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Insulin Sensitivity of Term Newborns Exposed *in Utero* to HIV and Antiretrovirals in Yaoundé

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Abstract

Introduction: Antiretrovirals (ARVs) and the human immunodeficiency virus (HIV) are implicated in the onset of insulin resistance. They cross the placental barrier thereby inducing early modifications of the fetal environment. The aim of our study was to assess insulin sensitivity in full-term newborns exposed *in utero* to HIV and ARVs in Yaoundé. **Materials and Methods:** We conducted an analytical cross-sectional study in 2 maternities in the city of Yaoundé from November 2021 to June 2022. We generated two groups of newborns (NBs): one group born to HIV positive mothers on ARVs and the other control group born to HIV negative mothers. Clinical data from mothers and NBs were collected. A homeostatic model assessment of insulin resistance (HOMA-IR) like index with C peptide served to assess insulin sensitivity. We used the Spearman correlation to measure the strength of association between insulin sensitivity and the different variables. A p-value < 0.05 was considered statistically significant. **Results:** Of 70 neonates included, 35 were born to HIV positive mothers on ARVs and 35 to HIV negative mothers. The median age of HIV positive and negative mothers was 30 (27 - 32) and 34 (24 - 47) years, respectively ($p = 0.791$). The body mass index before pregnancy as well as the average newborn weights were comparable in both groups. The ARV protocol associating Tenofovir, Lamivudine, Efavirenz was used by 97.1% of HIV positive mothers. In the exposed NBs group, C peptide was significantly lower ($p < 0.001$) and blood glucose significantly higher ($p < 0.001$). The median values of HOMA-IR were 1.4 (0.8 - 1.9) and 2

(1.4 - 2.6) (p = 0.001) for exposed and unexposed NBs, respectively. **Conclusion:** Newborns exposed to HIV and ARVs had lower C peptide levels and were more sensitive to insulin. Close metabolic monitoring of these newborns would allow early diagnosis and management of any glucose regulation disorder.

Keywords

Insulin Sensitivity, Newborns, Antiretrovirals, HIV, C Peptide, HOMA-IR

1. Introduction

Human immunodeficiency virus (HIV) infection remains a major public health problem worldwide. In 2021, according to the World Health Organization (WHO), 37.7 million people worldwide were living with HIV, including 1.3 million pregnant women, of whom 81% had access to antiretroviral treatment as part of the prevention of mother-to-child transmission initiative [1] [2]. Antiretroviral treatment has markedly improved the prognosis of people living with HIV and significantly reduced its transmission from mother-to-child to a bare minimum [3]. HIV infection and ARVs induce changes in carbohydrate and lipid metabolism leading to the development of diabetes mellitus, insulin resistance, metabolic syndrome and dyslipidemia [4] [5]. The mechanisms responsible for the development of these metabolic diseases are: lipodystrophy caused by lipolysis and the adipogenesis-inhibiting action of antiproteases, immune changes induced by HIV infection and ARVs, and mitochondrial cytopathy induced by nucleoside analogues [4] [5].

The developmental Origin of Health and Disease (DOHaD) theory is based on the concept that the origins of lifestyle-related disease are formed at the time of fertilization, embryonic, fetal stages by the interrelation between genes and environment during the intrauterine life [6] [7]. The mechanisms of intrauterine adaptation by the fetus are through transplacental effects and epigenetic effects [8]. As a result, HIV and ARVs crossing the placental barrier accumulate in amniotic fluid, thereby modifying the intrauterine environment to which the fetus must adapt. Moreover ARVs, especially nucleoside analogues, are responsible for mitochondrial toxicity through their inhibitory action on DNA polymerase δ and production of defective mitochondrial DNA (mtDNA), inefficient repair of error in mtDNA replication [9]. This results disruption of proper oxidative phosphorylation, thereby leading to mitochondrial dysfunction. This could disrupt fetal energy metabolism, leading to long-term changes in insulin sensitivity [9] [10] [11].

Studies have highlighted a high prevalence of obesity and lipid disorders in young children and adolescents born to HIV infected mothers, hence the importance of early screening for metabolic disorders and implementation of preventive measures such as lifestyle and dietary changes from early childhood [12] [13]. The aim of our study was to evaluate the insulin sensitivity in full-term new-

borns exposed *in utero* to HIV and ARV.

2. Materials and Methods

2.1. Study Type

This was a descriptive and analytical cross-sectional study conducted over a period of 08 months from November 2021 to June 2022 in two maternity wards in the city of Yaoundé: the maternity wards of the Central Hospital of Yaoundé and the Social and Health Center of Nkolndongo-Yaoundé.

Study population

The study population was selected by consecutive sampling. Eligible participants were newborns with gestational age between 38 and 41 weeks. Two groups of term newborns (NBs) were formed. A group of full-term NBs from HIV positive mothers (HIVp) treated with ARVs for at least three months at the time of inclusion, and a group of full-term NBs of HIV negative mothers (HIVn). We excluded NBs of mothers with a history of diabetes mellitus, hyperthyroidism, renal insufficiency, arterial hypertension, recent systemic corticosteroid therapy lasting ≥30 days, and NBs admitted to the neonatal intensive care unit at birth.

Sampling and sample size

This was a non-random consecutive sampling. Sample size was calculated using the Whitley *et al.* formula for estimating a difference in means. $N = (2 \times Cp)/d^2$, where N = number of patients required for each group, d = standard difference = expected difference/standard deviation; Cp = is a constant defined by the value chosen for statistical power and the p-value. This is given by statistical tables. With a statistical power of 80% and a p-value of 0.05, the constant (Cp) is 7.9. Considering an expected difference in insulin sensitivity of 20% between the 2 groups; we used the mean insulin sensitivity (M) of term newborns with a normal birth weight which is 1.03 ± 0.26 using the HOMA-IR test [14]. Thus $d = (0.20 \times 1.03)/0.26 = 0.79N = (2 \times 7.9)/(0.79)^2 = 25.31$. We required a minimum of 25 newborns per group.

2.2. Data Collection

Clinical data

With the help of midwives, we recruited women during their last prenatal visit and in delivery rooms. Data were collected using a pre-established questionnaire. These included sociodemographic, obstetrical and gynecological data, history of current pregnancy and HIV infection for HIV positive mothers and anthropometric parameters of all mothers. We also collected the anthropometric parameters of newborns, namely the weight, cranial circumference, thoracic circumference, arm circumference and length.

Biological data

A 10 milliliters blood sample was taken from the umbilical vein 2 cm from the fetal placental surface after expulsion of the placenta. It was equally distributed between a dry and a fluorinated tube. The blood samples were labeled and stored

in a cooler at 25˚C. They were transported to the Laboratory of the National Obesity Center within 12 hours of sampling. They were centrifuged at 3000 revolutions per minute for 10 minutes. Serum and plasma were separated and stored in cryovials using pipettes and frozen at minus 25˚C for subsequent assays. Venous blood sugar levels were measured using the endpoint enzymatic method by the glucose oxidase/peroxidase assay. Blood glucose was measured by a series of spectrophotometric micro curves. Measurement of fetal C peptide values was obtained from serum using the Eagle Biosciences Human C Peptide ELISA Assay Kit enzyme immunoassay. Reagents for the assay are ready to use and pre-dispensed in sealed reagent strips. The assay was performed manually. This kit allowed us to have C peptide values in pmol/l which were then converted in mIU/mL using the following formula: 1 μIU/mL = 6.00 pmol/L.

Assessment of insulin sensitivity

We used an HOMA-IR like index for insulin sensitivity assessment; it was determined by the HOMA-IR formula: Glucose (mmol/L) × Insulin (mU/L or μUl/mL)/22.5) [15]; where the insulin level was replaced by the C peptide level. In this study, we use C peptide because it's co-secreted in equimolar concentration with insulin, it isn't metabolized by the liver and doesn't undergo any extraction during the first hepatic passage. Therefore, it can be indirectly measured to access insulin secretion [16]. The HOMA-IR index is an alternative to the euglycemic insulin clamp. It is easier and more convenient to use [17] [18]. A newborn was considered insulin sensitive if the HOMA-IR value was <2.6 [15].

2.3. Statistical Analyses

Data were entered and saved using Excel 2013 software. Data analyses were performed using IBM-SPSS V.21.0 software. For sociodemographic, clinical and therapeutic parameters of the mothers, we calculated frequencies for qualitative variables. Quantitative variables were represented as medians (Interquartile Range) and means ± Standard Deviation. The same method applied to anthropometric parameters of newborns. The means were compared with the Student T test. For comparison of HOMA-IR values between the two groups of newborns, we used the Man Whitley and Fisher tests as needed. We used the Spearman correlation to measure the strength of association between insulin sensitivity and the different variables. A p-value of less than 0.05 was considered statistically significant.

2.4. Ethical Considerations

All pregnant women signed an informed consent form. We obtained authorizations from both hospitals in which the study took place, with codes as follows: N˚ 2022/065/AR/MINSANTE/SG/DHCY/UAF for the Central Hospital of Yaoundé and N˚/Ref: OEC/03/22/035/CASS/D/CE/ for Social and Health Center of Nkolndongo. We also obtained ethical clearance N˚28/UY1/FMSB/VDRC/DAASR/CSD from the Institutional Research Ethics Committee of the Faculty of Medicine

and Biomedical Sciences of the University of Yaoundé I.

3. Results

The study was offered to 98 pregnant women at term, including 45 women seropositive for HIV (HIVp) and 53 HIV negative (HIVn) women. Seventy women and their newborns were included in the study, distributed as follows: 35 newborns each of HIV negative and positive mothers (Figure 1).

3.1. Characteristics of Study Population

Mothers' Clinical Characteristics

Both groups were comparable in terms of age, level of education, gestational age and BMI (Table 1). HIVp mothers were more frequently concubines (31.4% vs 8.6%, p = 0.024) and self-employed (60% vs 28.6%, p = 0.023). The average age was 30.8 ± 5.1 years and 29.6 ± 6.9 years in the group of HIVp and HIVn mothers, respectively. Our study population was made up of young single women with a secondary school education. Most deliveries were vaginal. Regarding HIV treatment protocol, 97.1% of HIV positive women (34/35) were on triple therapy: Tenofovir, Lamivudine, Effavirenz.

Newborns Clinical Characteristics

Newborns in the HIV/ARVs exposed group were 51.4% male and 48.6% female. The mean weights were 3258 ± 296.9 g and 3305 ± 382.6 g in the exposed and unexposed group, respectively. We noted no significant difference in anthropometric parameters of newborns between the two groups (Table 2).

3.2. Insulin Sensitivity of Newborns

In the group of newborns exposed to HIV/ARVs, the median blood sugar values were higher (3.3mmol/l vs 1.3 mmol, p < 0.001) whereas HOMA-IR values were lower (1.4 vs 2, p = 0.001). Moreover, the median C peptide values were

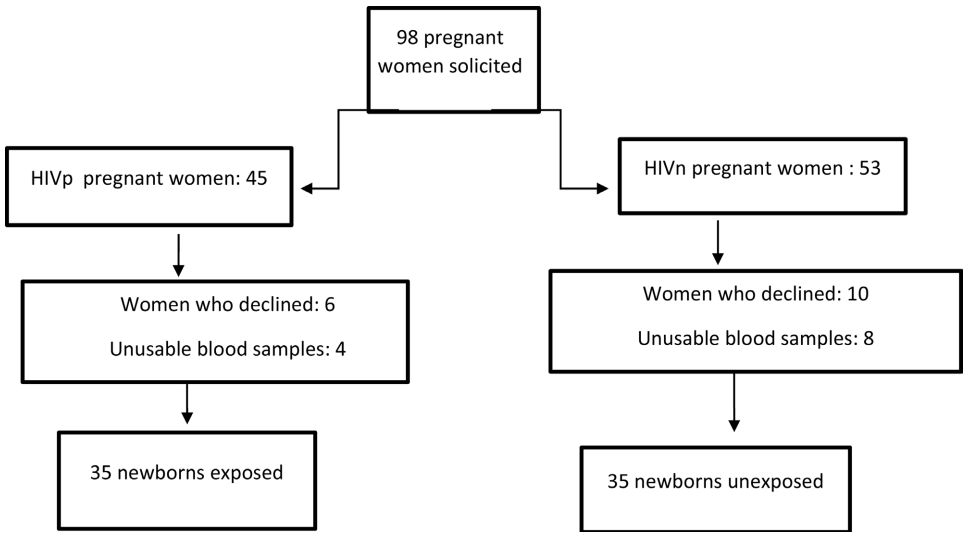

Figure 1. Participant flow chart.

Table 1. Sociodemographic and clinical characteristics of the women.

Characteristics	HIVp N = 35 (%)	HIVn N = 35 (%)	p
Age (SD), years	30.8 (5.1)	29.6 (6.9)	0.791
Matrimonial status (n, %)			
Single	17 (48.6)	17 (48.6)	0.024
Married	7 (20)	15 (48.9)	0.02
Concubine	11 (31.4)	3 (8.6)	0.035
Educational level			
None	2 (5.8)	0	0.082
Primary	4 (11.4)	1 (2.9)	0.075
Secondary	21 (60)	18 (51.4)	0.066
University	8 (22.9)	16 (45.7)	0.018
Profession			
None	6 (17.1)	5 (14.3)	0.023
Student	4 (11.4)	15 (42.9)	0.016
Self-employed	21 (60)	10 (28.6)	0.058
Private sector	4 (11.4)	4 (11.4)	0.089
Public sector	0	1 (2.9)	0.063
Gestational age (weeks)	39.1 ± 1.6	38.5 ± 1.2	0.096
Mode of delivery			
Vaginal	34 (97)	28 (80)	0.055
Cesarean	1 (2.7)	7 (20)	0.095
BMI (DS) (kg/m²) before pregnancy			
<18.5	1 (2.9)	14 (40)	0.746
18.5 - 24.9	12 (34.3)	15 (42.9)	0.084
25 - 29.9	15 (42.9)	6 (17.1)	0.79
>29.9	7 (20)	0 (00)	0.045

SD: standard deviation, BMI: body mass index, Kg/m²: kilogram per square meter

lower in HIV/ARVs exposed group (12.3 mIU/ml vs 30 mIU/ml, $p < 0.001$) See Table 3.

3.3. Association between Insulin Sensitivity and Duration of ARVs Treatment

There was no significant association between HOMA-IR values and duration of antiretroviral treatment as shown in Figure 2.

3.4. Association between Insulin Sensitivity and Newborn Birth Weight

According the bivariate analysis, in two groups of newborns, there was no significant

Table 2. Newborns clinical characteristics.

Characteristics	Exposed N = 35	Unexposed N = 35	p
Sex			
Female, n (%)	17 (48.6)	16 (45.7)	0.792
Male, n (%)	18 (51.4)	19 (54.3)	0.823
Length (SD), cm	49 ± 1.7	49.2 ± 2.4	0.69
Weight (SD), g	3258 ± 296.9	3305 ± 382.6	0.569
Head circumference (SD), cm	34.8 ± 0.9	34 ± 5.5	0.632
Chest circumference (SD), cm	33.7 ± 1.3	33.6 ± 1.7	0.836
Arm circumference (SD), cm	11.3 ± 1	11.2 ± 0.7	0.938

SD: standard deviation, cm: centimeter, g: gram.

Table 3. Distribution of blood glucose, C Peptide and HOMA-IR values of newborns.

Variables	Exposed N = 35	Unexposed N = 35	p
Blood glucose (Q1 - Q3), mmol/l	3.3 (1.3 - 4)	1.3 (1.1 - 4.6)	<0.001
C Peptide (Q1 - Q3), mIU/ml	12.3 (9.2 - 14.2)	30 (24.5 - 51.7)	<0.001
HOMA-IR (Q1 - Q3)	1.4 (0.8 - 1.9)	2 (1.4 - 2.6)	<0.001

Q1: first quartile Q3: third quartile, mmol/l: millimoles per liter, mIU/ml: milli-international units per milliliter.

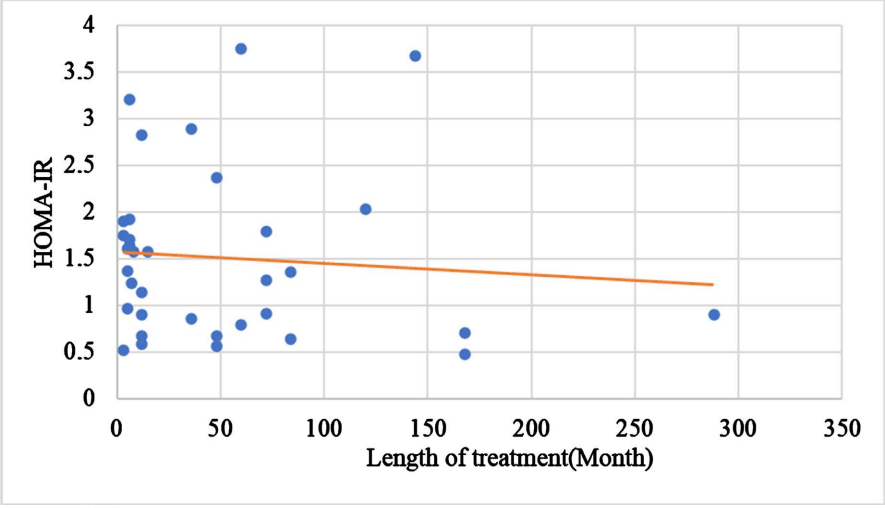

Figure 2. Association between insulin sensitivity and treatment duration.

association between HOMA-IR values and newborn birth weight. The relative risk of newborns with birth between 2500 - 3000, 3000 - 3500, 3500 - 4000 was 1.07 (95% CI: 0.87 - 1.33, p = 0.473), 1.02 (95% CI 0.7 - 1.02, p = 0675) and 1.33 (95% CI: 0.78 - 2.02, p = 0.284) respectively (Table 4).

Table 4. Association between insulin sensitivity and newborn birth weight.

Variables	HOMA-IR < 2.6		RR (95% CI)	p
	No	yes		
Birth weight (g)				
[2500 - 3000], n (%)	10 (90.9)	1 (9.1)	1.07 (0.86 - 1.33)	0.473
]3000 - 3500], n (%)	36 (81.8)	8 (18.2)	1.02 (0.70 - 1.02)	0.675
]3500 - 4000], n (%)	14 (93.3)	1 (6.7)	1.33 (0.78 - 2.02)	0.284

RR: Relative Risk, CI: Confidence Interval.

4. Discussion

The goal of our study was to assess insulin sensitivity of full-term newborns exposed *in utero* to HIV and ARVs using HOMA-IR. Therefore, we recruited 70 full-term pregnant women and their newborns from two maternity wards in the city of Yaoundé, who were divided into two groups: an exposed group consisting of 35 newborns of HIV positive mothers and a control group of 35 newborns of HIV negative mothers. Our main results were as follows: higher blood sugar levels, lower insulin values and HOMA-IR values in the group of newborns exposed *in utero* to HIV and ARVs compared to the control group.

In our study, we noted a predominance of single mothers with a secondary education and an average age of 30.8 ± 5.1 and 29.6 ± 6.9 years in the HIV positive and control group, respectively. This can be superimposed on the study population of Jao *et al.* [10]. About 97% (34/35) of the women were on the tenofovir, lamivudine, effavirenz protocol, and only one of the participants was on tenofovir, lamivudine, dolutegravir. Our results on ARV use are different from those of Jao *et al.* in 2015 who reported that 9.6% of women in their study population were not on ARVs, 21.1% on zidovudine only and 69.2% of women on triple therapy. This can be explained by the improvement of HIV care and strengthening of the prevention of HIV transmission from mother-to-child initiative in various maternities. The latter is likely due to capacity building of staff (midwives), regular supply of ARVs and sensitization of HIV-positive women on the risks of transmission. The median body mass index before pregnancy was 26.3 kg/m^2 (23 - 29.3) which is like that of Jao *et al.* but higher than observed by Simental-Mendia *et al.* [15] who found an average BMI of 23.8 ± 4.3 kg/m^2 prior to pregnancy. This may be due to the diverse dietary habits of different populations. Regarding anthropometric parameters of newborns, we did not note any significant difference between the group exposed to HIV/ARV and the unexposed one. The average weight of exposed and unexposed newborns was 3258 ± 296.9 g and 3305.5 ± 382.63 g respectively. This is similar to Simental-Mendia *et al.* who reported the mean weight as 3278 ± 321 g for newborns at term. We noted higher blood sugar levels in the exposed group versus the unexposed one (3.3 vs 1.3 mmol/l). Additionally, we recorded a drop in insulin secretion (according C peptide values) in exposed newborns which may be linked to mitochondrial toxicity

induced by tenofovir, an observation that could also explain hyperglycemia found in this group. Moreover, some of our maternities habitually administer 10% dextrose infusion to all parturients during labor. According to Pedersen's hypothesis, induced maternal hyperglycemia would lead to fetal hyperglycemia which would consequently induce fetal hyperinsulinism [19]. This physiological phenomenon was found in the control group where high insulin levels were observed for relatively low blood sugar levels compared to the exposed group. The insulin secretion deficit found in the exposed group would thus explain the failure of this physiological phenomenon, hence the relatively higher blood sugar levels in this group. Regarding insulin sensitivity, HOMA-IR values were lower in the exposed group, suggesting better insulin sensitivity in exposed newborns compared to unexposed. The same observation was made by both Jao *et al.* Better insulin sensitivity observed in the exposed group could also be explained by the sparing phenotype theory which stipulates early metabolic adaptations for the survival of the fetus in a more or less hostile intrauterine environment. The thrifty phenotype hypothesis proposes that the epidemiological associations between poor fetal and infant growth and the subsequent development of type 2 diabetes and the metabolic syndrome result from the effects of poor nutrition in early life, which produces permanent changes in glucose-insulin metabolism. These changes include reduced capacity for insulin secretion and insulin resistance which, combined with effects of obesity, aging and physical inactivity, genetic and environmental factors are the most important factors in determining type 2 diabetes field [20]. We could also speculate on the assay method used, namely HOMA-IR. The gold standard for measuring insulin sensitivity remains the hyperinsulinemic euglycemic clamp, a laborious test unsuitable for neonates. However, studies have demonstrated a significant correlation between the HOMA-IR and hyperinsulinemic euglycemic clamp [18] [21]. Thus, the HOMA-IR is the most suitable test for this type of study because it is cheaper and more practical for newborns. Study limitations include the absence of maternal blood glucose levels before and during labor as this would have permitted better correlation with fetal glycemia. In addition, in absence of reference values for HOMA-IR values in pediatric population, we used the references of another study evaluating the insulin sensitivity of newborns.

5. Conclusion

Newborns exposed *in utero* to HIV and ARVs have better insulin sensitivity and lower C peptide values compared to newborns of HIV negative mothers. Our results underline the importance of monitoring pregnant women living with HIV and the impact of the virus and ARVs on offspring metabolism. Close metabolic monitoring of these newborns in the medium and long term and evaluation of their insulin sensitivity with the euglycemic insulin test are necessary for early diagnosis and management of a possible glucose regulation disorder.

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Authors Contribution

Francine Mendane Ekobena and Hortence Fouedjio conducted the study and wrote the manuscript, Audrey Christance Donfack and Gabriel Loni Ekali collected data and did statistical analyses. Suzanne Ngo Um Sap, Martine Claude Etoa Etoga, Mesmin Dehayem and Anne Boli helped with data collection, analysis and interpretation. Jean Claude Mbanya and Eugène Sobngwi supervised the study. All authors read and approved the manuscript.

Ethics Statement

The study was approved by the institutional ethics committees of the Yaoundé Central Hospital and the Social and Health Center of Nkolndongo as well as by the ethics committee of the faculty of medicine and biomedical sciences of the university of Yaoundé 1.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

ARVs: Antiretrovirals
DOHaD: Developmental Origin of Health and Disease
HIV: Human Immunodeficiency viRus
HOMA-IR: Homeostasis Model Assessment-Insulin Resistance
mtDNA: Mitochondrial DNA
NBs: Newborns
WHO: World Health Organization