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Evaluation of *in utero* exposure to arsenic in South Africa

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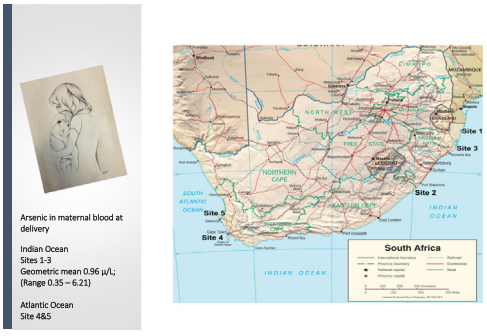
HIGHLIGHTS

- *In utero* exposure to arsenic in South Africa was assessed in blood and urine.
- Linear correlation between maternal and cord blood confirmed placental transfer.
- Maternal blood arsenic was negatively correlated with head circumference.
- Birth weight was positively correlated with maternal age, weight, height and parity.
- Socioeconomic status and nutrition was associated with maternal arsenic levels.

GRAPHICAL ABSTRACT



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ABSTRACT

Early life exposure to inorganic arsenic (iAs) has been shown to interfere with foetal and early childhood development, and is associated with morbidity and mortality in adulthood. The purpose of this study was to evaluate exposure to As *in utero*, to determine the association between maternal and cord blood of As and birth outcomes in South African populations. Total arsenic was measured in maternal blood of a total cohort ($n = 650$) and in paired cord blood and urine of a subset cohort ($n = 317$). Overall, the geometric mean (GM) of As in maternal blood was 0.62 µg/L (n = 650; 95% CI, 0.58–0.66). In the subset cohort, the GM of maternal blood As was 0.96 µg/L ($n = 350$; 95% CI, 0.91–1.02); in paired cord blood, the GM was 0.78 µg/L ($n = 317$; 95% CI, 0.74–0.83); and in urine (creatinine–corrected), the GM was 14.26 µg/g creatinine (n = 317; 95% CI, 12.64–16.09). A linear correlation was found between log maternal blood As and log cord blood As (rho = 0.80, $p < 0.001$). Birth outcomes showed geographical differences. in gestational age ($p < 0.001$), birth length ($p = 0.019$), head circumference ($p < 0.001$), Apgar score at 5 min ($p < 0.001$) and parity ($p < 0.002$). In a multivariate analysis, no association between maternal blood (AsB) levels and birth outcomes were found. However, the lower the gestational age, the higher the levels of maternal AsB ($\beta = -0.054$; 95% CI-0.087 to −0.020) and mothers who had had at least one child were less likely to have higher AsB if compared to those who had never had any child ($\beta = -0.177$; 95CI-0.322 to 0.031).
In both univariate and multivariate analyses, being single, and drinking water from communal outdoor taps, boreholes and rivers was associated with higher As levels. The findings suggest that more research is needed to evaluate the impact of low level As exposure on postnatal development.

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1. Introduction

It has been shown that exposure to arsenic (As) during pregnancy can have detrimental effects on foetal development, birth outcomes and early childhood development. Pregnant women and the population in general may be exposed to As through ingestion of food and drinking water, inhalation, and dermally, following contact with industrially contaminated soil and water and from naturally occurring contamination. In some geographical regions, mainly in Bangladesh, Taiwan and India, the major source of As is drinking well water which contains naturally occurring As concentrations many times exceeding the World Health Organization (WHO) guideline of 10 μg/L (Ahuja, 2008; IARC Monograph, 2012). It has been estimated that >100 million people worldwide rely on As-contaminated well water as the source of their drinking water (Fangstrom et al., 2009). In these areas, water is a primary contributor of exposure to As. In Bangladesh, it has been shown that cooked rice is also a significant source of population exposure (Bae et al., 2002). Similarly, Gilbert-Diamond et al., 2011 has reported that rice consumption contributed to exposure of US women to arsenic (Gilbert-Diamond et al., 2011). In areas where water As concentration is low, food and smoking are thought to be the primary contributors (Dictor, 2004).

Chemically, As is classified as a metalloid that exists naturally in the environment, both in inorganic and organic forms and in different oxidation states, each exerting potentially different toxic effects in humans (Marchiset-Ferlay et al., 2012). Arsenic is classified as a carcinogen and neurotoxicant by the IARC and the National Research Council (IARC Monograph, 2012; NRC, 2001). The main effects of As poisoning *via* drinking water are cancerous and non-cancerous skin lesions evident as hyperpigmentation and keratosis of the palms and feet (CHEN and WU, 1962). In endemic areas, an increase in primary cancers of the skin, lung, bladder and kidney have been observed. Some chronic diseases such as peripheral and cardiovascular diseases, neurological disorders, diabetes and hypertension are also thought to be associated with exposure to As (Abhyankar et al., 2012; De Vizcaya-Ruiz et al., 2009; Rahman et al., 2009a; Rahman et al., 2009b; States et al., 2009).

Some studies have examined the effect of high As exposure in pregnancy and the respective birth outcomes, both in animal models and in humans. Research indicates that pregnancy can alter the metabolism efficiency of inorganic As but this association is not yet well understood (Gebel, 2000; Kapaj et al., 2006; Vahter and Concha, 2001). This effect of As will depend on the dose and exposure duration, genetic and nutritional status, but also on co-exposure to other toxicants (Gebel, 2000). In animals, it has been shown that high doses of As have negative effects on the developing foetus (Golub et al., 1998). Similarly, in humans, reduction in birth weight, as well as increase in spontaneous abortions and infant mortality associated with As exposure have been observed (Ahmad et al., 2001; Hopenhayn et al., 2003; Huyck et al., 2007; Rahman et al., 2007; von Ehrenstein et al., 2007). Recently, Farzan et al., reported that *in utero* As exposure was associated with an increased risk of infections requiring medical treatment during the first year of life, particularly diarrhoea and respiratory symptoms (Farzan et al., 2016). In addition to inorganic As crossing into the human placenta and accumulating in the developing foetus, it also accumulates in the placenta disrupting its normal function, potentially resulting in lower birth weight at term, shorter birth length and smaller head and chest circumference (Ahmad et al., 2001; Concha et al., 1998; Laine et al., 2015; Rahman et al., 2009a; Tabacova et al., 1994). Thus, toxic effects of exposure to high levels of As (>10 μg/L) *via* drinking of contaminated water are well defined, health effects caused by exposure to low levels of As present in water and the diet are not clear (Rahman et al., 2009b). Studies from Chile, Argentina and Europe have reported similar disorders following exposures to much lower concentrations of As in drinking water, varying between undetectable levels and 3.6 μg/L (Hopenhayn et al., 2003; Rahman et al., 2009b; States et al., 2009). More recently, Farzan et al., 2013 have linked early-life As exposure to an increased risk of cancer in adulthood (Farzan et al., 2013).

To date, research investigating health effects of low level As exposure have produced conflicting results (Fei et al., 2013; Guan et al., 2012; Thomas et al., 2015), indicating the need for more research into the possible toxicity of As at low, long-term exposures, particularly in women of reproductive age and their offspring/babies (Rahman et al., 2009b).

In South Africa and other African countries the main sources of As originate from mining and related industries, as well as agricultural operations. However, there is a lack of information on natural levels of As in drinking water and soils. Smedley et al., 1996 has documented groundwater contamination with As in the Obuasi gold mining area of Ghana (Smedley et al., 1996) and Sami and Druzynski (2006) have examined geological occurrence of As in selected areas of South Africa. Nationwide, where 200 boreholes of 1514 boreholes sampled for As have been found to contain arsenic concentrations above WHO standards (Kempster et al., 2007; Sami and Druzynski, 2006).

The aim of this study was to assess *in utero* exposure to total As, as measured in maternal blood at delivery, and to examine the possible impact of As exposure on birth outcomes in populations residing along the Indian and Atlantic Oceans in South Africa. In a paired mother-child sub-cohort, the research team also assessed the association between maternal and cord blood and evaluated the correlation between As levels in three biological parameters, *viz.* maternal blood and maternal urine at delivery, and cord blood post-partum. Possible gender response to *in utero* As exposure was also examined.

2. Materials and methods

2.1. Study sites and participants

Five sites were included in the study: three sites (Sites 1 to 3) were situated along the Indian Ocean coast, and two sites (Sites 4 and 5) were situated along the Atlantic Ocean coast of South Africa. All study sites were rural, except for the city of Cape Town site (Site 4). Potential study candidates were recruited among women who were admitted for delivery at the local maternity sections at public hospitals. After the objectives of the study were explained, women who agreed to participate signed an informed consent form and agreed to donate blood and urine before delivery, and to the collection of cord blood after delivery. Participants agreed to answer a socio-demographic questionnaire which also included the topics of diet, lifestyle, and self-reported health status. The dietary part of the questionnaire recorded the frequency of intake of various basic foods during pregnancy. Participants also consented to access and use of hospital birth outcome data (including maternal and neonate characteristics such as weight, length and head circumference, gestational age, as well as birth complications, if any) for research purposes. In total, 650 women answered the questionnaire and donated pre-partum blood samples. Due to financial constraints, the collection of additional samples (pre-partum urine samples (n = 316) and post-partum cord blood samples (n = 317) was limited to women residing in Sites 1 to 3, which formed the sub-cohort of this study, along the Indian Ocean coast.

2.2. Sampling collection

A sterile venoject system was used for all blood collections. From each woman, a volume of 10 ml of venous blood was collected before delivery into a BD Vacutainer tube (10 ml capacity and containing EDTA). Participants from the sub-cohort also donated 30 ml of urine before delivery. Umbilical cord blood (10 ml) was collected post-partum by a nursing sister using a syringe.

2.3. Sample processing and analytical procedures

The analyses for total As content in whole blood (AsB) and urine (AsU) were performed using an Inductively Coupled Plasma-Mass