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Invited Review Article

In utero and early life arsenic exposure in relation to long-term health and disease

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ABSTRACT

Background: There is a growing body of evidence that prenatal and early childhood exposure to arsenic from drinking water can have serious long-term health implications.
Objectives: Our goal was to understand the potential long-term health and disease risks associated with in utero and early life exposure to arsenic, as well as to examine parallels between findings from epidemiological studies with those from experimental animal models.
Methods: We examined the current literature and identified relevant studies through PubMed by using combinations of the search terms "arsenic", "in utero", "transplacental", "prenatal" and "fetal".
Discussion: Ecological studies have indicated associations between in utero and/or early life exposure to arsenic at high levels and increases in mortality from cancer, cardiovascular disease and respiratory disease. Additional data from epidemiologic studies suggest intermediate effects in early life that are related to risk of these and other outcomes in adulthood. Experimental animal studies largely support studies in humans, with strong evidence of transplacental carcinogenesis, atherosclerosis and respiratory disease, as well as insight into potential underlying mechanisms of arsenic's health effects.
Conclusions: As millions worldwide are exposed to arsenic and evidence continues to support a role for in utero arsenic exposure in the development of a range of later life diseases, there is a need for more prospective studies examining arsenic's relation to early indicators of disease and at lower exposure levels.

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Introduction

Environmental toxicants can profoundly impact the health of individuals and chronic exposure to toxic metals, like arsenic (As), has been implicated in the development of a variety of diseases in adults. Arsenic exposure via contaminated groundwater is a global health concern. As a known carcinogen, As can cause cancers of the lung, bladder, and skin, with mounting evidence pointing to a role in liver cancer as well (International Agency for Research on Cancer, 2004). Studies from Taiwan, Bangladesh, and Chile found that moderate-to-high levels of As exposure (200–800 μg/L) are associated with both all-cause mortality and cardiovascular-disease related mortality (Argos et al., 2010;

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Chen et al., 2011; Wu et al., 1989; Yuan et al., 2007). Increases in cardiovascular disease occurrence, and modest, yet significant elevation in measures of hypertension also have been reported in As-exposed populations (Abhyankar et al., 2012; States et al., 2009).

We are now beginning to understand that pregnancy represents a particularly vulnerable window of susceptibility to toxicants for both mother and child and that many diseases may originate from environmental insults and alterations that occur during this sensitive developmental period. During pregnancy, As can pass through the placenta from mother to fetus, resulting in fetal exposure levels equivalent to those of the mother (Concha et al., 1998). Studies have found that in utero As exposure may have detrimental effects on pregnancy and birth outcomes, with higher levels of exposure associated with increased risks of spontaneous abortions and stillbirths, as well as increased infant mortality, preterm birth, low birth weight and fetal growth restriction (Ahmad et al., 2001; Hopenhayn et al., 2003; Hopenhayn-Rich et al., 2000; Huyck et al., 2007; Milton et al., 2005; Rahman et al., 2007, 2010; Vahter et al., 2006; von Ehrenstein et al., 2006). Fetal growth restriction has been linked to increased risk of later metabolic disease, which in turn can lead to chronic conditions such as hypertension, diabetes and increased risks of cardiovascular disease (Valsamakis et al., 2006).

In addition, in utero As exposure has been related to early life developmental effects, including neurodevelopmental defects in both animal studies (Goggin et al., 2012; Martinez et al., 2008, 2011; Martinez-Finley et al., 2009) and epidemiological studies among children (Hamadani et al., 2010, 2011; Parajuli et al., 2013; Parvez et al., 2011; Rosado et al., 2007; Roy et al., 2011; Tsai et al., 2003; von Ehrenstein et al., 2007; Wasserman et al., 2004, 2007). While the influence of in utero or early life As exposure on neurotoxicity also may impact risk of chronic disease, the long-term consequences of these early alterations have yet to be elucidated (Fig. 1).

Many of the early developmental effects of in utero exposure are likely influenced, at least in part, by epigenetic changes (Intarasunanont et al., 2012; Kile et al., 2012; Koestler et al., in press; Pilsner et al., 2012) and in turn, programming of ongoing health and risk of chronic conditions. Further evidence suggests in utero or early life exposure to As increases oxidative stress signaling (Ahmed et al., 2011, 2012), and deregulation of immune and inflammatory pathways (Ahmed et al., 2011, 2012; Fry et al., 2007). These are potential mechanisms underlying observed associations between maternal As exposure and increased susceptibility to infections among their offspring (Farzan et al., in press; Rahman et al., 2011; Raqib et al., 2009) as well as of chronic diseases. In light of accumulating epidemiological studies in conjunction with compelling animal model work, we review the literature highlighting newly published findings that address the potential role of in utero and early life exposure to As on long term health and risk of chronic disease, including cancer, respiratory disease and cardiovascular diseases.

Cardiovascular effects

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide and emerging data suggest that the determinants of CVD occur early in life. The Dutch Winter Hunger Study illuminated the link between fetal under-nutrition and growth restriction and later metabolic syndrome that leads to several chronic diseases, such as hypertension, diabetes and CVD (Valsamakis et al., 2006). While studies in adults suggest that high levels of As adversely affect glycemic control, blood pressure, systemic inflammatory markers, vascular endothelial function and CVD occurrence, few studies have been prospectively designed to examine the effects of early life As exposure on CVD risk. Nearly 40 years ago, a set of autopsy case reports from young children in Chile suggested a possible

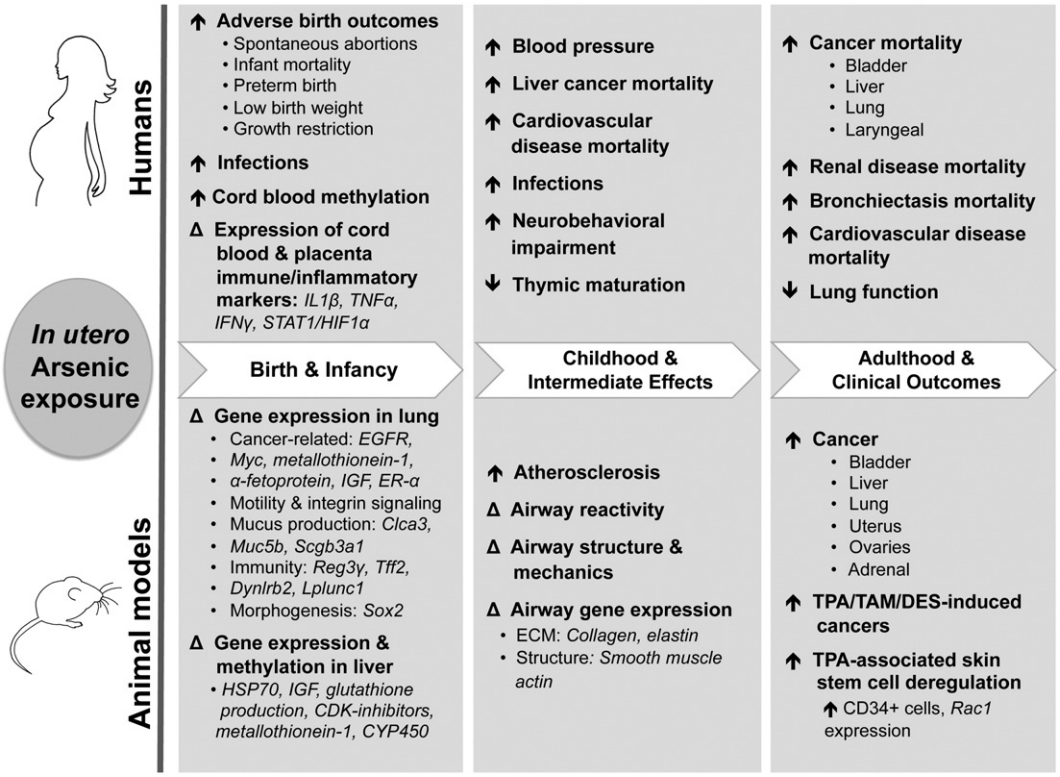

Fig. 1. In utero arsenic exposure and lifelong health effects. Human epidemiological studies (top) and experimental animal studies (bottom) demonstrate that in utero exposure to arsenic can impact health and disease development at different stages of life, from birth (leftmost gray panel) to childhood (center panel) and into adulthood (rightmost panel). In utero arsenic exposure may lead to different clinical presentation depending on the stage of life investigated, but examination of clinically relevant, intermediate endpoints in childhood may help to elucidate arsenic-related pathogenesis and later-life disease susceptibility.