International Journal of Hygiene and Environmental Health 217 (2014) 205–218

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

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

Birth outcome measures and maternal exposure to heavy metals (lead, cadmium and mercury) in Saudi Arabian population

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ARTICLE INFO

Article history:
Received 3 September 2012
Received in revised form 30 March 2013
Accepted 22 April 2013

Keywords:
Lead
Mercury
Cadmium
Birth outcome
Anthropometric measures
Small-for-gestational age
Umbilical cord blood
Maternal blood
Placenta
Saudi Arabia

ABSTRACT

This cross-sectional study was conducted to assess the association between exposure to heavy metals (lead, cadmium and mercury) during pregnancy and birth outcomes in 1578 women aged 16–50 years who delivered in Al-Kharj hospital, Saudi Arabia, in 2005 and 2006. The levels of lead, cadmium and mercury were measured in umbilical cord blood, maternal blood and the placenta. Outcome variables were anthropometric measures taken at birth, along with the risk of being small-for-gestational age (SGA). We selected the 10th percentile as the cutoff for dichotomizing measures of birth outcome. Cadmium, despite its partial passage through the placenta had the most prominent effect on several measures of birth outcome. After adjustment for potential confounders, logistic regression models revealed that crown-heel length ($p = 0.034$), the Apgar 5-minute score ($p = 0.004$), birth weight ($p = 0.015$) and SGA ($p = 0.049$) were influenced by cadmium in the umbilical cord blood. Significant decreases in crown-heel length ($p = 0.007$) and placental thickness ($p = 0.022$) were seen with higher levels of cadmium in maternal blood. As placental cadmium increased, cord length increased ($p = 0.012$) and placental thickness decreased ($p = 0.032$). Only lead levels in maternal blood influenced placental thickness ($p = 0.011$). Mercury in both umbilical cord and maternal blood was marginally associated with placental thickness and placental weight, respectively. Conversely, placental mercury levels significantly influenced head circumference ($p = 0.017$), the Apgar 5-minute score ($p = 0.01$) and cord length ($p = 0.026$). The predictions of these models were further assessed with the area under the curve (AUC) of the receiver operating curves (ROCs), which were modest (larger than 0.5 and smaller than 0.7). The independence of gestational age or preterm births on the observed effect of metals on some measures of birth outcome, suggested detrimental effects of exposure on fetal development. The magnitude of the estimated effects might not necessarily be of clinical significance for infants but may have a considerable public-health relevance given the high prevalence of exposure to heavy metals. Further research should be conducted to confirm these findings and to evaluate their long-term risks, if any.

Introduction

Even though *in utero* exposure to heavy metals has been well investigated over the last few decades (Yoshida, 2002; Bellinger, 2005; Thompson and Bannigan, 2008), our knowledge of the threats to the fetus at low levels of exposure remains either limited or inconsistent (Rahman and Hakeem, 2003; Jelliffe-Pawlowski et al., 2006; Tian et al., 2009; Gundacker et al., 2010; Shirai et al., 2010). Umbilical cord blood, as a noninvasive sample, has been frequently tested for assessing prenatal exposure to a variety of metals; other biological tissues such as maternal blood, human milk, urine, meconium and amniotic fluid can also be used (Gundacker et al., 2010; Shirai et al., 2010; Caserta et al., 2011). The placenta has recently been used as a tool for investigating and predicting some aspects of fetal developmental toxicity. It acts as a selective fetal–maternal barrier allowing nutrients and oxygen to pass to the fetus and is supposed to prevent potentially harmful compounds from crossing (Iyengar and Rapp, 2001). Heavy metals, however, do cross the placenta. Lead and mercury can easily cross placenta and accumulate in fetal tissues, while cadmium can partially cross (Iyengar and Rapp, 2001). Studies have suggested that placental metallothionein might play a protective role against cadmium toxicity by its binding to the metal (Kippler et al., 2010). The detection of cadmium in umbilical cord blood as reported in some studies (Tian et al., 2009; Lin et al., 2011), however, indicates that the role of placental metallothionein as a barrier to cadmium is inconclusive (Nakamura et al., 2012).

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http://dx.doi.org/10.1016/j.ijheh.2013.04.009

Associations have been reported between cadmium in umbilical cord blood and detrimental effects on the head circumference of newborns (Lin et al., 2011), thyroid hormone status at birth (Iijima et al., 2007) or child growth later in life (Tian et al., 2009). Different studies, though report conflicting results. Gundacker et al. (2010) found that placental and meconium lead were predictors of birth height, while birth weight was affected by lead in the placenta and maternal blood. Zhang et al. (2004) revealed that cadmium in umbilical cord blood, but not in maternal blood or the placenta, was negatively associated with neonatal birth height. On the other hand, Salpietro et al. (2002) reported that a decrease in birth weight was associated with cadmium in samples of maternal and umbilical cord blood. Gundacker et al. (2010) found that mercury in hair, but not in umbilical cord blood, maternal blood or the placenta, was associated with birth height.

Our previous study on the same population provided evidence that both the mothers and their newborns were substantially exposed to heavy metals, even though 88.7% of the participants were housewives at the time of the study, and all were non-smokers (Al-Saleh et al., 2011). Lead, cadmium and mercury were detected in the majority of the three compartments studied (placenta and umbilical cord and maternal blood), confirming their transplacental transfer. In the present study, we have expanded our data analyses by examining the influence of lead, cadmium and mercury measured in the placenta and in umbilical cord and maternal blood on measures of birth outcome.

Materials and methods

The data evaluated in this study originated from samples and questionnaires collected for the project "Exposure to environmental pollutants and its effect on pregnancy outcome" (Al-Saleh et al., 2011). The source population included 1578 women who delivered between June 2005 and 2006 in a main public hospital in the Al-Kharj area located about 80 km southeast of the capital city of Riyadh. None of the women smoked, but 26% had either a husband or at least one household member who smoked (cigarettes, sheesha and/or muaasal). Each woman was asked to join the study and completed a consent form. The women answered a detailed questionnaire and were interviewed after delivery by trained health-care personnel. The response rate was 99%. Umbilical cord blood and the placenta were obtained at the time of delivery, while maternal blood was collected within next hours of delivery. The details of sample collection and analytical procedures have been previously described elsewhere (Al-Saleh et al., 2011). The study protocol was approved by the Research Ethics Committee of King Faisal Specialist Hospital and Research Centre.

Birth anthropometric measurements. These data were obtained by the obstetrician at birth included birth weight (g), birth height (cm), head circumference (cm), crown-heel length (cm), Apgar 1-min score, Apgar 5-minute score, placental weight, placental thickness, and cord length. Ponderal index was calculated as birth weight (kilograms) divided by birth height^3 (m) cubed. The cephalization index was calculated as the ratio of head circumference (cm) to birth weight ($g \times 10^2$). Gestational age was calculated from the last menstrual period to the termination of pregnancy. The obstetrician examined each placenta and umbilical cord in the delivery room and recorded the placental weight, placental thickness and cord length.

Laboratory methods

Samples of umbilical cords and maternal venous blood were collected in Vacutainer tubes containing 10.5 mg of K_3-EDTA (tripotassium-ethylene diaminetetraacetic acid) as anticoagulant and stored at 4 °C until analysis. These tubes were tested for metal contamination before use. All blood and placental samples were analyzed for lead and cadmium using a Varian AA-280 Zeeman Atomic Absorption Spectrophotometer coupled to a GTA-120 graphite furnace (Varian Techtron Pty. Ltd., Australia). Mercury was analyzed by a Varian AA-880 Zeeman atomic absorption spectrophotometer coupled to a Vapor Generation Accessory VGA-77 (Varian Techtron Pty. Ltd., Australia). Details of the analytical procedure have been reported previously (Al-Saleh et al., 2011). The accuracy of the methods were verified by the analysis of two levels of certified reference materials for lead and cadmium (CONTOX Heavy Metal Blood Control A, Kaulson Laboratories, NJ, USA). The experimental values agreed well with the certified recommended values for both controls. The experimental values for levels I and III lead were 19.67 ± 2.72 μg/l $N = 88$ and 45.76 ± 6.98 μg/l $N = 87$ respectively, while the recommended values were 14.0–22.0 and 39.0–51.0 μg/l respectively. The measured values for cadmium for level I (10.34 ± 1.89 μg/l, $N = 79$) and level II (15.79 ± 3.31 μg/l, $N = 77$) were within the recommended ranges of 4–12 μg/l and 11–19 μg/l, respectively. Unfortunately, we were unable to use the reference materials for mercury analysis due to limited sample volumes. The bovine muscle powder (SRM 8414) reference material from the National Institute of Standards and Technology (NIST) was used for placental metal analysis. The results of our determinations were (0.47 ± 0.132 μg/g, $N = 44$) for lead, (0.014 ± 0.0058 μg/g, $N = 38$) for cadmium and (0.0054 ± 0.002 μg/g, $N = 23$) for mercury. The results are in good agreement with the recommended certified values for lead (0.38 ± 0.24 μg/g), (0.013 ± 0.011) μg/g for cadmium and (0.005 ± 0.003 μg/g) for mercury. The mean recoveries for spiked blood samples ranged from 102% to 104% for lead, 99% to 102% for cadmium and 102% to 107% for mercury with relative standard deviation (%RSD) ranging from 5.6% to 9.1%. The mean recoveries for placental samples were 99% to 103% for lead, 99% to 102% for cadmium and 100% to 109% for mercury, with %RSDs in the range of 6–11%. The method's detection limits (MDLs) in blood were 0.397 μg/dl, 0.42 μg/l, and 0.25 μg/l for lead, cadmium and mercury, respectively. The MDLs in placental tissues were 0.25 μg/g dry wt., 0.025 μg/g dry wt. and 0.033 μg/g dry wt. for lead, cadmium and mercury, respectively.

Due to the inaccuracy of self-reported smoking, urinary cotinine was measured as an index of smoking using the commercial Cotinine Direct ELISA Kit (Bio-Quant, Inc., USA). Values were corrected for creatinine which was measured by colorimetric assays (Oxford Biomedical Research, MI, USA).

Statistical analyses. Data were analyzed using SPSS for Windows (version 17; SPSS Inc., Chicago, IL, USA). A *p*-value of <0.05 was set as the level of statistical significance.

Data are given as arithmetic means, standard deviations (SDs) or proportions (%) unless otherwise stated. When required, skewed data were natural log-transformed to approximate normality before statistical analyses.

We selected the 10th percentiles as cutoffs for dichotomizing birth anthropometric measures (head circumference, heel-crown length, Apgar 1-min score, Apgar 5-minute score, birth weight, birth height, placenta weight, placenta thickness, cord length, ponderal index and cephalization index) to easily interpret the risk to fetal growth. A further binary outcome for small-for-gestational age (SGA) was created according to the method of Khanjani and Sim (2006) by comparing the birth weight below the 10th percentile of each newborn for that gestational age and gender.

Information on potential confounding variables related to demographic, socioeconomic, environmental and maternal and newborn health conditions were obtained from a detailed questionnaire. We also calculated total maternal weight gain by summing the average weight gains for the second and third trimesters. Among the socioeconomic indicators, only the highest