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Gestational Diabetes Mellitus and Dyslipidemia in HIV-Infected Pregnant Women Receiving PIs Based HAART

Natthawut Wetchitticharean MD,
Suvanna Asavapiriyanont MD.

Department of Obstetrics and Gynecology, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand

ABSTRACT

Objectives: To evaluate the incidence of gestational diabetes mellitus (GDM), altered lipid metabolism and birth weight in human immunodeficiency virus (HIV) infected pregnant women receiving protease inhibitor (PIs) based highly active antiretroviral therapy (HAART).

Materials and Methods: A cross-sectional descriptive study of 109 HIV-infected pregnant women receiving PI-based HAART to prevent vertical viral transmission from Rajavithi and Nopparatrachathani Hospital was conducted from October 2010 to July 2012. A 100-gm oral glucose tolerance test was performed in women with abnormal 50-gm glucose challenge test during 2nd to 3rd trimester and lipid profile was measured after the 4th week of treatment. Statistics such as number and percentage were used for descriptive data. Odds ratio (OR) with 95% confidence interval (CI), Chi-square, t-test and paired t-test were used for comparison with significance at p-value < 0.05.

Results: The patients' mean age was 28.9 years, most (79.8%) were naïve for HAART before pregnancy. The incidence of GDM was 7.3%. There was an increase in post treatment level of total cholesterol (TC) and triglyceride (TG) at 18.9 mg/dL (95%CI, 9.5-28.4) and 97.2 mg/dL (95%CI, 70.9-123.3), respectively. The incidence of low birth weight was 17.4%.

Conclusion: Use of PI-based HAART in pregnant women was associated with increased GDM and altered lipid metabolism.

Keywords: gestational diabetes mellitus, dyslipidemia, PIs-based HAART, HIV-Infected pregnant women, low birth weight

Introduction

In 2009, Ministry of Public Health of Thailand declared the new policy on Prevention of Mother to Child HIV Transmission (PMTCT) program with the goal of mother to child transmission rate of HIV beneath 3.5%. A boosted protease inhibitors (PIs) based highly active antiretroviral therapy (HAART) has been substituted for non-nucleoside reverse transcriptase inhibitors (NNRTI) based regimen prescribed earlier[1]. The PI-based regimen can reduce the risk of drug resistance and side effects from Nevirapine, but the safety of this regimen in pregnant women is still questioned. The PI-based regimens have been highly successful in controlling HIV viral load and can reduce vertical viral transmission but their benefits are

compromised by numerous undesirable side effects[2,3]. These include tissue insulin resistance and overt hyperlipidemia, which may be aggravated by the normal physiologic changes of carbohydrate and lipid metabolism during pregnancy[4-7]. Impaired fetal growth also has been concerned because higher incidence of low birth weight was reported[8].

The aim of this study is to evaluate the incidence of gestational diabetes mellitus (GDM), altered lipid metabolism and birth weight of the infants in HIV infected pregnant women receiving PI-based HAART.

Materials and methods

After approved by ethic review board committee, a cross-sectional descriptive study from Rajavithi and Nopparatrachathani Hospital was conducted from October 2010 to July 2012. A sample size was calculated using one single proportion with number of study equal to 101. The data was collected and reviewed from medical records of 112 HIV-infected pregnant women who receiving PI-based regimen (Lopinavir/Ritronavir; 400/100 mg twice daily) on PMTCT program. The women who had pregestational diabetes or received corticosteroids during pregnancy were excluded from the study. One hundred and nine cases met the criteria. They were closely monitored during pregnancy, delivery and puerperium. The information recorded including HIV history, obstetric data, GDM risk factors (previous GDM, BMI ≥ 30 kg/m^2, urine glucose ≥ 1$^+$, 1st degree relative with DM, history of stillbirth or DFIU, previous birth weight > 4,000 gm), body mass index (BMI), total weight gain and adverse drug effect from prior to current regimens.

In addition to routine prenatal blood test, fasting blood sugar, CD4 count, viral load and lipid profile were checked in the first prenatal visit, and reevaluated at the 4th weeks of therapy.

Screening for GDM with the O'Sullivan technique had been performed on all HIV-infected pregnant women at 24-28 weeks. In some cases, the pregnant women come to clinic lately such as 28 wks of GA, the test was postponed for four weeks (performing at 32 wks) after initiate drug regimens[9]. The patients whose 50-g glucose challenge test were ≥ 140 mg/dL had diagnostic 100-g oral glucose tolerance test. Regarding to the National Diabetes Data Group (NDDG) criteria[10], the abnormal fasting value or at least two from later three values of plasma glucose exceeded followings considered GDM (fasting glucose ≥ 105 mg/dL; 1 hr ≥ 190 mg/dL; 2 hours ≥ 165 mg/dL; or 3 hours ≥ 145 mg/dL).

Birth weight, Apgar score and route of delivery were recorded. All statistical analyses were performed using SPSS 16.0 software (SPSS, Chicago, IL, USA). Statistics such as number and percentage were used for descriptive data. Odds ratio (OR) with 95% confidence interval (CI), Chi-square, t-test and paired t-test were used for comparison with significance at p-value < 0.05.

Results

The pregnant women's mean age was 29.8 years old and mean body weight was 53.8 kg. One third was primigravida. Nearly 90% had no risk factors of GDM and one half of pregnant women had total weight gain less than 12 kg. Most (78.9%) were naïve for HAART. Most common side effect was dyslipidemia. Anemia was the second most common side effect.

Table 1. Characteristic data

Parameters	N (Percentage)
Age (year)	29.8 ± 5.4
BW (kg)	53.7 ± 9.7
Graida	
■ 1	42 (38.5)
■ 2-4	61 (54.0)
■ >4	6 (5.5)
Risk factors of GDM	
■ Presence	12 (11)
■ Absence	97 (89)
Total weight gain	
■ <12 kg	55 (50.5)
■ ≥12 kg	51 (46.8)
Previous ARV regimens	
■ Naïve	87 (79.8)
■ AZT/3TC/NVP	15 (13.8)
■ D4T/3TC/NVP	1 (0.9)
■ EFV-based	2 (1.8)
■ PI-based	3 (2.8)
Adverse drug effect	
■ Absence	39 (35.8)
■ Dyslipidemia	53 (48.6)
■ Anemia	15 (15.8)
■ Diarrhea	2 (1.8)

AZT = zidovudine, 3TC = lamivudine, NVP = nevirapine, D4T = stavudine, EFV = efavirenz Data presented as mean + SD or n(%)
Data presented as mean + SD or n(%)

The incidence of GDM was 7.3%, 2 out of 8 women were diagnosed with GDM A2 and they received insulin injection until delivery. None of the women who had BMI ≥ 30 kg/m^2 was diagnosed with GDM. The mean level of pretreatment and post treatment total cholesterol and triglyceride were significantly increased. (Table 2)

Table 2. Comparison of lipid profiles between pre and post treatment PIs based HAART

Lipid profile	Pretreatment (GA 24.09 ± 7.32 wks)	Posttreatment (GA 28.09 ± 7.32 wks)	p-value
Total cholesterol (mg/dL)	227.4 ± 45.0	242.8 ± 47.1	< 0.001
Triglyceride (mg/dL)	245.3 ±87.1	354.8 ± 125.2	< 0.001

Data presented as mean ± SD

One hundred and eleven babies (2 pairs of twins) were born from 109 HIV-infected pregnant women and 7.3% were delivered before 37 weeks. Eighty nine babies had birth weight between 2,500-3,999 gm and 1 case had birth weight more than 4,000 gm. Regardless of gestational age, the incidence of low birth weight (LBW) was 17.4%. The incidence of LBW in infants delivered after 37 weeks was13.9% (Table 3).

Table 3. Neonatal outcomes

Neonatal outcome	N (%)
Term (GA ≥ 37 wks)	101 (92.7)
Preterm (GA < 37 wks)	8 (7.3)
Birth weight	
■ < 2,500 g	19 (17.4)
■ 2,500 – 3,999 g	89 (80.7)
■ ≥ 4,000 g	1 (0.9)
Term infant	
■ < 2,500 g	14 (13.9)
■ ≥ 2,500 g	87 (85.1)

Discussion

The incidence of GDM in this study was comparable to prior study reported by González-Tomé MI et al[11]. However, the incidence was higher than general population at 2.2% reported from Phramongkutklao Hospital during 2003-2005[12]. The PI-based regimen cause tissue insulin resistance which was aggravated by the change of maternal carbohydrate metabolism during pregnancy. A mechanism of drug causing insulin resistance can be explained by direct inhibition of activity of the (GLUT-4) glucose transporter which facilitate cellular uptake of glucose[13].

Although, total cholesterol and triglyceride levels were increased, but these effects could be confounded by maternal hyperlipidemia during late pregnancy.

Basically, when the patients have high level of lipid profiles, we definitely concerned about atherosclerosis which causing by endothelial dysfunction. Finally, this event might lead to vascular occlusion but in fact during pregnancy, the vasodilatation state and increasing HDL level may alleviate this concerns[14]. The lipid lowering drug such as statin which generally used in hyperlipidemia patients is contraindicated during pregnancy because of it is considered potential teratogen.

The incidence of low birth weight was also higher than previously reported by Asavapiriyanont S, et al (9% with NNRTI-based regimen)[15]. This also was comparable to Nelfinavir/Idinavir-based regimen reported by Ramen Chmait, et al. at 15.4%[8]. Moreover,

13.9% of term infants had LBW which was remarkably greater than 3.7% incidence of LBW in normal pregnanct women in Rajavithi Hospital[16].

Although the women in this study had high incidence of GDM, the incidence of LBW wasalso high. These may be explained by the suppression of GLUT-4 which is essential for fetal growth, normal cellular glucose and fat metabolism[17].

The limitations of this preliminary descriptive study were small sample size and incomplete data. The variation of drug exposure duration was affected by the gestational age introducing regimens. Regarding to the remarkably higher incidence of GDM, the pregnant women who received the PIs-based regimens should be screened for GDM. Whenever impaired fetal growth is suspected, various tools should be used for fetal surveillance. Further studies are needed to clarify the long term maternal and neonatal side effects of the PI-based regimen.

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ภาวะเบาหวานขณะตั้งครรภ์ และไขมันผิดปกติในเลือดสตรีตั้งครรภ์ที่ติดเชื้อเอดส์ที่ได้รับยาต้านไวรัสสูตร 3 ตัวที่มีโปรทีเอสอินฮิบิเตอร์

ณัฐวุฒิ เวชจิตติเจริญ, สุวรรณา อัศวพิริยานนท์

วัตถุประสงค์ *: เพื่อศึกษาอุบัติการณ์การเกิดภาวะเบาหวาน การเปลี่ยนแปลงไขมันในเลือด และน้ำหนักทารกแรกเกิด ในสตรีตั้งครรภ์ที่ติดเชื้อเอดส์และได้รับยาต้านไวรัสเพื่อป้องกันการติดเชื้อจากแม่สู่ลูกชนิดสูตร 3 ตัวที่มี PI เป็น Lopinavir/ritonavir ในสูตร*

วัสดุและวิธีการ *: การศึกษาวิจัยเป็นแบบเชิงพรรณนา ตัดขวาง ทำในในสตรีตั้งครรภ์ที่ติดเชื้อเอดส์ และได้รับยาต้านไวรัสเพื่อป้องกันการติดเชื้อจากแม่สู่ลูกชนิดสูตร 3 ตัวที่มี PI ในสูตรจำนวน 109 ราย จากโรงพยาบาลราชวิถี และโรงพยาบาลนพรัตน์ราชธานี ในช่วงระหว่างตุลาคม 2553 ถึงกรกฎาคม 2555 ได้คัดกรองเบาหวานด้วยน้ำตาล 50 กรัม และยืนยันการเป็นเบาหวานด้วยการตรวจน้ำตาล 100 กรัม และตรวจระดับไขมันในเลือดในไตรมาสที่ 2 ถึง 3 หลังได้รับยาต้านไวรัสแล้ว 4 สัปดาห์ สถิติที่ใช้ได้แก่จำนวนและร้อยละ สำหรับบรรยายข้อมูล Odds ratio (OR) และ 95% confidence interval (CI), Chi-square, t-test และ paired t-test สำหรับเปรียบเทียบข้อมูลโดยมีนัยสำคัญที่ p น้อยกว่า 0.05*

ผลการศึกษา *: สตรีตั้งครรภ์ที่ติดเชื้อเอดส์มีอายุเฉลี่ย 28 ปี 11 เดือน ส่วนใหญ่ร้อยละ 79.8 ไม่เคยได้ยาต้านไวรัสสูตร 3 ตัวมาก่อนการตั้งครรภ์นี้ อุบัติการณ์เบาหวานระหว่างตั้งครรภ์พบร้อยละ 7.3 มีการเปลี่ยนแปลงระดับไขมันในเลือดโดยเพิ่มขึ้นหลังการได้รับยา ค่าเฉลี่ยคลอเลสเตอรอลและไตรกลีเซอไรด์เพิ่มขึ้น 18.9 มก/ดล (95%CI, 9.5-28.4) และ 97.2 มก/ดล (95%CI, 70.9-123.3) ตามลำดับ และพบอุบัติการณ์ทารกแรกเกิดน้ำหนักน้อย ร้อยละ 17.4 ซึ่งมากกว่ารายงานอื่นที่ได้ยาต้านไวรัสที่มี NNRTI ในสูตร*

สรุป *: การให้ยาต้านไวรัสสูตร 3 ตัวที่มี PI ในสูตรอาจมีความสัมพันธ์ในการเพิ่มระดับน้ำตาล และไขมันในเลือดในระหว่างตั้งครรภ์*