JMBR: A Peer-review Journal of Biomedical Sciences
June 2016, Vol. 15 No. 1 pp 55-61

THE RELATIONSHIP BETWEEN MATERNAL BLOOD CADMIUM, ZINC LEVELS AND BIRTH WEIGHT OF BABIES IN NON-OCCUPATIONALLY EXPOSED PREGNANT WOMEN IN BENIN CITY, NIGERIA.

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ABSTRACT

The delivery of babies with low birth weight is a prognosis of neonatal mortality, morbidity and poor health outcomes later in life. This study evaluates the levels of cadmium, zinc and calculated cadmium/zinc ratio in non-occupationally exposed pregnant women at delivery and their relationship with birth weight of babies.
Blood cadmium, plasma zinc and calculated cadmium/zinc ratio were determined in 200 pregnant women at delivery and 100 non-pregnant women which served as controls. Blood cadmium and plasma zinc were assayed by electrothermal Atomic Absorption Spectrometer and spectrophotometric method respectively.
Maternal blood cadmium and cadmium/zinc ratio were significantly higher in those with low birth weight ($p<0.001$) while plasma zinc was significantly lower than in those who gave birth to babies with normal weight ($p<0.001$). The anthropometric measurements: birth weight, head circumference and length were significantly lower in babies with low birth weight than in normal birth weight ($p<0.05$). Blood cadmium and cadmium/zinc ratio correlated inversely with birth weight ($r=-0.461$; $p<0.02$) while plasma zinc, head circumference ($r=0.392$; $p<0.05$) and length ($r=0.390$; $p<0.05$) correlated positively with neonatal birth weight ($r=0.482$; $p<0.02$) ($r=0.392$; $p<0.05$) ($r=0.390$; $p<0.05$) respectively. Concerted effort should be made to check environmental pollutions to avoid their harmful effects on human reproduction and birth weight of neonates.

Introduction:

The delivery of babies with low birth weight is a public health concern all over the world, because the weight of babies at birth is a prognosis of neonatal mortality, morbidity and poor health outcome later in life [1]. In our previous study, we observed increased levels of cadmium in non-occupationally exposed infertile males [2]. Since cadmium has been reported to affect fetus placental zinc dynamics leading to inadequate transfer of zinc to the fetus by utilizing the transport pathway normally used by zinc and its ability to act as endocrine disruptor this present study was designed to evaluate the levels of cadmium, zinc and calculated cadmium/zinc ratio in non-occupationally exposed pregnant women at delivery and their relationship with birth weight of babies. A baby is considered as low birth weight (LBW) when the weight at birth is less than 2500g while those above 2500g are regarded as normal birth weight [3]. The increasing incidence of LBW was attributed to maternal micro- and macro nutritional deficiency as well as exposure to toxic metals [1].

KEYWORDS: *Blood Cadmium, Zinc, Cadmium/Zinc Ratio and Low Birth Weight.*

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Maternal exposure to cadmium has been linked to the delivery of babies with low birth weight and spontaneous abortion elsewhere [1,4]. Toxic metals could gain entrance to the human body through environmental contamination, air, soil due to human activities such as the use of fossil fuels, industrial waste and mining as well as food and drinks [5-7]. Experimental studies have shown that cadmium is embryotoxic and teratogenic but there is an increasing evidence linking cadmium with adverse birth outcomes including low birth weight and premature delivery [8 9]. Tobacco smoke and products are major sources of cadmium exposure. Cigarette contains 1-2μg of cadmium on the average and a smoker who smokes one stick of cigarette could inhale 0.1-0.2μg cadmium [10-11]. Other sources of cadmium include diet especially sea foods, cereals, roots and leaves of vegetables [12-14]. It was estimated that about 8-25μg of cadmium is consumed per day in the United States of America through diet and the half-life of cadmium is up to 10years [15]. There is dearth of information on cadmium level and its impact on pregnancy outcomes from our center.

Zinc is one of the essential micronutrients that is useful to the human body. It acts as cofactor for numerous enzymes and it was believed until recently that zinc deficiency is rare because of its ubiquitous nature. It is now known that zinc deficiency is common due mainly to nutritional inadequacy [16]. Zinc is also required for normal growth and development of fetus during pregnancy. Deficiency in zinc level has been associated with delivery of babies with low birth weight.

MATERIALS AND METHOD

Study population

Two hundred (200) healthy pregnant women visiting antenatal clinic were consecutively enrolled for the study between January and December 2015 at the Departments of Obstetrics and Gynecology, Stella Obasanjo Hospital and Medical Laboratory Science, University of Benin, Benin City. The control group comprised of 100 age-matched non-pregnant women who were also recruited from among staff and students of the institutions.

Ethical Consideration

Institutional Ethical approval was obtained from Ethics Committee of the Edo State Hospitals Management Board and individual inform consent was obtained before the commencement of study. Demographic and clinical information were obtained using structured questionnaires.

Inclusion Criteria:

All healthy pregnant women of 18years and above expecting singleton, who attended antenatal clinic throughout the pregnancy and reported for delivery were included. Pregnant women who carried their pregnancy to full term and delivered either by vaginal and caesarean were also included.

Exclusion Criteria:

Pregnant women with complications such as diabetes mellitus, cardiovascular diseases, and those who had parity more than 4 were excluded. Obstetric conditions that could cause small for dates babies like preterm deliveries, bad obstetric history, intrauterine rupture abruption placenta previa, intrauterine death and congenital anomalies of the baby, pregnancy induced hypertension, polyhydramnios , clinical signs of infection and benign tumors or malignancies were excluded.

Sample Preparation:
Four milliliters (4mL) of venous blood was collected from each pregnant woman at the onset of labour into anticoagulated container and labeled. 2ml of the blood was kept refrigerated prior to analysis for cadmium while the other 2ml was spun at 3000rpm for 10minutes to obtain the plasma. The plasma was stored at -20^{0}C prior to analysis for zinc.
Demographic information was obtained using structured questionnaire while the birth weight of the infant, head circumference and baby's length were measured.

Determination of Cadmium
The concentration of Cadmium in maternal blood was analyzed with electrothermal Atomic Absorption Spectrometer (Perkin Elmer analyst 800, Norwalk, U.S.A) using method previously described by Olmedo et al [17].

The matrix modifier solution was prepared by mixing 50μL of 0.3g/L of $Mg(NO_{3)2}$ and 1mL of 0.33g/L of $Pd(NO_3)_2$ and 2mls of 0.2% v/v nitric acid 50μL of 0.1% Triton X-100. Then, 1 in 7 dilution of whole blood was made with 0.2% HNO_3 and 0.1% Triton X-100 and Cadmium standard working solution (1μg/L) was made by dilution with deionized water.
The light source (hollow cathode lamp) specific for cadmium was inserted into the ETAAS, the wavelength was adjusted to 228.8nm. The instrument was standardized with the standard blank (1% HNO_3) and cadmium standard.

An Aliquot of 20μL of whole blood was injected directly into the graphite furnace. Equal volume of matrix modifier was injected into the graphite furnace

The concentration of Cd (μg/L) was displayed on the screen after the run time (4mins). Plasma zinc was determined by colorimetric method using reagents supplied by Centronic, Germany. Quality control sera were included in the assay in order to ensure accuracy and precision of determinations.

Statistical Analysis
The data obtained were analyzed using statistical package for Social Science Program (SPSS) Version 16.0 (Chicago, IL, USA). The values obtained were presented as Mean ± Standard Error of Mean. Student's t-test was used to compare the means between the groups while Pearson correlation coefficient was used to assessed the relationship between the measured variables and birth weight of babies. A $P<0.05$ was considered as statistically significant.

Results:
The results of the study are as presented in tables 1-4. Table 1 shows the comparison of the measured variables in pregnant women at delivery with non-pregnant women. There was no significant different ($p>0.05$) in the mean age of pregnant women compared with non-pregnant women. Blood cadmium (0.78±0.04 vs 0.19±0.01) and cadmium/zinc ratio (0.0072±0.00 vs 0.001.3±0.00) were significantly higher ($p<0.001$) while plasma zinc (105.5±2.6 vs 142.1±2.4) was significantly lower ($p<0.001$) in pregnant women at delivery than non-pregnant women. Maternal blood cadmium (1.09±0.02 vs 0.62±0.06) and cadmium/zinc ratio (0.018±0.001 vs 0.008±0.001) were significantly higher ($p<0.001$) in those with LBW while plasma zinc was significantly lower (57.8±2.6 vs 71.8±2.4; $p<0.001$) than those who gave birth to babies with normal weight (table 2). The anthropometric measurements: birth weight (2.31±0.2 vs 3.40±0.5), head

Table 1: **Comparison of the levels of measured parameters in pregnant women at delivery and non-pregnant women (control) (mean ± SEM)**

Measured parameters	*Pregnant women at delivery*	*Non-pregnant women (control)*	*p-value*
Maternal age (years)	26.2±1.8	25.9±1.2	>0.05
Number of subjects	200	100	
Cadmium(µg/dL)	0.78±0.04	0.19±0.01	0.001
Zinc (µg/dL)	105.5±2.6	142.1±2.4	0.001
Cadmium/zinc ratio	0.0073±0.00	0.0013±0.00	0.001

Table 2: **Comparison of measured variables according to birth weight of babies**

Parameters	*Babies with low birth weight (n= 25)*	*Babies with normal birth weight (n=175)*	*p-value*
Cadmium (µg/dL)	1.09±0.02	0.62±0.06	0.001
Zinc (µg/dL)	57.8±2.6	71.8±2.4	0.001
Cadmium/zinc ratio	0.018±0.001	0.008±0.001	0.001

Table 3:Comparison of some Anthropometric measurements of babies with normal and low birth weight.

Anthropometric parameters	*LBW (n=25)*	*NBW (n=175)*	*p-value*
Birth weight (Kg)	2.31±0.2	3.41±0.5	0.05
Head circumference (cm)	32.6±1.1	34.8±3.0	0.05
Length (cm)	45.8±1.8	49.8±1.1	0.05

LBW=low birth weight; NBW= normal birth weight

Table 4: Correlation between birth weight of babies and measured parameters

Measured variables	*r-value*	*p-value*
Cadmium	-0.388	0.05
Zinc	0.482	0.02
Cadmium/Zinc ratio	-0.461	0.02
Head circumference	0.392	0.05
Length	0.390	0.05

circumference (32.6±1.1 vs 34.8±3.0) and length (45.8±1.8 vs 49.8±1.1) were significantly lower ($p<0.05$) in babies with low birth weight than normal birth weight (table 3). Table 4 indicates the correlation of birth weight of neonates with measured indices. Blood cadmium ($r=-0.388$; $p<0.05$) and cadmium/zinc ratio ($r=-0.461$; $p<0.02$) correlated inversely with birth weight while plasma zinc ($r=0.482$; $p<0.02$), head circumference ($r=0.392$; $p<0.05$) and length ($r=0.390$; $p<0.05$) correlated positively with neonatal birth weight.

Discussion:

The data presented in this study indicate that blood cadmium and cadmium/zinc ratio correlated negatively with neonatal birth weight while plasma zinc, head circumference and length correlated positively with birth weight of babies. Blood cadmium and cadmium/zinc ratio were significantly higher ($p<0.001$) while plasma zinc ($p<0.001$) was significantly lower in pregnant women than non-pregnant women. The observed increased in cadmium and decreased levels of zinc in pregnant women compared to non-pregnant women were consistent with previous studies [1,4,18]. Adam et al [4] reported increased levels of cadmium in pregnant women and association with high incidence of spontaneous abortion in Sudanese women. Tawari et al [1] reported on the influenced of increased cadmium levels on neonatal birth weight as well as possible amelioration by essential elements. An inverse correlation of blood cadmium with neonatal birth weight was reported in a large population of pregnant women by Johnston et al [18]. In that study over 60% of the study group had blood cadmium levels above the mean for the United States adults. The reported increase in cadmium levels was attributed to combination of exposure sources, which include cigarette smoke. Inconsistent findings were reported among pregnant women in the United States of America. Blood cadmium level of 0.18μg/L was reported in a group of pregnant women from North Carolina [19] while the National Health and Nutrition Examination Survey (NHANES) 2003-2004 observed mean cadmium level of 0.22μg/L in pregnant women compared to 0.33μg/L among non-pregnant women of child bearing age [20]. There are several proposed mechanisms by which cadmium exposure during pregnancy could adversely affect fetal growth and development. Studies have demonstrated that the human placenta is not a complete barrier since toxic metal levels in cord blood increased with maternal exposure [8,21-22]. In addition, cadmium concentrations in cord blood and in the placenta are correlated with maternal blood levels [8]. Higher maternal blood cadmium levels may adversely influence infant birth weight as a result of the indirect toxic effects of the metal on placental or direct effects on the fetus [18]. Cadmium toxicity may arise from its competition with zinc for divalent cationic sites in metalloenzymes. It is believed that zinc ion (Zn^{2+}) antagonizes the action of cadmium ion (Cd^{2+}) and a high Cd^{2+}/Zn^{2+} ratio may be responsible for cadmium toxicity [23]. Some authors have suggested that the toxic effects of cadmium may be mediated by altered metabolism of zinc and copper. Inadequate zinc or copper levels available to the fetus or early neonatal life may be teratogenic, retards growth and even affects cognitive function. Cadmium uses the same transport pathways normally utilized by essential elements and hence could cause death of cells through the disruption of vital pathways like electron transport chain [23-24]. Cadmium is a known endocrine disruptor and has the ability to reduce in-utero gene and protein expression associated with fetal growth [39]. It could activate macrophages to secrete numerous intracellular mediators and cytokines (nitric oxide, tumor necrosis factor-alpha, interleukins) as well as catalase and vaso-active amines [26]. The increased secretion of reactive oxygen species leading to oxidative stress and DNA damage could affect fetal growth [27]. High maternal cadmium levels may result in cellular dysfunction via abnormal signal transductions [28] and induction of metallothioneins synthesis [29-30]. Metallothioneins are members of a family of low molecular proteins that has affinity for cadmium. The protein helps to prevent cadmium within the placenta from reaching the fetus. In doing so, it affects fetus placental zinc dynamics leading to reduced zinc bioavailability to the fetus thereby contributing to weight reduction.

Conclusion:

Higher maternal blood cadmium, cadmium/zinc ratio and lower zinc concentration were observed in pregnant women who gave birth to babies with LBW compared to those with normal birth weight. Cadmium and cadmium/zinc ratio correlated negatively but plasma zinc, head circumference and length correlated positively with birth weight of babies. Concerted effort should be made to check environmental pollutions to avoid their harmful effects on humans.

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