Original Article

Cord Blood Leptin Levels and Anthropometric Indices in Virally Suppressed HIV-Positive and HIV-Negative Mother–Singleton Newborn Pairs: A Comparative Analysis

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ABSTRACT

Background: Despite the remarkable success of prevention of mother-to-child transmission interventions, in utero human immunodeficiency virus (HIV) exposure remains associated with increased morbidity and mortality. This has been linked to adverse anthropometric outcomes, and understanding the underlying mechanisms is crucial for designing effective interventions to improve health outcomes of HIV-exposed infants. **Aim:** This cross-sectional study compared the relationship between cord blood leptin levels and anthropometric indices in virally suppressed HIV-positive and HIV-negative mother–singleton newborn pairs at NAUTH from January to August 2023. **Methods:** Mother–newborn pairs were recruited using stratified random sampling. Data on sociodemographic, obstetric, and anthropometric indices and other medical variables were collected. Cord blood leptin levels were measured using an Elabscience® ELISA kit. Data were analyzed with SPSS version 22, with $P < 0.05$ considered significant. **Results:** Each group consists of 65 mother–newborn pairs. No significant differences were found in age, education, marital status, or social class between groups. Approximately 95% of the HIV-positive mothers were on Dolutegravir-based regimen. HIV-positive mothers had a significantly lower median third trimester weight gain rate ($P = 0.001$), intrapartum BMI ($P = 0.030$), and mean mid-arm circumference (0.017). HIV-exposed newborns had a significantly lower mean birth weight (p-0.002), birth weight-for-gestational age (GA) percentile and Z-scores ($P < 0.001$), ponderal index ($P = 0.002$), mid-arm/occipitofrontal circumference (OFC) ratio ($P < 0.001$), and OFC-for-GA Z-score ($P = 0.004$). HIV-exposed newborns also had significantly lower cord blood leptin levels ($P = 0.012$), with leptin showing moderate and weak positive correlations with birth and maternal anthropometric indices, respectively. Dolutegravir exposure had no effect on cord blood leptin levels. **Conclusion:** HIV-exposed neonates significantly had lower cord blood leptin levels and adverse anthropometric outcomes. Leptin levels correlated positively with neonatal and maternal anthropometric indices. Further research is needed to tailor interventions for improving outcomes in HIV-exposed infants.

Keywords: *Birth anthropometric indices, cord blood adipokines, Dolutegravir effects, maternal anthropometric indices, pregnancy outcomes, South-East Nigeria*

Introduction

In utero exposure to human immunodeficiency virus (HIV) and anti-retrovirals (ARVs) has been associated with elevated morbidity and mortality rates among HIV-exposed infants (HEIs), despite successful

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prevention of mother-to-child transmission (PMTCT) efforts.[1,2] Reports indicate that current PMTCT interventions cannot fully eliminate adverse outcomes among HEI.[3] This has the potential to erode the gains of PMTCT and other preventive child health initiatives, especially in high-HIV-burden countries like Nigeria.[4] The increased risk of morbidity and mortality has been attributed to in utero exposure to ARVs.[5] Pregnancy-induced physiological changes are believed to alter the pharmacokinetics of ARVs, potentially increasing drug toxicity in both maternal and fetal systems.[4] However, gaps in understanding the pathophysiological consequences of HIV and ARV exposure remain largely due to the exclusion of pregnant women from clinical trials and limited fetal sampling.

Additionally, the higher risk of morbidity and mortality among HEI has been linked to adverse birth anthropometric indices.[5-11] Reports consistently show a higher incidence of intrauterine growth restriction (IUGR) among uninfected HEI compared to their unexposed counterparts, which may contribute to increased morbidity and mortality risks.[5,7-11] Of particular concern is the recent adoption of Dolutegravir (DTG) as the preferred drug in first-, second-, or third-line ARV regimens, due to its efficacy, tolerability, safety, high resistance barrier, and low cost.[6] Initially avoided in women of childbearing potential because of risk of neural tube defects, DTG's association with excessive maternal weight gain and gestational diabetes now raises additional concerns about its impact on fetal development and growth. Other ARVs have also been shown to affect intrauterine growth.[5]

The mechanisms by which in utero HIV/ARV exposure influence fetal growth and development remain insufficiently explored. This gap in knowledge may hinder the development of interventions to mitigate potential adverse effects on fetal development, particularly concerning fetal growth processes. As a result, there is an urgent need to better understand the specific interactions between HIV/ARV exposure and fetal growth mechanisms, which could inform more targeted approaches to optimizing ARV regimens and improving maternal and infant health outcomes.

Leptin, an adipokine, plays a vital role in fetal growth and energy supply by enhancing placental lipolysis and nutrient transport, ensuring fuel availability for fetal metabolism.[12-15] It is predominantly produced by maternal adipocytes and the placenta, with levels significantly higher in pregnant women.[15] Its levels increase during pregnancy, correlating positively with fetal and maternal anthropometric indices. Elevated leptin levels are linked to pregnancy complications like obesity and gestational diabetes.[14] Cord blood leptin levels correlate positively with maternal leptin levels and have been reported to be approximately 50% of maternal levels. Therefore, altered cord blood leptin may not only influence intrauterine growth but also signal long-term metabolic risks, such as diabetes mellitus.[14,15]

Despite the role of adipokines like leptin in fetal growth and the association between HIV/ARV exposure and adverse anthropometric indices, this topic has not received sufficient research attention among HEI. A USA study linked in utero HIV/ARV exposure with increased fuel storage and inflammatory changes, potentially leading to metabolic alterations.[16] However, the study also found that HEI neonates had lower cord blood leptin levels compared to unexposed neonates, though this difference was not statistically significant.[16] Thus, the relationship between in utero HIV/ART exposure and metabolic parameters such as leptin remains unclear. Understanding the relationship between cord blood leptin and birth anthropometric indices among HIV-positive mother–newborn pairs is crucial for comprehending both the immediate and long-term metabolic risks associated with in utero HIV/ARV exposure and developing interventions to forestall adverse outcomes.

This study aimed to address these gaps by investigating the relationship between cord blood leptin and anthropometric indices among virally suppressed HIV-positive mother–singleton newborn pairs at NAUTH, Nnewi. Findings will contribute to a better understanding of the adverse consequences of in utero HIV and ARV exposure, leading to enhanced quality of care and outcomes for affected mothers and infants.

Subjects and Methods

Study Design and Setting: A cross-sectional analytic study was conducted between January and August 2023 among HIV-exposed newborn infants and HIV-unexposed controls delivered to mothers who received antenatal care (ANC) at Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, Anambra State. NAUTH is a referral tertiary center known for providing free comprehensive HIV services since 1999. Approximately 30% of mothers who deliver in the center are HIV-positive.[11] Delivery services are provided in NAUTH every day on a 24 hours basis. About one-quarter (26.3%) of multiparous HIV-positive women who deliver in the facility give birth to newborn infants with abnormal weight for gestational age (GA).[9,11] A review of PMTCT register showed that >95% of HIV-positive pregnant women accessing care in NAUTH were on DTG based regimen as at January 2023.

Eligibility Criteria: Live singleton HIV-exposed newborns and their virally suppressed HIV-positive mothers receiving highly active antiretroviral therapy (HAART) and ANC/PMTCT services at NAUTH were eligible. Controls included singleton HIV/ARV unexposed newborns and their mothers who received ANC at NAUTH. All HIV-positive mothers underwent a viral load test in the third trimester of pregnancy. Those who did not undergo the test, did not have a viral load result, or had unsuppressed viraemia (≥1000 copies/ml) were excluded from the study. All HIV-negative mothers were retested at labor, and those who seroconverted were also excluded. Mothers with coexisting medical conditions such as diabetes mellitus, hypertension, and cardiac diseases in pregnancy which could impact pregnancy outcomes were excluded from the study.

Sample size determination: The sample size for the study was calculated using a formula for comparing two groups with a quantitative endpoint ($2SD^2 [Z_{\alpha/2} + Z_{\beta}]^2/d^2$).[17] Given the standard deviation (SD) from a previous study (3.225),[16] a 95% confidence level ($Z_{\alpha/2} = 1.96$), a power of 80% ($Z_{\beta} = 0.84$), and an anticipated response rate of 80%, the minimum sample size of 62 was calculated, which was rounded off to 65 participants per group.

Sampling Technique: Mother–newborn pairs were recruited using stratified random sampling technique. Pregnant women presenting in labor were stratified according to their HIV status. Starting from the first day of enrolment, HIV-positive and negative women presenting in labor were given a number, in a sequential manner. Consecutive even-numbered HIV-positive subjects and HIV-negative controls who met eligibility criteria were enrolled until the required sample size was achieved. Where they failed to meet the inclusion criteria, the next person was recruited.

Data Collection: A pretested proforma was used to collect sociodemographic, obstetric, and other medical data of each mother–infant pair. Maternal data included age, educational status, occupation, parity, GA at booking, GA at delivery, HIV status, details of ARV therapy if HIV-positive, third trimester weight gain rate (g/week), other anthropometric parameters, and socioeconomic class of the family as described by Oyedeji.[18] Infant's data included sex, mode of delivery, GA at birth, and anthropometric measurements. For each neonate, GA, initially estimated from mother's last menstrual period (LMP), was confirmed within 24 hours of birth using Dubowitz's GA assessment chart.[19]

Anthropometric measurements: These followed established protocols for both mothers and newborns, ensuring accuracy and consistency across assessments.

The third trimester weight gain rate was calculated by dividing the difference between the first recorded third trimester weight (obtained from ante-natal record) and intrapartum weight by the duration of weight gain (in weeks). A normal weight gain rate was defined as 250–499 g per week, based on the Institute of Medicine's recommendations and previous reports.[20-22] The average weight gain for pregnant women in Nigeria has been reported to be 250 g per week.[22] Maternal intrapartum weight, BMI, and mid-arm circumference (MAC) were measured to reflect nutritional status at the time of delivery. Before weighing every day, the accuracy of the scale was checked with a 5 kg standard weight. On admission into the labor ward for delivery, maternal intrapartum weight was measured using a scale (SMIC Health Scale, Model ZT-120) on a flat, hard surface and adjusted for zero, with the mother standing barefoot and wearing light clothing. The weight was recorded to the nearest 0.1 kg. Height was measured after delivery using a stadiometer to the nearest 0.1 cm. Based on previous reports, the maternal weight and height cutoffs for this study were 65 kg and 157 cm, respectively, and a normal maternal MAC range was 25–30 cm.[21,23] Maternal BMI was calculated using the formula weight/height^2. The intrapartum BMI range of 25–29.9 kg/m² was adopted as a normal range for this study as the traditional normal BMI range of 18.5–24.9 kg/m² is less relevant during pregnancy.[21,24] A prior Nigerian study showed an increase in BMI from 23.3 kg/m² in the first trimester to 27.0 kg/m² in the third trimester, reflecting normal pregnancy-related weight gain.[24]

The MAC of the mothers and infants was measured on the left arm, midway between the acromion and olecranon with the elbow flexed at a 90° angle. The tape was snug but not compressing the tissue, and the measurement was recorded to the nearest 0.1 cm using an inelastic measuring tape.

Anthropometric measurements of the newborns, including weight, recumbent length, occipitofrontal circumference (OFC), and MAC, were performed as soon as possible within 24 hours of birth. The newborn infant was weighed naked using a SALTER Model 180 infant scale, with values recorded to the nearest 0.05 kg. The length of the infants was measured with an infantometer. The assistant gently cupped both ears and positioned the infant's head against the fixed headpiece, aligning the eyes in the vertical plane. With the left hand, the knees were pressed against the board, while the right hand positioned the movable foot piece against the heel, keeping it perpendicular to the board. The length was measured using the attached tape and recorded to the nearest 0.1 cm. The OFC was measured using a flexible,

inelastic tape, applied over the glabella, around the head at the same level on each side, and over the occipital prominence. The tape was pulled to compress the hair, and the OFC was recorded to the nearest 0.1 cm.

The anthropometric indices used to assess the infants' nutritional status included weight-for-GA, ponderal index (calculated as birth weight (g)/Length (cm)^3 × 100), and the MAC/OFC ratio. Birth weight-for-GA, length-for-GA, and head circumference-for-GA Z-scores were calculated from Fenton's intrauterine growth chart.[25] Based on Fenton's intrauterine growth chart, infants were categorized as small-for-GA (SGA) or large-for-GA (LGA) if their birth weight for GA was below the 10th or above the 90th percentile, respectively. Infants with a ponderal index below 2.32 g/cm^3 or above 2.85 g/cm^3 were classified as thin or obese, respectively, and those with a MAC/OFC ratio below 0.27 were also considered thin.[21,26]

Laboratory procedures

Cord Blood Sample Collection: Cord blood samples were collected with strict adherence to standard precautions to prevent exposure to blood-borne infections. Immediately after delivery of the infant and placenta, the umbilical cord was double-clamped, with the first clamp toward the placenta and the second on the baby's side 20 to 25 cm away from the first. The section between the clamps was then cut. Using sterile technique, the base of the umbilical cord and adjacent placenta surface were cleaned thrice with 70% isopropyl alcohol and then with betadine to remove maternal blood and contaminants. Subsequently, 10 ml of blood was drawn using an 18-gauge vacutainer needle or 10 ml syringe and distributed into appropriately labeled vacutainer bottles.

Sample Processing and Storage: Blood samples were centrifuged at 3000 revolutions per minute (rpm) for 5 minutes, and the supernatant plasma was harvested and stored at -20 degrees Celsius until analysis. All samples were brought to room temperature before assay.

Laboratory Analysis: Cord blood plasma total leptin was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit for human leptin produced by Elabscience®. Internal quality control of the entire assay was ensured using quality control sera provided by the manufacturer.

Data Analysis: Data were analyzed using SPSS version 22 software. The characteristics of HIV-exposed and HIV-unexposed groups were compared using the Chi-square test for categorical variables. Where conditions for Chi-square were violated, Fisher's exact test was used. Student's *t*-test and Mann–Whitney U test were used for normally distributed and non-normally distributed continuous variables, respectively. Test of normality for cord blood plasma leptin using the Kolmogorov–Smirnov test yielded a P value < 0.001, indicating it was not normally distributed. Hence, leptin level was compared between groups using Mann–Whitney U or Kruskal–Wallis tests as appropriate. The correlations between cord plasma leptin and anthropometric indices were assessed using partial correlation test while controlling for GA at birth. A P value less than 0.05 was considered statistically significant. Mothers and infants who had abnormal anthropometric indices were referred to appropriate staff for further evaluation and care.

Results

The sociodemographic characteristics of the study participants, consisting of 65 HIV-positive and 65 HIV-negative mother–newborn pairs, are summarized in Table 1. The age of the mothers ranged from 19 to 44 years, with a mean age of 30.7 years (±5.07) in the HIV-positive group and 31.0 years (±6.05) in

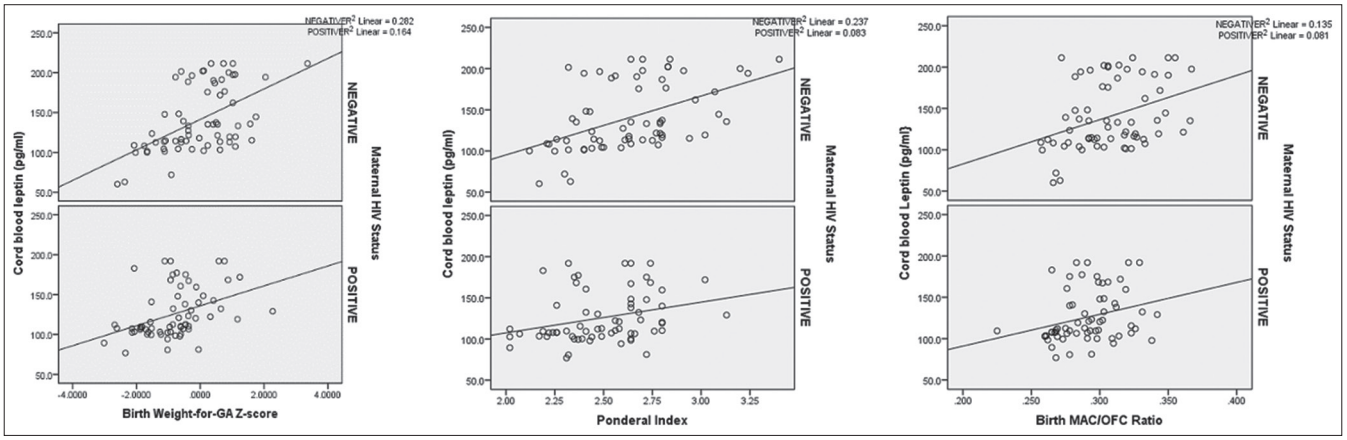

Figure 1: Scatter plot diagrams showing correlation between cord blood plasma leptin and anthropometric indices among HIV-exposed and HIV-unexposed neonates

Table 1: Sociodemographic characteristics of the HIV-positive and HIV-negative mothers

Characteristics	HIV-positive group	HIV-negative group	*P*	Total
Maternal age				
<25	6 (9.2)	9 (13.8)	0.504	15 (11.5)
25-29	20 (30.8)	20 (30.8)		40 (30.8)
30-34	22 (33.8)	15 (23.1)		37 (28.5)
>=35	17 (26.2)	21 (32.3)		38 (29.2
Mean±SD	30.7±5.07	31.0±6.05	0.754	30.8±5.56
Tribe				
Igbo	65 (100.0)	62 (95.4)	0.244	127 (97.7)
Others	0 (0.0)	3 (4.6)		3 (2.3)
Religion				
Christianity	65 (100.0)	64 (98.5)	1.000	129 (99.2)
Others	0 (0.0)	1 (1.5)		1 (0.8)
Highest educational attainment				
Completed Primary	10 (15.4)	7 (10.8)	0.156	17 (13.1)
Completed Secondary	48 (73.8)	43 (66.2)		91 (70.0)
Tertiary	7 (10.8)	15 (23.1)		22 (16.9)
Occupation				
Professional	0 (0.0)	3 (4.6)	0.010*	3 (2.3)
Civil servant	9 (13.8)	19 (29.2)		28 (21.5)
Trader	36 (55.4)	23 (35.4)		59 (45.4)
Artisan	10 (15.4)	4 (6.2)		14 (10.8)
Unemployed or student	10 (15.4)	16 (24.6)		26 (20.0)
Social class				
High	4 (6.2)	9 (13.8)	0.268	13 (10.0)
Middle	45 (69.2)	38 (58.5)		83 (63.8)
Low	16 (24.6)	18 (27.7)		34 (26.2)
Marital Status				
Married	63 (96.9)	65 (100.0)	0.496	130 (97.7)
Separated	1 (1.5)	0 (0.0)		1 (0.8)
Single	1 (1.5)	0 (0.0)		2 (1.5)
Place of residence				
Same state ≤15 km from site	31 (47.7)	53 (81.5)	<0.001*	85 (63.9)
Same state >15 km from site	33 (50.8)	12 (18.5)		47 (35.3)
Other states	1 (1.5)	0 (0.0)		1 (0.8)
Total	65 (100.0)	65 (100.0)		130 (100.0)

*Statistically significant, SD - Standard deviation

the HIV-negative group. Statistical analysis revealed no significant differences between the two groups regarding age, tribe, highest educational level, marital status, or social class. However, a higher proportion of HIV-positive participants resided at locations more than 15 km from the hospital compared to HIV-negative participants ($P < 0.001$). Additionally, a higher proportion of HIV-positive mothers were traders or artisans compared to the HIV-negative group ($P = 0.010$).

Table 2 compares the obstetric characteristics of HIV-positive and HIV-negative mothers. A significantly higher proportion of HIV-positive mothers were primiparous or grandmultiparous compared to HIV-negative mothers ($P = 0.004$). HIV-positive mothers also had a significantly lower mean GA at enrollment into ANC (18.5 weeks vs 22.3 weeks, $P = 0.008$). The mean GA at commencement of routine antenatal drugs was 18 weeks for both groups, with approximately three-quarters of mothers reporting always taking routine drugs in both groups. About three-quarters of HIV-positive mothers and two-thirds of HIV-negative mothers had vaginal delivery. There were no statistically significant differences between the groups in terms of

Table 2: Obstetrics characteristics of studied HIV-positive and HIV-negative mothers

Characteristics	HIV-positive group	HIV-negative group	*P*	Total
Parity				
P1	13 (20.0)	9 (13.8)	0.004*	22 (16.9)
P2-4	36 (55.4)	52 (80.0)		88 (67.7)
≥P5	16 (24.6)	4 (6.2)		20 (15.4)
Booking GA				
First trimester	8 (27.7)	16 (24.6)	0.010*	34 (26.2)
Second trimester	40 (61.5)	28 (43.1)		68 (52.3)
Third trimester	7 (10.8)	21 (32.3)		28 (21.5)
Mean±SD	18.5±6.59	22.3±9.18	0.008*	22 (13)
GA at starting routine drugs				
First trimester	20 (30.8)	23 (35.4)	0.500	43 (33.1)
Second trimester	40 (61.5)	34 (52.3)		74 (56.9)
Third trimester	5 (7.7)	8 (12.3)		13 (10.0)
Mean±SD	18.0±6.84	18.5±8.35	0.647	18.3±7.61
Frequency of routine drugs use				
Always	47 (72.3)	53 (81.5)	0.324	100 (76.9)
Often	8 (12.3)	6 (9.2)		14 (10.8)
Sometimes	10 (15.4)	5 (7.7)		15 (11.5)
Never	0 (0.0)	1 (1.5)		1 (0.8)
Mode of delivery				
Vaginal delivery	47 (72.3)	42 (64.6)	0.345	89 (68.5)
Cesarean section	18 (27.7)	23 (35.4)		41 (31.5)
Complication of labor				
No	47 (72.3)	51 (78.5)	0.250	98 (75.4)
Yes	11 (16.9)	9 (13.8)		20 (15.4)
Not applicable	7 (10.8)	5 (7.7)		12 (9.2)
Total (%)	65 (100.0)	65 (100.0)		130 (100.0)

*Statistically significant (chi-square test), GA - Gestational age, SD - Standard deviation

mode of delivery, GA at routine drugs commencement, frequency of routine drugs use, or occurrence of complications during labor in the index delivery.

The current ARV regimen of the studied HIV-positive women was abacavir, lamivudine, and dolutegravir (4.6%); tenofovir, lamivudine, and dolutegravir (90.8%); tenofovir, lamivudine, and atazanavir/ritonavir (3.1%); and tenofovir, lamivudine, and efavirenz (1.5%).

Table 3 displays the maternal anthropometric measurements for HIV-positive and HIV-negative mothers. HIV-positive mothers had a significantly lower median third-trimester weight gain rate compared to HIV-negative mothers (275 g/week vs 361.5 g/week, $P = 0.013$). In addition, the mean intrapartum BMI was significantly lower in HIV-positive mothers compared to the HIV-negative mothers (27.5 kg/m² vs 29.7 kg/m², $P = 0.03$). Similarly, the mid-arm circumference was significantly lower in HIV-positive mothers compared to HIV-negative mothers (28.8 cm vs 30.6 cm, $P = 0.017$). There were no significant differences observed between the two groups in terms of maternal height and intrapartum weight.

As shown in Table 4, there were no statistically significant differences in the sex distribution and GA at birth between HIV-exposed and HIV-unexposed neonates. However, neonates born to HIV-positive mothers had some noteworthy differences compared to those born to HIV-negative mothers, including a significantly lower median birth weight-for-GA percentile (22nd vs 54th percentile, $P < 0.001$), mean birth weight (3.0 kg vs 3.3 kg, $P = 0.002$), birth weight-for-GA Z-score (-0.8 vs -0.04, $P < 0.001$), ponderal index (2.49 vs 2.63, $P = 0.002$), mid arm circumference/occipito-frontal circumference (MAC/OFC) ratio (0.29 vs 0.31, $P < 0.001$), and OFC-for-GA Z-score (0.2 vs 0.5, $P = 0.004$).

The level of cord plasma leptin showed statistically significant differences between HIV-exposed and HIV-unexposed neonates, as detailed in Table 4. The HIV-exposed neonates exhibited a significantly lower

Table 3: Anthropometric characteristics of the HIV-positive and HIV-negative mothers

Characteristics	HIV-positive group	HIV-negative group	*P*	Total
Third trimester weight gain rate g/week)				
<250	22 (33.8)	11 (16.9)	0.013*	33 (25.4)
250-499	38 (58.5)	39 (60.0)		77 (59.2)
≥500	5 (7.7)	15 (23.1)		20 (15.4)
Median (IQR)	275.0 (119.4)	361.5 (188.8)	0.001*	306.3 (176.2)
Intrapartum weight (kg)				
<65	8 (12.3)	3 (4.6)	0.284	11 (8.5)
65-99.9	49 (75.4)	54 (83.1)		103 (79.2)
≥100	8 (12.3)	8 (12.3)		16 (12.3)
Mean±SD	79.2±13.96	82.3±12.90	0.192	80.7±13.48
Intrapartum BMI (kg/m^2)				
≤24.9	8 (12.3)	1 (1.5)	0.024*	9 (6.9)
25-29.9	35 (53.8)	32 (49.2)		67 (51.5)
30-34.9	22 (33.8)	32 (49.2)		54 (41.5)
Median (IQR)	27.5±6.4	29.7±5.3	0.030*	29.9±4.26
Maternal height (cm)				
<1.57	10 (15.4)	14 (21.5)	0.366	24 (18.5)
≥1.57	55 (84.6)	51 (78.5)		106 (81.5)
Mean±SD	164.8±4.93	163.9±5.22	0.341	164.4±5.08
Mid-arm circumference (cm)				
<25	12 (18.5)	4 (6.2)	0.033*	16 (12.3)
25-29.9	31 (47.7)	27 (41.5)		58 (44.6)
≥30	22 (33.4)	34 (52.3)		56 (43.1)
Mean±SD	28.8±4.19	30.6±4.33	0.017*	29.7±4.34

*Statistically significant, SD - Standard deviation, 1QR - Interquartile range

cord blood leptin level compared to HIV-unexposed infants (112.1 pg/ml vs 127.3 pg/ml, $P = 0.012$).

Table 5 demonstrates that cord blood leptin had statistically significant moderate positive correlations with all measured neonatal anthropometric indices and weak positive correlation with maternal anthropometric indices. A similar pattern was observed for both HIV-exposed and unexposed infants, as also shown in Figure 1. However, when the groups were analyzed separately, the association with maternal anthropometric indices was no longer significant except for maternal third-trimester weight gain rate among HIV-exposed and maternal mid-arm circumference among the HIV-unexposed neonates.

In HIV-exposed neonates, the median cord blood leptin levels were slightly lower among those exposed to DTG-based regimen (112.0 [IQR 44.5] pg/ml) compared to those exposed to non-DTG based regimen (119.2 pg/ml). However, the association was not statistically significant ($P = 0.827$).

Discussion

Our study revealed significant differences in anthropometric indices between HIV-positive and HIV-negative mother-newborn pairs, despite lack of significant difference in sociodemographic characteristics such as age, education, marital status, and social class of the two groups. This suggests that the observed disparities may not be directly attributable to such sociodemographic factors. This finding is consistent with reports of previous researches.[27,28] This is corroborated by the findings of a recent Lesotho study which reported a 2–3 times greater risk of adverse pregnancy outcomes among HIV-positive women, even with the use of HAART.[28] These findings underscore the complex interplay of HIV infection, ARV use, and pregnancy outcomes.

The observed patterns of variation in anthropometric indices between HIV-positive and HIV-negative mothers, as well as HIV-exposed and unexposed newborns, agree with previous findings.[7-11] HIV-positive mothers exhibited significantly lower anthropometric indicators of current nutritional status, whereas HIV-exposed neonates showed significantly lower levels in all assessed anthropometric indices except length-for-GA Z score. This pattern suggests that the anthropometric

Table 4: Characteristics of the HIV-exposed and HIV-unexposed neonates

Characteristics	HIV-exposed	HIV-unexposed	*P*	Total
Sex				
Female	36 (55.4)	30 (46.2)	0.293	66 (50.8)
Male	29 (44.6)	35 (53.8)		64 (49.2)
Birth GA Category				
<37 Completed weeks	5 (7.7)	7 (10.8)	0.545	13 (9.2)
≥37 Completed weeks	60 (92.3)	58 (89.2)		118 (90.8)
Mean±SD	39.0±1.68	38.8±1.97	0.473	38.9±1.82
Birth Weight Category (kg)				
<2.5	10 (15.4)	3 (4.6)	0.038*	13 (10.0)
2-5-3.9	53 (81.5)	55 (84.6)		108 (83.1)
≥4.0	2 (3.1)	7 (10.8)		9 (6.9)
Median (IQR)	3.0±0.55	3.3±0.51	0.002*	3.2±0.54
Birth Weight-for-GA				
<10th percentile (LGA)	19 (29.2)	9 (13.8)	0.047*	28 (21.5)
10th-90th percentile (AGA)	45 (69.2)	51 (78.5)		96 (73.8)
>90th percentile (LGA)	1 (1.5)	5 (7.7)		6 (4.6)
Median (IQR)	22.0 (31.0)	54.0 (56.0)	<0.000*	31.0 (53.0)
Weight-for-GA *Z*-Score				
<-2 *Z*-Score	8 (12.3)	4 (6.2)	0.519	12 (9.2)
-2 to +2 *Z*-Score	56 (86.2)	59 (90.8)		115 (88.5)
>+2 *Z*-Score	1 (1.5)	2 (3.1)		3 (2.3)
Mean±SD	-0.8±1.00	-0.04±1.14	<0.001*	-0.4±1.14
Ponderal Index				
2.32 to 2.85 (normal)	48 (73.8)	47 (72.3)	0.024*	95 (73.1)
<2.32 (thin)	15 (23.1)	8 (12.3)		23 (17.7)
>2.85 (obese)	2 (3.1)	10 (15.4)		12 (9.2)
Mean+SD	2.49±0.24	2.63±0.28	0.002*	2.56±0.27
MAC/OFC Ratio				
<0.27	16 (24.6)	6 (9.2)	0.019*	22 (16.9)
≥0.27	49 (75.4)	59 (90.8)		108 (83.1)
Mean±SD	0.29±0.02	0.31±0.03	<0.001*	0.30±0.03
OFC for GA *Z*-Score	0.2±0.62	0.5±0.53	0.004*	0.4±0.59
Length-for-GA *Z*-Score	0.0±0.70	-0.1±0.0.56	0.664	0.0±0.63
Cord blood leptin level				
Median (IQR)	112.1 (41.8)	127.3 (76.9)	0.012*	119.3 (56.2)

*Statistically significant OFC - Occipito-frontal circumference, MAC - Mid arm circumference

Table 5: Partial correlation coefficients of cord plasma leptin and anthropometric indices of HIV-exposed and HIV-unexposed neonates

Parameter	Total		HIV-exposed		HIV-unexposed	
	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*
Birth weight	0.49	<0.001*	0.40	0.001*	0.49	<0.001*
Weight-for-GA *Z*-score	0.53	<0.001*	0.40	0.001*	0.55	<0.001*
Ponderal index	0.44	<0.001*	0.25	0.043*	0.48	<0.001*
Birth length-for-GA *Z*-Score	0.36	<0.001*	0.36	0.003*	0.38	0.002*
Birth OFC-for-GA *Z*-score	0.41	<0.001*	0.32	0.010*	0.41	0.001*
3rd trimester weight gain rate	0.28	0.001*	0.28	0.023*	0.22	0.094
Maternal intrapartum BMI	0.21	0.015*	0.11	0.387	0.22	0.080
Maternal MAC	0.28	0.001*	0.11	0.387	0.33	0.007*

*Statistically significant OFC - Occipito-frontal circumference, MAC - Mid arm circumference

indices of HIV-exposed neonates are more closely linked to the mother's current nutritional status. As previously reported, the fetus relies entirely on the mother for the nutrients required for growth.[21,22] Therefore, poor maternal nutrition during pregnancy is expected to result in inadequate fetal growth. The lack of a significant difference in maternal height and intrapartum weight between HIV-infected and uninfected mothers is not surprising as these parameters do not reflect the mother's current nutritional status.

Cord blood leptin may serve as an indicator of maternal adiposity, being primarily produced by maternal adipocytes and the placenta. Previous reports indicate that maternal factors such as BMI and weight gain rate during pregnancy influence cord blood leptin levels.[29] Since leptin plays a key role in pregnancy-associated energy balance changes, the significant difference in cord blood leptin levels between HIV-exposed and unexposed neonates is not surprising. This difference aligns with the observed significant difference in anthropometric pattern and the positive correlation between cord blood leptin levels and anthropometric indices. These findings highlight the need for interventions to improve the nutritional status of HIV-positive pregnant women to ensure a healthier start and optimal outcomes for their offspring.

The observed statistically significant difference in cord blood leptin levels between HIV-exposed and HIV-unexposed neonates contrasts with the findings of a previous study conducted in USA, which did not find a statistically significant difference in the cord blood leptin of HIV-exposed and HIV-unexposed newborns (11.7 vs 12.4 ng/ml, $P = 0.84$).[16] This may explain the lack of statistically significant difference in the mean birth weight-for-GA Z-scores of the HIV-exposed and HIV-unexposed neonates (-0.50 vs -0.25, $P = 0.47$) in the USA study in contrast to the index study. The above may be attributed to the fact that the HIV-positive mothers in the USA study had a slightly higher though not statistically significant pre-pregnancy BMI (26.4 vs 25.0 kg/m^2, $P = 0.39$), in contrast to the index study where HIV-positive mothers significantly had poorer nutritional status. This implies that maternal nutritional status is a major determinant of cord blood leptin levels in HIV-positive populations. Reports indicate that in utero exposure to altered adipokine levels can disrupt fuel homeostasis and create an inflammatory environment, significantly impacting HIV-exposed infants in both short and long terms.[30-33] Therefore, effort should be intensified at ensuring the optimal nutritional status of childbearing HIV-positive women, considering its impact on cord blood adipokines such as leptin.

The pattern of cord blood leptin levels among neonates exposed to DTG in utero does not suggest a trend toward increased growth, in contrast to some prior reports.[34-36] DTG has been reported to affect adipose cells by influencing the secretion of adipokines and cytokines, potentially contributing to metabolic effects such as increased weight gain.[34,35] Hence, DTG has been linked to excessive weight gain and gestational diabetes.[37-39] The fact that more than 95% of the HIV-positive subjects were on DTG-based regimen limited the power of the index study to make robust comparisons. However, the absence of significant relationship between exposure to DTG-based regimen and cord blood leptin agrees with some studies which found no relationship between exposure to DTG and maternal or newborn anthropometric indices.[40,41] Larger prospective comparative studies with an adequate number of DTG-unexposed infants of HIV-positive mothers are still needed to confirm this relationship.

Conclusion

HIV-exposed neonates had a lower cord blood leptin level and poorer anthropometric outcomes compared to HIV-unexposed infants. Cord blood leptin level correlated positively with neonatal anthropometric indices and indicators of current maternal nutritional status.

Recommendation

The significant correlation between cord blood leptin levels and neonatal or maternal anthropometric indices implies that leptin plays a vital role in fetal growth and development. There is a need to implement targeted nutritional interventions for HIV-positive pregnant women to optimize maternal weight gain and fetal growth.

Limitations of the study

The study did not measure maternal leptin levels and hence could not examine the effect of maternal leptin on cord blood leptin levels. Additionally, there were only a few HIV-exposed neonates whose mothers were not on a DTG-based regimen, limiting the ability to compare the effects of DTG and non-DTG regimens. Despite these limitations, findings of the study provide useful evidence for the development of targeted nutritional interventions among HIV-positive mothers.

Ethics approval and consent to participate

All aspects of the study were carried out in accordance with declaration of Helsinki. Approval was obtained from the NAUTH Research and Ethics Committee (Approval No.NAUTH/CS/66/VOL.15/VER.3/339/2021/114), with additional permissions from relevant departmental

heads. Written informed consent was obtained from all participating mothers. Voluntary participation and confidentiality were ensured throughout the study.

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Conflicts of interest

There are no conflicts of interest.

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