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Arsenic and Cadmium Levels in Maternal and Umbilical Cord Blood and their Associations with Birth Outcomes

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Exposure to heavy metals as cadmium and arsenic during pregnancy may have unfavorable effects on pregnant women and their offsprings. The aim of the study is to characterize the concentrations of arsenic and cadmium in umbilical cord blood and maternal blood and to clarify their associations with certain epidemiological maternal variables and birth outcomes. This cross- sectional study was conducted on randomly chosen 113 pregnant mothers and their newborns. Full history and sociodemographic data were recorded. Inductively Couples Plasma Mass Spectrometry was used to assess the levels of arsenic and cadmium in maternal and cord blood serum samples. There was a significant negative association between gestational age and maternal serum level of arsenic (r=-0.368, P=0.04). There was a significant negative correlation between maternal serum levels of arsenic and cadmium with Apgar score at 1-minute (r=-0.352, -0.361, P= 0.04, 0.032 respectively). No significant correlation was found between maternal serum levels of arsenic and cadmium and neither maternal education nor maternal age. The current approach states that maternal exposure to arsenic and cadmium during pregnancy has been found to be harmful to the developing fetus. The outcomes of the present work highlight the importance of avoiding prenatal exposure to heavy metals.

Keywords: Arsenic; Birth Outcomes; Cord Blood; Cadmium; Pregnant Women.

Exposure of mothers during pregnancy to various trace elements and heavy metals, which incorporate lead, cadmium, arsenic, mercury and aluminum could be of damaging impact to the developing fetus,[1, 2], even at low levels of exposure.[3] Also, exposure to environmental contaminants during pregnancy may have an extended harmful effects in early childhood and later in life.[4] A significant positive correlation has been demonstrated between maternal serum levels of mercury and cord blood mercury concentration[5] which may induce a hazard to the fetus. Some investigators detected an inverse relationship between total mercury concentration in cord blood and fetal growth.[6] Cord blood lead concentration showed significant positive correlation with head circumference and birth weight.[7]

Cadmium pollution of the environment is omnipresent due to activities of the industries, usage of phosphate fertilizers, burning of motor fuels in means of transportations and particles released by tyre wear, all of which produce emissions to air, soil and water.[8, 9] In non-smokers, diet is considered the main significant source of exposure to cadmium. In smokers, tobacco is the main significant source, as tobacco, like other plants, takes up cadmium, which is inhaled in the smoke.[10] Also, cadmium can be present at increased levels in food for instance shellfish, organ meats, cereals, root vegetables, and green leafy vegetables.[11]

Cadmium exposure is considered of great importance owing to its probable burden on fetal health in spite that the placenta acts as a barrier, which protect the fetus from exposure to cadmium by enhancing metallothionein expression.[12] This metal has been shown to be correlated with reduced birth weight[1, 13], premature delivery[14] and changed thyroid hormone condition of newborn.[15]

Exposure to arsenic (AS) is primarily oral, which results mostly from drinking water sources. In areas of the world in which water contains arsenic concentrations of more than 50µg/L, the small children can be at considerable risk for both cancer and neural deterioration.[16] The evidence of the contribution of arsenic in causing unfavorable human reproductive outcomes is increasing. It has been supposed that maternal exposure to arsenic early in pregnancy negatively influences newborn's birth weight.[17] Fish, shellfish, poultry, dairy products, meat and cereals are sources of arsenic in diet, though exposure from these foods is much lower in comparison to exposure through contaminated groundwater. Now, human bodies are continuously being tainted by dietary and commercial product ingredients and become simply over burdened by toxins. This could be elucidated by changes in modern life styles.[18] Comparable data, solely for pregnant women, have been studied confirming that. Unfortunaly, there are no safe blood level values for any of the heavy metals that have any degree of transfer through the placenta to the fetus during pregnancy. The only way of decreasing fetal exposure is to lessen maternal exposure.[19]

The goals of the present work were to characterize the concentrations of arsenic (As) and cadmium (Cd) in umbilical cord blood and maternal blood and to clarify their associations with certain epidemiological maternal variables and birth outcomes (gestational age, head circumference, and Apgar score at 1-5 minutes) .

Subject and methods

This cross- sectional study was conducted on 113 newborn -mother couples who were randomly chosen from those attending Al-Galaa Maternity Educational Hospital in the period between September 2016 to June 2017. The mothers' ages ranged between 16 and 45 years. Pregnant mothers with history of chronic diseases or major illnesses during pregnancy were excluded. Elective caesarean sections were enrolled in the study. Neonates with any apparent congenital anomalies, metabolic, genetic or neurological problems were also excluded. This study was funded by the National Research Centre11th research plan, entitled "Immunological profile in cord blood and growth assessment of the newborn in relation to maternal exposure to environmental contaminants". The study protocol was approved by the Medical Ethical Committee of the National Research Centre (Approval code: 16/295). Written informed consent was provided by all mothers who participated in this study after explaining the background, objectives, and benefits of the study. The mothers also signed the informed consent on behalf of the neonates enrolled in the study. Verbal oral consent was obtained from illiterate mothers.

All Mothers were subjected to the Followings

Full history taking laying stress on: mother's age, education, occupation, residence, the order of child birth, water source availability, sanitary disposal, and smoking status during pregnancy. Exposure to environmental tobacco smoke (ETS) was defined as exposure to tobacco smoke from smoking by others in the household.[20]

Perinatal history : Included gestational age (in weeks), type of labor, history of delivery problems.

Maternal anthropometric measures: The height and weight of mothers were recorded just before delivery according to a standard protocol suggested by the World Health Organization.[21] Body weight was measured in lightweight clothing to the nearest 0.1 kg using a portable digital balance (Tanita scale). Height was measured to the nearest 0.1 cm without shoes, using a portable stadiometer (Harpenden stadiometer) .

All the included neonates were subjected to the following

Physical examination: Neonates were subjected to thorough clinical examination by the pediatrician that included chest, heart, abdomen, and central nervous system examination. The Apgar score was also measured to assess neonatal condition at birth on a scale from 1 to 10, at 1 and 5 minutes after delivery. Infants were evaluated on a scale of 0 to 2 according to five categories (skin color, muscle tone, reflexes, respiratory effort, and heart rate), and the points from each category added together to determine the total score[22].

Anthropometric data were measured, before breast feeding started. Newborns were weighed (in kilograms) without diapers and using an electronic digital infant scale (Laka). Length (in centimeters) was measured in the supine position, using a stadiometer (Seca 416) composed of a stationary head-board and a movable foot board. Head and mid upper arm circumferences (cm) were also measured.[23]

Sample collection

Ten ml of venous blood was collected from the mothers at the time of labor either in normal or section delivery, and then centrifuged under cooling (4°C) at 1800 xg to separate serum samples which were stored at -70°C pending laboratory analysis.

10 ml of cord blood was collected from an immediate clamped ,isolated piece of the umbilical cord of the newborn during delivery before placental separation and put on EDTA free tubes, then centrifuged under cooling (4°C) at 1800 x g to separate serum samples which were preserved at – 70°C until laboratory investigation.

Determination of heavy metals (arsenic and cadmium) in serum samples

Principle Determination of toxic elements in traditional medicine was done using Inductively Couples Plasma Mass Spectrometry (Perkin Elmer ELAN ICP-MS DRC II), PIN 5989-559 IEN. This method is provided to determine As, Cd, and other metals in biological samples.

METHOD

Sample Preparation

For the determination of serum heavy metals, the serum samples were diluted with an equal volume of deionized water (1:5). The dilution ratio was adjusted to insure that concentration fall within a suitable absorbance range.

Estimation of As, and Cd, in serum samples

The diluted samples were injected into Inductively Couples Plasma Mass Spectrometry (ICP mass) and the calibration curve for each metal was plotted. Then the concentration of each metal in each sample was estimated from the corresponding curve of each metal. Good precision and accuracy 1_3% for solution mode.

Accuracies and precisions for most elements are typically on the order of 1_3% for solution mode.

Statistical analysis

Analysis was performed using SPSS[21] (SPSSINC, Pennsylvania, USA). Mean + SD and percent were used for parameters' distribution calculations. Correlation was done using pearson's correlation. $P<0.05$ value was considered as significant and $P<0.005$ value as highly significant.

RESULTS

A total of 113 mother-newborn pairs were enrolled in this study. The mean of maternal age was 26.7 + 5.6 years. The mean of gestational age was 36.9 + 2.1 weeks. 45.1% of the newborns were males and 54.9% were females. 55.8% of the newborns were delivered vaginally and 44.2% had caesarean section delivery. About 93% of mothers had history of passive smoking exposure. The source of drinking water in 99% of the study population was tap water which is a safe source of water compared to those depending on other sources such as the shallow wells. The maternal and neonatal sociodemographic characteristics are shown in Table (1).

The anthropometric measurements of mothers and neonates are shown in Table (2)

The mean concentrations of maternal serum arsenic and cadmium levels were 59.7+9.2 and 0.7+0.4 respectively. The mean concentrations of cord blood levels of arsenic and cadmium were 3.5+7.6 and0.7+0.3 respectively as shown in Table (3).

There was a significant negative correlation between maternal serum level of arsenic and gestational age ($P<0.05$). On the other hand, no significant correlation could be detected between maternal serum level of cadmium and cord blood concentrations of arsenic and cadmium and gestational age (P>0.05). There was no significant correlation between serum levels of arsenic and cadmium in maternal and cord blood with the head circumference of the newborns (P>0.05). There was a significant negative correlation between serum level of arsenic in maternal blood and the Apgar score at 1- minute and 5- minutes (P<0.05). In addition, there was a significant negative correlation between maternal serum level of cadmium and the Apgar score at 1-minute (P<0.05). No significant correlation between serum levels of arsenic and cadmium in maternal and cord blood and maternal education could be detected. The correlations of the study were shown in Table (4).

The serum levels of cadmium and arsenic in maternal blood and cord blood cadmium concentration were significantly higher in mothers who were passively exposed to environmental tobacco smoke compared to the non- exposed mothers (P<0.05) as shown in Table (5).

Table 1. The maternal and neonatal sociodemographic characteristics

Parameters	Range (No=113)	Mean ±SD
Maternal age (years)	16-43	26.7 ±5.6
Gestational age (weeks)	32- 42	36.9 ±2.1
Apgar at 1-minute	2- 8	5.8±1.6
Apgar at 5- minute	5-10	8.1±1.6
	Number	Percentage
Sex of infants		
Male	51	45.1%
Female	62	54.9%
Delivery mode		
Normal	63	55.8%
Caesarean section	50	44.2%
Smoking exposure		
Yes	93	82.3%
No	20	17.7%
Mother education		
Illiterate	10	8.8%
Read and write/ basic education	49	43.4%
Secondary education	41	36.3%
High education	13	11.5%
Availability of tape water		
Available at home	112	99.1%
Outside home	1	0.9%

DISCUSSION

The intrauterine environment doesn't constantly protect the fetus from environmental factors as shown by different epidemiological studies. Exposure of mothers to stress, dietary factors, and environmental chemicals have a considerable impact on fetal growth and fetal development[24]. Consequently, deficiency or over exposure of certain trace elements might be harmful to the health of both pregnant women and their fetuses[25].

The present study showed a significant negative correlation between serum level of arsenic in maternal blood and gestational age (P< 0.05). This comes in line with Xu *et al*[26] and Enas *et al* 13 who reported that gestational age was inversely related to arsenic concentration in mothers' whole blood. Also, Shi *et al*[27] found that preterm birth has a stronger spatial relationship with ground water arsenic than term low birth weight implying an inconsistency in the effect of arsenic on the two reproductive outcomes. A study done in

Table 2. The anthropometric measurements of mothers and neonates

Parameters	Range	Mean± SD
Newborn weight (kilogram)	1.9-4.4	2.9± 0.6
Newborn length (centimeter)	35.2-56.4	47.4± 3.3
Head circumference (centimeter)	26.5-38.3	34.2± 1.9
Mid arm circumference (centimeter)	6.2-13.3	10.2± 1.5
Maternal weight (kilogram)	46.8-102.5	75.4± 14.8
Maternal height (centimeter)	142.4-180.5	157.7± 6.7

Table 3. The mean of concentrations of arsenic and cadmium in maternal and cord blood

Parameters	Mean	Std. Deviation
Maternal As mcg/L	59.7	9.2
Maternal Cd ng/mL	0.7	0.4
Cord blood As mcg/L	3.5	7.6
Cord blood Cdng/mL	0.7	0.3

Table 4. Correlations between maternal and cord blood levels of arsenic and cadmium and gestational age, head circumference, Apgar score of the newborns, and maternal education:

		Gestational age	Head circumference	Apgar 1-minute	Apgar 5-minutes	Maternal education
Maternal arsenic	Pearson Correlation	-0.36	-0.01	-0.35	-0.38	-0.124
	Sig. (2-tailed)	0.042	0.936	0.04	0.03	0.35
Maternal cadmium	Pearson Correlation	-0.15	-0.01	-0.36	-0.07	-0.122
	Sig. (2-tailed)	0.05	0.91	0.032	0.05	0.36
Cord blood arsenic	Pearson Correlation	-0.18	0.19	-0.18	-0.10	-0.241
	Sig. (2-tailed)	0.17	0.05	0.15	0.44	0.07
Cord blood cadmium	Pearson Correlation	-0.21	-0.03	-0.18	-0.10	-0.229
	Sig. (2-tailed)	0.11	0.07	0.13	0.48	0.36

Table 5. Comparison between mothers who were passively exposed to tobacco smoke and the non-exposed mothers as regards the maternal and cord blood levels of arsenic and cadmium

	Passive smoke exposure	Non-exposed	P. value
Number	93	20	
Maternal arsenic mcg/L	52.61 ± 9.54	43.26 ± 4.80	0.01
Maternal cadmium µg/mL	1.27 ± 0.25	0.57 ± 0.53	0.03
Cord blood arsenic mcg/L	3.52 ±7.5	2.39±5.83	0.23
Cord blood cadmium µg/mL	0.91±0.45	0.52±0.86	0.04

* P<0.05 : significant

India found that exposure to high concentrations of arsenic (200 µg/L) during pregnancy was correlated with a six- fold raised risk of stillbirth[28]. The probable explanation could be that inorganic arsenic (iAs) traverses the human placenta, and accumulates in the developing organs and systems of the fetus, promoting an increased risk potential.[29] Observational evidence proposes that iAs accumulates in and disrupts placental function[30] and changes DNA methylation in cord blood[31]. It has been reported that abnormal placentation is a powerful risk factor for preterm delivery and restricted fetal growth.[32]

There was non -significant correlation between serum level of cadmium in maternal blood and gestational age (P >0.05).

Similarly, Johnston *et al*,[1] reported that gestational age at delivery did not differ by blood cadmium levels. On the other hand, Röllin *et al*,[20] stated that mothers of infants who were born preterm had a higher geometric mean for cadmium level in blood in comparison to the mothers of infants born at term but this finding was not significant. The findings of Amaya*et al*,[33] indicated that gestational age was associated with placental cadmium concentration. Here in, we did not detect a significant correlation between cord blood arsenic and cadmium concentrations and gestational age (P>0.05). However, the existence of cadmium in cord blood has been related with increased incidence of preterm delivery.[14]

Our study demonstrated no significant correlation between serum levels of arsenic and cadmium in maternal blood and cord blood with head circumference of the newborn (P>0.05). This result agrees with is in accordance with Johnston *et al*, 1 and Röllin *et al*,[20] who also found that cadmium levels were not associated with head circumference. This could be attributed to the function of the placenta as being an efficient barrier against cadmium passage [34]. On the other hand, Rahman *et al*, [35] demonstrated that a one µg g/L increase in averaged urine inorganic arsenic values was associated with a 0.05 mm head circumference reduction (P=0.04).

The present study revealed a significant negative correlation between serum level of arsenic in maternal blood and the Apgar 1-minute and Apgar 5-minute score ($P<0.05$).In addition, there's a significant negative correlation between serum level of cadmium in maternal blood and the Apgar 1-mimute score ($P<0.05$) but not with Apgar 5-minute score ($P>0.05$). No significant correlations could be detected between cord blood cadmium and arsenic concentrations and the Apgar 1-minute and 5-minute scores ($P>0.05$).These results were in contrast with the findings of other studies. Mokhtar *et al*,[36] registered a negative association between cord blood cadmium and the 5-miunte Apgar score, in 100 Egyptian newborns who had a mean cord blood cadmium level of 0.66 µg/L. Garcia- Esquinas*et al*,[37] stated that newborns with cord blood cadmium concentrations over 0.29µg/L had less 1-minute and 5-minute Apgar scores than those with lesser concentrations. The study carried out in Saudi Arabian population[38], found that newborns who had Apgar 5-minutes scores less than the 10th percentile (0-8) had high levels of umbilical cord blood cadmium. Apgar scoring permits the evaluation of the state of infants directly after birth.[39] In addition, there is a proof that lower 5-minute Apgar scores at birth may be linked with lower survival and neurological outcomes at the age of one year [40] and during early adulthood.[41] The causal biological mechanisms that explain this association stays unclear.

The serum levels of arsenic and cadmium in maternal blood and cord blood cadmium concentration were significantly higher in mothers who were passively exposed to environmental tobacco smoke compared to the non- exposed mothers ($P<0.05$). Our findings are consistent with other studies .Butler Walker *et al*,[42] found that geometric mean blood cadmium in moderate smokers (1-8 cigarettes/day) and in heavy smokers (>8 cigarettes /day) was 7.4 fold higher and 12.5 fold higher, respectively, comparative to non- smokers. Guan *et al*[43], and Röllin *et al*[20] also stated that maternal blood levels of cadmium were significantly elevated among mothers who exposed to second-hand smoke during pregnancy. In addition, Garcia- Esquinas *et al*[37] found that cadmium concentration was 22% higher in newborns from mothers who smoked during pregnancy than those who non-smoked ones. The smoke of cigarette is a well recognized source of human exposure to cadmium. An average cigarette has 1-2 µg of cadmium, of which smokers take up a part via inhalation.[44] One cigarette has been found to raise the blood cadmium level by 0.1-0.2 µg/L.[45]

Our study revealed that there was no significant correlation between maternal blood arsenic and cadmium concentrations and cord blood concentrations of arsenic and cadmium ($P>0.05$) (results not shown). Similarly, Rudge *et al*,[46] and Röllin *et al*[20] stated that there was no significant correlation between maternal and cord blood as regards cadmium concentration. However, other studies demonstrated a significant positive correlation between maternal and cord blood concentration of arsenic and cadmium.[47, 43 ,37] The contradictory results between studies could be attributed to the dose, timing of exposure, and the dynamic physiological changes that occur in pregnant women.[48] The current study did not find significant correlations between maternal and cord blood concentrations of arsenic and cadmium and either maternal age or education ($P>0.05$). Similarly, Röllin *et al*[20] found that maternal age and education had no effect on cadmium levels. In contrast, Liu *et al*,[48] demonstrated that among different age intervals, the concentration of maternal serum arsenic and cadmium significantly increased with increasing age. Age is the one of the first parameters that has an effect on the body burden of trace elements.[49] Parajuli *et al*,[50] reported that the maternal age was negatively associated with the cord blood arsenic level and the cord blood arsenic level from less educated mothers was higher than those from educated mothers. Less educated mothers mostly come from families with lower socioeconomic status. Some studies stated that children with lower socioeconomic status have higher exposure to several chemical pollutants than those with higher socioeconomic status [51]. Shi *et al*,[27] showed that younger maternal age has stronger spatial correlations with ground water arsenic. The positive spatial relationship between low birth weight and arsenic level is observed for maternal age <25 years.[27]

We have some limitations in this study. The small sample size which could not help to identify significant relation between variables.

Therefore, carefulness is required during analysis of the results. In addition, concern should be taken as regards the design that choose productive couples during the third trimester of pregnancy, which means that if metals influence fertility or lessen pregnancy length, the concentration in our adult sample could be undervalued the levels in the general population. Also, we did the anthropometric measurements one time on infants, leading to a possible resource of measurement error.

CONCLUSION

It becomes clear that prenatal exposure to heavy metals such as arsenic and cadmium may have a direct influence on birth outcomes. For that reason, improving socioeconomic status and educating mothers as regards the sources of exposure to these heavy metals could potentially decrease the hazards on their newborns.

Recommendations

The study highlights the possible hazardous effect of prenatal exposure to arsenic and cadmium on newborns and emphasizes the require for better understanding the role of dietary, occupational, environmental, and life style which affect their exposure levels. Mothers should be advised to avoid tobacco smoke exposure as it's a significant avoidable source of heavy metal exposure in newborns.

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