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FETAL BIOMETRY SIMILAR WITH DOLUTEGRAVIR OR EFAVIRENZ EXPOSURE

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BACKGROUND

Pregnant women living with HIV (PWLHIV) are increasingly receiving dolutegravir (DTG) worldwide and in Botswana. Few studies have assessed fetal biometry in PWLHIV on DTG-based antiretroviral therapy (ART).

OBJECTIVE

To evaluate fetal biometry in PWLHIV on DTG-based or efavirenz (EFV)-based ART compared to HIV-uninfected (HIV-U) pregnant women in Botswana.

METHODS

Study Design: Cross-sectional analysis within cohort study.
Inclusion Criteria: PWLHIV receiving tenofovir and emtricitabine plus DTG or EFV and HIV-U pregnant women 16-36 weeks gestational age (GA) from antenatal clinics in Gaborone, Botswana.
Exclusion Criteria: Pregnancies with multiple gestations or ending in fetal demise.
Primary Outcome: Fetal biometry obtained via ultrasound exam at 24-36 weeks GA. Head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC), and femur length (FL) were measured.
Primary Exposure of Interest: 1) Fetal exposure to HIV, 2) Fetal exposure to DTG vs EFV among HIV/ART-exposed fetuses.
Statistical Analysis: Z scores for HC (HCZ), BPD (BPDZ), AC (ACZ), and FL (FLZ) were calculated using Intergrowth-21st references. Linear regression models were fit to assess the association of *in utero* HIV/ART exposure with each fetal biometric Z score. Sub-group analyses were performed among PWLHIV to assess the association of DTG vs. EFV with fetal biometry.

TABLE 1. CHARACTERISTICS OF PREGNANT WOMEN AND THEIR FETUSES BY HIV/ANTIRETROVIRAL EXPOSURE AT ENROLLMENT

WOMEN	PWLHIV (n=268)	HIV-uninfected (n=167)	*p* value
Maternal age, years	28.9 (25.2, 34.4)	24.5 (21.3, 29.1)	*<0.01*
Gravidity	3 (2,3)	1 (1,3)	*<0.01*
Married	17 (6.3)	18 (10.8)	*0.10*
Highest education level			
Secondary school or less	243 (90.7)	115 (68.9)	*<0.01*
Tertiary school or higher	25 (9.3)	52 (31.1)	
Alcohol use during pregnancy	16 (5.9)	6 (3.6)	*0.27*
Tobacco use during pregnancy	0 (0.0)	1 (0.6)	*0.38*
History of chronic HTN pre-pregnancy	9 (3.4)	2 (1.2)	*0.22*
Maternal height	160.8 (155.5, 165.0)	161.0 (157.0, 165.0)	*0.56*
Systolic BP, mm Hg	109 (102, 119)	109 (103, 118)	*0.67*
Diastolic BP, mm Hg	69 (62.0, 75.5)	67 (62, 73)	*0.06*
FETUSES			
	HIV/ARV-exposed	HIV/ARV-unexposed	*p* value
GA at ultrasound, weeks	28 (25, 31)	26 (25, 29)	*0.01*
Head circumference z score	-0.30 (-1.04, 0.28)	-0.26 (-0.97, 0.39)	*0.15*
Biparietal diameter z score	0.09 (-0.63, 0.82)	0.07 (-0.64, 0.68)	*0.22*
Abdominal circumference z score	0.00 (-0.40, 0.82)	0.00 (-0.54, 0.84)	*0.57*
Femur length z score	1.45 (0.67, 2.05)	1.24 (0.45, 2.04)	*0.22*

Continuous variables expressed as median (Interquartile range) and categorical variables as n (%). P values calculated from Wilcoxon, Chi-square or Fisher's exact tests as appropriate. ARV=Antiretroviral, BP=Blood pressure, GA=Gestational age, HTN=Hypertension, PWLHIV= Pregnant Women Living with HIV

TABLE 2. CHARACTERISTICS OF PREGNANT WOMEN LIVING WITH HIV AND THEIR FETUSES BY ANTIRETROVIRAL EXPOSURE AT ENROLLMENT

WOMEN	TDF/FTC/DTG (n=176)	TDF/FTC/EFV (n=92)	*p* value
Maternal age, years	28.2 (24.7, 33.1)	30.5 (26.8, 36.0)	*0.01*
Gravidity	2 (2,3)	3 (2,4)	*0.13*
Married	7 (4.0)	10 (10.9)	*0.03*
Highest education level			
Secondary school or less	157 (89.2)	86 (93.5)	*0.25*
Alcohol use during pregnancy	11 (6.3)	5 (5.4)	*0.79*
Tobacco use during pregnancy	0 (0.0)	0 (0.0)	*1.00*
History of chronic HTN pre-pregnancy	6 (3.4)	3 (3.3)	*0.95*
Maternal height	160.3 (155.8, 165.0)	161.0 (155.0, 166.0)	*0.61*
Systolic BP, mm Hg	109 (102, 119)	109.0 (102.5, 118.5)	*0.88*
Diastolic BP, mm Hg	69 (63, 76)	69 (62, 75)	*0.46*
CD4 cell count, cells/mm³			
<200	12 (6.8)	3 (3.3)	*0.30*
201-500	86 (48.9)	41 (44.6)	
>500	78 (44.3)	48 (52.1)	
HIV RNA level, copies/mL			
<40	160 (90.9)	87 (94.6)	*0.36*
40-1000	10 (5.7)	5 (5.4)	
1001 – 10,000	2 (1.1)	0 (0.0)	
>10,000	4 (2.3)	0 (0.0)	
Duration on ART, weeks	15.3 (9.5, 24.6)	27.6 (24.9, 30.4)	*<0.01*
FETUSES			
GA at ultrasound, weeks	28 (25, 31)	28 (25, 30)	*0.43*
Head circumference z score	-0.39 (-0.98, 0.30)	-0.62 (-1.11, 0.14)	*0.15*
Biparietal diameter z score	0.14 (-0.60, 0.89)	0.34 (-0.35, 0.71)	*0.27*
Abdominal circumference z score	0.31 (-0.42, 0.74)	0.34 (-0.35, 1.03)	*0.15*
Femur length z score	1.42 (0.56, 1.96)	1.49 (0.82, 2.15)	*0.24*

Continuous variables expressed as median (Interquartile range) and categorical variables as n (%). P values calculated from Wilcoxon, Chi-square or Fisher's exact tests as appropriate. ART=Antiretroviral therapy, BP=Blood pressure, DTG=dolutegravir, EFV=efavirenz, FTC=emtricitabine, GA=Gestational age, HTN=Hypertension, TDF=tenofovir

TABLE 3. LINEAR REGRESSION MODELS FOR FETAL BIOMETRIC MEASUREMENT OUTCOMES COMPARING MATERNAL HIV INFECTION VS NON-INFECTION AND TENOFOVIR/EMTRICITABINE/DOLUTEGRAVIR VS TENOFOVIR/EMTRICITABINE/EFAVIRENZ EXPOSURES

	HCZ		BPDZ		ACZ		FLZ	
Exposure of Interest	Coefficient	*p* value	Coefficient	*p* value	Coefficient	*p* value	Coefficient	*p* value
Maternal HIV infection vs. non-infection *	-0.11	0.32	-1.68	0.15	-0.19	0.30	0.14	0.32
TDF/FTC/DTG vs TDF/FTC/EFV ^	0.14	0.29	0.21	0.21	-0.21	0.33	-0.13	0.42

ACZ=abdominal circumference z score, BPDZ=biparietal diameter z score, DTG=dolutegravir, EFV=efavirenz, FLZ=femur length z score, HCZ=head circumference z score, TDF=tenofovir, FTC=emtricitabine.
**Model adjusted for maternal age, gravidity, education level, height, and alcohol use in pregnancy.*
^Model adjusted for maternal age, gravidity, education level, height, alcohol use in pregnancy, and CD4

RESULTS

- Of 435 pregnant women, 176 received DTG-based ART, 92 efavirenz (EFV)-based ART, and 167 were HIV-U.
- PWLHIV were older (28.9 vs 24.5 years, *p=<0.01),* higher in gravidity (3 vs 1, *p<0.01),* and less likely to have completed tertiary education (9.3% vs 31.1%, *p<0.01*) than HIV-U women. (Table 1)
- GA at ultrasound was higher in PWLHIV than HIV-U women (28 vs 26 weeks, *p=0.01).*
- Among PWLHIV, women on DTG were younger (28.2 vs 30.5 years, *p=0.01*) with shorter ART duration prior to ultrasound (15.3 vs 27.6 weeks, *p<0.01*) than those on EFV. (Table 2)
- In unadjusted analyses, median HCZ, BPDZ, ACZ, and FLZ did not differ between fetuses of PWLHIV vs HIV-U women (-0.30 vs -0.26, *p=0.15*; 0.09 vs 0.07, *p=0.22*; 0.00 vs 0.00, *p=0.57* and 1.45 vs 1.24, *p=0.22,* respectively). (Table 1)
- This relationship persisted after adjusting for maternal age, height, education level, gravidity and alcohol use in pregnancy. (Table 3)
- There were no differences in fetal biometry between fetuses exposed to DTG vs EFV (HCZ: -0.39 vs -0.62, *p=0.15*, BPD: 0.14 vs 0.34*, p=0.27*, ACZ: 0.31 vs 0.34, *p=0.15,* and FLZ: 1.42 vs 1.49, *p=0.24*). (Table 2)
- This relationship remained after adjusting for maternal age, height, education level, gravidity, alcohol use, as well as CD4 count. (Table 3)

CONCLUSIONS

In this small Botswana cohort, there does not appear to be a substantial association between *in utero* HIV/ARV exposure and fetal biometry or between *in utero* DTG vs EFV exposure and fetal biometry. While these results are reassuring and support continued use of these regimens in pregnancy, larger studies with serial ultrasounds are needed to validate these findings.

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