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Intrauterine Exposure to Arsenic Affect Infant Development

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The ICDDR,B Child Development Unit (CDU) conducted a longitudinal observational study on a sample of 1562 pregnant mothers in Matlab, Bangladesh, to examine the intrauterine effects of arsenic on infants. Drinking water consumed by the mothers during their pregnancy was assessed for arsenic concentration using atomic-absorption spectroscopy. Infants were assessed for cognitive and psychomotor development at the age of 7 months. Sixty-three percent of all functioning tube wells had arsenic contamination above 50µg/L. Infants whose mother drank water from wells with >50µg/L of arsenic had slightly lower developmental scores than those whose mother's drinking water had lower arsenic levels. While the clinical importance and long-term implications of these developmental differences need to be determined, these results provide further evidence of the urgent need to reduce the arsenic contamination in Bangladesh.

Arsenic is a widely distributed environmental pollutant. Many peoples are exposed to arsenic contaminated drinking water in different regions of the world due to elevated levels in ground water. It is neurotoxic and known to cause cancer, skin diseases and other chronic diseases. Recently a few cross sectional studies in school-aged children reported a negative association of arsenic exposure with children's development. Siripityakunkit and colleagues[1] found a significant association between high arsenic levels in hair and impaired visual perception in 6-9 year old Thai children who were chronically exposed to arsenic contaminated drinking water. Calderon[2] and Rosado[3] reported co-exposure of arsenic and lead in primary school children from smelter areas in Mexico associated with lower verbal intelligence and long-term memory. Similarly, in Taiwan, long-term arsenic-exposure through drinking water was associated with lower scores in three out of four performance tests in a dose response manner[4]. Two studies in Bangladesh reported an association between exposures to high well water arsenic and reduced intellectual function, even after adjusting for covariates[5,6]. These studies indicate that children as young as 6 years old may suffer from subtle developmental deficits due to arsenic exposure.

Arsenic has been reported to pass through the placenta in humans[7]. It is also reported to cross the blood-brain barrier in animal models[8] and to influence the synthesis of

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brain enzymes[9]. In humans, observational studies have shown that exposure to highly arsenic contaminated drinking water is associated with reduction in birth weight[10] and increase in fetal loss[11] but we are unaware of any study that reported the effect of arsenic exposure during pregnancy on the later neuro-behavior of infants. Considering the ability of arsenic to cross both the placental and blood-brain barriers we hypothesized that arsenic exposure during pregnancy might be harmful to the developing brain and lead to lowered cognitive function in infancy[12].

Based on a study in 41 districts of Bangladesh, the British Geological Survey estimated that 21 million Bangladeshis are exposed to water with arsenic concentrations >50µg/L, the maximum allowable level by the Government of Bangladesh[13]. A large randomized community based food and micronutrient supplementation trial (MINIM at) was conducted on 5,000 pregnant women in rural Bangladesh where almost 70% of tube wells exceeded the WHO cut-off for excess arsenic which is 10µg/L and 63% exceeded the Bangladeshi national cut-off of 50µg/L. At the same time a parallel study (As Mat) assessed the tube wells' arsenic concentration in that region, using atomic-absorption-spectroscopy to estimate the life time exposure of that population to arsenic. We combined data from these two studies and assessed the association between prenatal arsenic exposure and later infant development. Information on water arsenic exposure was available for 1,562 mothers of MINIM at study whose children were assessed for developmental outcome at the age of 7 months.

We used two problem-solving tests, Support and Cover, to assess infants' cognitive function. The Support test involves placing a long cloth on a table in front of the child, then placing a toy out of the child's reach at the farthest end of the cloth. The infant has to pull the cloth to retrieve the toy. In the cover test a toy is covered with a cloth while the infant is watching. The infant is then required to remove the cloth to retrieve the toy. These procedures were videotaped and scored later. Four trials were given in both problem-solving tests. Three behaviors were scored in each trial: cloth-behavior (the way the child handled the cloth), fixation behavior (the way the child fixed his/her vision on the toy) and toy-behavior (the way the child grasped the toy). Each behavior was scored on a 3 point scale, starting from 0 for no evidence of intention, 1 for possible ambiguous intention and 2 for clear evidence of intention. The scores for each behavior were summed to give an intention score for each trial that ranged from 0 to 6, and the scores of 4 trials were then summed to give a total score ranging from 0-2,4.

For assessment of motor function we used Psychomotor Developmental Index (PDI) of Baylcy Scales of Infant Development-II. These are simple non-language dependent and culturally modified tests designed to detect early behavioral changes from intrauterine insults. The problem solving tests were chosen because they are sensitive to small differences, are relatively easy to perform, and can be scored from videotape which facilitates on going quality control. A detailed questionnaire concerning socioeconomic status and anthropometric measurements of the mother-infant pairs were also available from the MINIM at study. The water arsenic levels were categorized under 3 groups: <10µg/L; 10-50µg/L and >50µg/L for one-way analyses of variance.

Infants whose mothers drank water from wells with >50µg/L of arsenic had slightly lower developmental scores than infants whose mother's drinking water contained less arsenic (Table-I). Using water-arsenic level as a continuous variable and adjusting for all available socio-demographic covariates, the negative effect of arsenic remained significant for both the Support (B±SE:-0.003±0.001, p=0.008) and cover (-.002±0.001,p=0.035) problem-solving tests. Data showed a significant over all linear-trend for both the Cover (p<0.007) and Support tests (p<0.002) with declining scores from the lowest to the highest exposed-group. There was no significant effect of arsenic on Psychomotor Developmental Index (B±SE:-0.003 ±0.002, p=0.199).

We measured small negative effects of arsenic exposure on problem solving tests in sevenmonth old infants. There was a trend towards a lower score on the Psychomotor Developmental Index with higher arsenic exposure, but this difference was not statistically significant.

The infants in our study were measured for developmental scores at a very young age (7 months) and over 65% of them were predominantly breast--fed until 6 months of age (personal communication with Dr. Iqbal Kabir, MlNIM at study). In Matlab, from 1978 to 1987, the median duration of exclusive breast feeding fluctuated around 6 months[14]. We found a higher percentage of predominantly breast-fed children at 6 months compared to the previous report of Matlab[14] and to the other national statistics. This is because counseling on exclusive breast feeding for the first 6 months was one of the interventions in the main MINIM at study. Breast milk excretes

Table-I

Means (SD) of developmental outcomes by concentration of arsenic in drinking water during pregnancy

Arsenic exposure (µg/L)	N	Total Cover mean ±SD*	Total Support mean ±SD*	Psychomotor Developmental Index – mean ±SD
0.5-9.99	538	13.6±6.7	12±7.5	104.4±15
10-49.99	190	13.4±6.6	11.7±7.3	104.2±16
≥ 50	834	12.6±7.1	10.6±7.6	103±16
Total	1,562	13.06±6.9	11.2±7.6	103.6±15
Group difference P-value		0.017	0.002	0.36

ANOVA controlling for age (Cover and PDI) and age and sex (support)
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very little arsenic[7] and arsenic exposure through foods/plain water in partial breast-fed children is unlikely to be very high and generally requires several months to exert its chronic impact. Thus, the effect of arsenic seen in this study is likely to be due to intrauterine exposure.

The exact mechanism of action of chronic arsenic exposure on the brain is not clear. The retention of arsenicals in tissues suggests that they could exert certain biological effect[15]. Functional damage of the brain might occur without causing any structural damage to the brain. In animal models arsenic has been reported to alter brain enzymes[8,9]. In experimental pregnant rats arsenic drinking solution resulted in reduced spontaneous locomotors activity and altered special learning task in the pups[16]. Some animal studies also report arsenic induced oxidative stress on the brain[17].

One study reported that methylation increases during pregnancy and it might be protective for the developing fetus[7,18]; however, our report shows that there is a subtle harmful effect of prenatal arsenic exposure on infant development. The difference is small but statistically significant. We do not know its functional implication, but it is a matter of concern. Our study was part of a large community-based food and micronutrient intervention and all the pregnant mothers received micronutrients supplements, like folic acid that is known to be protective against oxidative damage of arsenic. We also do not know at what point of pregnancy the mothers knew that their tube well contains high arsenic concentrations 'and whether they switched to a drinking' water source with lower arsenic concentrations after getting this information. It is likely that receiving ·antioxidants and changing water source (if any) reduced the toxic effect of arsenic on the developing fetal brain, leading to a very small effect size. This is a large longitudinal study and the children are being followed later in life. We will therefore be able to report the long-term effects of intrauterine and concurrent arsenic exposure on children's development. The effect on problem solving behavior of infants was small but concerning and provides additional evidence highlighting the need to reduce arsenic exposure in Bangladesh.

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