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Effects of Heavy Metals on the Health of Pregnant Women and Fetus: A Review

Azad Gull[1], Ashaq Ahmad Dar[2] and Manoj Sharma[3]
[1]SOS in Zoology Jiwaji University Gwalior, (Madhya Pradesh), India
[2]SOS in Environmental Science Jiwaji University Gwalior, (Madhya Pradesh), India
[3]SOS in Pharmaceutical Science Jiwaji University Gwalior, (Madhya Pradesh), India

(Corresponding author: Azad Gull)
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ABSTRACT: The goal of this research is to further scientific understanding of prenatal exposure to heavy metals among pregnant women and fetus. This review will explore the association of these exposures with growth and development of the children. This review will also focus on the intersection of environmental problems related to metals as well as the particular susceptibility that children may have to these environmental contaminants.

Keywords: Heavy metals, women, health children

I. INTRODUCTION

Occupational exposure is regarded a risk factor for female fertility and early pregnancy loss among working females. The miscarriages are the most common negative pregnancy outcome with increased emotional consequences that effect individuals and families [1]. This is a critical indicator of embryotoxicity that may occur due to exposure of heavy metal. The embryotoxic effects of chemicals including environmental contaminants and drugs have been studied widely [2, 3, 4] and its effects on overall development of children and maternal health have also been investigated.

Heavy metals found in the environment are released from a wide variety of sources [5] and humans are exposed to these metals through occupational, accidental and sundry exposures. Abnormal occurrence of pregnancies like miscarriages, menstruation or sperm properties may each serve as an indicator of reproductive toxicity in humans due to heavy metals [4].

To our understanding no systematic review has reported on the effect of heavy metals on maternal and child health in developing nations. The widespread use of heavy metals and their exposure and the impact of As, Pb, Cd and Hg on maternal and fetal health is relevant for public health policy. To fill this gap, this review studies the current state of knowledge about the link between heavy metals and maternal and child health. For the purpose this review included Mercury, Lead, Cadmium and Arsenic to quantify the problem posed by these heavy metal exposures to women and children.

The different developmental effect due to environmental pollutants is a major concern that is affecting the female reproductive system and development of babies. Among the different environmental pollutants heavy metals have also caused great damage to human health, especially to reproductive system and developmental babies.

Few reports revealed that the exposure to heavy metals *viz* lead, cadmium, copper could promote the pregnancy implications *viz*, spontaneous abortions, toxemia and anemia. Most of the problems occur due to lipid peroxidation. Preterm infants were delivered by woman living close to the vicinity in areas high lead and cadmium in the soil.

The toxic metals when present in the maternal blood stream may cause abnormal placental function and deviate nutrient transport to the fetus through the indirect formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that cause oxidative stress by reacting with macromolecules and damaging them. When the vascular endothelium is damaged endothelins are released causing the smooth muscle around the blood vessels to contract.

II. METHODOLOGY

The different search engines were used for the literature collectively. The different key words like heavy metals, pregnant mothers and foetus, reproductive problems, developmental concerns were used to download the literature.

About 200 articles were downloaded and only 87 were retained for the present study due to their relevance with our objectives.

Heavy metals and their health effects

A. Impact of Arsenic

The main exposure to arsenic is due to underground drinking water with its principal source the aquifers contaminated with arsenic. The contamination of ground water is associated with chronic diseases like cancer of skin and internal organs and with several non malignant adverse health effects. similarly, reports from Chile, Sweden, Hungary and Taiwan have also found associations between high arsenic exposure and spontaneous abortion, still birth and preterm birth rates with almost similar results from Massachusetts and Texas that included 533 woman and found abortion, stillbirths and neonatal death among women consuming various concentrations of arsenic in their drinking water [6].

A non-significant association between the arsenic contamination and pregnancy outcomes are reported by most of the studies. However, few studies in the region of Bangladesh has found that spontaneous abortions, still birth, abortions and preterm birth are high in women having high concentration of arsenic in their drinking water. The study of 32126 pregnant women in rural Bangladesh found preterm birth of 22.3% and the incidence of low birth weight babies is found to be 31% to47% [7].

The study found a strong association between arsenic exposure and the health of pregnant mother and foetus. The concentration of arsenic was calculated by taking the urine samples of 1578 pregnant mothers. However, no association was found between the dosage and birth size. Further, significant negative dose effects were found with birth weight and head and chest circumference at a low level of arsenic exposure. It was found that birth weight was decreased by 1.68g for each 1-ug/L increase of arsenic in urine. For head and chest circumference, the corresponding reductions were 0.05mm and 0.14mm per 1-µg/L, respectively [8].

Similarly, another study that involved 3426 pregnant woman in an area with highly elevated concentration of arsenic in tube wells. The analysis showed a considerable variation in its concentrations with a total range 1-1,470 µg/L, adjusted to specific gravity 1.012 g/ml with an overall median concentration of 80µg/L (25^{th} and 75^{th} percentiles were 37 and 208 µg/L respectively). A negative association was found socioeconomic classes and marked geographical variations in its exposure have been found [9].

A cohort of 1616 pregnant woman in Bangladesh were studied to evaluate the relationship between long term dietary habits and total arsenic concentration with microwave assisted acid digestion and inductively coupled mass spectrometry. It was observed that changes in the metabolism and dietary habits were positively correlated [10].

The defects in cognitive functions of children were observed by the studies conducted in Bangladesh [11], Mexico [12, 13], Taiwan [14], India [15] and US [16]. Two recent studies in Bangladesh in children 6 and 10 years of age [17,18] showed that arsenic concentration in their drinking water was related to deficits in global and performance IQ that were larger at 10 than 6 years of age. In arsenic a high dose of arsenic is associated with detrimental effects on the developing embryo [19, 20, 21]. In humans chances of foetus loss due to arsenic contamination has been observed [22, 8]. There is a marked change in behavior and developing brain due to neurotoxicity of arsenic.

A cohort was established to obtain national level biomonitoring data for approximately 2000 pregnant women and their infant between 2008 and 2011.The of Arsenic measured in the urine were lower than national population figures for Canadian women of reproductive age (20-39 years). The higher levels of Arsenic were found in older women [23] as well. The profile of Arsenic metabolites in urine was determined during first trimester and in children of seven year old. The median of the Arsenic species found in the four year old children was 9.71 µg/L (arsenobetanic AsB), 3.97 µg/L (dimethylarsenic acid-DMA), 0.44 µg/L (monomethylarsonic acid-MMA) and 0.35 µg/L (i-As) [24].

Arsenic has been related to increased risk of cardiovascular, lung, bladder, skin, prostate and liver diseases [25, 26, 27]. It is associated with increased systematic inflammation via oxidative stress [28] and with chronic metabolic disorders like diabetes [29]. The high levels of Arsenic inhibits antigen presentation of macrophages [30] and T-cell proliferation [31], decreased $CD_4\beta$ T cell number in the spleen [32] and inhibit contact hypersensitivity responses [33]. The increased urinary Arsenic concentration is linked with fever and diarrhea during pregnancy [34]. The in-utero Arsenic exposure with the fetal immune repertoire [35] and infectious outcomes during early childhood [36, 37] has been established. The understanding of the immunomodulatory properties of Arsenic that susceptibility to specific infections in humans is poorly understood. The liver is known target of Arsenic carcinogensis [26] and emerging data support immunotoxicity [38] but its susceptibility during pregnancy has not been investigated.

The direct and indirect effects of arsenic exposure revealed that arsenic exposure is related to low birth weight, gestational age and menstrual health. This is also associated with increased risk of nausea and vomiting during pregnancy. This in turn contributes to pour nutritional status of the pregnant mothers that later results developmental change of the babies. Arsenic exposure has been associated with changes in development pathways of the babies. The dependent relationship has been found in most of the studies although the results vary considerably.

B. Impact of Cadmium

A study by Laudanski *et al.* the concentration of cadmium in mothers who delivered preterm infants was higher as compared to mothers who delivered full term babies. This was attributed to the higher concentration of cadmium in the soil of area. The relation between the decreased birth weight and cadmium exposure was found significant by some studies. The exposure to Lead and Cadmium promoted the complications like threatened spontaneous abortion, toxemia and anemia. The low concentration of Cadmium reveled increase in the contractile activity among pregnant women. The Cadmium may enter into the infant by way of breast feeding that will cause different types of developmental problems to them [39].

The relationship between the cadmium levels during pregnancy and infant birth outcomes in a prospective pregnancy cohort was evaluated. The study participants (n=1027) had a mean cadmium level of 0.46 mg/L with a range of 0.08 to 2.52 mg/L. In multivariable models, high maternal blood cadmium levels (s0.50 mg/L) during pregnancy were inversely associated with the birth weight percentile by gestational age (p=0.007) and associated with increased odds of infant being borne small for gestational age (p,0.001). The observed effects were independent of cotinine-defined smoking status [40].

Most of the studies found association between the decreased birth weight of new borne infants and increased cadmium concentration in maternal blood or the placenta. However few studies have argued the effect of cadmium on pregnancy outcome or growth of infants were not significant [41, 42]. Further low concentration of cadmium was found to enhance the contractile activity induced by Ca^{2+} and oxytosin. Moreover, breast milk is another route by which maternal exposure to cadmium has an impact on neonatal infants, but no relation has been found between maternal exposure to cadmium and concentration of cadmium in breast milk in previous studies because of the low concentration of cadmium in breast milk. However, a survey of cadmium transport to breast milk in Japanese woman might give different results, because the concentration of cadmium in Japan is known to be higher than that in European countries.

It is believed that the maternal exposure of cadmium is another rise to neonatal infants although no relation has been found between exposure to cadmium and its presence in the breast milk and few studies showed negative results in this regard. This study is an attempt to review the impacts caused by some of the well known heavy metals on pregnant mothers and infants.

This study was to investigate whether exposure to Cadmium during pregnancy is associated with an increased risk of adverse birth outcomes in a sex dependent manner. Cadmium concentration in maternal urine samples were measured in 237 subjects and the study found increased risk of adverse birth outcomes. A significant inverse association between Cadmium concentration and birth anthropometry (birth weight, birth length, head circumference and Apgar scores). Placental accumulation of Cadmium hinders transfer to the fetus with little information about Cadmium uptake and body burden related to pregnancy. The concentration of Cadmium in the blood, urine and placenta in relation to iron status among women followed for 2 years beginning in early pregnancy [43].

The adsorbed has a long half life in the body and can adversely affect kidney and bone and to increase the risk of cancer [44] and overall mortality [45] endocrine disruptor [46, 47] affect reproductive and child development [48]. Cadmium is associated with embryotoxic and teratogenic in variety of animal species [49]. An increasing evidence of maternal Cadmium and adverse pregnancy outcomes like reduced birth size [50, 51] and preterm delivery [52].

Several animal studies have shown a considerable embryo fetotoxic activity of Cadmium compounds and the placenta seems to be one of the target organs for Cadmium toxicity in humans. Relatively high levels were found in human placental tissue by many workers that may cause morphological and functional impairment of organs [53, 54]. An association between maternal Cadmium level and risk of gestational age (SGA) infant in Chinese population revealed that Cadmium exposure at middle gestational stage increase the risk of SGA in contrast to early gestational stage [55].

C. Impact of Mercury

The history of occupational exposure to mercury is reported since 2000 years ago by the Spanish who found salves working in the mercury mines die due to mercury poisoning.

The minimata episode of the Japan reveled that mercury is a neuro toxic and causes birth defects. The different studies across the world further reported that mercury can cause damage to children brain if mother are exposed to mercury during pregnancy. Even the smaller doses of mercury is associated with low I.Q among children.

The relationship between average fish consumption as well as the type of fish consumed and levels of mercury in the blood of pregnant women were examined. The maternal blood mercury level in late pregnancy was positively correlated with mercury levels of cord blood which was almost twice the level found in maternal blood. Pregnant women who consume a large amount of fish may have high blood mercury levels. Further, cord blood mercury levels were much higher than that of maternal blood. Because the level of fish intake appears to influence blood mercury level, preconceptual education might be necessary in order decrease fish consumption. A cohort of children in the Faeroe Islands was followed up until 7 years of age to document mercury levels and neurobehavioral effects of methyl mercury exposure from maternal consumption of pilot whale meat [56]. Neuropsychological tests found pronounced dysfunction in the domains of language, attention, and memory at exposure levels less than what is considered safe. Conversely a study of mother child pairs from ocean fish consuming population of the Seychelles Islands found no adverse developmental outcomes associated with prenatal or postnatal methyl mercury exposure [57, 58, 59].

Prenatal consumption of fishes contaminated with Mercury is associated with no deleterious outcomes to the offspring in regard to child behavior. The total maternal blood Mercury available in blood samples indicated the possible effects of prenatal mercury exposures on offsprings behavior in this cohort. A study of an Inuit in Arctic Quebec (where exposure is greater from consumption of sea mammals rather than fishes), showed an increase in attention problems and disruptive behavior at age 11 with increasing prenatal mercury exposure [60]. The maternal Mercury levels in pregnancy were related to inattentive at impulsive behavior at age 8 [61]. Conversely in Seychelles archipelago, where eating fish daily, their prenatal Mercury levels were unrelated to the behavior of their offsprings at 5 years [62] at age 9 there was evidence of negative association between prenatal Mercury exposure levels and hyperactive behavior [59].

Behavior and spatial learning deficits were observed in animal models of methyl mercury exposure in utero and through lactation [63, 64]. Coluccia *et al.* noted that low levels of exposure to Methylmercury during the postnatal brain growth spurt in mice induced subtle and persistent motor and learning deficits. An association between the mercury contamination that cause serious offspring brain damage resulting from prenatal exposure to very high levels of mercury has been found [65]. Surprisingly, studies have shown positive benefits to neurocognition of the offspring if the mother consumes fish contaminated with mercury [66, 67, 68, 69].

The concern for pregnant women and their fetuses is exposure to Methyl mercury [70, 71] as Mercury is actively transported across the placenta and impaired neurodevelopment as a result of fetal exposure. Human exposure to Methyl mercury (MeHg) in some areas occur mainly due to consumption of fishes contaminated with Mercury. As Methyl mercury is transferred to the children [72, 73, 74, 47, 75] through placenta, maternal exposition represents a risk for offspring is obvious. Adverse health effects following prenatal exposure to [76, 77] Methyl mercury have been described by various studies.

D. Impact of Lead

The high concentration of the lead in human body will change CNS and brain that may coma, convulsions and even death. The survival group of children's is associated with behavioral changes and intellectual impairment. Adults having high level of lead in their body become even the victims of kidney diseases and high blood pressure. The low concentration lead produce a spectrum of injury like lead affects brain development in children, resulting in reduced I.Q. behavioral changes such as shortening of attention span and increased antisocial behavior and reduced educational attainment. Most of the effects cannot be reversed.

In study of 185 in Boston, Massachusetts, Bellinger and his associated demonstrated a consistently negative relationship between umbilical cord blood lead level and Bayley Mental Development Index (MOI) at 6 and 12 months. At each age, the difference between the low and high cord blood lead group was equal to about one third of standard deviation. The Australian infants had on average higher postnatal PbB levels than typically found among US infants living in good housing. However this level of intoxication is commonly found urban, inner city infants who reside in old deteriorating residences where lead is found in dust, soils and flaking paints. In an interim study of 185 inner city infants an indirect adverse effect of prenatal lead exposure on the six month Bayley MOI and psychomotor Development Index (POI) was observed. The effect was mediated by lead related deficits in fetal growth and maturation.

The possible investigation of incidences of intrauterine-growth retardation (IUGR) revealed that the main level of Zinc was also higher in the maternal blood of IUGR cases the mean cord blood Lead level was greater than 10 µg/dL which is greater than Centers for Disease Controls invention level, in 54% of newborns. There is a weak relationship between cord blood Lead levels and birth weight of newborns [78]. Blood Lead levels among a cohort of pregnant women was investigated among the cohort of pregnant women. Maternal blood Lead levels from Lead remobilization from historic verses contemporaneous exposures reveled the impaired cognitive development [79].

Lead exposure is associated with mental disorders that compelled many governments to reduce the amount of Lead exposure to prevent adverse outcomes. Further the fetal nervous systems sensitivity to neurotoxins [80] is another concern. An inverse association between prenatal Lead exposure and infant neurodevelopment has been documented [81, 82, 83, 84]. The umbilical cord blood Lead level as the index of prenatal exposure were measured [81] and prenatal maternal bone Lead level as an index of mobilizable maternal Lead during the course of pregnancy were correlated [85]. Lead levels in different compartments and at different stages of pregnancy are only modestly correlated, suggesting that each measure captures different aspects of fetal exposure [86]. The vulnerability of developing organ systems, including the birth to environmental pollutants vary widely over the course of pregnancy [80].

Table 1: Effects of heavy metals on the health of pregnant women and infants.

Author	Study Area	Heavy Metal	Sample Size	Effects
Mbongwe	Botswana	Arsenic	63	IQ deficits, attention-related behaviours, and poor academic achievement.
Rahman *et al.* 2008	Bangladesh	Arsenic	1,578	Effect on birth weight, birth length, head and chest circumferences.
Vahter *et al.* 2006	Bangladesh	Arsenic	3,426	Reproductive effects
Nishijo *et al,* 2002	Japan	Cadmium	57	Lower birth weight
Dietrich *et al.* 1989	Boston, Massachusetts, Bellinger	Lead	185 infants	Negative relationship between umbilical cord blood lead (PbB) level and Bayley Mental Development Index (MOl) at 6 and 12 months.
Dietrich *et al.* 1989	Australia	Lead	600 infants	The Bayley MOl was inversely related to early postnatal PbB levels measured at 6 months.
Dietrich *et al.* 1989	Cincinnati, Ohio	Lead	185 innercity infants	Indirect' adverse effect of prenatal lead exposure on the 6-month Bayley MOl and Psychomotor Development Index (POI).
Kile *et al.* 2016	Bangladesh	Arsenic	1764 pregnant women	Lower birth weight.
Tofail *et al.* 2009	Bangladesh	Arsenic	4,436 pregnant women	Effects on infant development.
Tofail *et al.* 2009	Bangladesh	Arsenic	1,799 infants	Effect on development.
Jedrychowski *et al.* 2006	Poland	Mercury	233 infants	Delayed psychomotor or mental performance in infants.
Johnston *et al.* 2014	North Carolina	Cadmium	1027	Effects on birth weight.
Lin *et al.* 2017	Bangladesh	Arsenic	1616 pregnant women	Accumulation of As in Toenail.
Abul Hasnat and Milton 2005	Bangladesh	Arsenic	533 women	Increase the risk of fetal and infant death.
Kim *et al.* 2006	Korea	Mercury	63 pregnant women	High blood mercury levels, effects on CNS

The whole blood Lead levels in a pregnant women might not be the optimal marker for Lead concentration in the fetal brain. About 99% of Lead in whole blood is bound to red cells and thus not available to cross the placenta [87]. The economic condition, lifestyle, residential location, use of traditional cosmetics and food habits are positively correlated with toxicity [88] and sources need to be identified [89].

III. CONCLUSION

This mini review concludes that heavy metals if present in very less concentration may cause different adverse effects on pregnant women and developing fetus. The effects that are recognized include IQ deficits, attention-related behaviours, poor academic achievement, birth length, head and chest circumferences, reproductive effects, lower birth weight, negative relationship between umbilical cord blood lead (PbB) level and Bayley Mental Development Index (MOl) at 6 and 12 months, the Bayley MOl was inversely related to early postnatal PbB levels measured at 6 months, indirect adverse effect of prenatal lead exposure on the 6-month Bayley MOl and Psychomotor Development Index (POI),effects on infant development, delayed psychomotor or mental performance in infants, accumulation of As in Toenail, increase the risk of fetal and infant death, high blood mercury levels, effects on CNS, no adverse effects of maternal prenatal mercury levels on the behaviour of the offspring, increase in risk for SGA in infants born to women exposed to mercury and arsenic Arsenic in blood and urine, significant impact on fetal development, effects on neonatal neurodevelopmental, inverse associations between Cd concentrations and birth anthropometry in female neonates, urinary As metabolites show a strong ability to methylate i-As to monomethylarsenoic acid (MMA) especially for pregnant women and 7-year-old children, association between maternal Cd exposure and birth size, influence of As exposure and Ft concentrations on 8-oxodG concentrations and Cd-induced oxidatively damaged DNA, effect on neurodevelopment, enhance susceptibility to HEV (Hepatitis E Virus) infection, extremely detrimental to human health and elevates the risk of SGA in contrast to early gestational stage.

Hence measures to prevent the toxicity of heavy metals among pregnant women should be undertaken and as such if the area is suspected that it is contaminated with heavy extreme caution must be taken to avoid the consumption of any food from these areas.

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