,26]. Birth weight was measured with electronic scales (UNICEF Uniscale; SECA, Hamburg, Germany; precision of 10 g). Birth length was measured with a locally made wooden infantometer with 1 mm precision. Also for the children that were measured at home, we ensured valid and precise weight measurements, by routinely standardizing and calibrating the scales. In addition, the health workers periodically received refresher training on anthropometric measurements, and an independent team repeated the anthropometric measurements for a random sample of approximately 5% of the newborns [18].

2.4. Covariates

Information on the women's age, weight, height, parity, education, and socioeconomic status as well as the date and place of delivery, and the newborns' sex were available from the MINIMat trial and the HDSS. The maternal body mass index (BMI, kg/m^2) was calculated based on women's weight and height at enrollment (approximately GW 9). Pregnancy weight gain (in kg) was calculated by subtracting the weight measured in early pregnancy (GW 9) from the weight measured at GW 30. Gestational age (weeks) was calculated by subtracting the date of the last menstrual period (LMP) from the date of delivery. If the LMP was not known (n = 26), the gestational age was estimated based on ultrasound measurements [21]. Parity was defined as the number of live or dead