Original Article

Blood lead levels in antenatal women and its association with iron deficiency anemia and adverse pregnancy outcomes

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Abstract

Objectives: Lead is one of the most toxic heavy metal prevalent in the environment, which affects almost all major organs including heart, brain, intestines, kidneys as well as reproductive organs. It has been known that serum iron deficiency is associated with increased serum lead levels as lead is a particularly pernicious element to iron metabolism. Lead is also known to freely cross the placenta too; hence, this study was planned to determine any association between antenatal iron deficiency anemia (IDA), raised blood lead levels (BPb), and adverse pregnancy outcomes. **Materials and Methods:** This was an observational study done on 99 antenatal women with IDA and 41 nonanemic antenatal women. Lead levels were assessed in these 140 antenatal women and they were followed for adverse pregnancy outcomes. Chi-square test was used to find a difference in quantitative variables and Pearson's correlation test was used to assess association between BPb and hemoglobin levels. **Results:** We found that in 11 out of 99 (11.11%) women with IDA, BPb levels were high as compared to high BPb levels in only 1 out of 41 (2.4%) women without IDA and the high BPb levels ranged from 4 μg/dl–16.9 μg/dl with a mean BPb of 8.1 μg/dl. The difference in BPb among anemic and nonanemic antenatal women was significant ($P < 0.05$) and there was a negative dose effect relationship between BPb levels and hemoglobin levels. This difference in antenatal outcomes among women with and without high BPb levels was also significant with increased incidence of pre-eclampsia, FGR, and preterm deliveries in women with raised BPb levels. The incidence of NICU admission was also higher in the neonates of mothers with high BPb levels. **Conclusions:** We propose screening of high-risk women based on their social, occupational, environmental, and personal factors, with serum lead levels in the preconception period itself. All public and personal measures must be taken to reduce lead consumption and exposure in the preconception and antenatal period.

Keywords: Adverse pregnancy outcomes, blood lead levels, iron deficiency anemia

Introduction

Lead is one of the most toxic heavy metal prevalent in the environment, which affects almost all major organs including heart, brain, intestines, kidneys as well as reproductive organs. Exposure to lead is inadvertent as it is widely used in construction, plumbing, batteries, and cosmetics. Effect on lead on a pregnant mother and the newborn was first identified a century ago when women who worked at lead industries were reported to have increased chances of miscarriages, stillbirths, preterm delivery, and neonatal deaths as compared to women in other occupations. Similar observations were later made in populations living in close proximity to the lead industries. Researchers have even described

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increased risk of minor fetal malformations even with lower blood lead levels. These observations were further confirmed by prospective studies which found that raised blood levels were also associated with pregnancy-induced hypertension.[1-4] Lead is known to freely cross the placenta as proved by studies which showed strong correlation between maternal blood lead levels and cord blood lead levels; however, all the short and long term effects of increased lead exposure due to placental transfer in new-borns are largely unknown besides some evidence indicating impaired neurodevelopment in the children.[5]

It has been known that serum iron deficiency is associated with increased serum lead levels as Lead is a particularly pernicious element to iron metabolism.[6] Lead is taken up by the iron absorption machinery, and secondarily blocks iron through competitive inhibition. Further, lead interferes with a number of important iron-dependent metabolic steps such as heme biosynthesis. This is an important consideration which needs to be introduced in the antenatal care of pregnant women in developing countries wherein the obstetricians deal with iron deficiency anemia not responding to adequate iron therapy. Obstetric population in India is especially at high risk for increased lead exposure largely because of continued use of lead-laden cosmetics (vermillion, lipsticks), use of earthen pots for cooking, PICA, and use of traditional ayurvedic medications during pregnancy.

America College of Obstetrics and Gynaecology[7] recently recommends that obstetric care providers should screen pregnant women for being at risk for increased lead exposure and should screen them for blood lead levels in the early antenatal period itself. With increasing industrialization in west Rajasthan, we plan to study lead levels in pregnant women to identify whether antenatal anemia and other antenatal complications are associated with increased blood lead levels (BPb) to provide evidence for initiating changes in the environmental policies and public health care programs directed toward reduction in lead exposure in the high-risk obstetric population.

Materials and Methods

This pilot study was conducted over a period of one year among the antenatal mothers visiting the antenatal clinic of All India Institute of Medical Sciences (AIIMS), Jodhpur, Rajasthan. The study was approved by institutional ethics committee, AIIMS, Jodhpur. A total of 156 pregnant women who were suspected to have iron deficiency anemia (IDA) and 50 nonanemic pregnant women were enrolled in our study between 2018 and 2019. Antenatal mothers with hemoglobin levels <11 gm% diagnosed at any trimester were investigated to ensure IDA based on the hematocrit levels, red blood cell (RBC) count, mean corpuscular volume indices (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and serum ferritin and transferrin saturation levels (serum iron/total iron-binding capacity). The presence of microcytic hypochromic anemia on peripheral blood smear, serum ferritin levels <12 ng/ml, and transferrin saturation of <20% were considered confirmatory parameters for IDA.

Women with anemia other than iron deficiency like known hemoglobinopathies, anemia due to chronic disease, iron deficiency anemia secondary to nonconsumption of iron, noncompliance to iron therapy or with confounding factors causing nonabsorption of iron were excluded from study. Antenatal women with high-risk obstetric factors like chronic hypertensives, gestational diabetes mellitus, mothers with previous history of hypertensive disorders of pregnancy, and mothers with bad obstetric history secondary to identifiable causes like APLA syndrome, endocrinological abnormalities, anatomical defects (cervical incompetence, mullerian anomalies), genetic abnormalities, and prior history of preterm births were also excluded from the study. Women with history of blood transfusion prior to enrolment in the study were also excluded. Since our population were antenatal women, confounders like smoking, blood loss during menstruation were naturally eliminated.

After taking informed consent, high-risk assessment with respect to lead exposure was done based on their social, occupational, dietary, and environmental surroundings through a questionnaire. A detailed information through questionnaire was taken about their exposure to lead through their occupation, usage of cosmetic products like vermillion (sindoor), lipsticks, hair dyes, pica, and compact powders was taken. Women were also asked about usage of ayurvedic medications, tobacco chewing, recent paint at home, and usage of types of pipes in potable water supply. Women with hemoglobin levels <11 gm% were defined to be anemic and were subjected to further investigation to confirm iron deficiency anemia and rule out chronic liver and renal disorders.

Venous blood was collected in EDTA vials and Lead levels were estimated by FDA approved Lead Care 11 analyzer in the department of Biochemistry, AIIMS, Jodhpur after ensuring proper quality control. The lead level of 3.5 μg per dl was taken as the cut-off limit. All women (with or without IDA) with evidence of lead in serum (>3.5 μgm/dl) were followed for adverse pregnancy outcomes.

The primary outcome measure was estimation of BPb in antenatal women with and without IDA and to find out any dose effect relationship between BPb and IDA. The study also tried to establish adverse maternal and neonatal outcomes in relation to elevated lead levels.

Results

A total of 156 pregnant women who were suspected to have iron deficiency anemia (IDA) and 50 nonanemic pregnant women were enrolled in our study between 2018 and 2019. Among the 156 anemic women enrolled for further investigations to confirm

IDA, 99 women were confirmed to be iron deficient, 21 women had normal ferritin and transferrin saturation, 10 women had normocytic normochromic anemia, and 26 women did not return for delivery at our institute and hence, they were excluded from the study. Among 50 nonanemic antenatal women, 41 women were included in the study as serum lead levels were not available for the remaining 9 mothers. Hence, a total of 140 women were recruited, 99 (70.7%) women with IDA and 41 (29.2%) women without IDA were further assessed for elevated lead levels and pregnancy outcomes.

Lead levels and high-risk practices for increased lead consumption

Demographic parameters among women with high BPb levels were comparable with the women with normal BPb levels. Age and parity were comparable between anemic and nonanemic women ($P < 0.05$) and the mean age was 25.6 years. Most of the women in our study were housewives (114 out of total 140, i.e. 81.4%). Only one woman was working in a job with high lead exposure, but she had normal lead levels. A total of 12/140 women were found to have high BPb levels ranging from 4 μg/dl–16.9 μg/dl with a mean BPb of 8.1 μg/dl.

Most of the women in our study were using cosmetics especially sindoor as part of their local religious habits and it was found that 94.5% of women who had normal lead levels were sindoor users while 90% women with high lead levels were using sindoor. This difference was not significant. The women with or without high lead levels were comparable in terms of source of drinking water, type of water supplying pipes, and area of residence (rural/urban) [Table 1]. Although the difference was not significant, it was noted that among women with high BPb levels, 91% were using cosmetics, 63.6% women had history of pica, and 81.8% women were residing in urban areas.

Lead levels among anemic and nonanemic antenatal women

We found that in 11 out of 99 (11.11%) women with IDA, BPb levels were high as compared to high BPb levels in only 1 out of 41 (2.4%) women without IDA. The difference between the two groups is significant ($P < 0.05$). There was a negative dose effect relationship between BPb levels and hemoglobin levels as calculated by Pearson's correlation test, (Pearson's Correlation is -.175) which is significant at the 0.05 level (2-tailed).

Antenatal outcomes due to high BPb levels in pregnancy

On analyzing the effect of high-lead level on maternal outcome, we found that in group with lead level less than 3.5 μg/dl, 17/128 (13.2%) women had poor antenatal outcomes and the most common antenatal complication was mild preeclampsia contributing to 35.2% of high-risk pregnancies, followed by fetal

Table 1: Demographic parameters and factors associated with high risk for lead consumption in women with and without high BPb levels

Demographic Parameters	Normal Lead Levels	High Lead Levels	P
Age (in years)			0.852
<20	17	2	
21-30	94	9	
>=31	17	1	
Occupation			
Housewife	104	10	>0.05
Jobs without lead exposure	023	02	
Ceramic/dye work/paint/battery repair/construction/jewellery/car repair	01	00	
Usage of products			
Sindoor	122	7	0.31
Cosmetic	105	10	
Tobacco/Supari	002	01	
Ayurvedic/Herbal medicine	02	01	
Pica (consuming clay, pieces of earthen pots)	24	08	0.05
Address			
Rural	49	2	0.190
Urban	80	10	
Recent paint at home			
Yes (<2 years)	52	2	0.04
No	77	10	
Source of drinking water			
Well/Filter Can	5	00	0.823
Municipal supply	110	10	
Handpump/Boring	14	02	
Type of pipes at home			
No pipes	5	0	0.148
Metallic pipes	51	8	
PVC pipes	73	4	

growth restriction (FGR) in 23.5% (4/17) women, 23.5% (4/17) women had PROM.

Out of 12 patients with high-lead levels, 7/12 (58.3%) women had adverse antenatal outcomes including 42.85% (3/7) women with FGR pregnancy, 14.2% women having preterm rupture of membranes (PROM), 28.5% women had preterm delivery, and 1 baby (14.2%) had neural tube defect [Table 2]. Among the two preterm deliveries, one woman was terminated pre-maturely at 32 weeks due to severe pre-eclampsia with uncontrolled hypertension. This difference in antenatal outcomes among women with and without high BPb levels is significant with the Chi-square statistic of 5.194 and ($P = 0.0226$) [Table 3].

Neonatal outcomes due to high BPb levels

Mean baby weight was 2.68 kg in women with high BPb levels as compared to 2.957 kg in other women with a mean difference of 277 g. Out of 12 babies in high BPb group, 7 (58.3%) babies had good neonatal outcomes, while 5 babies (41.6%) had poor neonatal outcomes including 4 neonates requiring NICU admission for respiratory distress and prematurity and one neonatal death due to poor APGAR at birth (underlying cause FGR with reversed end-diastolic flow). In women with normal BPb, 12 (9%) neonates required NICU admission due to respiratory distress, low birth weight, and suspicion of neonatal sepsis; there were no neonatal deaths in this group. The difference in neonatal outcomes among the two groups is significant with the Chi-square statistics of 7.3327 and *P* value of 0.006771 [Table 4].

Table 2: Various adverse antenatal outcomes in women with respect to BPb levels

Antenatal complications	BPb ≤3.5 μg/dl (n=128)	>3.5 μg/dl (n=12)
Pre-eclampsia	6 (4.6%)	1 (8.3%)
Fetal growth restriction	4 (3.12%)	3 (25%)
Premature rupture of membrane	4 (3.12%)	1 (8.3%)
Preterm labor	1 (0.7%)	2 (16.6%)
Intrahepatic cholestasis of pregnancy	2 (1.5%)	0
Neural tube defect	0	1 (8.3%)

Table 3: Blood lead levels (BPb) and adverse antenatal outcomes

ANTENATAL Outcome	Blood lead levels		Total antenatal women
	≤3.5 μg/dl	>3.5 μg/dl	
Normal antenatal outcome	107 (83.59%)	05 (41.6%)	104
Adverse antenatal outcome	21 (16.40%)	07 (58.3%%)	36

*Chi-Square value=5.194. ***P* (<0.05)

Table 4: Blood lead levels and adverse neonatal outcomes

Neonatal Outcome	Blood lead levels		Total antenatal women
	≤3.5 μg/dl	>3.5 μg/dl	
Normal neonatal outcome	117 (91.4%)	07 (58.3%)	124
Adverse neonatal outcome	11 (8.5%)	05 (41.6%)	16

*Chi-Square value=7.3327. ***P* (<0.05)

Discussion

Lead is a toxic heavy metal which is omnipresent in the environment and is associated with many adverse health effects.[8] Despite the ban on leaded gasoline and lead containing paints, lead remains to be continually used in lead acid batteries for electronic vehicles, paints, solder, stained glass, lead crystal glassware, ammunition, ceramic glazes, jewellery, cosmetics, vermillion, toys, traditional medicines, metallic pipes used for plumbing, and earthen cooking pots. Adverse health effects are known at BPb of <10.5 μg/dl but there is no safe lower limit defined and levels as low as 2 μg/dl have been found to be associated with increase in both cardiovascular and all-cause mortality.[9]

In a pilot study, conducted by Chambial *et al.* in the school teachers of jodhpur city, it was found that 49% of study population had lead levels >3.5 μg/dl.[10] High-lead levels were found despite the absence of any occupational exposure proving the presence of environmental exposure in Jodhpur city. The authors proposed that drinking water could be the source of lead exposure as 55% of the population with lead levels >3.5 μg/dl were using metallic pipes for plumbing and 25% of this affected population did not use any water purification system. In our study, antenatal women with high BPb levels, 83.4% were housewives and none of them used any water purification system. However, we found no significant difference in the BPb levels among the subjects using metallic or PVC pipes indicating elevated lead levels in the major water body of the city. Cosmetic use was similar in women with both high and low lead levels but pica (consumption of clay, broken pieces of earthen pots, pencil peels) was more common in women with high lead levels (66.66% v/s 28%).

Lead exposure has long been correlated with adverse hematological effects mainly IDA as lead causes interference with both heme biosynthesis and red blood cell survival.[11-14] Hseih *et al.*[15] studied the risk of anemia in both male and female population of lead manufacturing industry. They found that BPb had significantly negative correlation with hematological parameters in male workers but not in female workers. The authors explained this difference on the basis of relatively lower BPb levels in female workers and gaps in data in terms of number of pregnancies or menstruation patterns in the female population. In a recently published cross-sectional study by Hamadneh *et al.*,[16] no significant difference was found between BPb levels and hemoglobin or Fe levels among pregnant women; however, the authors noted that BPb levels were higher among women belonging to low socioeconomic status and those using multivitamins. However, in this study the cut-off limit to define high BPb level was >10 μg/dl, but there are several studies which quote that the adverse maternal and fetal outcomes can be noted with lower BPb levels.[17-19]

In our study, we found a significant difference in lead levels among women with and without IDA, 11.11% and 2.4%, respectively. The mean BPb level was 8.45 μg/dl in IDA mothers as compared to just one mother with BPb of 4.2 μg/dl out of 41 mothers without IDA. We also found a significant negative correlation between BPb levels and hemoglobin levels and these findings are in coherence with those reported by other studies in pediatric and pregnant populations.[20,21] In our study, 90% of women with high BPb levels belonged to lower socioeconomic status.

Lead has been known to readily cross the placenta[22,23] and is excreted in breast milk;[24,25] hence, lead has been associated with adverse perinatal outcomes like preeclampsia, spontaneous abortion, preterm labor, premature rupture of membranes (PROM),[26-30] fetal growth restriction, and neural tube defects.[31] Pregnant mothers who have been previously exposed to lead are even more vulnerable during pregnancy because remobilization process in response to increased calcium requirement ends up remobilizing lead into blood.[32,33] In our study, there was a higher incidence of adverse antenatal outcomes in women with higher lead levels. There was a markedly significant difference in the incidence of fetal growth restriction (25% and 3%), pre-term labor (16% and 0.7%), and neural tube defects (8.3% and 0%) in women with and without elevated BPb levels, respectively. Elevated lead levels can cause abnormal placental function leading to abnormal nutrient transfer and oxidative stress, thus increasing the risk of FGR and pre-eclampsia.[34,35] Lead can induce reactive oxygen species which can cause collagen damage and hence structural weakness of placental membranes leading to PROM and preterm labor.[30] Ladele *et al.* studied lead levels in maternal and umbilical cord blood and found that 75.6% mothers and 66.8% umbilical cords had BPb > 5 μg/dl and they observed that calcium supplementation was significantly associated with a lower maternal BPb.[36]

Taylor *et al.*,[19] in their large cohort study, investigated the association of prenatal BPb levels with birth weight, head circumference (HC), crown-heel length (CHL), preterm delivery and birth weight. They sampled around 4285 antenatal women for BPb assessment and followed them for neonatal outcomes. The mean BPb levels in their study were 3.67 ± 1.47 μg/dl and they concluded that raised BPb levels in maternal blood increase the incidence of preterm delivery and decrease birth weight, head circumference, and crown-heel length although similar results were not demonstrated in other studies wherein no association was found between BPb and HC or CHL.[37-39] In our study, mean birth weight of neonates was lower in women with high BPb but the difference was not statistically significant; however, a significantly higher incidence of NICU admissions was seen with high BPb as compared to normal BPb, 41.6% and 9%, respectively, and the most common reason for NICU admission was respiratory distress. In the high BPb group, one neonate had neural tube defect and there was one neonatal death secondary to intrapartum hypoxia in a severely growth-restricted baby.

In the above study, BPb levels are found to be significantly higher in anemic antenatal women and the lead levels negatively corelate with hemoglobin concentration. Increased lead levels have also been found to be associated with adverse maternal and neonatal outcomes. In a primary care setting, it is important to screen antenatal mothers for serum blood lead levels especially women who are anemic or do not respond to conventional iron treatment. More awareness must be spread to reduce lead consumption among pregnant women by limited cosmetic use, vermillion use, PICA, and occupational exposure to lead in order to improve maternal and neonatal well-being. BPb measurement must be included as a compulsory antenatal investigation in women living in areas with untreated water supplies or in areas with lead-based industries.

Conclusion

Lead remains a public health problem despite measures taken to reduce its environmental contamination. Antenatal mothers and neonates are the most vulnerable groups as high BPb levels adversely affect the well-being of both. We propose screening of high-risk women based on their social, occupational, environmental, and personal factors, with serum lead levels in the preconception period itself. All public and personal measures must be taken to reduce lead consumption and exposure in the preconception and antenatal period. Government must make policies on reducing environmental consumption of lead and treating physicians must spread awareness about the deleterious effects of this ubiquitous metal.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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