Effects of Arsenic on Maternal and Fetal Health

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Abstract

Arsenic, which is commonly found in drinking water, is a potent toxicant, but little is known about its effects on maternal health. Arsenic's modes of action include enzyme inhibition and oxidative stress as well as immune, endocrine, and epigenetic effects. A couple of studies reported increased blood pressure and anemia during pregnancy. Susceptibility to arsenic is dependent on the biomethylation, which occurs via one-carbon metabolism. Methylarsonic acid and dimethylarsinic acid are main metabolites in urine, and elevated methylarsonic acid is considered a general risk factor. Arsenic easily passes the placenta, and a few human studies indicate a moderately increased risk of impaired fetal growth and increased fetal and infant mortality. The fetus and infant are probably partly protected by the increased methylation of arsenic during pregnancy and lactation; the infant is also protected by low arsenic excretion in breast milk. Early-life exposure may induce changes that will become apparent much later in life.

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INTRODUCTION

Arsenic is a ubiquitous metalloid element in the bedrock, sediments, and soils. From these minerals and deposits, it is easily dissolved to surrounding aquifers. Therefore, drinking water derived from groundwater is a common source of human exposure to inorganic arsenic (50, 90). In addition, people may be exposed via ambient air in areas with industrial emissions or coal burning, particularly when arsenic-rich coal is used for indoor stoves in poorly vented homes (134). More than one hundred million people worldwide are at risk of elevated arsenic exposure. The situation is particularly problematic in Southeast Asia, where a large fraction of the many hand-pumped wells yield drinking water with arsenic concentrations above 10 μg/L (9), the drinking water guideline value of the World Health Organization (138), but millions of people in the United States, Europe, and China are also currently exposed to drinking water arsenic levels above 10 μg of As/L (50, 88). An increasingly important source of exposure to inorganic arsenic is food, such as cereals and vegetables, especially in areas where arsenic-rich groundwater is used for irrigation (see, e.g., Reference 1). Highly elevated arsenic concentrations in seafood consist mainly of arsenobetaine, arsenocholine, and arsenosugars (**Figure 1**), which are of less toxicological significance but need to be considered when arsenic in urine is used as an indicator of exposure to inorganic arsenic.

HEALTH EFFECTS OF ARSENIC

Inorganic arsenic is an established potent human carcinogen, causing cancer in skin, lungs, urinary bladder, and kidney, and possibly also in liver, prostate, and ovaries (50, 122). Even drinking water concentrations around 10 μg/L, which is the standard in many countries, are associated with an appreciable cancer risk, on the order of 0.1%–0.3% (90). In addition, chronic arsenic exposure is associated with increased risk of numerous noncancer effects, e.g., hyperkeratosis; pigmentation changes; cardiovascular diseases including hypertension; respiratory effects; neurological, liver, and kidney disorders; and diabetes mellitus (50, 90, 139).

Arsenic targets a wide range of functional groups in the body, giving rise to biological effects by different mechanisms depending on the tissue, dose, duration of exposure, and metabolism of arsenic. Arsenic in its trivalent forms is highly reactive, binding preferentially to sulfhydryl (SH-) groups, which results in inhibition of numerous enzymes (139), such as DNA repair enzymes (132) and antioxidant-related enzymes, e.g., thioredoxin reductase and glutathione peroxidase (29, 69). Low doses of arsenic also induce reactive oxygen and nitrogen species, resulting in oxidative DNA damage (15, 59, 107, 139) and lipid peroxidation (30,

92). Proteins to which arsenite may bind in vivo include tubulin, poly(ADP-ribose)polymerase (PARP-1), thioredoxin reductase, estrogen receptor-alpha, arsenic(+3)methyltransferase (AS3MT), and Keap-1 (58). A growing number of experimental studies show that arsenic also causes endocrine disruption, altered cell signaling, altered cell cycle kinetics, epigenetic effects (affected DNA methylation), and altered transcription (19, 20, 57, 60, 90, 101).

All these modes of action are highly relevant for maternal and fetal health. Still, the arsenic-related health effects have mostly been documented in adult populations in general, and little is known about variation in susceptibility depending on gender and age (125). Usually, the developing organism is particularly vulnerable to toxic insult, because of rapid cell division and differentiation, especially in the brain (32). Because arsenic easily passes the placenta (16), exposure during pregnancy may be critical. In the following, the state of the art concerning the consequences of arsenic exposure for maternal health and early-life development is discussed. Most of the available information concerns exposure via drinking water, but other routes of exposure, e.g., inhalation of airborne arsenic, are likely to cause similar effects, although the metabolism of arsenic may be somewhat different.

METABOLISM OF ARSENIC

Arsenic Methylation

The susceptibility to arsenic-induced toxicity is affected by its biotransformation in the body. It has long been known that absorbed arsenate (protonized form is arsenic acid, shown in **Figure 1**) is first reduced in the blood (126), and then the formed arsenous acid (arsenite, which is protonized at physiological pH) is methylated, mainly in the liver. The methylation occurs via one-carbon metabolism, using S-adenosylmethionine (SAM) as methyl donor (79), as shown in **Figure 2**. Much later, arsenic(+3)-methyltransferase (AS3MT) was identified as the main enzyme transferring the methyl groups from SAM to arsenic in its trivalent form in the presence of glutathione or other thiols (3). Although the exact sequence and mechanism of the addition of methyl groups to arsenite (arsenous acid) have not been entirely elucidated (89, 118), it is clear that the main metabolites excreted in urine are monomethylarsonic acid (MMA, about 10%–20% of total metabolites in urine) and dimethylarsinic acid (DMA, 60%–80%), besides some 10%–30% inorganic (unmethylated) arsenic. The concentrations of these metabolites can be used as a measure of exposure to inorganic arsenic and the relative amounts as a measure of metabolism efficiency. Although an efficient methylation of inorganic arsenic to DMA facilitates the excretion and can be considered a detoxification mechanism (124), highly reactive and toxic intermediate arsenic metabolites, in particular MMA(III), the reduced form of MMAs (see, e.g., 93, 118), are retained in the tissues together with inorganic arsenic. It is well documented that the fraction of MMA(V) in urine, which may be related to MMA(III) in tissues, is associated with an increased risk of adverse health effects (see, e.g., 15, 48, 72, 140). The fact that pregnant mice given periodate-oxidized adenosine, known to inhibit arsenic methylation (79), showed increased developmental toxicity of arsenic (64) supports the view that impaired methylation efficiency is a general risk factor for arsenic toxicity also in early life. Recently, it was discovered that the urine of arsenic-exposed women from Bangladesh also contained thiodimethylarsinic acid (thio-DMA) at low concentrations (98), but the potential health implication of this metabolite has not yet been elucidated. The chemical structures of inorganic arsenic and its mono- and dimethylated metabolites are shown in **Figure 1**.

One-Carbon Metabolism

Because arsenic metabolism is closely linked to one-carbon metabolism, the factors influencing the transmethylation and transsulfuration

SAM: S-adenosylmethionine

MMA: methylarsonic acid

DMA: dimethylarsinic acid

SAH: S-adenosylhomocysteine

Hcy: homocysteine

BHMT: betaine-homocysteine S-methyltransferase

GSH: glutathione

PEMT: phosphatidylethanolamine N-methyltransferase

reactions (**Figure 2**) may also impact arsenic biotransformation. Indeed, folate status and genetic polymorphisms in one-carbon metabolism enzymes have been found to affect arsenic methylation (28, 37, 106, 115). Before going into details concerning susceptibility factors for maternal and fetal arsenic toxicity, a short review of one-carbon metabolism is pertinent. For recent comprehensive reviews of this complex metabolic network, which consists of several connecting cycles stretching over both cytosol and mitochondria, see, e.g., References 82, 87, 99, 100, and 135. Activation of the essential amino acid methionine by methionine adenosyltransferase (MAT) produces SAM, which is the universal methyl donor in the body; so also for arsenic, catalyzed by AS3MT. The methyl transfer produces S-adenosylhomocysteine (SAH), which is hydrolyzed by SAH hydrolase to homocysteine (Hcy). This reaction is reversible, and elevated Hcy, via SAH, is a strong feedback inhibitor of the SAM-dependent transmethylation reactions. Therefore, Hcy must be efficiently removed. This is accomplished by remethylation back to methionine, either by the folate-dependent or the betaine-dependent pathway. The folate-dependent remethylation uses the vitamin B12-dependent enzyme methionine synthase (MS) for the transfer of a methyl group from 5-methyltetrahydrofolate to Hcy. Betaine-homocysteine S-methyltransferase (BHMT) catalyzes the remethylation of homocysteine using betaine derived from choline oxidation. A third way of removing Hcy is the transsulfuration pathway, yielding cysteine via the irreversible conversion of Hcy to cystathionine by cystathionine ß-synthase (CBS). Cysteine is further metabolized to biologically important compounds, such as glutathione (GSH) and taurine.

Gender Differences

It general, women have a higher fraction of DMA and a lower fraction of MMA in urine than do men (46). Recently, it was shown that this efficient methylation of arsenic in women is limited to the childbearing-age period (70, 71). Before puberty and after menopause, girls and women showed a methylation pattern similar to that in boys and men, respectively. This indicates an involvement of sex hormones in arsenic methylation, probably related to the endogenous production of choline in women, which after oxidation to betaine is the only source of methyl groups, besides folate, for the remethylation of homocysteine to methionine (14, 39, 145, 147). Choline is synthesized in the body by SAM-dependent methylation of serine or recycled from lecithin (phosphatidylcholine). The synthesis of phosphatidylcholine by phosphatidylethanolamine N-methyltransferase (PEMT) was recently shown to be up-regulated by estrogen (25, 102), which likely explains why the arsenic methylation is particularly efficient in women of fertile age only.

ARSENIC EXPOSURE AND MATERNAL HEALTH

Observed Health Effects

Despite the high prevalence of elevated arsenic exposure worldwide and the documented toxicity of arsenic, very few studies have investigated the effects on maternal health. In a large cross-sectional study in Inner Mongolia, even fairly low water arsenic concentrations (20–50 μg/L) were associated with increased systolic blood pressure in women (N = 8790) six weeks post partum (63). It was suggested that the cardiovascular challenge in pregnancy increased the susceptibility to arsenic. There is also certain evidence that arsenic may cause anemia, probably by destabilizing membranes (5) and decreasing the delta-aminolevulinic acid dehydratase activity (55), especially during pregnancy. Exposure to moderately elevated arsenic concentrations in drinking water (40 μg/L) in Antofagasta, northern Chile, was found to be associated with a higher rate of anemia during pregnancy compared to that in Valparaiso, a town with essentially no arsenic in the drinking water (43). As pregnancy progressed, the

prevalence of anemia increased more sharply among the exposed women. This may be a serious effect of arsenic as iron deficiency in women is a common phenomenon in late pregnancy and may result in complications for both mother and child (61, 77). Interestingly, a recent study from Bangladesh showed a negative association between individual measures of arsenic exposure (urine concentrations) and hemoglobin concentrations in men but not in women (36). Only in the small fraction of women with hemoglobin concentrations below 100 g/L was elevated arsenic exposure (more than 100 μg/L in urine) associated with decreased hemoglobin concentrations.

Given that arsenic interacts with steroid hormones, and estrogen in particular, it seems likely that arsenic exposure may have additional adverse effects on maternal health and child development as well as on women's health more generally. Indeed, recent studies indicate increased age at menarche in Indian girls exposed to arsenic through drinking water (108, 109). Exposure of female rats to arsenite in drinking water over seven estrous cycles caused a significant reduction in plasma levels of leutinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol, along with a significant follicular and uterine cell degeneration and decreases in ovarian steroid-metabolizing enzymes and ovarian and uterine glutathione peroxidase (11). Selenium supplementation restored the plasma hormone levels and prevented the arsenic-induced histopathological changes in ovaries and uterus. In utero exposure of mice to fairly high arsenic concentrations (42 or 85 mg/L in drinking water during gestational days 8–18) showed a marked increase in ovarian and lung tumors as well as uterine and oviduct hyperplasia in the females at adult age (122). This indicates that arsenic-related effects on women's health may be induced prenatally.

Our understanding of gender differences in arsenic toxicity is very poor. It seems clear, however, that women are less susceptible than are men to arsenic-induced hyperkeratosis and pigmentation changes (for a review, see Reference 125). Our ongoing population-based study on arsenic-induced health effects in Bangladesh, which is one of the few designed to evaluate gender differences in arsenic-related health effects (96), showed that the lower risk of arsenic-related skin lesions in women largely is explained by the more efficient metabolism of arsenic in women compared to men (72). On the other hand, epidemiological studies that have reported data for men and women separately, although not directly comparable, indicate that women may be more sensitive to certain arsenic-related toxic effects (125). Obviously, more studies designed to evaluate these issues are needed.

Mechanistic Considerations

Pregnancy implies considerable stress on maternal metabolism. This is particularly true for one-carbon metabolism because methyl groups, as well as folate and choline, are critical for placental and fetal development. Elevated levels of Hcy in maternal plasma have been associated with preeclampsia, placental abruption, adverse pregnancy outcomes, and infertility (7, 26, 100). To support the remethylation of produced Hcy and to meet the fetal demand of choline for brain development, PEMT is up-regulated in pregnancy to increase the de novo synthesis of choline in maternal liver (145). Betaine, the oxidation product of choline and the form delivering the methyl group to Hcy, becomes increasingly important during pregnancy for adjusting the Hcy level (128), especially in women with low serum concentrations of folate and methionine (131). Obviously, this betaine-dependent remethylation of Hcy by BHMT is particularly important for arsenic-exposed women. In fact, the methylation of inorganic arsenic to DMA increases during the course of pregnancy (16, 45, 127), apparently in parallel with the improved one-carbon metabolism. In women from both northern Argentina and northern Chile, more than 85% of arsenic in urine was in the form of DMA at the time of delivery. Because this efficient methylation is associated with increased excretion of arsenic in maternal urine (124), it likely protects

both the mother and her fetus from arsenic-induced toxicity. It is important to stress, however, that there is a wide interindividual variation in maternal arsenic methylation, especially in early pregnancy (16, 34, 45, 67).

On the other hand, elevated arsenic exposure may aggravate the pregnancy-induced stress on one-carbon metabolism and related complications, as it is associated with elevated Hcy levels (19, 140), possibly by inhibition of BHMT (19). Arsenic is also known to inhibit several other methyltransferases, e.g., AS3MT, involved in its own methylation (58, 116). Even moderately elevated exposure to arsenic inhibits the methylation, in particular the further methylation of MMA to DMA (67, 70). The resulting increase in urinary MMA, as mentioned above, is associated with increased risk for toxic effects. Moreover, arsenic-induced oxidative stress may shift one-carbon metabolism to the transsulfuration pathway, giving preference to formation of glutathione (to combat the stress) before the remethylation of homocysteine (86). Although all the links between arsenic-induced oxidative stress (142) and impaired one-carbon metabolism remain to be elucidated, recent in vitro studies, using human prostate epithelial cells, indicated that the arsenic-related GSH depletion in a similar way channels Hcy into the irreversible transsulfuration pathway, in favor of de novo glutathione synthesis via cysteine (19). Taken together, these results provide strong evidence that arsenic disrupts one-carbon metabolism by several different mechanisms, which may lead to complications in maternal health and subsequently in fetal health.

ARSENIC IN THE PLACENTA

Placental Transfer

Studies of pregnant women exposed to arsenic via drinking water in Argentina showed arsenic concentrations in cord blood similar to those in maternal blood (16), a finding recently confirmed in Bangladeshi women (34). It is clear that both inorganic arsenic and the methylated metabolites easily pass the placenta (16, 34, 53, 73). The passage of inorganic arsenic with subsequent binding to fetal tissues was confirmed in the marmoset monkey, which is one of the very few animal species that are unable to methylate arsenic (73). As mentioned above, the methylation of arsenic in women is induced during pregnancy (16, 45), and studies from Argentina showed that essentially all arsenic in the blood plasma and urine of newborn babies was in the form of DMA. Thus, it seems that it is mainly this less toxic metabolite (41) that reaches the fetus in late gestation (16). This finding is supported by studies on mice showing mainly DMA in fetal blood and tissues, in spite of appreciable concentrations of MMA in maternal blood and tissues in response to exposure to high arsenic concentrations in drinking water (10–85 mg/L) during gestation (21, 53). However, a recent study on Bangladeshi mothers with high-level arsenic exposure reported that about 30% of the arsenic in cord blood was in the form of MMA and 25% was inorganic arsenic (34). To what extent these apparently conflicting results reflect an efficient methylation of transferred inorganic arsenic to MMA in the fetus or are related to the obvious problems in correctly speciating arsenic in blood and tissues (113) remains to be elucidated. Still, it is obvious that the fetus is exposed to more inorganic arsenic and MMA in early gestation, before the induction of maternal one-carbon metabolism. Similarly, at high exposure levels, when the methylation is inhibited, the fetus will be exposed to more inorganic arsenic and MMA.

Probably, arsenic is transported to the fetus by GLUT1, one of the main transplacental glucose transporters (54). Both human and rat GLUT1 have been shown to catalyze the cellular uptake of trivalent forms of inorganic arsenic and MMA (75, 103). In addition, GLUT4, the insulin-responsive isoform expressed in early pregnancy (54), was recently found to catalyze the transport of arsenite and MMA(III) (103). Arsenate [As(V)] is likely taken up by phosphate transporter (66, 103), although data for placenta are missing. Whether pentavalent MMA and

DMA are transported via the similar mechanisms is not known.

Placenta Toxicity

Arsenic is also accumulating in the placenta (16, 117). Although the form and consequences of such accumulation have not been the focus of much research, it is likely that arsenic may give rise to toxic effects in the placental tissue mediated, e.g., via oxidative stress (81), and possibly also by impaired transport of nutrients to the fetus. Arsenic is a strong inhibitor of thioredoxin reductase (69, 76), which is one of the major stress-protection systems in the placenta (85, 105). An intact antioxidant system is essential for both maternal and fetal health, as the placental throphoblasts are exposed to extensive oxidative stress that if not neutralized may lead to placental pathology and preeclampsia (52). Mice exposed to arsenite in drinking water from conception through weaning showed placental dysplasia especially in the vasculature (35), indicating that arsenic-related spontaneous abortions and fetal growth impairment (see below) may be mediated via placental insufficiency.

ARSENIC-INDUCED FETAL TOXICITY

Fetal Loss and Malformations

Arsenic is shown to be embryotoxic and teratogenic in experimental animals (38, 133). However, reliable human data are needed, as the kinetics and toxicity of arsenic vary dramatically among animal species (123), making extrapolation of dose-response data from animal experiments to humans difficult. Most experimental animals are more efficient in methylating arsenic to DMA and less susceptible to toxicity. Still, mechanistic findings may be highly relevant. It is worth noting that although neural tube effects are a consistent finding in experimental studies (see, e.g., 38), there are essentially no convincing human data (8, 110). Also, findings of aberrant migration and delayed maturation of Purkinje cells following low-dose arsenic exposure during the rapid brain-growth period in rats (22) warrant further studies on early human development.

Several of the few available human studies are ecologic in design, with potential bias in assessment of exposure. A study in the United States comparing reported data on public tapwater quality for 286 women having spontaneous abortions with that of 1391 women having live births reported that an increased frequency of spontaneous abortion was associated with high levels of arsenic, besides mercury, potassium, and silica, after adjustment for potential confounders (4). A similar increase in spontaneous abortions with increasing water arsenic levels was observed in Hungary (6); however, the full report is not available. Evaluation of time trends in register data on pregnancy outcomes in Antofagasta in northern Chile, where before 1970 the drinking water contained high arsenic concentrations (about 100 μg/L before 1957 and 800 μg/L during 1958–1970), indicated elevated rates of late fetal loss (overall 3%) during the period with high water arsenic concentrations relative to the mortality rates in Valparaiso, which has essentially no arsenic in the drinking water (47). The rate ratio for stillbirth was 1.7 [95% confidence interval (CI), 1.5–1.9] after adjustment for location and calendar time. In a similar ecological study in Bangladesh, outcome data of about 30,000 pregnancies in 600 villages, grouped geographically in 16 centers included in a nongovernmental-organization health-care network, were related to the average water arsenic concentrations in the centers (each based on 7–14 wells) (13). After adjustment for several socioeconomic and health factors, the rate of stillbirths (overall 3.4%) was found to increase with increasing water arsenic concentration, the odds ratio being 1.80 (95% CI, 1.14–2.86) at 50–80 μg/L, compared with less than 10 μg/L. Increased risks of spontaneous abortion, stillbirth, and preterm birth were also reported from three smaller cross-sectional studies, two in Bangladesh (192 and 533 women) and one in West Bengal (202 women), in which women were interviewed retrospectively about drinking water sources and

outcomes of previous pregnancies (2, 84, 130). The risk ratios were 2–3 for both spontaneous abortions (two studies) and stillbirths (all three studies) in high-exposure groups.

Two fairly large population-based studies in Bangladesh with individual exposure data have been reported. In the first, pregnancy outcome data for 2000 women were obtained from centers providing care to all pregnant women in three areas with known elevated arsenic concentrations in drinking water (62). The results showed a weak but statistically significant association between arsenic concentrations in drinking water (sampled at personal follow-up interviews) and birth defects (odds ratio 1.005 for all defects combined), but no other adverse effects on pregnancy outcomes. Another study involved a large cohort of 29,134 pregnancies in Matlab, a rural area of Bangladesh, where fetal and infant survival data were obtained from the well-established health and demographic surveillance system (94). Data on individual arsenic exposure were based on interviews, carried out in a parallel study, about the history of drinking water sources, and screening of arsenic concentrations in all functioning tube-wells in Matlab (96). There was a tendency of increased fetal loss, and women drinking water with 277–408 μg/L (fourth quintile) showed a significant increase in relative risk of 1.14 (CI 1.01–1.30) compared with those drinking water with less than 10 μg/L (94).

It should be noted that the reported studies may have underestimated the effects of arsenic in early gestation, particularly if arsenic exposure affects fetal survival at an early stage, as indicated in experimental studies (10, 91). The earliest spontaneous abortions, which constitute the majority of all fetal losses, are not detected by the surveillance systems or interviews.

Impaired Fetal Growth

There are certain indications of impaired fetal growth in mothers exposed to arsenic via drinking water during pregnancy (44, 143). Two ecological cross-sectional studies from northeastern Taiwan (up to 3600 μg/L; 85% above 50 μg/L in the drinking water) and northern Chile (on average 40 μg/L in the water) showed nonsignificant decreases in birth weight of 30 and 57 grams, respectively (from 3133 and 3398 g, respectively). Our recent population-based cohort study involved 1578 mother-infant pairs in rural Bangladesh, with measurements of arsenic concentrations in maternal urine samples collected in early and late gestation (median 80 μg/L, 90th percentile 400 μg/L) (95). Arsenic exposure showed a significant negative association with size at birth at urine arsenic concentrations below 100 μg/L, but no further effect at higher exposure levels. The reason for this dose-response pattern is not known. The total As-associated decrease in birth weight was 170 g (average birth weight 2681 g), and the head and chest circumferences were reduced by 5 mm and 14 mm, respectively.

Mechanisms of Fetal Toxicity

Considering the high placental transfer of arsenic and its documented toxicity, the reported effects on fetal development seem to be less strong than could be expected, especially in populations with prevalent poor nutrition. Possibly, the increased methylation efficiency during pregnancy results in less arsenic being transferred to the fetus (42), either because of the increased rate of excretion in maternal urine with advancing gestation (16) or variation in the rate of transfer among the arsenic metabolites, as discussed above. Also, the methylated arsenic metabolites, at least in their pentavalent form, are less fetotoxic (41, 51). As there is a wide interindividual variation in arsenic methylation, it is important to evaluate whether women with low methylation capacity, either due to genetic polymorphisms or otherwise impaired one-carbon metabolism, are more susceptible to arsenic-induced adverse pregnancy outcomes.

The mechanisms involved in the arsenic-induced effects on the fetus loss likely include direct toxic effects of arsenic on enzyme activities, e.g., that of thioredoxin reductase, methyltransferases and DNA repair enzymes, oxidative stress, hormone interaction, and

perturbation of one-carbon metabolism. Because arsenic inhibits several methylation reactions and causes elevated Hcy levels, a known risk factor for adverse pregnancy outcomes including neural tube defects and other congenital malformations, the implication of arsenic exposure in such effects needs to be verified in humans. A recent evaluation of arsenic-related gene expression changes in babies born to mothers exposed to arsenic in drinking water during pregnancy detected a set of 11 transcripts that were influenced by the prenatal arsenic exposure (27). In particular, pathways involving stress, inflammation, metal exposure, and apoptosis in the newborn were affected by arsenic. Studies on hematopoietic progenitors derived from human cord blood and murine bone marrow cells showed toxicity of arsenic on colony-forming units, indicating immunosuppression by arsenite and MMA(III) at μM concentrations (24). Surprisingly, very low concentrations of arsenite increased the proliferation rate of both human and murine female cells, whereas male cells showed no significant modulation. As discussed below, these effects may not be detected until after birth or even later in life.

The fact that all of the above-mentioned potential mechanisms of arsenic are related to the nutritional status of the mother suggests that malnourished women may be at particular risk of arsenic-induced adverse pregnancy outcomes (127). Indeed, in utero exposure to arsenic in mice with inactivated folate-binding protein 2 (Folbp2) gene showed exencephaly in 40% of the embryos compared with 24% in control embryos with intact Folbp2 (136). The effect of arsenic was further exacerbated when the dams were fed a folate-deficient diet. Moreover, Selenium deficiency was found to enhance the accumulation of arsenic in fetal brain, with a concomitant dramatic increase in the activity of the selenoenzyme DI-II activity, compared with the Selenium-adequate mice (85). Finally, arsenic-induced oxidative stress and apoptosis in developing rat brain cells were partly reversed by vitamins C and E (10). There is an obvious need for information on risk factors in humans.

ARSENIC IN INFANCY

Infant Mortality

In contrast to the transfer of arsenic over the placenta to the fetus, the passage over the mammary gland is limited, with little arsenic being excreted in breast milk (17, 23). Thus, the infant is protected against arsenic exposure during an exclusive breast-feeding period, whereas formula prepared from the drinking water may result in very high exposure. Studies of arsenic metabolites in the urine of breast-fed infants at three months of age in rural Bangladesh showed about 1 μg/L in breast milk, which increased marginally (90th percentile 4 μg/L) with increasing maternal arsenic exposures (23). An interesting finding was that almost all arsenic in the breast milk was in the trivalent inorganic form. Probably arsenic is transported via aquaglyceroporins, which, as mentioned above, are the main transporters of inorganic arsenic in most organisms (74, 103) and are present in the mammary gland (83).

Because of the very low arsenic exposure during breast-feeding, it seems likely that the reported effects of arsenic during infancy are due to prenatal exposure. In the town of Antofagasta in northern Chile, where the public water contained highly elevated arsenic concentrations until about 1970, especially after the installation of a new water source in 1958 (at which time concentrations were about 800 μg/L), the register data showed an elevated infant mortality rate, particularly neonatal (before three months of age) mortality (relative risk 1.5) compared to that in the town of Valparaiso, which has essentially no arsenic in the drinking water (47). There was, however, a marked decrease in infant mortality during this period, even more marked in Antofagasta than in Valparaiso, which indicates that other factors had a much stronger impact on infant mortality than did arsenic. The above-mentioned cohort study carried out in rural Bangladesh showed a significant 29% increase in infant mortality when mothers had been exposed at 275–400 μg/L in drinking water, compared to those whose mothers had been drinking water with less than

10 μg/L (94). Obviously, this was largely due to prenatal exposure as most women are practicing exclusive breast-feeding for about three months and partial breast-feeding for more than a year (104). Possibly, the increased mortality is mediated via immunosuppressive effects of arsenic, as discussed above.

Protection Against Infant Arsenic Toxicity

Breast-fed infants may also to a certain degree be protected against toxic effects of the arsenic ingested with supplementary food and water by an efficient one-carbon metabolism, resulting in efficient methylation of arsenic. We observed very high fractions (nearly 90%) of DMA in urine of three-month-old infants in Bangladesh, considerably higher fractions than in the urine of their mothers (23). Most likely, the efficient methylation is related to the high levels of circulating free choline in the newborn child in response to the up-regulated maternal synthesis of choline during pregnancy (49) and the presence of appreciable amounts of choline already in the first mature milk (40, 49). The milk choline derives from active uptake from maternal circulation as well as de novo synthesis from phosphatidylethanolamine in the mammary gland (144). In addition, the newborn child has much folate stored in the liver, the concentration being about 50% higher than in the maternal liver (78, 131), whereas folate in breast milk first reaches maximum levels some months post partum (56).

Breast milk also contains appreciable amounts of antioxidants, which likely protect against arsenic-induced oxidative stress. Taurine, the most abundant free amino acid in breast milk (129), has antioxidant properties and has been shown to protect against arsenic-induced cytotoxicity, including lipid peroxidation, in murine hepatocytes (112). Thioredoxin levels also are high in breast milk (119). It is possible that these mechanisms contribute in an integrated way to the protection against certain arsenic-induced effects, e.g., developmental effects (120). There is, however, an increasing body of evidence both from experimental and epidemiological studies that early-life arsenic exposure may affect health later in life.

LATER EFFECTS OF EARLY-LIFE ARSENIC EXPOSURE

Increased Health Risks Later in Life

The specific historic arsenic exposure scenario in northern Chile, with highly elevated arsenic levels in drinking water before 1970, particularly between 1958 and 1970, has been used for investigations of the effects of early-life exposure on effects later in life in humans. Liaw and coworkers (68) compared cancer mortality rates in individuals from this region under the age of 20 with those in a region with low water arsenic concentrations, dividing the children into those born before, during, or after the peak exposure period. The results showed that those who had been exposed to the very high arsenic concentrations as young children had an increased liver cancer mortality, with an overall relative risk of 10.6 (95% CI, 2.9–39.2), whereas mortality from the most common childhood cancers, leukemia and brain cancer, was not increased (68). Similar investigations of mortality in lung cancer and other lung diseases in Antofagasta in the age group 30–49 years, in relation to early-life exposure, showed a significantly increased standardized mortality ratio (SMR) for lung cancer (SMR 7.0, CI 5.4–8.9) and bronchiectasis (SMR 12.4, CI 3.3–31.7) for those born just before the high-exposure period (1950–1957) and exposed in early childhood (114). For those born during the high-exposure period (1958–1970) with probable exposure in utero and early childhood, the SMR for lung cancer was 6.1 (3.5–9.9), whereas that for bronchiectasis was as high as 46 (21.1–87.7). The increased susceptibility in early life, however, may not apply to all the health effects related to arsenic exposure. A recent study from Bangladesh did not find a higher risk for arsenic-related skin effects in individuals exposed since birth, or before, compared with those who started being

exposed after one year of age (72, 96). If anything, individuals who had been moderately exposed from birth, or before, were less prone to develop arsenic-related skin lesions than were those who were more than one year of age when they started using tube well water.

Arsenic and Fetal Imprinting

Because of the increasing evidence that early-life environment is critical for organ function and chronic diseases later in life (31, 65, 146), it is plausible that a toxic element such as arsenic, which easily passes to the fetus, contributes to such effects. There is increasing evidence during recent years that arsenic acts via epigenetic effects at very low exposure levels, mainly by interfering with DNA methylation (18, 19, 101) and histone acetylation (97), effects that are implicated in long-term fetal programming. Recent studies confirmed such effects of arsenic in mice following prenatal exposure (12, 141). In particular, newborn male mice showed a significant reduction in global methylation in GC-rich regions (141). There was also enhanced expression of genes encoding for GSH production and aberrant expression of genes related to insulin growth factor–signaling pathways and cytochrome P450 enzymes.

The endocrine disrupting effects of arsenic are likely to occur at very low concentrations and to have long-term consequences, particularly if induced early in life. The above-mentioned important series of experimental studies demonstrated marked sex-dependent increases in tumor induction in adult mice exposed to arsenic prenatally (dams exposed to 42 or 85 mg/L arsenic in drinking water during gestational days 8–18) and indicate that the estrogen-signaling system is essential for the induction or promotion of carcinogenic processes (for a review, see Reference 122). At adult age, the female mice showed an increased risk of ovarian and lung tumors as well as uterine and oviduct hyperplasia, whereas male mice showed a highly elevated incidence of liver and adrenal tumors. Arsenic exposure in utero caused long-lasting *ER-α* overexpression, probably by hypomethylation of the promoter region of the gene (111, 121). Similarly, mice given water with 50 μg/L arsenic during the perinatal period showed impaired regulatory interactions between the hypothalamic-pituitary-adrenal axis and the serotonergic system in the dorsal hippocampus at adult age, indicating predisposition for depressive-like behavior, which was also indicated in behavioral studies (80).

SUMMARY POINTS

1. There is increasing evidence that arsenic impairs intrauterine growth and increases the risk of fetal and, especially, infant mortality, but little is known about the impact on maternal health.
2. Although the mother, fetus, and breast-fed infant seem to be partially protected by the induced maternal one-carbon metabolism during pregnancy and lactation, leading to improved arsenic methylation and excretion in urine, arsenic is known to induce epigenetic effects, oxidative stress, and immune suppression and to inhibit numerous enzymes, all of which are essential functions for both maternal health and early-life development, including fetal programming.
3. In particular, the interactions with DNA methylation and steroid hormones indicate that changes induced by arsenic in early life may give rise to adverse health effects later in childhood or in adult life.
4. Such effects may be particularly severe in undernourished populations. The increasing exposure to environmental pollutants, such as arsenic, in low-income countries is likely

to exacerbate the adverse effects of poverty and related risk factors, such as inadequate food and poor sanitation, which are estimated to prevent at least 200 million children from attaining their developmental potential (33).

FUTURE ISSUES

1. Inorganic arsenic is a well-documented potent human carcinogen and toxicant, but little is known about its adverse effects on maternal health.
2. Future research should include effects of arsenic on age at menarche and menopause as well as on fertility in women. Such effects may be induced prenatally and need to be considered in future studies.
3. It seems clear that women are less susceptible to arsenic-related skin lesions than are men, but more studies designed to evaluate the risk of other toxic effects of arsenic in women are needed. Such information would not only identify a potential risk group for arsenic exposure, but may also provide important information on the mechanisms and modes of action.
4. Inefficient arsenic biotransformation to DMA, resulting in elevated percentage of MMA in urine, is associated with an increased risk of adverse health effects, but little is known about the impact or the consequences of early-life exposure to arsenic.
5. Arsenic accumulation in placenta seems to cause oxidative stress, both directly and via impaired antioxidant systems, and possibly also causes impaired transport of nutrients to the fetus, but the results of studies need further confirmation. If confirmed, it is important to elucidate how the effects may affect fetal health and development.
6. In particular, more information on the interaction of arsenic with thioredoxin reductase, an important maternal antioxidant, is needed.
7. Arsenic is known to pass the placenta and may induce global DNA hypomethylation and modulated histone acetylation in the fetus, but little is known about the consequences of such effects on health later in life.

DISCLOSURE STATEMENT

The author is not aware of any biases that might be perceived as affecting the objectivity of this review.

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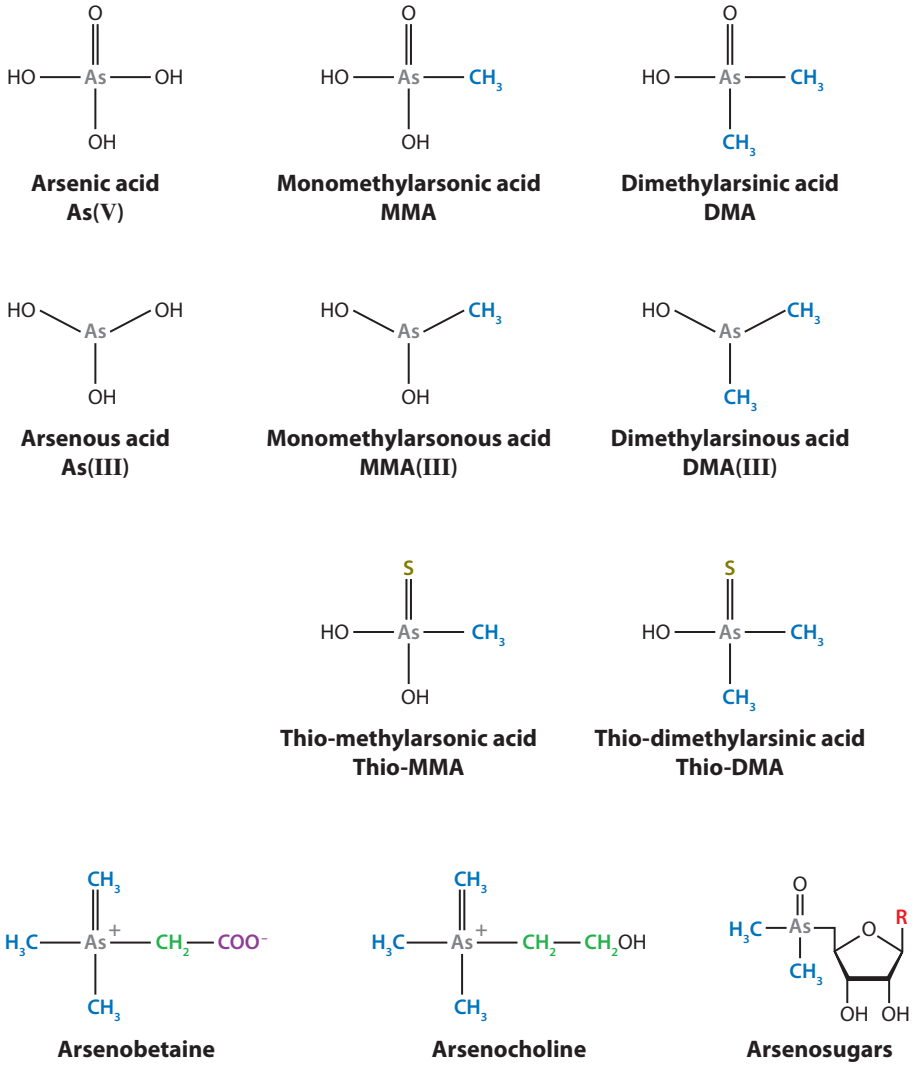

Figure 1

Chemical forms of arsenic in human exposure and metabolism: inorganic arsenic, the main form in drinking water, its methylated metabolites, and other organic arsenic compounds, commonly found in seafood.

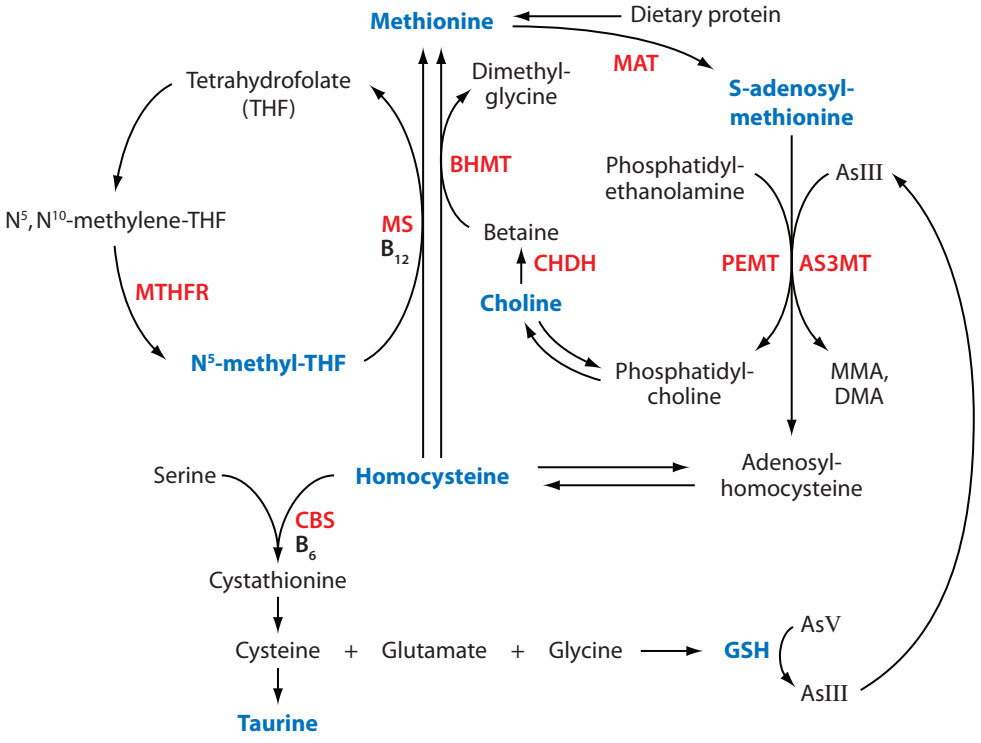

Figure 2

Metabolic pathway of human metabolism of inorganic arsenic by one-carbon metabolism, with indicated choline and folate-mediated remethylation of homocysteine to methionine and homocysteine catabolism via the transsulfuration pathway. The key factors influencing arsenic metabolism are depicted in blue and all enzymes in red. MAT, methionine adenosyltransferase; AS3MT, arsenic(3+)methyltransferase; PEMT, phosphatidylethanolamine-N-methyltransferase; CHDH, choline dehydrogenase; BHMT, betaine homocysteine methyltransferase; THF, tetrahydrofolate; MTHFR, methylene tetrahydrofolate reductase; B_{12}, vitamin B_{12}; MS, methionine synthase; B_6, vitamin B_6; CBS, cystathionine ß-synthase; GSH, glutathione.

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Errata

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