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Original article

Maternal post-absorptive leucine kinetics during late pregnancy in US women with HIV taking antiretroviral therapy: A cross-sectional pilot study

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SUMMARY

Background: Despite the success of combination antiretroviral therapy (cART) for the prevention of mother to child transmission of HIV, infants exposed to cART *in utero* frequently are born smaller and have mild cardiac abnormalities. The mechanisms responsible for lower birth weight and cardiac abnormalities in children exposed to cART are unclear but could be related to dysregulation of maternal amino acid metabolism during pregnancy. Previous data in HIV(−) women have shown a relationship between abnormal maternal protein metabolism during pregnancy and low infant birth weight and animal data demonstrate a relationship between altered maternal protein metabolism and increased risk for offspring cardiovascular abnormalities.

Objective: The objectives of this study were to: 1) characterize post-absorptive maternal leucine kinetics during late pregnancy and 2) examine the relationships between maternal leucine kinetics and offspring birth weight and cardiac function.

Design: Post-absorptive maternal leucine kinetics (evaluated by using stable isotope tracer methodology) in 16 HIV(+) women receiving cART and 14 HIV(−) US women during the 3rd trimester of pregnancy were compared. Relationships between post-absorptive maternal leucine kinetics, cardiac function (echocardiography) and birth weight were statistically examined.

Results: Maternal plasma leucine concentration (HIV(−): 82.8 ± 10.7 vs. HIV(+): 72.3 ± 13.5 μM, $p = 0.06$) and leucine oxidation rate (HIV(−): 6.1 ± 1.6 vs. HIV(+): 4.9 ± 1.8 μmol/kgBW/min, $p = 0.03$) were lower in HIV+ women compared to controls. Total leucine turnover rate, non-oxidative leucine disposal rate and post-absorptive maternal glucose and palmitate kinetics did not differ between groups. Left ventricular fractional shortening tended to be lower in children born to HIV(+) compared to controls (HIV(−): 42 ± 1 vs. HIV+: 36 ± 5%, $p = 0.08$) and associated with lower maternal plasma leucine concentration ($r = 0.43$, $p = 0.08$).

Conclusions: Preliminary results indicate that post-absorptive maternal leucine metabolism during late pregnancy is mildly altered in HIV+ US women taking cART. The clinical significance of maternal leucine metabolism on adverse infant outcomes is unclear and should be further explored in more expansive studies.

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1. Introduction

Annually over 1.4 million children are born to women with HIV-infection world-wide [1]. Combination antiretroviral treatment (cART) is effective in preventing the vertical transmission of Human Immunodeficiency Virus (HIV) from mother to child during pregnancy and parturition [2–4]. However children exposed to cART *in utero*, regardless of their HIV status appear to be at a greater risk for lower birth weight [5,6] and stunted growth and wasting [7,8], particularly in less developed countries. In addition, children exposed to cART *in utero* are born with minor cardiac abnormalities [9] that persist into pre-adolescence [10].

Mechanisms for lower birth weight and impaired cardiac abnormalities in offspring exposed to cART are unclear. In HIV(−) women, abnormalities in protein metabolism (i.e. intake) during pregnancy is associated in lower offspring birth weight [11,12]. In non-HIV animal models, maternal protein restriction during pregnancy results in lower offspring birth weight [13] and abnormalities in molecular regulators of cardiac growth [14]. In addition, in a rodent model of intrauterine growth restriction (a condition where offspring are born smaller and frequently have cardiovascular abnormalities), maternal leucine turnover, concentration and fetal leucine delivery is blunted [15,16].

Disruptions in amino acid metabolism are well-known in HIV(+) adults both taking and not taking cART [17–19], however, little is known regarding maternal amino acid metabolism during HIV(+) pregnancy and its potential effects on infant birth weight and cardiac function. Based on previous findings of insulin resistance [20,21] and impaired fatty acid oxidation [22] in non-gravid HIV(+) adults, we hypothesized that maternal leucine utilization (i.e. oxidation rate) during HIV(+) pregnancy would be higher in order to meet maternal energy needs (i.e. to compensate for insulin resistance and lower fatty acid oxidation) leaving less leucine (i.e. lower plasma concentration and leucine non-oxidative disposal rate) available for fetal growth and metabolism. Subsequently, reduced maternal amino acid delivery to the fetus could contribute to lower birth weight and cardiac function in the offspring by limiting the amount of leucine or by disrupting growth signaling needed for fetal organ growth and maturation. Therefore, our primary aim was to compare post-absorptive maternal leucine kinetics in late pregnancy between women with and without HIV taking cART. Our secondary aim was to examine the relationships between maternal post-absorptive leucine kinetics and infant birth weight and cardiac function. We also measured maternal glucose and fatty acid kinetics in order to examine leucine kinetics in the context of overall maternal substrate metabolism. Identification of mechanisms for abnormalities in infant body composition and cardiac structure and function in children exposed to HIV and cART may lead to nutritional optimization strategies for HIV+ pregnancy; especially important in resource limited countries and in those who are socio-economically disadvantaged, where nutrition is often sub-optimal.

2. Participants

Pregnant women were recruited from January 2009–December 2010. HIV-infected women (n = 16) were recruited from the AIDS Clinical Trials Unit and the Infectious Diseases Clinics at Washington University School of Medicine (WUSM), and HIV-negative women (n = 14) were recruited from the WUSM/Barnes Jewish Hospital Women's Health Clinic. Twenty HIV(+) pregnant women were screened and 16 agreed to participate and were enrolled; and 19 HIV(−) pregnant women were screened and n = 14 agreed to participate and were enrolled in the study (total n = 30). All HIV(+) women were infected less than 10 years and did not have Acquired Immune Deficiency Syndrome (AIDS). HIV(+) women were taking combination antiretroviral therapy (cART) during their pregnancy and all but three HIV(+) women had undetectable viral loads at the time of the metabolic study (Table 1). Twelve (n = 12) of 16 HIV(+) women were taking combivir (lamivudine/zidovudine) and all were taking a protease inhibitor. Eleven (n = 11) of 16 HIV(+) women received intravenous zidovudine during parturition. All enrolled HIV(+) and HIV(−) women were excluded if they had current or a history of gestational diabetes, were not sedentary (exercise ≥ 2×/week), had multiple pregnancies, had a fetal abnormality (as determined by routine standard of care

Table 1
Maternal demographic and metabolic variables.

Variable	HIV(−) (n = 14)	HIV(+) (n = 16)	p-Value
Age (yrs)	26 ± 5 (23,29)	26 ± 4 (24,28)	0.89
Race (n, white/black)	4/10	2/14	0.13
Height (cm)	164.7 ± 4.7 (162.2,167.2)	165.5 ± 8.6 (161.3,169.7)	0.68
Weight at study (kg)	86.0 ± 24.3 (73.3,98.7)	85.3 ± 22.1 (74.5,96.1)	0.70
GWG (kg)	17.2 ± 6.9 (13.6,20.8)	17.7 ± 21.2 (7.3,28.1)	0.20
Smoking during pregnancy (n)	4	7	0.39
HIV duration (yrs)	N/A	5.3 ± 3.4 (3.6,8.7)	
3rd trimester CD4 (cells/dL)	N/A	509 ± 205 (409,609)	
3rd trimester viral load (copies/mL)			
<400 (%)	N/A	88	
400–1000 (%)	N/A	12	
Hematocrit	31.0 ± 1.9 (30,32)	28.7 ± 3.3 (27.1,30.3)	0.05
HbA1C (%)	5.1 ± 0.8 (4.7,5.5)	5.4 ± 1.4 (4.7,6.1)	0.65
Fasting glucose (mg/dL)	77.4 ± 5.8 (74.4,80.4)	76.9 ± 7.1 (73.4,80.4)	0.76
Fasting insulin (μU/mL)	12.9 ± 12.3 (6.5,19.3)	9.1 ± 5.4 (6.5,11.8)	0.79
TG (mg/dL)	150.2 ± 36.2 (131.2,169.2)	160.3 ± 61.1 (130.4,190.2)	1.00
HDL (mg/dL)	65.5 ± 15.6 (57.3,73.7)	60.0 ± 12.1 (54.1,72.1)	0.36
LDL (mg/dL)	109.1 ± 22.9 (97.1,121.1)	86.8 ± 36.6 (68.9,104.7)	0.24
Chol (mg/dL)	204.7 ± 38.9 (184.3,225.1)	178.9 ± 38.2 (160.2,197.6)	0.10
FFA (μmol/L)	467.9 ± 103.7 (413.6,522.2)	555.0 ± 122.5 (495.0,615.0)	0.06
βHB (μmol/L)	318.1 ± 149.7 (239.7,239.7)	317.2 ± 166.4 (235.7,398.7)	0.92
Growth hormone (ng/ml)	0.48 ± 0.69 (0.12,0.84)	0.39 ± 0.34 (0.22,0.56)	0.53
Cortisol (ug/dL)	23.4 ± 6.9 (19.8,27.0)	21.7 ± 4.7 (19.4,24.0)	0.53
IGF-1 (ng/mL)	375.8 ± 211.2 (164.6,486.4)	249.8 ± 101.6 (200.0,299.6)	0.11

Values are mean ± SD (95% CI). GWG: gestational weight gain, TG: triglyceride, HDL: high density lipoprotein, LDL: low density lipoprotein, Chol: total cholesterol, FFA: free fatty acid, βHB: beta hydroxy butyrate, IGF-1: insulin-like growth factor 1.