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Incidence of Gdm in Hiv Positive Antenatal Women on Anti-Retroviral Theraphy (ART)

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ABSTRACT

Background – Multidrug regimen for HIV infected pregnant women to eliminate vertical transmission to children is practiced in India from 2013.
Objectives – To find out if protease Inhibitors used in multidrug regimen increases the incidence of GDM in pregnant women.
Materials and methods – 100 HIV positive pregnant women on ART were included in the study. The incidence of GDM associated with ART was studied at a tertiary care hospital Chennai between the study period of September 2014 to August 2015. Oral glucose test was done to identify GDM mothers.
Results – Increased incidence of GDM was found in women with increasing parity, increasing BMI, Previous IUD, First degree relative with diabetes and previous big baby. 11.1% on Tenofovir, Lamivudine and Lopinavir developed GDM. 5.6% of patients on Zidovidine, Lamivudine, Nevrapine developed GDM. There was no statistical significance for development of GDM in these patients.
Conclusion – No significant increase in overall incidence of GDM in HIV women on ART. No significant association between ART and GDM was found in this study. The 11% incidence in our study is associated with other maternal risk factors.

KEYWORDS Anti retroviral therapy, Gestation Diabetes mellitus, HIV in pregnancy.

Introduction
HIV prevalence among adult population has declined in the past decade from 0.4% in 2000 to 0.27% in 2011. [1] But reduction in HIV infection in children is only 35% which indicates the high level of transmission from mother to child. 1.42 lakh children are living with HIV in India and 14000 new infections annually. Mother to child transmission is the primary route of infection for HIV in children. HIV accounts for 10,000 deaths in India every year. Based on recommendations of WHO 2010 India had adopted Multidrug regimen for Prevention of Parent to Child Transmission (PPTCT) to achieve decrease in transmission rates. [2]

Drugs used in Antiretroviral therapy
Nucleoside and Nucleotide reverse transcriptase inhibitors: Zidovudine, Lamivudine, Stavudine, Abacavir, Emtricitabine, Didanoside, Tenofovir (NtRTI).

Non Nucleotide Reverse Transcriptase Inhibitors – Efavirenz, Nevirapine.
Integrase Inhibitor – Raltegravir.
Fusion Inhibitor – Enfuviritide.
Protease Inhibitor – Ritonavir, Lopinavir, Atazanavir, Nelfinavir, saqiunavir, Indinavir.
Entry Inhibitors – Maroviroc.

Toxicity of NRTI

Drugs	Zidovudine	Stavudine	Lamivudine
Short Term	Headache, Nausea, Vomiting, Malaise, Diarrhea, Bone marrow Supression, Anemia (Macrocytic)		Skin rash
Medium term	Bone Marrow suppression, Anemia, Hyperpigmentation, Lactic acidosis.	Lactic acidosis, Peripheral neuritis, Pancreatitis.	
Long Term		Lipodystrophy, Dyslipedemia.	

Adverse effects of NNRTI

Drug	Adverse effects
All NNRTIs	Skin Rash, Hepatitis, CNS Manifestations.
Nevirapine	Hepatitis, Skin Rash, Steven Johnson's syndrome.
Efavirenz	Confusion, Abnormal thinking, Agitation, Anxiety, Fetal Malformation during first four weeks of gestation, Gynecomastia.

Protease Inhibitors side effects – Dyslipidemia, Lipodystrophy, Rise in transaminase, **Hyperglycemia**, Increased bleeding episodes in hemophiliacs, Osteoporosis, Avascular necrosis.

As per December 2013 NACO guidelines, if a women is diagnosed as HIV positive she is started immediately on ART TDF, Tenofovir(300mg) + 3TC Lamivudine (300mg) + EFV efavirenz (600mg). If she is already on a particular regimen of ART the same is continued throughout the pregnancy irrespective of CD4 count.

Materials and Methods
100 HIV positive women on ART were studied in a government tertiary care institute Chennai.

Exclusion criteria
- Women on corticosteroid
- Who are pregestational diabetic
- Not willing for followup

Inclusion criteria
- Not on corticosteroids
- Not a known case of type 2 DM
- Willing for follow up

Information related to HIV history, Obstetric data, GDM risk factors (previous GDM, BMI >30 kg/m^2 , first degree with diabetes mellitus, History of still birth, Previous birth weight >4kg, weight gain) adverse effects were noted. In addition routine prenatal blood tests, fasting blood sugar, CD4 count, viral load was done. Screening for GDM was done with DIPSI criteria at 16 weeks, 24 – 28 weeks and 32 weeks. The women were given 75mg glucose irrespective of fasting state and a cut off of <140mg/dl was diagnostic of GDM. They were followed up for 6 weeks after delivery and various details were collected.

Results

Table 1 – ART regimen and GDM

ART regimen	GDM		Total
	No	Yes	
TL/Lpr	1 (100%)	0	1
TLE	72 (88.9%)	9 (11.1%)	81
ZLN	17 (94.4%)	1 (5.6%)	18
Total	90	10	100

Table 2 – Parity and GDM

		GDM		Total
		No	Yes	
GRAVIDA	1	52 (96.3%)	2(3.7%)	54
	2	34 (87.2%)	5 (12.8%)	39
	3	4 (66.7%)	2 (33.3%)	6
	4	0	1 (100%)	1
		90	10	100

In our study incidence of GDM is 11%.(Table 1) There is increased risk of GDM with increasing parity. Primi - 3.7%, 2nd gravida -12.8%, 3rd gravida – 33.3% and 4th gravida almost 100%. The P value is 0.015 (<0.05) which is statistically significant. (Table 2)

The multivariate binary logistic regression analysis was done and it was found that previous IUD/Still birth, Weight gain in the present pregnancy and 1st degree relative were significantly associated risk variables in predicting the outcome with their odds ratio respectively.

1. Weight gain – odds ratio 3.588
2. IUD/Still born – odds ratio 89.299
3. 1st relative with DM – odds ratio 18.298

With previous IUD or still born the risk increased to 66.7%. The P value is <0.05% which is statistically significant. Pervious GDM increases the risk by 75%. The p value is 0.001% (<0.05%) which is statistically significant. BMI more than 30 the risk of GDM increases by 50%. The p value is 0.036 which is statistically significant. Presence of a first degree relative increased the risk by 35.3%-p value 0.001 statistically significant. There was no statistically significant in occurrence of GDM based on ART - P value (0.782). P value is insignificant with respect to the outcome of pregnancy.

Discussion

The overall incidence of GDM was 11% in our study. Seshiah et al reported that the prevalence of GDM in Chennai were 17.8% in urban, 13.8% in semiurban and 9.9 % in rural. [3]

The relationship between protease inhibitors and impaired glucose tolerance has not been well-defined. [4-6]. Various studies have continued to document a possible relationship between protease inhibitors and insulin resistance, particularly in conjunction with impaired lipid metabolism, hyperlipidemia, and peripheral lipodystrophy.[7–10] One study evaluating possible mechanisms for the deterioration of glucose tolerance with protease inhibitors found that it may occur in two ways: 1) inducement of peripheral insulin resistance in skeletal muscle and adipose tissue, and 2) impairment of the ability of the β-cell to compensate.[11]

The effect of protease inhibitors on glucose tolerance during pregnancy is controversial. Until 2004 there were only 2 small studies with opposing results. One study retrospectively compared the impact of highly active antiretroviral therapy with protease inhibitors on 41 HIV-infected pregnant patients with 23 HIV-infected pregnant patients receiving only zidovudine. It concluded that highly active antiretroviral therapy and protease inhibitor therapy was associated with an increased rate of impaired glucose tolerance in pregnancy and impaired fetal growth.[11] The other study prospectively evaluated 41 HIV-infected pregnant women, 14 of whom were taking protease inhibitors and 27 of whom were not. They found that the use of protease inhibitors did not significantly increase the risk of an elevated glucose result, nor was the mean glucose result increased in the women taking protease inhibitors.[12] Between 2004 to 2006 the results of 2 large multicenter trials were published.[13] Both address gestational diabetes in relation to antiviral therapy; specifically type and duration of antiretroviral therapy use. The Pediatric AIDS Clinical Trial Group (PACTG) 316 trial results reported an association between protease inhibitor use and gestational diabetes, specifically with long-term antiviral use.[14] However, the Women and Infants Transmission Study, reported in 2005, and did not find an association between protease inhibitor use and gestational diabetes. [15]. However, the length of protease inhibitor exposure before pregnancy was not collected in this study. The varying findings in the above four studies may also be explained by differences in patient population and methods of diagnosis of gestational diabetes along with BMI differences which were not analyzed. The strength of this study is that it is a single-center study with a stable population, BMI data available, and a uniform method of diabetes detection.

Our study also did not find any association between ART use and gestational diabetes. The overall incidence of gestational diabetes in HIV mothers was 11% in our study. This occurrence could be explained by associated maternal risk factors. The risk factors studied were parity, previous IUD/still birth, previous GDM, previous big baby BMI, Obesity, Family history. Our study demonstrated that women with increasing parity, increasing BMI and a positive family history for a first degree with diabetes had higher incidence of GDM similar to the findings reported seshiah et al [3.] Women with a history of GDM, Big baby or IUD/still birth in the previous pregnancy also had an increased risk of developing GDM in the present pregnancy similar to the findings reported McMohan et al [(16)].

Our study had a few of limitations. We did not look at period of protease inhibitor exposure. It is possible that those with elevated results had been exposed for shorter or longer periods. In addition, we did not look at neonatal outcomes; we do not know what impact of ART use in our population had on neonatal hypoglycemia or fetal growth. Finally, the numbers are limited because this is a single center study.

Conclusion

Our study with 100 HIV positive mothers on ART found out that there is no significant increase in the overall incidence of GDM. The observed incidence could be explained by the other risk factors associated with GDM present in those women. Thus concluding that multidrug regimen in HIV positive pregnant women effectively decreases vertical transmission with no increased risk of GDM.

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