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ORIGINAL PAPER

Effects of Maternal HIV Infection and Alcohol Use in Pregnancy on Birth Outcomes in Uganda

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Abstract
Alcohol use and HIV infection are prevalent in sub-Saharan Africa (sSA), and both are associated with low birth weight. Yet, few studies have evaluated the combined effects of maternal HIV infection and alcohol use on birth outcomes. We analyzed data from a prospective cohort study of HIV-related placental changes in Ugandan women. We defined alcohol use as self-reported alcohol use within the last year, using the AUDIT questionnaire and used linear and logistic regression to measure associations between maternal alcohol use, HIV serostatus, and birth weight. In a subsample, we measured alcohol exposure using phosphatidylethanol (PEth) in neonatal heelstick dried blood spots to confirm maternal alcohol use. Of 352 participants, 176 (50%) were women with HIV (WHIV). Three of 176 (2%) HIVuninfected women and 17/176 (10%) of WHIV self-reported alcohol use (P = 0.002). Maternal HIV infection was associated with lower birth weight (β = −0.12, 95% CI [−0.20, −0.02], P = 0.02), but self-reported alcohol use was not (β = 0.06, 95% CI [−0.15, 0.26], P = 0.54), and the interaction between HIV serostatus and alcohol use was not significant (P = 0.13). Among the PEth subsample, neither HIV status nor PEthconfirmed alcohol use were associated with low birth weight. Maternal HIV infection was associated with lower birth weight, but alcohol use was not, and there was no significant interaction between maternal HIV infection and alcohol use. Alcohol use was more prevalent in WHIV and under-reporting was common. A larger study of the effects of laboratory-confirmed alcohol and HIV exposure on birth outcomes is warranted.

Keywords Maternal HIV · Alcohol · Birth Outcomes · Uganda

Introduction

Alcohol use disorders and HIV infection are both common throughout sub-Saharan Africa (sSA) [1], including Uganda. A cohort study of Ugandan and South African pregnant women with HIV (WHIV) found that up to 40% had biomarker confirmed alcohol use during pregnancy [2]. Furthermore, multiple studies have demonstrated the deleterious relationship between alcohol and HIV in the general population and in pregnancy [1, 3–5]. Despite this, few studies have evaluated the combined effect of HIV and alcohol on low birth weight, especially in sub-Saharan Africa (sSA). Low birth weight is an independent risk factor for morbidity and mortality in the perinatal period and also has far reaching neurodevelopmental consequences on the growth of a child [6–8].

Maternal HIV infection affects birth outcomes and has been associated with low birth weight (LBW) and preterm delivery irrespective of antiretroviral therapy (ART) use [9]. The effects of alcohol use in pregnancy may extend far into childhood, presenting as fetal alcohol spectrum disorders [10, 11].The sole published study measured maternal alcohol use by self-report in a population-based South African cohort [12]. In this study, recent and lifetime alcohol use was associated with LBW, but maternal HIV infection was not, and there was no observed synergistic effect of maternal HIV infection and alcohol use on birth outcomes [12].

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However, the findings of this study were limited by unconfirmed maternal self-reported alcohol use. Prior studies have demonstrated that self-reported alcohol use is an unreliable measure of true alcohol intake, with under-reporting common in both the general population [13, 14] and pregnant WHIV [2], affecting the validity study findings relying on self-reported alcohol intake.

Thus, there remains a gap in knowledge about the combined effects of maternal HIV infection and alcohol use in pregnancy. In response, we analyzed data collected from a prospective cohort of pregnant WHIV and HIV-uninfected comparators in Uganda to examine the combined effects of alcohol and HIV on birth outcomes in sSA using maternal self-reported alcohol use. We also performed a sub-analysis using laboratory-confirmed alcohol use measured as phosphatidylethanol (PEth) concentration in neonatal heelstick dried blood spots for a subsample of the participants' infants. We hypothesized that the combined effects of maternal HIV and alcohol use in pregnancy are associated with a higher risk of adverse birth outcomes than either maternal alcohol use or HIV infection alone.

Methods

This was a cross-sectional secondary analysis of data collected from participants enrolled in a comparative prospective cohort study of placental changes in WHIV, the HIV Infection, Antiretroviral Therapy and Placental Inflammation in Uganda: Potential mechanisms for poor outcomes in HIV-Exposed Infants (PI-study). Participants were recruited in 2017–2018 from Mbarara Regional Referral Hospital (MRRH) in Uganda. Pregnant women were eligible for enrollment into the PI study if they presented to MRRH in labor for delivery, were aged ≥ 18 years, spoke English or Runyankole (the local language), available by phone after discharge, and had a single intrauterine pregnancy. In addition, WHIV were eligible if they reported taking ART in the last 30 days prior to delivery. WHIV and HIV-uninfected women were enrolled consecutively in a 1:1 sampling ratio and questionnaires were administered by trained research assistants during the latent phase of labour. Additional details of the larger study are reported elsewhere [15].

Ethical Considerations

The study was approved by the institutional ethics review boards at Mbarara University of Science and Technology (MUST 11/03–17), Partners Healthcare (2017P001319/MGH) and the Uganda National Council for Science and Technology (HS/2255). All participants provided written informed consent prior to enrollment.

Data Collection

Data was collected by an interviewer-administered structured questionnaire and entered into a Research Electronic Capture (REDCap) database [16]. Data gathered included sociodemographic information, medical and obstetric history, and birth outcomes. Gestational age was calculated using participant-reported last normal menstrual period, or chart documentation if participant report was missing.

Sample Collection

Women who reported HIV-negative serostatus were tested for HIV using a point-of-care antibody-screening test (Determine HIV 1 and 2, Abbott, USA). CD4 + T-cell count and HIV viral load were measured among WHIV if these results were not available in their clinic records within the last six months. Neonatal heelstick was performed within 48 h of birth to prepare dried blood spots (DBS), which were stored at -80 °C prior to shipment for PEth testing. Placentas were collected at the time of delivery and weighed to the nearest 0.1 kg (kg), we used standardized placental weight percentiles to correct the measured placental weight for gestational age.

Alcohol Use

Our primary exposure, maternal alcohol use, was defined as any self-reported alcohol use during the last year. We assessed alcohol use with the AUDIT instrument [17] [18], the AUDIT assesses alcohol use in the past 12 months, we thought this would be important as pre-natal and perinatal alcohol use affects the growing fetus and therefore affecting birth outcomes. We measured PEth in DBS for all neonates with LBW and a randomly selected sample of neonates with normal birth weight to achieve at least a 4:1 ratio of normal:LBW, this was an exploratory case-control sub-analysis to estimate the effect of confirmed alcohol exposure on LBW as we were not able to analyze PEth levels for all neonates. PEth concentration was measured using liquid chromatography and tandem mass spectrometry (LC-MS/MS) [19] at the United States Drug Testing Laboratory (Des Plaines, USA), and reflects the amount of fetal alcohol exposure during the previous 2–3 weeks [20, 21]. A PEth value of ≥ 8 nanogram/mililiter (ng/mL) in neonatal heelstick dried blood spot was considered positive [22].

Birth Outcomes

Neonatal weight was measured within 24 h of delivery, to the nearest 0.1 kg by trained midwives using a weighing scale that was calibrated. Our primary outcome was birth

Table 1 Baseline characteristics of study participants ($N=352$) and unadjusted associations with birth weight

	n [%]	Unadjusted β (95% CI[c])	*P*-value
Maternal characteristics			
Age in years, median [IQR[a]]	26 [22–30]	0.02 (0.01, 0.02)	< 0.001
Married	317 [90]		< 0.001
HIV-positive	176 [50]	0.11 (0.02, 0.21)	0.01
Self-reported alcohol use in the last year	20 [6]	0.01 (-0.17, 0.19)	0.89
Completed primary education or less	207 [59]	0.06 (-0.03, 0.16)	0.20
Household asset index		0.05 (-0.06, 0.17)	0.37
Low	118 [34]		
High/medium	234 [67]		
Parity, mean [SD[b]]	2.9 [1.6]	0.05 (0.01, 0.08)	< 0.001
Neonatal characteristics			
Birth weight (kg), mean [SD]	3.2 [0.5]		
Gestational age (weeks), mean [SD]	39.1 [1.9]	0.06 (0.03, 0.09)	< 0.001

[a]IQR: interquartile range, [b]SD: standard deviation [c]95% CI: 95% confidence interval

weight [23] measured as a continuous variable. LBW was defined as birth weight < 2.5 kg and selected as an additional outcome because it is an independent risk factor for neonatal mortality and morbidity. [6, 7].

Statistical Analysis

Continuous variables were described using frequencies and proportions for categorical variables and means and standard deviations (SD) for continuous variables. Our primary analysis was a linear regression model with birth weight in kgs as the outcome measure and self-reported maternal alcohol use and HIV serostatus as exposures. In an exploratory linear regression model limited to WHIV, we included variables associated with birth weight in prior studies (parity, gestational age, maternal age and asset index as a measure of socioeconomic status) as potential confounders. We assessed for interaction between maternal HIV serostatus and alcohol use. We also created a logistic regression model restricted to participants with PEth measurements, with LBW as the outcome and PEth-confirmed alcohol use (PEth ≥ 8 ng/mL in heelstick blood) and maternal HIV serostatus as exposure variables.

We used STATA™ version 13 to perform the above analyses.

Table 2 Unadjusted and adjusted associations of HIV infection and alcohol use with birth weight (N = 352)

Variable	Unadjusted β coefficient (95% CI[a])	*P*-value	Adjusted β coefficient (95% CI)	*P*-value
Self-reported alcohol use in the last year	0.01 (-0.19, 0.22)	0.90	0.06 (-0.15, 0.26)	0.54
HIV-positive serostatus	-0.11 (-0.21, -0.02)	0.02	-0.12 (-0.20, -0.02)	0.02
HIV · alcohol product term			-0.43 (-0.98, 0.13)	0.13

[a]95% CI: 95% confidence interval

Results

The analysis included 352 women. Of these, 176 (50%) were WHIV, of whom 74% (130/176) had undetectable HIV viral load (< 40 copies/ml). Median CD4 + T-cell count was 436 (interquartile range [IQR] 308–617) cells/mm^3. The median age was 26 years [IQR 22–30], and mean parity was 2.6 (standard deviation [SD] 1.64). The majority, 90% (317/352), were married, and 59% (207/352) completed at least primary-level education. Mean gestational age was 39.1 (SD 1.9) weeks. (Table 1)

Overall, 6% (20/352) self-reported any alcohol use in the prior 12 months. Prevalence of self-reported alcohol use was higher among WHIV than HIV-uninfected participants (10% [17/176] versus 2% [3/176], $P=0.002$). The gestational age corrected placental weight percentile did not vary by HIV status (p = 0.23). Among the subsample with PEth-measured alcohol use ($n=79$), 18% (14/79) were LBW. Alcohol exposure prevalence (by self-report and/or PEth positivity) was 21% (3/14) among LBW neonates and 22% (14/65) among normal birth weight neonates. PEth was positive in 17% (13/75) of women reporting no alcohol use, of whom 62% (8/13) were WHIV. Of the sub-sample, only 8% (6/79) had confirmed heavy alcohol use, i.e., PEth levels ≥ 50ng/mL.

In the primary linear regression model including all participants, maternal HIV serostatus was associated with lower birth weight, (β=-0.12, 95% CI [-0.20, -0.02], $P=0.02$), but self-reported alcohol use was not (β = 0.06, 95% CI [-0.15, 0.26], $P=0.54$, Table 2). In an exploratory linear regression model limited to WHIV and adjusting for potential confounders, the association between maternal alcohol use and birth weight was not statistically significant (Table 3). The interaction term between maternal HIV infection and alcohol use was not significant (β=-0.43, 95% CI [-0.98, 0.13], $P=0.13$, Table 2). Among the subsample with PEth-measured alcohol use, neither HIV serostatus (adjusted odds ratio [aOR] = 0.67, 95% CI [0.19, 2.36], $P=0.52$) nor confirmed alcohol use (aOR = 0.68, 95% CI [0.15, 3.15], $P=0.63$) were associated with low birth weight.

Table 3 Unadjusted and adjusted associations with birth weight in an exploratory model limited to WHIV (n = 176)

Variable	Unadjusted β coefficient (95% CI[a])	*P*-value	Adjusted β coefficient (95% CI)	*P*-value
Self-reported alcohol use in the last year	-0.01(-0.23, 0.20)	0.91	-0.03 (-0.23, 0.17)	0.76
Age	0.02 (0.01, 0.03)	0.002	0.01 (-0.01, 0.03)	0.07
Low asset index	0.01(-0.02, 0.05)	0.51	0.01 (-0.02, 0.02)	0.52
Parity	0.11(0.02, 0.19)	0.02	0.02 (-0.03, 0.76)	0.52
Gestational age (weeks)	0.06 (0.03, 0.09)	< 0.001	0.06 (0.03, 0.09)	< 0.001

[a]95% CI: 95% confidence interval

Discussion

We examined the combined effects of maternal alcohol use and HIV infection on birth outcomes among women living in Uganda who presented in labor. We found that maternal HIV infection was associated with a small, but statistically significant decrease in birth weight, but that self-reported alcohol use in the past year was not. The interaction term between maternal HIV serostatus and alcohol use was not statistically significant, indicating that the effects of alcohol on birth weight did not appear to meaningfully differ by maternal HIV status. In an adjusted model restricted to WHIV, we again found no significant association between maternal alcohol use and birth weight. Moreover, in the logistic regression model restricted to participants with PEth measurements, confirmed alcohol use was also not associated with LBW.

Prior studies have also reported an association between maternal HIV infection and lower birth weight. [9, 24, 25] Low birth weight in WHIV may result from HIV replication in the placenta, [26] altered cytokine profiles, [27] placental insufficiency and intrauterine growth restriction, [28] especially in WHIV with incomplete ART response. In prior studies, maternal CD4 count < 200 or < 350 cells/ml^3 were associated with lower birth weight. [29, 25] The median CD4 count in our cohort was over 400 cells/ml^3 implying greater immune reconstitution, likely minimizing negative effects on birth weight seen at lower CD4 counts. Furthermore, 74% of participants had undetectable HIV viral load, suggesting HIV replication leading to inflammation and placental insufficiency is unlikely the sole cause of LBW in children born to these women.

Similar to other studies of low-moderate maternal alcohol use [30, 31], neither self-reported nor PEth-confirmed alcohol use was associated with birth weight in our study. By contrast, heavy alcohol use has been associated with lower birth weight in previous studies. [32] Because few participants in our cohort were heavy alcohol users, we were unable to explore this relationship. Also, the effect of alcohol on birth outcomes is more pronounced when used in the first trimester, [33] and first trimester use would not be captured by neonatal PEth results. Thus, our analysis may have missed potential associations between pre- or early-pregnancy alcohol use and birth weight.

Our finding of lack of a combined effect of maternal HIV infection and alcohol use on birth weight is similar to a published study of 667 mother-infant dyads, 131 (20%) of whom were WHIV taking ART. Only 3% (21/667) self-reported heavy alcohol use, and the effect of alcohol use on birth weight was the same in WHIV and HIV-uninfected women. [12].

Strengths of our study include large cohort size with equal-sized populations of WHIV and HIV-uninfected women, and biomarker confirmation of alcohol use in a subsample of participants. The latter is especially important because more WHIV underreported their alcohol use than HIV-uninfected women (62% vs. 38%, consistent with data from other cohorts of WHIV [2] and may result from social desirability bias. [34] Limitations of our study include inability to confirm self-reported alcohol use with PEth testing for the all participants due to limited funds, this could have resulted in misclassification. Furthermore, self report may capture some first-trimester alcohol use, but neonatal PEth concentrations may not reflect alcohol use in early pregnancy that could have a greater impact on birth weight. In addition, only 8% of the PEth-measured subsample had heavy alcohol use in pregnancy, which limited power to detect an association between heavy alcohol use and birth weight. Finally, our analysis used secondary data collected as part of a larger study and the relatively small number of LBW neonates meant that logistic regression models could not be adjusted for potential confounders. A larger study of the combined effects of maternal alcohol use and HIV on birth outcomes including objective measures of fetal alcohol exposure is warranted.

Conclusions

Maternal HIV infection was associated with lower birth weight, but low-to-moderate alcohol use was not. We found no statistically significant interaction between HIV infection and alcohol use in regression models, indicating no large differential effect of alcohol use on birth weight by maternal HIV serostatus. Self-reported alcohol use was more prevalent in WHIV than HIV-uninfected pregnant women and under-reporting was common, especially among WHIV.

Furthermore, efforts should be made to reduce alcohol use among pregnant WHIV in sSA.

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Declarations

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Conflict of Interest None of the authors have a commercial or other association that might pose a conflict of interest.

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