Research Article

Association between Leptin, Adiponectin, Resistin and Maternal Body Mass Index and Sex of Newborn Infants

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Abstract

Background: Maternal and cord blood adipokine levels are associated with birth weight and intra-uterine retardation in neonates. It is not however clear whether there exists any association between adipokine concentrations and gender of newborn infants. This prospective study correlates the levels of resistin, leptin, and adiponectin in maternal and cord blood with maternal body mass index (BMI) and gender of the newborn babies.

Methods: Blood resistin, leptin, and adiponectin concentrations were determined in 200 maternal and cord blood at delivery by Enzyme linked Immunosorbent assay technique. The mean values of maternal adipokines were associated with maternal body mass index while the cord blood adipokines levels were correlated with gender of neonates.

Results: Maternal blood leptin levels were significantly higher (P<0.001), while resistin and adiponectin levels were significantly lower (P<0.001), than in cord blood. Resistin (p<0.025), and leptin (p<0.001), increased with increasing maternal BMI while adiponectin (p<0.001), decreased with increasing maternal BMI. Also, cord blood resistin was significantly higher (p<0.002), among male gender than female, while leptin and adiponectin were lower (p<0.001), among male than female gender. Resistin (r -0.10; p<0.024), and leptin (r=0.47; p<0.001) correlated negatively while adiponectin (r=0.27; p<0.001), correlated positively with gender among the newborn babies.

Conclusion: The measured adipokines are differentially expressed between male and female newborn infants. The need to pay attention to adipokine levels during pregnancy and postnatally is suggested because of their possible influence on cardiometabolic disorders later in life.

INTRODUCTION

The changes in adipocyte number and volume in neonates may be associated with enhanced risk of cardiometabolic diseases later in life. Despite the lack of established biomarkers of adipocyte number and volume, adipose derived hormones assayed at birth could serve as markers of adipose tissue function [1]. Adipose tissue derived hormones play vital roles in the control of feeding habit, reproductive function and inflammation [1,2]. Evidence suggests that adiponectin, and leptin are associated with adipocyte size and obesity in adult population [3]. Also, abnormal levels of adipokines during pregnancy may be associated with adverse pregnancy outcomes such as small for gestational age babies [4,5]. Authors elsewhere have reported association between adipokines and maternal body mass index [6], but it is not clear whether there is sex dimorphism in the levels of adipokines in cord blood of neonates. An insight into their relative concentrations in maternal and fetal circulation is of public health importance.

Maternal cardiometabolic changes affect fetal metabolism resulting in an increased risk of developing chronic diseases later in life [6]. The cardiometabolic derangements separately and interdependently can progress to a reasonable increase in cardiovascular disease (CVD), morbidity, and mortality; making the cardiometabolic syndrome an established risk factor for premature and severe cardiovascular disease and stroke [4]. However, Umbilical cord blood cardiometabolic characteristics is a reflection of maternal, placental, and fetal conditions, and may also indicate potential derangements in the endocrine or metabolic intrauterine fetal environment with the possibility of affecting fetal growth [1]. Our group earlier reported a significantly lower concentration of adiponectin and leptin in small for gestational age babies than appropriate for gestational age babies [4].

Adiponectin is a protein hormone that regulates several metabolic processes including glucose regulation and fatty acid oxidation [6]. 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 exerts some of its weight-reduction effects via the brain. It is of thought that adiponectin is mainly derived from fetal tissues and not from maternal tissues or placental [7]. At birth, cord blood concentrations of adiponectin are approximately 4–7 fold higher than maternal serum [8]. However, this is followed by a progressive decline in adiponectin levels in the first year of life [9]. Since maternal adiponectin does not cross the placenta, the associations between cord blood adiponectin and measures of fetal adiposity reflect an independent role of fetal adiponectin.

On the other hand, leptin is the hormonal product of the obesity (ob) gene and it is centrally sourced in adipose tissues and this hormone is produced in both maternal and fetal adipose tissues during pregnancy [10]. The placental is, however, believed to be an important contributor to the fetal leptin concentration due to the decline in neonatal levels following birth [11]. Also, there is an increase in serum leptin concentrations in maternal plasma throughout human pregnancy and it increases substantially in the fetus after 34 weeks gestation relative to the rapid body fat mass accumulation during the latter half of the third trimester [12]. So, Fetal leptin concentrations, lower than maternal levels, are detectable at term and are possibly due to production by fetal adipose tissue [13]. Therefore, leptin appears to be an important factor for fetal growth and development.

Resistin is a cysteine-rich adipose-derived peptide hormone that is encoded by the RETN gene in humans [14] and its physiologic role has been the subject of so much debate. In humans, the serum concentration of resistin ranges from 7 to 22ng/ml and it is primarily produced by cell populations other than adipocytes which include macrophages, peripheral blood mononuclear cells (PBMCs), and bone marrow cells [14]. It has been proposed by some authors that there is endogenous Resistin production by the placenta and a weak association between placental resistin expression and circulating Resistin has been reported [15].

Despite the reports that elevated cord blood adipokines are associated with higher birth weight [4], intra-uterine growth restriction [16], and indicators of future risk of childhood obesity, it is not clear whether maternal BMI is associated with cord blood Adipokines or there are gender differences in the expression of these adipokines in cord blood of Nigerian neonates. Several studies elsewhere have reported conflicting findings of association between cord blood levels of adiponectin, leptin, resistin and birth weight of infants [8,16]. There appears to be dearth of information on the relationship between maternal and cord blood adipokine concentrations among Nigerians. The objective of this study therefore was to determine the association of maternal and cord blood levels of resistin, leptin, and adiponectin at term gestation with maternal BMI and gender of newborn infants.

MATERIALS AND METHODS

Study population

This is a prospective 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 between January and December 2018 in the study and later admitted with the onset of confirmed labor for deliveries in the same facility.

Sample size

The sample size was determined using sample size determination formula for health studies by Lwanga and Lemeshow, (1991) [17] N = Z2×P (1-P)/ d^2 and 20.8% prevalence of cardiometabolic disorders among pregnant women in Nigeria [16].

Ethical consideration

Institutional Ethical approval was obtained from the Ethics Committee of the Edo State Hospitals Management Board (A.926/438 dated 5/1/2018), and individual inform consent was obtained before the commencement of the study.

Demographic and clinical information were obtained using structured questionnaires. Medical history, height and weight of mothers, height, weight and head circumference of neonates were measured by trained staff. A Seca scale was to measure the weight of the neonates.

Inclusion criteria

All healthy pregnant women of 18 years 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 section 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, abruptio 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 labor, five (5ml), of venous blood was obtained from the antecubital vein of the mother and immediately after delivery, the cord was clamped at both ends and cut. Five (5) milliliters (5mL), of blood was collected from the umbilical vein into lithium heparin containers and labeled appropriately. The blood was spun at 3000 rpm for 10minutes to obtain plasma. The Plasma was stored at -20^0 C until analysis for leptin, adiponectin, and resistin. Demographic information was obtained using a structured questionnaire

Determination of leptin, adiponectin, and resistin

The concentration of leptin, adiponectin, and resistin in maternal and cord blood was analyzed by the Enzyme-Linked Immunosorbent Assay (ELISA) with the use of reagent Kits from Elabscience Biotechnology Inc (Bethesda, USA), with sensitivity of 9.38pg/mL, 0.18ng/mL, 18.75pg/mL as well as intra-assay

and inter-assay coefficient of variation of <10% respectively. 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, ADP/Acrp30, and RETN 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 parameters in maternal and cord blood. A $P < 0.05$ was considered statistically significant.

RESULTS

The results of the study areas are presented in Tables 1-6. Table 1 shows the demographic data of studied participants while Table 2 shows the comparison between the levels of measured adipokines in maternal and cord blood samples. It was observed that leptin levels were significantly higher ($P < 0.001$), while resistin and adiponectin levels in maternal blood were significantly lower ($P < 0.001$) compared with their levels in cord blood.

Table 3 indicates the correlations of measured adipokines between maternal and cord blood samples. A positive correlation existed between maternal and cord blood levels of resistin ($r = 0.16$ $P = 0.023$), and leptin ($r = 0.03$ $P = 0.623$), while adiponectin ($r = -0.076$ $P = 0.285$) shows negative correlation.

Table 4 shows that the levels of resistin ($p < 0.025$), and leptin ($P < 0.001$), increased with increasing maternal BMI while adiponectin levels (($p < 0.001$) decreased with increasing maternal BMI.

The cord blood resistin level was significantly higher ($p < 0.001$), among male newborn than female newborn, while leptin and adiponectin were significantly lower ($p < 0.001$), among male newborns than female newborns. There were no differences in the mean levels of the measured adipokines in the mothers who had male newborns and female newborns (Table 5).

Cord blood leptin ($r = 0.47$ $p < 0.001$), and adiponectin ($r = 0.27$ $p < 0.001$), correlated positively, while resistin ($r = -0.16$ $p < 0.024$) correlated negatively with gender among the newborns. There was however no significant correlation in the measured parameters in the maternal blood with the gender of their offsprings (Table 6).

DISCUSSION

Adipokines such as leptin, adiponectin, and resistin are used to assess metabolic function in humans, and elevated levels of these adipokines have been associated with birth weight [18,19], small for date babies [4], and intrauterine growth restriction

Table 1: Demographic data of the study population.

Measured Variables	Mothers (n=200)	Neonates(n=200)
Age(Years)	26.9±2.8 (17-39)	-
Weight(Kg)	51.6±3.6 (44.6-58.8)	-
Height(cm)	142.5±2.3(138.1-147.0)	-
BMI	25.4±2.9(19.5-31.2)	-
Birth weight(Kg)	-	3.28±0.2(2.26-3.48)
Head circumference(cm)	-	34.5±2.1(32.4-36.5)
Recumbent length(cm)	-	53.8±0.2(53.6-54.1)
Ponderal Index(g/cm³)	-	2.42-±0.2(2.20-2.62)
Range in parenthesis		

Table 2: Comparison of the Levels of Measured Adipokines in Maternal and Cord Blood Samples (Mean ± SD).

Measured Adipokines	Maternal	Cord	t value	p-value
Resistin (ng/ml)	13.9±10.4	23.1±10.3	8.86	0.001
Leptin (ng/ml)	41.5±21.2	5.36±2.89	23.9	0.001
Adiponectin (ug/ml)	8.73±5.19	62.2±2.07	25.5	0.001

Table 3: Correlations of Measured Adipokines between Maternal and Cord Blood Samples.

Correlation	R-value	P-value
Resistin (ng/ml)	0.16	0.023
Leptin (ng/ml)	0.03	0.673
Adiponectin (ug/ml)	-0.076	0.285

Table 4: Comparison of the Levels of Measured Adipokines in Maternal Blood Samples with their BMI (Mean ± SD).

BMI (Kg/m2)	18.5-24.9	25.0-29.9	≥30.0	F Value	P-value
Resistin (ng/ml)	8.71 ± 3.13	13.2 ± 14.5	15.7 ± 3.66	3.75	0.025
Leptin (ng/ml)	13.7 ± 7.05	30.5 ± 14.5	58.1 ± 15.0	121	0.001
Adiponectin (ug/ml)	14±4.53	11±5.12	5.31±2.76	57.2	0.001

[18]. It is important to know if the alterations in the levels are associated with the gender of newborn infants in our setting. The data presented in this study indicate that leptin levels in maternal blood were higher, but resistin and adiponectin were comparably lower in maternal blood relative to their levels in cord blood. The levels of leptin and resistin increased with increasing maternal BMI while adiponectin decreased with increasing maternal BMI. Cord blood leptin and adiponectin were lower while resistin was higher among male than female newborn infants.

The significantly lower levels of resistin in maternal blood compared with their levels in cord blood and the significantly positive correlation between maternal and cord blood levels of resistin observed in this study, are consistent with other authors [20,21]. This observation may be because there is endogenous resistin production by the placenta as a result of the expression

Table 5: Comparison of the Levels of Measured Adipokines in Maternal and Cord Blood and Gender of Newborn (Mean ± SD).

Parameters		Newborn Gender		P-Value
		Male N=88	Female N=112	
Resistin (ng/ml)	Maternal	14.9±11.0	13.1±4.05	0.333
	Cord	26.8±2.85	21.8±0.514	0.002
Leptin (ng/ml)	Maternal	40.3±20.3	41.6±27.1	0.775
	Cord	1.67±1.14	6.13±2.53	0.001
Adiponectin (ug/ml)	Maternal	6.3±3.86	7.88±5.36	0.151
	Cord	37.3±5.92	66.9±1.26	0.001

Table 6: Correlation of Measured Adipokines in Cord and Maternal Blood with Newborn Gender.

Parameters	Maternal		Cord	
	R Value	P Value	R value	P value
Resistin (ng/ml)	0.0278	0.684	-0.1	0.024
Leptin (ng/ml)	0.041	0.559	0.47	0.001
Adiponectin (ug/ml)	-0.079	0.219	0.27	0.001

of the human resistin gene in the syncytiotrophoblasts of the placenta and it could also be linked to an increase in placental mass during gestation [15]. However, the high molecular weight of resistin (15 kDa), makes it impossible for trans-placental transfer from maternal to fetal circulation. So, it is most unlikely that maternal serum resistin contributes to the resistin levels in fetal circulation. This is due to the scientific evidence which shows that substances with molecular weights of over 500 Da will not be able to pass through the placental barrier [14]. High resistin level in fetal circulation plays a vital role in ensuring the survival of the neonate by providing adequate substrate glucose for Central Nervous System utilization through the inducement of hyperglycemia [22]. This is quite suggestive that resistin may also be involved in fetal energy metabolism during pregnancy apart from its involvement in maternal energy metabolism. Also, the production of resistin by fetal adipose tissue may be accountable as one of the reasons for the observed increase in cord blood resistin levels [23]. It was reported that male and female fetuses respond differently to the same intrauterine environment, suggesting an important biological differences in both cellular and molecular levels. The growth of the male fetuses may be greater than the female fetuses beginning from the early stages of pregnancy. It was suggested that the sex of the fetus may determine placental function and differences in fetal programming [24].

The increased level of resistin in maternal blood with increasing BMI and its positive correlation with BMI is consistent with previous studies [24,25]. These observations show that resistin protein is present in maternal adipose tissue and bloodstream and further demonstrates that there is significantly more resistin in the serum of obese individuals. This postulation was supported by another researcher who reported that there was more serum resistin protein in obese than lean individuals [24]. However, in obese mice induced by a high-fat diet, there

was elevated body mass, blood glucose, insulin resistance, and increased resistin level [26].

In the same vein, it was demonstrated that elevated resistin concentration in maternal blood correlates negatively with maternal BMI [27], which suggests that umbilical cord blood resistin level is independent of maternal adipose tissue production and this is further supported by the fact that cord blood resistin levels are majorly accounted for by placental production and not transfer from maternal adipose tissue or blood.

The higher levels of maternal and cord blood Resistin in male newborns, when compared with female newborns observed in this study, is inconsistent with other studies [28,29]. The authors reported no significant differences in resistin levels between the female and male neonates and no significant association between umbilical cord blood resistin level and neonate's gender respectively. The differences in findings on resistin levels concerning the gender of the neonates in this present study and other authors may be due to the variations in the bodyweight of babies in our study, and those in previous studies. It could also possibly be due to the large sample size in our work. However, in women, both the level of RETN gene in adipose tissues and the plasma resistin concentrations are higher than those in men and this has been attributed to relatively greater body fat contents or reproductive hormones [20].

The significantly higher mean level of leptin in maternal blood compared with the mean level in cord blood as well as the non-significant positive correlations between maternal and cord blood levels of leptin seen in this study, was consistent with other authors [11,13,30]. This was possibly due to an increase in serum leptin concentrations in maternal plasma throughout human pregnancy which also increases substantially in the fetus after 34 weeks of gestation relative to the rapid body fat mass accumulation during the latter half of the third trimester [12].

It was, however, reported that the placenta is a source of both fetal and maternal leptin [31]. Despite this, other authors have shown that fetal adipose tissue is capable of producing leptin at the beginning of lipogenesis and differentiation [32]. Thus, these data suggest that fetal leptin concentrations are directly correlated to fetal fat mass (similar to adults), with negligible contributions by the mother. This assertion was corroborated by the findings from our previous work which showed that Cord blood leptin was significantly lower in small for gestational age than appropriate for gestational age neonates [4]. Another research has demonstrated that the human placenta, though being a site for both maternal and fetal leptin production, most of the placental leptin is transported into the maternal circulation [32]. This possibly accounted for the increased concentration observed in maternal circulation when compared with fetal circulation in this study.

Also, the increase in the leptin (P< 0.001), with increasing maternal BMI is also consistent with the previous study [33]. An increase in BMI is associated with a significantly elevated plasma leptin concentration which is due to an increase in the white adipose tissue when compared with individuals with lower BMI [34]. Also, Persson et al. [35], reported that obese pregnant women have significantly elevated plasma leptin concentrations compared with non-obese pregnant women throughout pregnancy.

The observed lower levels of maternal/cord blood leptin in male neonates when compared with female neonates in this study, aligns with the findings of other authors [36]. The reason for differences in leptin concentration between the genders is not quite clear. However, there is ample evidence providing differences in the leptin concentration between sexes, at the same time, various mechanisms have been postulated to explain this difference. It was reported that in women, both the levels of ob mRNA in adipose tissues and the plasma leptin concentrations are higher than those in men and this has been attributed to relatively greater body fat contents or reproductive hormones present in females [30]. This therefore, makes compelling evidence to support the postulation that the differential in adiposity between the genders could be due to the heightened hypothalamic feedback loop in leptin adiposity regulation in the female [37]. The observable dimorphism in leptin production in early life may also indicate the genetic difference in leptin production.

The significantly lower levels of adiponectin in maternal blood when compared with their levels in cord blood and the non-significant negative correlation between maternal and cord blood adiponectin levels observed in this study, is in line with previous reports [31,8], but is however inconsistent with another author [38], who reported significantly higher levels of adiponectin in maternal blood when compared to cord blood. This inconsistency might be due to the small sample size used in their study.

However, the source of adiponectin in cord blood is unclear, but it is most likely that it is derived mainly from fetal tissues and not from maternal or placental tissues, since maternal adiponectin does not cross the placenta. There are several supportive lines of evidence to this postulation. The First one is that there was no positive correlation between the cord and maternal levels of adiponectin coupled with the significantly higher concentration of adiponectin in cord blood compared to their levels in maternal circulation. The findings from this study do not support the likelihood that placental adiponectin synthesis, may contribute to the high levels of adiponectin in cord blood. The report from previous studies showed that the separation of the fetoplacental unit during birth, the removal of the placental does not cause a fall in the levels of serum adiponectin after birth, assuming that the circulating half-life of this adipocytokine is in the range of several hours [38].

The Second evidence is that the regulatory mechanisms of plasma adiponectin levels in the fetus are still not well understood but it appears to be produced and secreted exclusively by adipocytes. Therefore, it is possible that a rise in fat mass results in the down-regulation of adiponectin, however, a reduction in body weight of obese and that of normal-weight subjects could lead to an elevation in adiponectin concentrations, reflecting the possibility that fat mass may have negative feedback on the production of adiponectin. The absence of such negative feedback may be responsible for the hyper adiponectinemia seen in neonates. Expressly, body fat is significantly lower in terms of percentage in neonates (13%) when compared with children or adults (25–30%) [39].

Nevertheless, the mechanisms underlying the correlation between larger adipocytes and down-regulation of adiponectin were not elucidated. Based on these studies, and with the assumption that adiponectin in the fetus originates mainly from adipose tissue, an additional explanation for the extremely high levels of adiponectin in the cord blood might be the lack of adipocyte hypertrophy in neonates. Histological analysis of adipose tissue of fat cells in neonates shows two populations of cells in the adipose tissue: small cells that do not contain fat and larger cells that contain fat but are small in their diameter compared with adult fat cells [39]. It may not be incorrect to conclude that, the hyper adiponectinemia in cord blood samples seen in this study may be due to a lack of negative feedback exerted in the large adipocytes.

The finding of a significantly lower level of adiponectin with increasing maternal BMI in this study is consistent with the report of some authors [40], who reported a reduced level of plasma adiponectin in obese humans, especially those with visceral obesity, and with inverse correlation with insulin resistance. It was reported in some prospective studies that lower adiponectin levels are associated with higher cases of diabetes. It was also shown that low serum adiponectin is independently associated with metabolic syndrome. In reality, it is more prominent than any other inflammatory markers. Reduced plasma adiponectin levels are also commonly seen in a variety of conditions frequently associated with insulin resistance, such as cardiovascular disease and hypertension [40].

The mechanism by which increased BMI results in lower adiponectin levels in the maternal system is quite unknown. However, data suggesting that oxidative stress inhibits the expression of adiponectin is available in literature. Although the mechanism underlying this regulation is unclear, this may have contributed to the decreased level of plasma adiponectin as observed in obesity, a condition that is associated with increased

oxidative stress in adipose tissue. Again, reduced adiponectin levels can be caused by interactions of genetic factors such as SNP 276 in the adiponectin gene itself and environmental factors, i.e., lifestyle changes that cause obesity, such as a high-fat diet and sedentary lifestyle. These lower levels of adiponectin in turn appears to play an important causal role in the development of insulin resistance, type 2 diabetes (T2D), and metabolic disease, thereby indirectly causing atherosclerosis. Moreover, reduced adiponectin levels also directly play a causal role in the development of atherosclerosis [33].

Maternal anthropometric characteristics have been reported to influence sex-specific growth with male advantage over female neonates among women with low BMI as against those with higher BMI [41]. A negative association between maternal BMI and SGA births in males was reported among women with singleton pregnancies without history of diabetes mellitus [42].

The limitation of this study is that only Nigerian women were evaluated and the results may not be extrapolated to other ethnicities.

CONCLUSION

The leptin level in maternal blood was higher than in cord blood while resistin and adiponectin were comparably lower in maternal blood than in cord blood. Also, resistin and leptin levels in maternal and cord blood correlated positively, while adiponectin correlated negatively with the gender of newborn infants. The relationship between maternal/cord blood level of resistin, adiponectin, and leptin with BMI and neonatal gender indicates that adipokines have an intrinsic role in influencing body weight and are differentially expressed according to the gender of neonates. This is in addition to key roles in the maintenance of normal pregnancy as well as the overall fetal growth and development, hence there is a need to pay attention to their levels during pregnancy and postnatally concerning the possible influence on cardiometabolic disorders later in life.

ACKNOWLEDGMENTS

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