

Effect of Maternal HIV Infection on Treatment with HAART on Neonatal Birth Weight and Other Anthropometry: A Cohort Study of HIV Sero-Positive Women in Enugu, South-East Nigeria

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ABSTRACT

Introduction: Low Birth Weight (LBW) is associated with poor health conditions during neonatal period, infancy and in adult life. It is possible that some form of fetal growth restriction occurs in babies of HIV sero-positive women.

Aim: To determine the effect of maternal HIV infection on neonatal birth weight and other neonatal anthropometric indices.

Materials and Methods: The study was prospective cohort in design. Neonatal birth weight, head circumference, and crown-heel length of babies of 87 consecutive consenting HAART experienced HIV sero-positive pregnant women on HAART (study group) were compared with those of 92 matched HIV sero-negative women (control group). Data analyses were both descriptive and inferential at 95% confidence level.

Results: The incidence of low birth weight was 25.3% (22/87) among the HIV sero-positive group and 14.1% (13/92) among the control group ($p=0.060$, R.R=1.8, 95% CI: 0.96-3.33). The mean neonatal head circumference in the study and control groups were 33.7 ± 2.93 cm and 34.5 ± 2.31 cm respectively, $p=0.036$ while the mean crown-heel length was 47.9 ± 4.59 cm versus 48.7 ± 4.02 cm, $p=0.217$.

Conclusion: Maternal HIV treatment with Highly Active Antiretroviral Therapy (HAART) was not associated with high incidence LBW in Enugu, Nigeria. However, the head circumference was reduced. Careful measurement of the head circumferences of neonates of HIV sero-positive mothers, during routine new-born examination, is encouraged, so that any disproportionate growth would receive further appropriate assessment.

Keywords: Crown-heel length, HAART experienced, Head circumference, Low birth weight, Maternal HIV sero-positivity

INTRODUCTION

Birth weight is a clinical parameter used for monitoring and analysing events during the antenatal period and also the pregnancy outcomes [1]. LBW is either the result of preterm birth or restricted fetal growth [2] and the later is due to hostile intra-uterine environment. A reduced weight, length and a head circumference of newborn at birth is characteristic of LBW [3]. Newborns with LBW have increased risk of infection and death during neonatal period and infancy [4].

There is now increasing evidence that LBW is associated with several poor health conditions in adult life such as adult onset Diabetes Mellitus, Hypertension, Ischaemic heart diseases, intellectual and sensory disabilities [4]. Hence identifying the determinants of LBW is vital because of the enormous health challenges associated with it.

The burden of HIV/AIDS is still one of the serious health challenges in the world today with the developing countries worse affected while sub-saharan Africa remains by far the most affected region [5,6]. It is believed that HIV per se seem not to affect pregnancy and vice versa [7,8]. However, a previous study has documented some association between anaemia, preterm labour, Intrauterine Growth Restriction (IUGR), fetal distress, still birth and LBW and maternal HIV infection [9]. Furthermore, some studies done in the developing countries reported increased risk of preterm deliveries and delivery of LBW newborns among HIV infected pregnant women [10-13]. However other studies from the developed countries have shown no significant difference in birth weight [14,15]. The pathogenesis of LBW among infants of HIV infected women is not clear. It is being suggested that HIV infected mothers

may have more subclinical chorio-amnionitis compared to those without the virus [16,17].

There are literature that addressed the relationship between HIV infection and pregnancy, however most of these were concerned with the risk of mother-to-child transmission and just few on adverse pregnancy outcome with regards to pregnant women infected with HIV [11]. The proportion of LBW infants especially those exposed to HIV can serve as measures of socio-economic development as well as a measure of quality required mother and child health care needs. This study was aimed at determining the effect of maternal HIV infection on neonatal birth weight, head circumference, and crown-heel length at the University of Nigeria Teaching Hospital, Enugu Nigeria.

MATERIALS AND METHODS

The study was prospective cohort in design. The study participants were drawn from pregnant women attending antenatal care at the antenatal clinic of the University of Nigeria Teaching Hospital (UNTH), Enugu, who intended to deliver at the labour ward of the hospital. The study period was from May 2015 to May 2016. The prevalence of HIV in pregnancy, in Enugu State of Nigeria is the third highest in the South-Eastern geopolitical region of Nigeria [18] while it is 12.4% among antenatal clinic attendee at UNTH [19]. The approval for this study was obtained from the Institutional Review Board (IRB) of the hospital (NHREC/05/01/2008B-F-WA00002458-1RB00002323). There was individual counselling of each women recruited for the study, after which her consent was obtained.

The sample size was calculated using the formula [20]; $n=2 \times (Z\alpha + Z\beta)^2 \times P(1-P) / (P_0 - P_1)^2$ where n =sample size, p =average proportion exposed, $Z\beta$ =Z score determined from statistical table based on acceptable level of power of comparison between groups, $Z\alpha$ =Z score determined from statistical table based on value of level of significance, $P_0 - P_1$ is effect size (difference in proportion expected from previous studies for cases and control). Using the incidence rate of LBW among HIV negative controls in a previous study in Abakalili, Nigeria in 2009 [21], and this study designed to detect a 10% increase in the proportion of low birth weight newborn among pregnant women with HIV infection at 5% (0.05) level of significance and 80% (0.80) power and assuming a 20% loss to follow-up, 200 participants were eligible for the study.

The exposure (study) group consisted of 100 consenting HIV sero-positive pregnant women, at a gestational age of 24 week or less, who were on Highly Antiretroviral Therapy (HAART) and sero-negative to Venereal Disease Research Laboratory (VDRL) test. Exclusion criteria were HIV clinical stage 3 to 4, multiple pregnancy, maternal diabetes mellitus, pre-eclampsia, intrauterine fetal death, women who react to Sulphonamides, women with kidney disease, autoimmune disorders, hypothyroidism, severe vomiting in pregnancy and history of illicit drug use and tobacco. The control group consisted of equal number of HIV negative pregnant women matched for age and parity groups, attending the antenatal clinic of the UNTH and who also intended to deliver at hospital.

Both study and control groups' participants were encouraged to sleep under insecticide treated nets provided for them. Additionally, they received intermittent preventive treatment for malaria with sulphadoxine-pyremethazine (IPT-SP) during the pregnancy according to the prevailing national guideline [22] two doses starting after 16 weeks gestation and separated by interval of one month, for the HIV sero-negative women while the HIV sero-positive women received 3 doses after 16 weeks gestation, separated by the same interval of one month. The HIV sero-positive women received ARV drugs according to the national guideline [23].

At recruitment, relevant information that included maternal age, parity, marital status, occupation, level of education, husband's occupation, history of alcohol and complication during pregnancy was collected using proforma. Clinically evaluation for signs and symptoms of AIDS was done using the WHO clinical case definition [24]. Social classification described by Olusanya BO et al., was used to classify the women into social classes [25]. This was based on education of the woman and the occupation of her husband. This comprised five social classes (I-V). Social classes I and II represented the elites, class III represented the middle class and classes IV and V represented the lowest class. Anthropometric measurements such as, booking weight and height were performed using standard methods [26] and maternal weight was measured at every antenatal visit. Data was obtained from the newborns of participants in both groups and included gestational age at birth, sex, mode of delivery, birth weight, crown-heel length, and the head circumference. The gestational age at birth was determined from the first day of the mother's Last Normal Menstrual Period (LNMP). Calculations from first trimester ultrasound scan were used in cases where the LNMP was not recalled with certainty. LBW was regarded as birth weight less than 2.5 kg [27]. The normal head circumference at term is 35 ± 2 cm [28].

The primary outcome measured was the incidence of low birth weight amongst newborn of HIV sero-positive women and the control group. The secondary outcome measures included the mean head circumference and crown-heel length of newborn in each group.

STATISTICAL ANALYSIS

Data collected was keyed into the Statistical Package For Social Sciences (SPSS) computer software version 20 for windows. Continuous variables were analysed using the mean \pm SD and compared between the two groups using the student t-test.

Proportions were compared using the Pearson's chi square test. Relationships were expressed using relative risks at 95% confidence interval. All tests were two sided and p-value of <0.05 was considered statistically significant.

RESULTS

Two hundred participants were recruited for the study-100 HIV sero-positive women (study group) and a matched control of 100 HIV sero-negative women. Thirteen (13.0%) and 8 (8.0%) participants were lost to follow-up in the study and control groups respectively. Thus, the number of participants analysed was 87 for the study group and 92 for the control group. Basic characteristics of the participants were similar between the study and control groups [Table/Fig-1]. The mean ages of participants were 32.8 (5.38) and 32.9 (5.17) for the study and control groups respectively ($p=0.880$). A majority of the participants belonged to multiparous group (70.1%, 61/87 versus 72.8%, 67/92), and social class III (41.4%, 36/87 versus 46.7%, 43/92).

Characteristics		HIV +ve women (n=87)	HIV -ve women (n=92)	p-value
Age (years)	<20	0 (0.0%)	0 (0.0%)	0.984
	20-24	7 (8.0%)	8 (8.7%)	
	25-29	16 (18.4%)	14 (15.4%)	
	30-34	29 (33.3%)	30 (32.6%)	
	35-39	26 (29.9%)	30 (32.6%)	
	>40	9 (10.3%)	10 (10.9%)	
Parity	1	21 (24.1%)	20 (21.7%)	0.920
	2-4	61 (70.1%)	67 (72.8%)	
	>5	5 (5.7%)	5 (5.4%)	
Social class	Elite (I&II)	19 (21.8%)	26 (28.3%)	0.218
	Middle (III)	36 (41.4%)	43 (46.7%)	
	Low (IV&V)	32 (36.8%)	23 (25.0%)	
Ethnic group	Igbo	64 (73.6%)	65 (70.7%)	0.569
	Hausa	5 (5.7%)	9 (9.8%)	
	Yoruba	8 (9.2%)	11 (12%)	
	Others	10 (11.5%)	7 (7.6%)	
Mode of delivery	Vaginal delivery	42 (48.3%)	51 (55.4%)	0.338
	Caesarean section	45 (51.7%)	41 (44.6%)	

[Table/Fig-1]: Distribution of participants' basic characteristics.

[Table/Fig-2] shows that the major predictors of neonatal birth weight did not differ between the two groups. The mean (SD) weight gain in pregnancy was similar between the HIV sero-positive group {9.4 (2.20) kg} and the control {9.6(2.0 kg)}, $p=0.560$. A majority of the participants in both groups had weight gain in the pregnancy of 10 kg or more (51.7%, 45/87 versus 57.6%, 53/92). The gender distribution of the newborns (male or female) did not differ between the two groups ($p>0.05$). Also, the incidence of preterm delivery in the HIV positive group (11.5%, 10/87) did not differ significantly from that of the control group (16.3%, 15/92), $p=0.353$.

Characteristics	Sub-groups	HIV +ve women (n=87)	HIV -ve women (n=92)	p-value
Weight gain in pregnancy (kg)	<10	42 (48.3%)	39 (42.4%)	0.429
	>10	45 (51.7%)	53 (57.6%)	
Gestational age at delivery (wks)	<37	10 (11.5%)	15 (16.3%)	0.542
	>37	77 (88.5%)	77 (83.5%)	
Gender of newborn	Male	45 (51.7%)	50 (54.3%)	0.725
	Female	42 (48.3%)	42 (45.7%)	

[Table/Fig-2]: Distribution of major predictors of birth weight.

The incidence of low birth weight was 25.3% (22/87) among the HIV sero-positive women and 14.1% (13/92) among the control group; the observed difference was not statistically significant ($p=0.060$, $R.R=1.8$, 95% CI: 0.96-3.33). Likewise, the mean neonatal birth weights of the participants' babies were similar between the two groups {2.9 (0.73) kg versus 3.0 (0.67) kg}, $p=0.413$. The mean head circumference of babies of HIV sero-positive women {33.7(2.93) cm} was significantly lower than 34.5 (2.31) cm observed for the HIV sero-negative control ($p=0.036$). The mean neonatal crown-heel length did not differ between the 2 groups ($p=0.217$). Further details of the anthropometric measurements of babies in the two groups are shown in [Table/Fig-3].

Characteristics	HIV +ve women (n=87)	HIV -ve women (n=92)	p-value
	Mean (SD)	Mean (SD)	
Birth weight (kg)	2.9 (0.73)	3.0 (0.67)	0.413
Head circumference (cm)	33.7 (2.93)	34.5 (2.31)	0.036
Crown-heel length (cm)	47.9 (4.59)	48.7 (4.02)	0.217

[Table/Fig-3]: Effect of maternal HIV infection on birth weight, neonatal head circumference, and crown-heel length.

DISCUSSION

This study showed no significant difference in proportion of low birth weight neonates of HIV positive mothers when compared to the HIV negative controls. This result is similar to the findings of several studies from both developing countries [29,30] and developed countries [15,31]. It is also in keeping with the results of a systematic review by Brocklehurst P et al., [11]. Nevertheless, a significant association between LBW and maternal HIV infection has been reported by few other studies [10,12,27]. The mechanism by which maternal HIV infection could cause adverse prenatal outcome including LBW is currently not well understood [21]. The lack of association between maternal HIV infection and LBW in this study could be due to the use of anti-retro viral therapy like the newer protease inhibitors in the study center. This therapy has been shown to significantly reduce viral load and improve neonatal outcome including birth weight [32].

Low birth weight has strong relationship with maternal weight gain in pregnancy [13]. The maternal weight gain, in this study, did not differ between the HIV positive group and its control. It therefore follows that the comparable neonatal birth weight and LBW incidence, might have been influenced by the comparable maternal weight gain in pregnancy between the HIV positive and the control group. Furthermore, LBW babies are associated with women with poor antenatal attendance [21]. In this study however, participants were compliant with antenatal care services which may explain the comparable LBW between the two groups. Preterm delivery as observed in this study was not associated with maternal HIV infection. This was similar to findings in Rwanda [33] and Lagos, Nigeria [10]. The reason for this could be attributed to the exclusion of participants with factors that could predispose to preterm labour such as use of illicit drugs, smoking and tobacco. HIV infection, no doubt is more common in persons with behavioural attributes such as illicit drug abuse, smoking and alcohol, and these factors may lead to prematurity [12]. Different times of initiation of anti-retroviral therapy in pregnancy, with regard to the trimesters, have been reported to have different influence on the risk of preterm delivery [34]. Initiation of HAART in second trimester was reported by Lopez M et al., to be associated with iatrogenic preterm delivery as against initiation in first trimester [35]. In the present study, participants who were not already on HAART at the time of recruitment, in the second trimester, were excluded. This might also have contributed to the apparent lack of association reported in this study. Newborns exposed to HIV in-utero, have been previously reported vulnerable to stunting,

and their head circumference and crown heel length generally less than the unexposed newborns [36].

The mean head circumferences of newborns in the two groups in the present study are similar to the findings in similar studies in Lagos [10], Nigeria and Kenya [12]. There was a statistically significant difference in the mean head circumference of the newborns of HIV positive mothers when compared to infants of HIV negative mothers. While some previous authors observed similar significant difference [33,37], some others did not find any significant association [10,12,38]. The mechanism by which maternal HIV infection causes reduced head circumference is still unclear. However, the observed difference could be assumed to be due to the direct effect of antiretroviral drugs themselves on fetal development. Nucleoside reverse transcriptase inhibitors have been associated with mitochondrial toxicity and protease inhibitors with endometrial dysfunction [35]. These mechanisms have been related to placenta and vascular damage resulting in disproportionate fetal growth which could affect fetal head development. However further studies with 'strong power' are needed to support this assumption.

The mean crown-heel length in the present study was similar to that found in similar studies [10,12]. There was no statistically significant difference in the mean crown-heel length of newborn of HIV positive mothers and newborns of HIV negative mothers. This was also similar to findings from similar studies [12,38]. However, some studies [10,33,37] reported a significant difference in the crown-heel length between the two groups. The reason for this is unclear and would require further studies. Clinical staging, as was used in the study, is useful in the determination of severity in resource poor settings [12].

LIMITATION

CD4 count and viral load could not be used to determine the severity of HIV infection in the study. Furthermore, the wide confidence intervals obtained in the results of this study suggests that a larger sample size could have improved the study's precision.

CONCLUSION

This study demonstrated that in a population of HAART experienced women, maternal HIV infection had no significant association with the incidence of low birth weight among newborns. On the other hand, while maternal HIV infection did not affect the neonatal crown-heel length, the average neonatal head circumference was significantly lower than that of HIV sero-negative pregnant women. Therefore, during routine newborn examination, clinicians should carefully assess the head circumferences of neonates of HAART experienced HIV sero-positive mothers for any disproportionate growth that may require further assessment and possible intervention.

DECLARATION

We wish to declare that the abstract of this article was presented as 'oral presentation' at the FIGO world congress 2018 at Rio de Janeiro Brazil. No part of the manuscript has been submitted for or has been published.

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