Comparison Of Leptin And Adiponectin Levels In The Cord Blood Of Small For Gestational Age Neonates And Appropriate For Gestational Age Neonates At Birth

Osaretin James Agbonlahor
1. Department of Medical Laboratory Science, School of Basic Medical Sciences, University of Benin, Benin, Nigeria,
2. Medical Laboratory Science Council of Nigeria, Abuja, Nigeria

Mathias Abiodun Emokpae
Department of Medical Laboratory Science, School of Basic Medical Sciences, University of Benin, Benin, Nigeria.
Correspondence to: Prof Mathias Abiodun Emokpae, E-mail: mathias.emokpae@uniben.edu
ORCID iD:0000-0002-6266-1774; Cell phone; +2348034511182

Abstract

Background: Fetal birth weight is one of the key indicators of neonatal mortality and morbidity. It may lead to several perinatal and long-term complications such as mental development, future physical growth, and survival.

Objective: To evaluate the levels of Leptin and Adiponectin in cord blood and their relationship with birth weight, head circumference, recumbent length, and Ponderal index in small for gestational age babies.

Methods: Cord blood leptin and Adiponectin were determined in 200 neonates at delivery. Cord blood leptin and adiponectin levels were determined by Enzyme-linked immunosorbent assay using reagents kits supplied by Elabscience Biotechnology Inc (Bethesda, USA).

Results: Cord blood Leptin and Adiponectin levels were significantly lower (P< 0.001) in Small for Gestational Age babies when compared with appropriate for Gestational Age babies. The anthropometric measurements: birth weight (P<0.01), head circumference (p<0.04), recumbent length (p<0.04) and ponderal index (p<0.02) were significantly lower in Small for Gestational Age babies than in Appropriate for Gestational Age babies (p<0.05). Cord blood Leptin (r=0.49 P=0.001) and Adiponectin (r=0.26 P=0.001) correlated positively with birth weight.

Conclusion: Cord blood adiponectin and leptin were significantly lower in small for gestational age than appropriate for gestational age neonates. The possible long-term implications of the findings are discussed. The need for pregnant mothers to pay attention to those intrinsic factors that predispose them to having small for gestational age babies is emphasized.

Keywords: Small for gestational age, cord blood, leptin, adiponectin.

Introduction

Birth weight of babies is one of the most important public health concerns worldwide and is still the leading cause of prenatal and neonatal deaths (Maznah *et al*., 2016). In developed countries, most of the low birth weight neonates are born premature, but in low resource settings, most of the full-term infants who experienced growth restriction in-utero often result in small for gestational age (SGA) babies (Rizzo and Arduini, 2009). SGA is defined as birth <10th percentile for gestational age using the INTERGROWTH-21(Villar et al., 2014). SGA may occur as a result of pathologic process of intrauterine growth restriction (IUGR) in which a fetus does not attain it's in utero growth potential, or due to normal variability in which a fetus attains it's in utero growth potential but is constitutionally small (Blake et al., 2016). Despite the relatively high rate of SGA births in Nigeria, information on cord blood cardiometabolic status is scanty. Growth restriction occurs in ~10% of all human pregnancies and is characterized by birth weight of <2.5 kg (Farr *et al*., 2015). There are reports from some epidemiological studies which identified that growth-restricted fetuses have an increased risk of developing several diseases in adulthood, including cardiovascular and metabolic diseases (Flier and Maratos-Flier, 2017). In developing countries like Nigeria, the documented main cause of small for gestational age babies is maternal undernutrition (Adinma *et al.*, 2017). Specifically, intrauterine growth restriction is frequently associated with inflammation and infarcts within the villi, resulting in lesion formation or severe cases a reduction of the villous surface area, implying abnormal villous development (Farooqi and Rahilly, 2014). However, recent studies suggest that certain adipokines such as Leptin and Adiponectin play some roles in intrauterine growth,

thus influencing neonatal birth weight (Marialena *et al.*, 2008).

Adiponectin is a protein hormone that regulates many metabolic processes including glucose regulation and fatty acid oxidation (Emilio *et al.,* 2010). It is mainly secreted from adipose tissues and also from the placenta in pregnancy into the bloodstream with higher plasma levels relative to many hormones. It may play a vital role in fetal growth, probably enhancing the growth-promoting effect of insulin through its insulin-sensitizing action (Laudes *et al*., 2009). However, the relationship between fetal adiponectin and birth weight is not conclusive. In small for gestational age (SGA) newborns, a low concentration of adiponectin has been observed (Matsubara *et al*.,2002) but other studies did not find significant differences between small for gestational age and appropriate for gestational age (Martinez-Cordero *et al*., 2006).

On the other hand, leptin is the hormonal product of the obesity (ob) gene and it is centrally sourced in adipose tissues and it is produced in both maternal and fetal adipose tissues during pregnancy (Hoggard *et al*., 2001). Because leptin hormone plays a role in the development of several fetal organ systems; control of food intake, energy balance, and fat storage as well as the regulation of cell multiplication and differentiation in adipose tissues, pancreas, kidney, liver arteries, stomach and immune cells (Dijiane and Attig, 2008). Any condition that reduces fetal leptin concentrations is likely to reduce fetal growth and development, predisposing these offspring to many diseases in adulthood (Marzaki-Tovis et al., 2005). The placental is, however, believed to be an important contributor to the fetal leptin concentration due to the decline in neonatal levels following birth (Yura *et al*., 2003). Fetal leptin appears to be vital in overall fetal growth and development and as a result, there are different growth patterns in utero due to specific variations in leptin levels. The limitations of some of the previous studies are small sample size and presence of controversies for differentiation between IUGR and early gestational age of (SGA) neonates. The objective of this study was to compare the cord blood levels of adiponectin and leptin among small for gestational age and appropriate for gestational age babies. It also correlates cord blood Leptin and Adiponectin with head circumference, recumbent length, and Ponderal Index in the neonates.

Materials and Methods

Study Population

This is a cross-sectional study of 200 healthy pregnant women attending antenatal clinics at the Departments of Obstetrics and Gynecology, Stella Obasanjo Hospital, Benin City. They were consecutively enrolled for the study between January and December 2018 and later admitted with the onset of confirmed labor for deliveries in the same facility. The ultrasound derived gestational age was used to determine SGA status.

Ethical Consideration

Institutional Ethical approval was obtained from the 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 apparently 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 cesarean were also included.

Exclusion Criteria:

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

Sample Preparation:

The pregnant women were admitted at the onset of labour and immediately after delivery, the cord was clamped at both ends and cut. Four milliliters (4mL) of blood was collected from the umbilical vein into Lithium Heparin containers and labeled. The blood was spun at 3000 rpm for 10minutes to obtain plasma. The Plasma was stored at -20^0 C until analysis for leptin and adiponectin.

Demographic information was obtained using a structured questionnaire while the birth weight of the neonates, head circumference, and recumbent length was measured by digital infant scale, flexible metal tape measure, and Seca 416 portable Infantometer respectively. The ponderal index (PI) was calculated as Birth weight (gr)/ Body length $(cm)^3$ x 100, to assess the fetal growth pattern.

Determination of Leptin and Adiponectin

The concentration of leptin and Adiponectin in cord blood was analyzed by the Enzyme-Linked Immunosorbent Assay (ELISA) with the use of kits from Elabscience Biotechnology Inc (Bethesda, USA). The Elabscience protocols outlined in each kit were followed. All standard precautions outlined by the manufacturer were observed with the inclusion of Quality Control sera in the laboratory assays.

This ELISA kit uses the Sandwich-ELISA principle with a micro ELISA plate that has been pre-coated

with an antibody specific to Human LEP and ADP/Acrp30 respectively.

Statistical Analysis

The data obtained were analyzed using the statistical package for the Social Science Program (SPSS) Version 21.0 (Chicago, IL, USA). The values obtained in this study are represented as Mean ± Standard Deviation. Student's t-test, Chi-Square, and Analysis of Variance (ANOVA), were used to compare means between the groups while Pearson correlation coefficient was used to assess the relationship between the measured variables and the birth weight of babies. A P<0.05 was considered statistically significant.

Results

The results of the study are presented in tables 1-5. Table 1&2 shows the comparison of measured Parameters in cord blood samples according to Birth Weight. In table 1, the Cord blood Leptin and Adiponectin were significantly lower (P< 0.001) in small for gestational age babies than appropriate for gestational age babies.

The anthropometric measurements: Birth weight, Head circumference, recumbent length, and ponderal index were significantly lower (P< 0.05) in babies with small for gestational age when compared to normal birth weight babies (Table 3).

Table 4 shows the Comparison of anthropometric measurements of Babies according to the mode of delivery. Birth weight, Head circumference, recumbent length, and Ponderal Index were not significantly different (P>0.05) in babies delivered by spontaneous vaginal delivery when compared to those delivered by cesarean section.

Table 5 indicates the correlation of birth weight of neonates with measured indices. Cord blood Leptin (r=0.49; P=0.001), Adiponectin (r=0.26; P=0.001), head circumference (r=0.394; P= 0.05), Recumbent length (r= 0.025; P = 0.725) and Ponderal Index (r=0.59; P = 0.001) correlated positively with neonatal birth weight.

Table 1: Comparison of Measured Parameters in Cord Blood Samples according to Birth Weight (Mean ± SD)

Birth weight (Kg)	Leptin (ng/mL)	Adiponectin (ug/mL)
Small for gestational age babies (<2.5) n=41	1.97±1.14 (1.61-2.33)	37±5.92 (25- 48.9)
Appropriate for gestational age babies (>2.5) n=159	6.23±2.53 (2.33-6.63)	67.2±1.26 (64.7-69.7)
t value	10.5	7.78
P value	0.001	0.001

Table 2: Comparison of the Levels of Measured Parameters in Cord Blood Samples with Birth Weight Ranges (Mean ± SD)

Birth weight Ranges (Kg)	Leptin (ng/ml)	Adiponectin (ug/ml)
2.0-2.5 (n =41)	1.97±1.14	37±5.92
2.6-3.0 (n =38)	3.17±1.14	49.5±9.72
3.1-3.5 (n =85)	6.63±1.53	67.3±7.46
3.6-4.0 (n =26)	8.28±2.05	82.8±7.88
>4.0 (n =10)	9.14±3.36	92.3±7.74
F-value	112	36.6
P-value	0.001	0.001

Table 3: Comparison of Some Anthropometric measurements of Babies with Normal and SGA.

Anthropometric Parameters	Small for gestational age babies(n =41)	Appropriate for gestational age babies (n=159)	P-value
Birth weight (Kg)	2.34±0.3	3.47±0.4	0.01
Head Circumference (cm)	32.3±1.3	34.4±2.8	0.04
Recumbent length (cm)	50.2±0.5	54.6±0.3	0.04
Ponderal Index (g/cm3)	2.14±0.5	2.45±0.2	0.02

Table 4: Comparison of Some Anthropometric Measurements of Babies according to Mode of Delivery

Parameters	Spontaneous vaginal Delivery (n =176)	Caesarean Section (n=24)	P-value
Birth weight (Kg)	3.31±0.2	3.39±0.5	0.06
Head Circumference (cm)	33.8±1.5	34.3±1.8	0.07
Recumbent length (cm)	52.1±0.7	51.6±0.5	0.08
Ponderal Index (g/cm3)	2.44±0.3	2.39±0.7	0.08

TABLE 5: Correlation of Measured Parameters in Cord Blood with Birth weight

Parameters	R-value	P-value
Leptin (ng/ml)	0.49	0.001
Adiponectin (ug/ml)	0.26	0.001
Head Circumference	0.394	0.05
Recumbent Length	0.025	0.725
Ponderal Index	0.59	0.001

Discussion

The data presented in this study indicate that cord blood leptin and adiponectin were lower in SGA babies than appropriate for gestational age babies. In the same vein, Cord blood adiponectin and leptin concentrations correlated positively with head circumference and the Ponderal Index with the birth weight of babies. There was a significant correlation between the recumbent lengths of babies with adipokines.

The above observations are consistent with previous studies (Eyal et al., 2003; Marzaki-Tovis et al., 2005; Saneyard et al., 2018). It was reported that leptin levels in umbilical cord blood at term were highly correlated with birth weight. Remarkably, the role of leptin in fetal development has not been completely understood. What is factual is that leptin plays a role in the development of many fetal organ systems, therefore, any condition that reduces fetal leptin concentrations is likely to reduce fetal growth and development, predisposing these offspring to several diseases in adulthood. SGA babies grow rapidly during the early postnatal period as a result of increased insulin sensitivity. These babies, therefore, gain excess body fat mass during childhood and adulthood, thereby leading to a higher risk of insulin resistance in adulthood (Duffield et al., 2009; Seneyard et al., 2018). It was reported that leptin is directly associated with body fat mass in neonates and fat storage increases significantly in the last week of pregnancy and small for gestational age neonates are likely to have lower levels of leptin than normal neonates (Seneyard et al., 2018). The reasons for the 20.5% (41/200) high rate of SGA babies are not clear.

The causes of growth-restricted babies are multifactorial, which includes maternal size and poor nutrition, social exclusion, infections, congenital abnormalities, teratogens chronic hypoxia, renovascular disease of the mother as well as placental and umbilical cord disorders (Cunningham et al.,2005; Seneyard et al., 2018). Our group previously associated lower levels of some micronutrients and higher concentrations of toxic metals like cadmium and lead with a low birth weight of neonates (Agbonlahor and Emokpae, 2016; Emokpae et al., 2016). Some of these causes are associated with inflammation and infarcts within the villi, resulting in lesion formation or in severe cases a reduction of the villous surface area, implying abnormal villous development (Farooqi and Rahilly, 2014). On the other hand, maternal malnutrition results in an increased villous surface area, with no changes in placental volume, potentially suggesting an attempt to compensate for the maternal malnutrition by increasing villi branching. Based on these findings, the potential effects of programming in these different groups are likely to vary significantly.

Despite these varied results in the maternal plasma leptin concentrations, there is a significant reduction in fetal leptin concentrations in growth restriction that is associated with both maternal malnutrition and placental insufficiency (Laudes *et al*., 2009). Thus, there is either reduced leptin transportation or reduced placental leptin production, which decreases offspring leptin concentrations. From the findings in this study, it may not be incorrect to suggest that low cord leptin concentrations may increase the risk of developing metabolic syndrome in adulthood.

The significant positive correlation of leptin levels in cord blood with ponderal index observed in this study was consistent with other authors (Christou *et al*., 2002; Fazeli *et al*., 2019) but inconsistent with that of Geary et al.(1999), who reported a negative correlation of cord blood leptin with ponderal index. During human pregnancy, leptin physiologically regulates fetal growth and conceptus development (Henson and Castracane, 2000). It was reported by Christou et al.(2002) that leptin levels in infants whose birth weights were classed as large for gestational age were threefold higher than those for whom body weights were considered appropriate for gestational age and 12-fold greater than for those infants classed as small for gestational age. It has been proposed, therefore, that leptin in umbilical cord blood may originate exclusively from fetal and/or placental

sources and, in light of correlations with birth weight and/or ponderal index, may play a role in conceptus growth and development (Christou *et al*., 2002).

The observed significantly lower cord blood adiponectin levels in SGA babies when compared with appropriate for gestational age babies as well as a significant positive correlation between adiponectin levels in cord blood and birth weight, are consistent with Eyal Sivan et al. (2003) and Weyermann et al*. (*2019). The mechanism by which increased cord blood adiponectin results in high birth weight is not well understood. However, maternal adiponectin is predicted to reduce gluconeogenesis in maternal liver, increase fatty acid oxidation and glucose utilization, and improve insulin sensitivity in liver and skeletal muscle. In the placenta, maternal adiponectin decreases placental insulin-signaling and reduces insulin-stimulated amino acid transport and subsequently decreases fetal growth. Fetal adiponectin is reported to increase fetal adiposity and growth, possibly via increased lipogenic enzyme expression in the fetal liver (Mantzros *et al*., 2009).

Besides, a study that used genetic approaches to manipulate fetal adiponectin gene expression in mice and reported data to suggest a direct link between elevated adiponectin and increased size of fat depots in early life (Qiao *et al*., 2012). Similar to the findings in humans, neonatal adiposity in mice was positively correlated with circulating neonatal adiponectin concentrations, whereas adiponectin knockout fetuses displayed lower body weight and fat content. However, the effect of adiponectin gene-knockout on body weight and body fat was no longer observable after the 15th postnatal day. While the mechanisms underlying the delayed expansion of adipose tissue in adiponectin knockout fetuses remain unclear, it may be related to decreased transcription of lipogenic genes in the fetal liver. The above support the possibility of the linkage between reduced adiponectin levels in cord blood and small for gestational age babies as observed in this study.

Conclusion

Lower cord blood leptin and adiponectin concentrations were observed in SGA babies compared to normal birth weight babies. Also, cord blood leptin, and adiponectin correlated positively with neonatal birth weight, head circumference, recumbent length, and Ponderal Index. Adequate preventive care and treatment of pregnant women with suspected intrauterine growth restriction could help reduce the rate of SGA babies to avoid the associated consequences.

Acknowledgments: This study would not have been possible without the contributions of the Management and staff of Stella Obasanjo Hospital especially those of the Department of Obstetrics and Gynecology and Medical Laboratory Services. Additional help was obtained from Dr. Andrew Evbuomwan (Senior Registrar in the Department of O& G, Stella Obasanjo Hospital) and Mr. Ehijie Iyamah (Chief Medical Laboratory Scientist, Haematology Department, University of Benin Teaching Hospital). Worthy of mention is the invaluable contributions of the Academic and Non-Academic Staff of the Department of Medical Laboratory Science, University of Benin.

Source of fund: None

Conflicts of interest: None declared

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