Published in final edited form as:

Environ Int. 2018 March ; 112: 23–32. doi:10.1016/j.envint.2017.12.004.

Prenatal arsenic exposure, child marriage, and pregnancy weight gain: associations with preterm birth in Bangladesh

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Abstract

Background: Preterm birth is a disease of multifactorial etiologies that has environmental, social, and maternal health components. In Bangladesh, environmental arsenic exposure, child marriage, and low maternal weight gain during pregnancy are highly prevalent. These factors are often studied individually in relation to preterm birth; although, they may have interactive effect.

Objective: To evaluate the associations between prenatal arsenic exposure, child marriage, pregnancy weight gain, and preterm birth in a prospective birth cohort in Bangladesh.

Methods: During 2008–2011, we recruited 1,613 pregnant women aged 18 years at 16 weeks of gestation and followed them throughout pregnancy. We measured arsenic in drinking water (n=1,184) collected at enrollment and in maternal toenails (n=1,115) collected 1-month postpartum using inductively coupled plasma mass spectrometry. Child marriage (<18 years old)

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Conflict of interest: No conflicts of relevant to this article to disclose.

was defined using self-reports. 2nd and 3rd trimester pregnancy weight gain was calculated using monthly records. Gestational age was determined by ultrasound.

Results: In multivariate modified Poisson regression models, the risk ratios for preterm birth were 1.12 (95% CI: 1.07–1.18) for a unit change in natural log water arsenic exposure, 2.28 (95% CI: 1.76–2.95) for child marriage, and 0.64 (95% CI: 0.42–0.97) for a pound/week increase in maternal weight during the 2nd and 3rd trimesters. 2. Mediation analysis revealed that both arsenic exposure and child marriage have small but significant association with preterm birth via lowering pregnancy weight gain. Similar associations were observed for maternal toenail arsenic exposure.

Conclusions: Reducing arsenic exposure and ending child marriage could reduce the risk of preterm birth in Bangladesh. Nutritional support to ensure adequate weight gain during pregnancy may provide additional benefits, especially among women with a history of child marriage.

1. Introduction

Preterm birth (livebirth <37 weeks of gestation) is the leading cause of neonatal mortality and the second leading cause of mortality among children under five years of age; the surviving infants are at lifelong risk of neurological impairments and chronic lung diseases (1). Worldwide, more than 15 million babies are born preterm each year, and more than a third of them are in South Asia (2). In Bangladesh, the incidence of preterm birth is estimated to be 14% (2), which is one of the highest in the world; the estimates are as high as 19–22% in rural areas (3, 4). Common risk factors for preterm birth include prenatal arsenic exposure, child marriage (marriage <18 years old), and poor maternal weight gain during pregnancy. These factors often co-exist in Bangladesh and part of the South Asia. Nonetheless, no studies yet have used an integrative approach to examine if these factors interact with each other in relation to preterm birth, creating critical research gap for both practitioners and policy makers to tackle preterm birth, which is one of the priorities for the United Nations 2030 agenda for sustainable development (5).

The ground water contamination by inorganic arsenic is a global health issue. However, the mostly affected region in terms of the number of population exposed is the Ganga-Brahmaputra plain in Bangladesh and West Bengal. An estimated 30–70 million people in Bangladesh (6) and an additional 26 million in West Bengal (7) are exposed to arsenic through contaminated drinking water sourced from ground water at levels higher than the World Health Organization (WHO) recommendation of <10µg/L. Arsenic can cross the placenta readily, and thereby pose a significant risk to the developing fetus (8, 9). Several studies have reported the link between prenatal arsenic exposure and adverse birth outcomes, including spontaneous abortion (10), stillbirth (10, 11), low birth weight (12–14), and neonatal mortality (15, 16). However, the epidemiological evidence for an association between arsenic exposure and preterm birth is less consistent (17). Although, most studies have reported a positive association between arsenic exposure and preterm birth, other than three ecological studies in Bangladesh (18) and the United States (19, 20), the associations were not statistically significant (21–26). On the other hand, a significant negative association between arsenic exposure and gestational age was reported in few other studies (27), including three recent prospective cohort studies in Bangladesh (14), Mexico (28), and

the United States (29), while two studies reported non-significant positive associations (30, 31). Such inconsistency is likely due to the differences in study design and arsenic exposure level among the study populations, ecological exposure assessment strategy used by many studies, small sample size, and inadequate adjustment for confounders, indicating the need for large prospective studies with individual-level exposure measurements (17, 32).

Another social factor impacting maternal and child health in Bangladesh is child marriage, defined by the United Nations Children's Fund (UNICEF) as marriage or in union for girls before age 18 years. Bangladesh has one of the world's highest prevalences of child marriage. According to a recent report from Bangladesh Demographic and Health Survey (DHS), 66% of the girls are married before age 18 years, while 29% are married before age 15 (33). The prevalence of child marriage is also very high in other South Asian countries, including India, Nepal, Afghanistan, and Pakistan. Every two out of five girls in South Asia are married or in union before age 18 (33). Child marriage often forces girls into pregnancy before they reach biological maturity, as child brides have less control over their reproductive decision and are less likely to use contraception prior to first childbirth (34). Studies have shown that child brides experience higher risk of complications during pregnancy or childbirth, which is the 2nd leading cause of death among 15–19 year-old girls globally (33). Infants born to child brides are also at higher risk of low birth weight, preterm birth, and neonatal death (35–37). It is debatable if the biological immaturity of child brides intrinsically increases the risk of adverse birth outcomes, or it is the heightened socio-economic vulnerability for girls to get married at a young age (38, 39) and/or shared maternal health characteristics of child brides, such as multiple and closely-spaced pregnancies (34, 40), higher risk of perinatal infections (41), and lower quality and quantity of perinatal health care (40) that increase the risk. Nonetheless, current research on child marriage has focused on the short-term effects of young maternal age on reproductive and perinatal health outcomes, while our understanding of the long-term effects of child marriage in subsequent pregnancies when the mother reaches her adulthood is limited.

Both prenatal arsenic exposure and child marriage have been shown to impact maternal perinatal health status, resulting in inadequate weight gain during pregnancy (42–44), which is an independent risk factor for preterm birth (45, 46). For instance, studies in the developing and developed countries reported increased risk of preterm birth among women gaining less total weight over the gestational period or, less weekly weight during the 2nd and 3rd trimesters (46–50). These researches suggest that pregnancy weight gain may acts as a mediating or intermediate variable influencing the effect of prenatal arsenic exposure and child marriage on preterm birth.

However, despite the intricate relation between prenatal arsenic exposure, child marriage and pregnancy weight gain, these factors were often studied individually and our understanding of any interactive effects these factors might have on preterm birth is not known. To model this intricate relationship, here we used mediation analysis technique hypothesizing that pregnancy weight gain will mediate the effect of arsenic exposure and child marriage on preterm birth. Using this modeling approach, we quantified the direct effects of prenatal arsenic exposure and child marriage on preterm birth as well as the indirect effects mediated via maternal weight gain during pregnancy (51).

2. Methods

2.1 Study participants

We used data from a prospective birth cohort established in Bangladesh during 2008–2011. The details of this study, including details of recruitment and enrollment have been previously reported (13). Briefly, women were eligible to participate if they were 18 years old with an ultrasound confirmed singleton pregnancy of 16 weeks' gestation; used a tube well as their primary source of drinking water; had been using the same drinking water source for >6 months; and intended to live in her current residence throughout pregnancy. A total of 1,613 pregnant women were recruited and followed until delivery (Fig. 1). At the end of follow-up, 1,184 singleton livebirths were recorded after loss of contact with participants (n=99), participation withdrawal (n=121), miscarriage (n=132), stillbirth (n=72), and multiple pregnancies (n=5). Missing data were reported for maternal toenail arsenic (n=69) and secondhand smoke exposure (n=1). Women who remained in the study were similar with those who dropped out in respect to chronological age, age at marriage, exposure to secondhand smoke, no. of past pregnancies, household income, education, and enrollment BMI and toenail arsenic exposure (data not shown).

All subjects provided written informed consent before participation. Participants were informed and counseled on safe drinking water options if their water samples contained arsenic above the Bangladesh standard of <50 µg/L. Prenatal care and multivitamins were provided to all participants through our community outreach clinics, which were among the few healthcare providers in that catchment area. All protocols were reviewed and approved by the Human Research Committees at Harvard T.H. Chan School of Public Health and Dhaka Community Hospital Trust.

2.2 Exposure assessment

Arsenic was measured in drinking water collected from the tube well that each woman identified as their primary source of drinking water at the time of enrollment and has been previously described (13). Briefly, nitric acid-preserved water samples were analyzed for total arsenic concentrations by inductively coupled plasma mass spectrometry (ICP-MS) following US EPA method 200.8 (Environmental Laboratory Services, North Syracuse, New York). The average percent recovery of drinking water arsenic was 101% (range: 92% – 110%). Samples with arsenic concentrations below the limit of detection (LOD) ranging from 0.5–1.0 µg/L (n = 242) were reassigned LOD/2 for statistical analysis.

Arsenic was also measured in maternal toenail clippings collected 1-month post-partum and has been previously described (13). We collected toenail material from all 10 toes and pooled them for analysis. Briefly, nitric acid-digested pooled toenail samples were diluted with Milli-Q water before analyzing for total arsenic concentrations using ICP-MS. The reported arsenic concentrations were blank-corrected and normalized using arsenic concentration of certified human hair reference material (CRM Hair; Shanghai Institute of Nuclear Research, China). Toenail clippings were collected from 1,115 participants with a history of singleton livebirth at 1-month post-partum; 1,091 of them were used in the analysis after excluding samples with toe mass <5 mg (n = 16) and relative standard

deviation 25% (n = 8). Samples with arsenic concentrations below the LOD ranging from 0.09–0.7 ng/L (n=1) were reassigned LOD/2 for statistical analysis. The average percent recovery and relative standard deviation of CRM hair for arsenic was 76% and 5.2%, respectively.

Child marriage was defined as formal marriage before 18 years of age based on the legal age of marriage for girls in Bangladesh during the study period. A Structured questionnaire was used to collect self-reported age at marriage at the time of enrollment. Maternal height and weight was measured at first clinic visit and at monthly house visits following enrollment on an adult scale that was calibrated before each measurement and rounded to the nearest gram. We estimated maternal rate of weight gain during the 2nd and 3rd trimesters in pound/week (lb/wk) as a measure of pregnancy weight gain using longitudinally collected maternal monthly follow-up visit weights. We fit a linear regression model with maternal monthly weight as a dependent variable (y) and gestational week from 14th week to the last available weight measurement week before delivery as an independent variable (x). The estimated slope of the linear model reflected the rate of weight gain per week during the 2nd and 3rd trimesters for each participant.

2.3 Outcome and covariates

Preterm birth was defined as livebirth before 37 completed weeks of gestation. Health care workers attended all births to collect detailed birth records. Gestational age was determined by ultrasonography by a licensed general practitioner using either (1) gestational sac mean diameter if the pregnancy was between 4–7 weeks or, (2) crown-rump length if the pregnancy was between 7–16 weeks (52, 53). Other demographic information, including maternal age, education, number of past pregnancies, secondhand smoke exposure was collected at the time of enrollment using a structured questionnaire. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters and was categorized into underweight, <18.50; normal weight, 18.50 – 24.99; overweight, 25.00.

2.4 Statistical analysis

Arsenic concentrations in drinking water and maternal toenail were right skewed and subsequently transformed to their natural log (ln). The distribution of selected characteristics across the preterm birth group was assessed using Student's *t*-test, Man-Whitney *U*-test, or Chi-square test when appropriate. All *P*-values were two-sided.

We conducted mediation analysis to estimate the direct and indirect effects of arsenic exposure and child marriage on preterm birth considering pregnancy weight gain a mediator. Mediation analysis was conducted by fitting two separate models: model for preterm birth (outcome model, Model 1) and model for pregnancy weight gain (mediator model, Model 2). We used multivariate Poisson regression with robust error variance to model for preterm birth, and estimated risk ratios (RR) (Model 1) (54). We used multivariate linear regression to model for pregnancy weight gain (Model 2).

$$\log(\pi_i) = \theta_0 + \theta_1 \ln(\text{arsenic})_i + \theta_2 \text{Child marriage}_i + \theta_3 \text{weight gain}_i + \theta_4 C'i \quad (1)$$

$$E(\text{pregnancy weight gain}_i) = \beta_0 + \beta_1 \ln(\text{arsenic})_i + \beta_2 \text{Child marriage}_i + \beta_4 \mathbf{C}'_i \quad (2)$$

The notation, π_i denotes the probability of preterm birth, and $\mathbf{C}'_i$ denotes covariate matrix for subject i . Prenatal arsenic exposure and child marriage were considered as two independent exposure of interests, while we used a common outcome model (Model 1) in the mediation analysis. The model for preterm birth and the model for pregnancy weight gain were combined to estimate the direct, indirect and total effects for mediation analysis. We used the following list of covariates to adjust for the outcome and mediator models based on a priori evidence and causal diagram using DAG (55): maternal age (continuous), education (no formal education, primary, secondary or higher), number of past pregnancies (0, 1, >1), BMI categories (<18.50, 18.50–24.99, 25.00), and secondhand smoking (yes, no). Analysis was conducted in the full cohort as well as stratified by the child marriage groups.

The direct effect of arsenic exposure on preterm birth is given by $\exp(\theta_1)$, which represents the RR for preterm birth for a unit increase in natural log arsenic exposure when pregnancy weight gain takes a value what it would have been in absence of arsenic exposure. Similarly, indirect effect of arsenic on birthweight is given by $\exp(\theta_3 * \beta_1)$, which represents the RR for preterm birth for a unit increase in natural log arsenic exposure comparing pregnancy weight gain in the absence of arsenic exposure versus what pregnancy weight gain would be if arsenic exposure were increased to one unit in natural log scale. The total effect of arsenic exposure can be estimated as the product of the direct and indirect effect risk ratios and represents the risk ratios for preterm birth for a unit increase in natural log arsenic exposure via both pathways.

Similarly, the direct effect of child marriage on preterm birth is given by $\exp(\theta_2)$, which represents the RR for preterm birth for child marriage compared to adulthood marriage if pregnancy weight gain were what it would have been in case of adulthood marriage. The indirect effect is given by $\exp(\theta_2 * \beta_2)$, which represents the RR for preterm birth comparing pregnancy weight gain between child marriage and adulthood marriage groups, had women experienced child marriage. The total effect of child marriage can be estimated as the product of direct and indirect effect risk ratios and represents the risk ratios for preterm birth for child marriage compared to adulthood marriage via both pathways. The proportion of the total effect mediated via the mediating variable (proportion mediated, PM) was estimated as $PM = \frac{RR_d \times (RR_i - 1)}{(RR_d \times RR_i - 1)}$, where RR_d is the direct-effect risk ratio, RR_i is the indirect-effect risk ratio.

Analyses were conducted with and without an exposure-mediator interaction term and in the full cohort as well as stratified by child marriage groups. Direct and indirect effects were averaged across all individuals. Bias corrected confidence intervals were estimated from 1,000 bootstraps. Analyses assume that conditional on the covariates, there is no confounding of 1) the exposure-outcome relation, 2) exposure-mediator relation, 3) mediator-outcome relation and that 4) there is no effect of the exposure that itself confounds

the mediator-outcome relation (56). Analyses were implemented with STATA (Version 14.0, StataCorp LP, College Station, Texas).

3. Results

3.1 Descriptive statistics

Of 1,183 singleton livebirths included in our analysis, 260 (21.9%) were born preterm. Approximately, 70% of the infants born preterm were born to women who had a history of child marriage. The mean age of marriage was 17.4 years (range: 11–29 years); 45% of the women were married before age 18 years, compared to the national average of 66% (33). The lower proportion of child marriage in our cohort was because women had to be at least 18 years old at the time of enrollment to be included into the study. Women with a history of child marriage were more likely to have low educational attainment, low household income, low BMI, but high chronological age, and multiple past pregnancies compared to women with no history of child marriage (data not shown). The study subjects were ethnically similar. All were married and non-smoker, although 42% of the participants reported to be exposed to secondhand smoking during pregnancy. Arsenic exposure was relatively modest with median concentration of 2.2 µg/L (range: <LOD–1400 µg/L) and 1.2 µg/g (range: <LOD–46.6 µg/g), respectively for drinking water and maternal toenail arsenic, but spanned a wide range. Nearly 22% of the women included in our analysis were exposed to drinking water arsenic at concentrations above the national standard of 50 µg/L, contributing to over 35% of all preterm births in our cohort. Mother's weight gain during the 2nd and 3rd trimesters followed a linear trend with a mean of 0.80 lb/wk (interquartile range, IQR: 0.55–0.98). Other population characteristics and their bivariate associations with preterm birth are presented in Table 1.

3.2 Regression analyses

3.2.1 Associations with preterm birth—Table S1 and Fig. 2 displays the associations between prenatal arsenic exposure, child marriage, pregnancy weight gain, and preterm birth in the full cohort as well as stratified by child marriage groups. For drinking water arsenic exposure (Fig. 2, A1-A3), we observed that every unit increase in natural log arsenic exposure increased the risk of preterm birth by 12% (95% CI: 1.07, 1.17; $P<0.0001$) after adjusting for maternal age, education, enrollment BMI, number of past pregnancies, 2nd and 3rd trimester weight gain, child marriage and secondhand smoking. In stratified analysis, the risk of preterm among women with no history of child marriage (RR = 1.15; 95% CI: 1.05, 1.26, $P=0.003$) and women with a history of child marriage (RR= 1.10; 95% CI: 1.04, 1.17); $P<0.0001$) remained consistent. Our results also showed that child marriage was positively associated with preterm birth. Specifically, the risk of preterm birth among women with a history of child marriage was 128% higher (95% CI: 1.76, 2.95; $P<0.0001$) compared to women with no history of child marriage.

Pregnancy weight gain, on the other hand, showed an inverse association with preterm birth. For instance, every lb/wk increase in maternal weight gain during the 2nd and 3rd trimesters were associated with 36% decreased risk of preterm birth (95% CI: 0.42–0.97; $P=0.04$) in the full cohort. Interestingly, in stratified analysis, pregnancy weight gain was associated

with decreased risk of preterm birth only among women who had a history of child marriage (RR = 0.58; 95% CI: 0.37, 0.92; $P=0.02$), but not among women who had no history of child marriage (RR = 0.86; 95% CI: 0.37, 2.01; $P=0.72$). Similar magnitude and direction of associations were observed for maternal toenail arsenic exposure, although the associations were not statistically significant when analyses were conducted stratified by child marriage groups.

3.2.2 Associations with pregnancy weight gain—Table S2 and Fig. 2 summarizes the associations between prenatal arsenic exposure, child marriage and pregnancy weight gain adjusted for maternal age, education, enrollment BMI, number of past pregnancies, and secondhand smoking. Our results showed that both drinking water arsenic exposure and child marriage were associated with lower weight gain during the 2nd and 3rd trimesters. For instance, each unit increase in natural log water arsenic exposure was associated with 0.016 lb/wk lower weight gain during the 2nd and 3rd trimesters (95% CI: -0.024, -0.009; $P<0.0001$). The associations remained consistent among women with no history of child marriage ($\beta = -0.011$; 95% CI: -0.02, -0.025; $P=0.03$) and women with a history of child marriage ($\beta = -0.021$; 95% CI: -0.032, -0.011; $P<0.0001$). Additionally, women who had a history of child marriage gained 0.037 lb/wk less weight during the 2nd and 3rd trimesters (95% CI: -0.07, -0.004; $P=0.03$) compared to women with no history of child marriage.

In case of maternal toenail arsenic, significant negative associations between arsenic exposure and pregnancy weight gain were observed in the full cohort and among women who had a history of child marriage, but not among women who had no history of child marriage. However, the associations between toenail arsenic exposure and pregnancy weight gain did not differ between women with a history of child marriage and women with no history of child marriage, as the confidence intervals overlapped each other. We also tested for an interaction between toenail arsenic exposure and child marriage in the full cohort, which was not statistically significant (data not shown).

3.3 Mediation analysis

3.3.1 Arsenic exposure → pregnancy weight gain → preterm birth—

Mediation analysis showed that prenatal arsenic exposure had small but statistically significant indirect effect on preterm birth mediated via pregnancy weight gain (Table 2). For instance, each unit increase in natural log drinking water arsenic exposure was associated with 1% increased risk of preterm birth (95% CI: 1.00, 1.02) that was mediated via lowering mother's weight gain during the 2nd and 3rd trimesters. The total effect risk ratio for water arsenic exposure on preterm birth was 1.13 (95% CI: 1.07 – 1.18); the proportion of the total effect mediated via pregnancy weight gain was 6.3%. The direct, indirect, and total effect associations between water arsenic exposure and preterm birth were consistent between women with a history of child marriage and women with no history of child marriage. However, the contribution of the indirect effect pathway to the overall effect of water arsenic exposure on preterm birth was 9.5 times higher among women with a history of child marriage compared to women with no history of child marriage (PM = 11.4% vs 1.2%).

Similar magnitude of associations was observed for maternal toenail arsenic exposure, although the associations were not statistically significant among women with no history of child marriage. However, the contribution of the indirect effect pathway to the overall effect of toenail arsenic exposure on preterm birth was 13.7 times higher among women with a history of child marriage compared to women with no history of child marriage (PM = 23.3% vs 1.7%), suggesting possible scope of intervention to minimize the effect of arsenic exposure on preterm birth by improving perinatal nutrition among this group.

3.3.2 Child marriage → pregnancy weight gain → preterm birth—Child marriage also showed a small but statistically significant indirect effect on preterm birth (indirect effect RR = 1.02; 95% CI: 1.00, 1.05) via lowering mother's weight gain during the 2nd and 3rd trimesters (Table 3). The total effect risk ratio was 2.32 (95% CI: 1.76 – 3.00); the proportion of the total effect mediated via pregnancy weight gain was only 2.9%.

4. Discussion

Our study demonstrates that prenatal arsenic exposure and child marriage were associated with increased risk of preterm birth in Bangladesh; a small proportion of the effects were mediated via low maternal weight gain during the 2nd and 3rd trimesters. The association between arsenic exposure and preterm birth showed a dose-response relationship, where every unit increase in natural log water arsenic exposure was associated with 7 – 18 % increased risk of preterm birth. The association was consistent for arsenic exposure measured in drinking water at the time of enrollment and maternal toenails collected within 1-month post-partum. Our results also showed that mother's history of child marriage was associated with 76 – 200 % increased risk of preterm birth after adjusting common risk factors, suggesting that child marriage may have long-term consequence on perinatal health. Conversely, maternal weight gain during the 2nd and 3rd trimesters was associated with decreased risk of preterm birth, particularly among women who had a history of child marriage, suggesting possible scope of intervention to reduce the risk of preterm birth among this high-risk group by improving perinatal nutrition.

The positive association between arsenic exposure and preterm birth was reported in previous studies among populations exposed to varying levels of arsenic in drinking water. A recent cross-sectional study in Ohio, USA assessed the link between arsenic levels in community water system and birth outcomes using records of 428,804 birth certificates during 2006–2008, and found that each unit ($\mu\text{g/L}$) increase in annual county-level average arsenic exposure was associated with 10% increased odds of preterm birth (95% CI: 1.05, 1.15) (19). Another ecological study in Taiwan comparing infants born to arsenic-exposed villages (0.15 $\mu\text{g/L}$ – 3.59 mg/L) with infants born to arsenic non-exposed villages (<0.9 $\mu\text{g/L}$) reported 10% increased odds of preterm birth (95% CI: 0.93, 1.33) after adjusting for potential confounders (26). Furthermore, an ecological study in New Hampshire, USA reported that preterm birth was spatially correlated with higher levels of ground water arsenic in that region (20). In Bangladesh, a retrospective cross sectional study reported an increase in preterm birth among women living in arsenic-exposed village (200 – 1371 $\mu\text{g/L}$) compared to those living in less exposed village (< 20 $\mu\text{g/L}$) (18). Ours is the first prospective study with individual-level exposure data to establish this association.

We also found that the effect of prenatal arsenic exposure on preterm birth was partly mediated via lowering maternal weight gain during the 2nd and 3rd trimesters. The mediating role of pregnancy weight gain was previously reported for the association between arsenic exposure and birth weight by Kile et al. (42). These results indicate that pregnancy weight gain may lie within the causal pathway between prenatal arsenic exposure and adverse birth outcomes. However, the magnitude of the indirect effect association and its relative contribution to the overall effect of arsenic exposure and preterm birth was minimum, except for women who had a history of child marriage. Specifically, among women who had a history of child marriage, 23.3% of the total effect of maternal toenail arsenic exposure on preterm birth was mediated via lowering maternal weight gain during the 2nd and 3rd trimesters (indirect effect RR = 1.03; 95% CI: 1.01, 1.06 for a unit increase in natural log arsenic exposure). These results suggest that by improving maternal perinatal nutrition, it might be possible to minimize some of the toxic effects of prenatal arsenic exposure on preterm birth, particularly among the high-risk women with a history of child marriage.

Additionally, several studies have reported that the risk of preterm birth is higher among adolescent mothers (35, 36, 57, 58). However, previous studies in the field of child marriage, have focused on examining the effect of young maternal age on perinatal health outcomes; although, some have suggested that the risk associated with child marriage may extend beyond adolescent pregnancy (59), perhaps to subsequent adulthood pregnancies. A hospital based case-control study in Saudi Arabia reported that women with a history of child marriage (<16 years) experienced higher odds of spontaneous abortion, fetal death, and infant mortality, which extended throughout their childbearing period (60). Some argue that the health and wellbeing of girls at adolescence (when the girl herself is undergoing biological maturation) can be compromised by child marriage, resulting in long-term maternal and child health consequences (61). Our results provide critical insights into the long-term effect of child marriage on preterm birth in subsequent adulthood pregnancies. The inverse association between pregnancy weight gain and preterm birth was reported in several other studies (46–48, 50, 62). A large meta-analysis of 37 cohort and 18 case-control studies, involving a total of 3,467,638 women found that the overall risk of preterm birth was significantly higher among women gaining less weight during pregnancy, measured as total pregnancy weight gain (overall RR=1.64; 95% CI: 1.62–1.65) and weekly weight gain (overall RR=1.56; 95% CI: 1.26–1.94) compared to that recommended by the Institute of Medicine (IOM) guidelines (47, 63). Previous studies have reported that the association between pregnancy weight gain and preterm birth was modified by the mother's pre-pregnancy BMI status (48, 62) and adolescent pregnancy (64). The current IOM guidelines, thus provide weight gain recommendations by women's pre-pregnancy BMI statuses (63). The IOM guidelines also suggest for relatively higher weight gain for pregnant adolescents to minimize their risk of adverse perinatal outcomes (65, 66). In our study, we observed an inverse association between pregnancy weight gain and preterm birth, which was modified by the mother's prior history of child marriage, highlighting the importance of adequate perinatal nutrition among this group even in subsequent adulthood pregnancies.

The mechanism how prenatal arsenic exposure may affect preterm birth is not well understood, although there is a strong link with inflammation and infection (67). Studies have found that arsenic exposure during pregnancy is associated with increased

inflammatory markers in newborn cord blood (68, 69), and altered expression of cord blood microRNAs that are integral to inflammation and immune responses (70). Moreover, arsenic exposure has been associated with altered angiogenesis leading to dysplastic placental development (71), which is considered as a major risk factor for preterm birth (72).

The biological plausibility for an increased risk of preterm birth among women with a history of child marriage is not known either. Child marriage often forces girls into pregnancy before their biological maturity. Women with a history of child marriage are less likely to use contraception before first childbirth, and are more likely to experience multiple unwanted pregnancies, closely spaced pregnancies, and high fertility (34). Hence, they have higher risk of entering a reproductive cycle with reduced nutritional reserve in the body (73), which might trigger maternal-fetal competition for nutrients during the intrauterine period. The maternal-fetal competition for nutrients has been linked with smaller placental mass, less uterine and umbilical cord blood transfer, and less placental transfer of nutrients and oxygen to the fetus, predisposing to low birth weight and preterm birth (74).

Our study has some limitations. Approximately, 13.6% of the enrolled participants in our cohort either lost to follow-up (n=99), or withdrew from the study (n=121). Participants who remained in the study were similar in exposure and most demographic characteristics with those who dropped out of the study (data not shown). Hence, there is little chance for selection bias in our results. However, generalizability could be an issue, as our study participants were originated primarily from rural and peri-urban areas of the country with varying levels of arsenic in ground water aquifers and a relatively higher prevalence of adolescent marriage. Furthermore, we determined gestational age relying solely on ultrasound measurements taken at 4–16 weeks of gestation. Pregnancy dating using ultrasound is considered gold standard if measurements were taken in early pregnancy, but the estimates are increasingly inaccurate after the end of first trimester (75). We did not have reliable data on maternal last menstrual period (LMP) in our cohort, as few participants could recall their LMP date. Therefore, we were not able to use LMP information in conjunction with ultrasound measurements to validate pregnancy dating, particularly for women enrolled after 14 weeks of gestation. So, we acknowledge that there is a chance for misclassification in gestational age, but we argue that the effect of this misclassification will likely be non-differential, as we previously have showed that arsenic exposure was not associated with the timing of enrollment (14). Furthermore, recall bias and potential inaccuracies in reporting maternal age and age at marriage were a possibility, as no reliable birth or marriage registry existed in the region to validate such information. Also, it is unlikely that the toenail clippings collected from participants were in the same length for all study participants, where longer clippings will represent a longer duration of exposure. We previously explained that any exposure misclassification resulting from different lengths of toenails among the study participants will likely be non-differential (13) and any bias introduced by this will be towards the null. There were 242 samples (20.5%) with drinking water arsenic concentrations below the LOD (range: 0.5 – 1.0 µg/L), for which we reassigned a value of LOD/2 for statistical analysis. Studies have shown that simple imputation methods for data points below the LOD (e.g. replacement by zero, LOD, LOD/2, LOD/ 2) may result in meaningful bias (76, 77). However, as Richardson and Ciampi

pointed out, any bias introduced by assigning a value of LOD/2 for measurements below the detectable limit would likely be minimum (77).

As in any observational study, ours may be limited by unmeasured confounding. For instance, child marriage is associated with a number of factors, including low socioeconomic background, poor quality and quantity of antenatal care, higher frequency of perinatal infection, pregnancy spacing, physically demanding work, and higher levels of stress, and other adverse psychological factors (78–80), which could independently increase the risk of preterm birth. While, these factors could potentially confound the association between child marriage and preterm birth in our cohort, we did not collect reliable information on these variables in our cohort. So, our results for the association between child marriage and preterm birth could partly be explained by unadjusted factors in our analysis that are related to child marriage, and should be interpreted with caution. We carefully selected a list of covariates based on a priori knowledge and causal diagram using DAG. The study subjects were ethnically similar and all were married and non-smoker. All study subjects received the same level of prenatal care and vitamin supplements with reportedly 99% compliance through our community outreach clinics. Studies have shown that folate supplementation can reduce arsenic's toxicity by promoting arsenic methylation efficiency (81). Therefore, there is a possibility that the use of multivitamins during pregnancy might have attenuated the association between arsenic exposure and preterm birth in our cohort

We measured pregnancy weight gain during the 2nd and 3rd trimesters based on the assumption that weight increases linearly during that period. So, it is possible that our estimated weight gains were measured in error, which would bias our downstream analysis where pregnancy weight gain was used as a mediator. Studies have shown that maternal weight gain is relatively higher and linear during the 2nd and 3rd trimesters of pregnancy (66). Studies have also reported that the association with preterm birth is strongest for maternal weight gain during the later trimesters of pregnancy (49, 82). Therefore, we argue that the bias introduced by our estimated weight gain would likely be minimum. Some studies have used maternal total weight gain during pregnancy to assess the association between pregnancy weight gain and preterm birth. The total weight gain will be systematically lower for mothers delivering preterm. Also, weight gain during pregnancy is not uniform; it is relatively low during the 1st trimester and higher and linear during the 2nd and 3rd trimesters (66). Therefore, for mothers delivering preterm, the total weight gain will disproportionate include relatively lower 1st trimester weight gain (46). In addition, women were enrolled into our study at different stages of gestation (4–16 weeks), and most of them did not know their pre-pregnancy body weight, precluding us to estimate their total pregnancy weight gain without errors.

Our study has several strengths. We measured arsenic exposure in drinking water collected from the tube well that each woman identified as her primary source of water. Previous studies in Bangladesh reported that drinking water arsenic exposure show little temporal variability (83), thus may represent subject's long-term exposure if the main source of water remains unchanged (84). However, arsenic measured in drinking water will not capture other sources of arsenic exposure, especially arsenic exposure from food sources, such as rice and fish. The modest correlation ($\sigma_{\text{spearman}} = 0.48$; 95% CI: 0.44 – 0.53) between drinking water

and maternal toenail arsenic exposure indicates other sources of arsenic exposure in this population. We also measured arsenic in maternal toenails, as a biomarker for the internal dose, reducing the risk of exposure misclassification. Previous studies have showed that arsenic exposure measured in maternal toenails collected 1-month post-partum represents individual's cumulative exposure over the past 9–12 months (85), essentially corresponding to the entire pregnancy. We also collected maternal toenails at the time of enrollment, and discarded data for toenails with low mass (<5 g). Hence, we argue that arsenic levels measured in toenails collected within 1-month post-partum will reflect gestational exposure. Additionally, the prospective nature of this study with relatively larger sample size and individual-level arsenic measurement is another strength not shared by most studies in this field. Finally, this is the first study to assess the interactive effect of prenatal arsenic exposure, child marriage, and pregnancy weight gain on preterm birth. Because these environmental, social and maternal health factors often coexist in Bangladesh and part of the South Asia, where more than a third of the global preterm babies are born, our results could provide critical insights to empower public health interventions in this region.

5. Conclusions

Our results show that prenatal arsenic exposure, child marriage, and low maternal weight gain during the 2nd and 3rd trimesters are associated with increased risk of preterm birth in Bangladesh. Public health interventions to minimize arsenic exposure during pregnancy and end child marriage may improve perinatal outcomes in Bangladesh. Improving maternal nutritional status during pregnancy could provide additional benefits, particularly to the high-risk women who have a history of child marriage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH) grant R01ES015533

Source of Funding: The National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH) supported this work [grant number: R01ES015533]

Abbreviations:

LOD	Limit of Detection
IOM	Institute of Medicine

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Fig. 1.
Study participation

Fig. 2.

Directed acyclic graphs showing associations between prenatal arsenic exposure, child marriage, pregnancy weight gain, and preterm birth in Bangladesh. Analyses were conducted separately for A) drinking water and B) maternal toenail arsenic exposure in the full cohort (A1, B1) as well as stratified by child marriage: among women with no history of child marriage (A2, B2) and women with a history of child marriage (A3, B3). The solid lines with arrow represent the direction of associations, accompanied by respective effect sizes in risk ratios (95% CI) or beta coefficients (95% CI). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; NS= Non-significant

Table 1:

Distribution of selected characteristics by preterm birth among 1,184 pregnant women recruited in a prospective birth cohort in Bangladesh, 2008–2011.

Characteristic	Preterm Birth (n = 260)	Term Birth (n = 924)	P-value
Maternal age (years)	22.97 ± 3.94	22.95 ± 4.29	0.941
History of child marriage, n (%)			
Yes	182 (70.0)	350 (37.7)	<0.0001
No	78 (30.1)	574 (62.3)	
2 nd & 3 rd trimester weight gain (lb/wk)	0.74 ± 0.26	0.81 ± 0.27	0.0002
Enrollment BMI, n (%)			
18.5 kg/m ²	70 (27.0)	266 (28.7)	0.017
>18.5 to 25.0 kg/m ²	177 (68.0)	563 (61.0)	
>25.0 kg/m ²	13 (5.0)	95 (10.3)	
No. of past pregnancies, n (%)			
0	85 (32.8)	391 (42.3)	0.013
1	82 (31.7)	271 (29.4)	
> 1	93 (35.5)	262 (28.3)	
Maternal education, n (%)			
No formal education	49 (18.9)	123 (13.3)	0.001
Primary education	60 (23.2)	320 (34.7)	
Secondary or higher	151 (57.9)	481 (52.0)	
Secondhand smoke, n (%) ^a			
Yes	121 (46.9)	375 (40.6)	0.077
No	138 (53.1)	549 (75.4)	
Toenail arsenic (µg/g), median (IQR) ^b	1.65 (0.72)	1.10 (1.7)	<0.0001
Water arsenic (µg/L), median (IQR)	16.7 (64.3)	1.80 (25.2)	<0.0001

Values are mean ± Standard deviation except where indicated

IQR= Inter quartile range; lb/wk= pound/week

^aMissing data reported for second hand smoking, n=1

^bA total of 1,090 participants (229 preterm births) were included in the analysis for toenail arsenic exposure

Table 2:

Direct, indirect, and total effects of prenatal arsenic exposure on preterm birth considering pregnancy weight gain a mediator. Analyses were conducted in the full cohort as well as stratified by the history of child marriage. The models for pregnancy weight gain were adjusted for maternal age, education, enrollment BMI, number of past pregnancies, secondhand smoking, and child marriage (in full cohort). The models for preterm birth were additionally adjusted for pregnancy weight gain.

Effects	Drinking Water Arsenic Exposure				Maternal Toenail Arsenic Exposure			
	Full Cohort (n= 1,183)		History of Child Marriage		Full Cohort (n= 1,090)		History of Child Marriage	
			No (n= 652)				No (n= 596)	
	RR (95% CI)	PM%	RR (95% CI)	PM%	RR (95% CI)	PM%	RR (95% CI)	PM%
Direct effect	1.12 (1.07, 1.17)		1.15 (1.05, 1.26)	1.10 (1.04, 1.17)	1.13 (1.03, 1.24)	1.15 (0.97, 1.36)	1.11 (0.99, 1.23)	
Indirect effect	1.01 (1.00, 1.02)	6.3	1.00 (0.99, 1.01)	1.2	1.02 (1.00, 1.04)	12.1	1.03 (1.01, 1.06)	23.3
Total effect	1.13 (1.07, 1.18)		1.15 (1.04, 1.25)	1.12 (1.06, 1.18)	1.15 (1.04, 1.26)	1.15 (0.97, 1.36)	1.14 (1.02, 1.27)	

● Effect estimates were consistent adding an arsenic-pregnancy weight gain interaction term in the model for preterm birth

● Bias corrected standard error was derived from 1,000 bootstraps.

● RR = Risk Ratio; CI = Confidence Intervals; PM = Proportion Mediated

Table 3:

Direct, indirect, and total effects of child marriage on preterm birth considering pregnancy weight gain a mediator. The model for pregnancy weight gain was adjusted for maternal age, education, enrollment BMI, number of past pregnancies, secondhand smoking, and water arsenic exposure. The model for preterm birth was additionally adjusted for pregnancy weight gain.

	Adjusting for Water Arsenic		Adjusting for Toenail Arsenic	
	RR (95% CI)	PM%	RR (95% CI)	PM%
Direct effect	2.28 (1.73, 2.96)		2.35 (1.82, 3.17)	
Indirect effect	1.02 (1.00, 1.05)	2.9	1.03 (1.01, 1.08)	5.7
Total effect	2.31 (1.76, 3.00)		1.43 (1.86, 3.30)	

- Effect estimates were consistent adding an interaction term between child marriage and pregnancy weight gain in the model for preterm birth
- Bias corrected standard error was derived from 1,000 bootstraps.
- RR= Risk Ratio; CI= Confidence Intervals; PM= Proportion Mediated