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Safety Profile of Tenofovir in Hepatitis B Pregnant Patients

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1. Abstract

1.1. Introduction: Hepatitis B Virus (HBV) is a major cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. There are three possible routes of transmission of HBV from infected mothers to infants: transplacental transmission of HBV in uteri, natal transmission during delivery or postnatal transmission during care of infant or through breast milk.

1.2. Aim: To study safety profile of prenatal use of Tenofovir for the mothers and infants, including the adverse events and outcomes, risk of congenital anomalies for infants exposed in utero, and other potentially toxic effects in the neonates like growth, bone, or other abnormalities.

1.3. Methods: Three hundred and thirty pregnant women were found to be positive for serum HbsAg. In all of them liver function test, renal function test, HbeAg and HBV DNA analysis was done by Polymerase Chain Reaction (PCR). Out of them 32 patients, as per scientific protocol were treated with Tenofovir 300 mg.

1.4. Observations: These thirty-two patients on Tenofovir were followed during whole pregnancy, delivery period and till new born achieved one year of age. None of the newborn had any congenital formation during pregnancy as evidenced by ultra-sonogram of pregnant mothers and follow up by Neonatologist for period of one year.

1.5. Conclusion: Tenofovir is safe in pregnancy for both mother and newborn as none of the thirty two infants develop any kind of congenital malformation.

2. Introduction

Hepatitis B virus is a pan global health problem worldwide and is a major cause of chronic hepatitis, cirrhosis and Hepatocellular Carcinoma (HCC). There are three possible routes of transmission of HBV from infected mothers to infants: transplacental transmission of HBV in uteri, natal transmission during delivery or postnatal transmission during care of infant or through breast milk [1-3]. Tenofovir Disoproxil Fumarate (TDF) is a potent Nucleotide analogue Reverse Transcriptase Inhibitor (NRTI) and has potent activity against Hepatitis B Virus (HBV) infection and is approved for its treatment [4-6]. It is classified as a Pregnancy Category B drug, meaning there is no adequate evidence of risk in humans. Thus, safety information on TDF during pregnancy has important public health implications.

2.1. Aim

The aim was to study safety profile of prenatal use of Tenofovir for the mothers and infants, including the adverse events and outcomes, risk of congenital anomalies for infants exposed in utero, and other potentially toxic effects in the neonates like growth, bone, or other abnormalities.

3. Methods

This study was carried out at Pt BDS PGIMS Rohtak under Department of Medical Gastroenterology, in collaboration with Department of Obstetrics & Gynecology, for a period of two years i.e. from 01.05.2019 to 30.04.2021. Women in any trimester of pregnancy who tested HbsAg positive were enrolled in the follow up study after an informed consent. Personal history, history of risk factors

and obstetric history was obtained. The biochemical & virological tests done were complete haemogram, liver & renal function tests, INR, blood sugar, serum electrolytes, anti HCV antibody, anti HIV antibody, HBV DNA Quantitative, HbeAg, HBe Ab, IgM anti Hbc and ultra-sonogram abdomen including fetal wellbeing. The thirty two (32) pregnant patients whose HBV DNA titers were 107 or more copies/ml with or without HbeAg positivity were started on tablet tenofovir 300 mg on daily basis from seventh month of pregnancy and continued till three months after delivery i.e. in post-partum period. At the time of admission for delivery, again, a detailed history was taken and general, systematic and obstetrical examination was done. Data on mode of delivery, indication for cesarean section, weight and maturity of babies were recorded. The every new born was given single dose of 0.5 ml hepatitis B immunoglobulin intramuscularly and zero dose hepatitis B vaccination at time of birth and later full hepatitis B vaccination schedule was completed. These infant were followed till one year of age for detection of any congenital malformation and HbsAg positive status. The data pertaining to these thirty-two pregnant patients who were started on Tenofovir and their infant were analyzed in detail.

3.1. Observations

A total of 330 women were found positive for HbsAg on Enzyme Linked Immunoassay Method (ELISA). The highest prevalence was observed in the age group of 20-25 years (62.5%) followed by the 25-30-year age group (28.12%). Maximum women (65%) were multiparous and belonged to rural background (59%) and were having lower socio-economic status (51.5%). Out of these total pool of 330 pregnant, 298 (90.30%) were asymptomatic chronic carriers, two women (0.6%) had acute hepatitis B and 30 (9.09%) were having chronic hepatitis B in active stage. The HBV DNA Quantitative level varies from 107 to 1011 copies/ml (mean of 109 copies/ml) and HbeAg was positive in 28 pregnant patients (75%). In total 32 pregnant patients belonging to last two categories whose HBV DNA titers were 107 or more copies/ml with or without HbeAg positivity were started on tablet tenofovir 300 mg on daily basis from seventh month of pregnancy and continued till three months after delivery i.e. in post-partum period. Out of these 32 women, twenty-seven women (84.37%) delivered vaginally and rest 5 (15.63%) underwent cesarean section which was mainly done for obstetric indications. Majority of the babies were term and having birth weight in the range of 2.5-3.2 kg (51.9%). Every new born was given 0.5 ml of hepatitis B immunoglobulin intramuscularly, along with zero dose hepatitis B vaccination at time of birth. All the babies received breast feeding. The safety profile of prenatal use of Tenofovir for the mothers and infants was good and there were no adverse events and outcomes, congenital anomalies or toxic effects in the neonates like growth, bone, or other abnormalities (Table 1 and 2).

Table 1: Showing Distribution of Patients According to Stage of Disease

Total Hepatitis B Pregnant Patients	Chronic Inactive Carriers	Patients Put on Tenofovir Treatment
330	298	32

Table 2: Showing Age Distribution, Viral load parameters and Congenital Malformations

Pregnant Patients on Tenofovir	Age (20-25 yrs)	Age (25-30yrs)	HBV DNA (Copies/ml)	HbeAg Positivity	Adverse Events	Congenital Malformations and HbsAg Positivity
32	20 (62.5%)	9 (28.12 %)	10^7 to 10^{11} (mean of 10^{11})	28 (75%)	0 (0%)	0 (0%)

4. Discussion

In the present study, the highest prevalence was observed in the age group 20-25 years (62.5%) followed by 25-30-year age group (28.12%). However other studies have reported an increase in seropositivity with increasing age of antenatal women. We also found a higher frequency of HbsAg positivity in multiparous women (65%). In a study by MacLean et al [7], mean age and parity was 25.79 and 2.81 respectively. HbeAg positivity rate among HbsAg positive women vary widely. In the group of 32 HbsAg positive pregnant patients who were started on Tenofovir, HbeAg positivity was seen in 25 (78.12%) patients. In the present study, no adverse pregnancy outcome was found in association with positive HbsAg status. Pasorek et al in a retrospective comparison between maternal HbsAg positive cases and controls found no relationship between positive mothers and pregnancy outcomes [8]. In contrast, Tse KY et al reported an association of increased risk of gestational diabetes, ante partum hemorrhage and threatened preterm labour with HbsAg carrier state [9]. In the present study group of 32 patients, twenty-seven (84.37%) women delivered vaginally and rest 5(15.63%) underwent cesarean section for obstetric indications. The results were similar to study by Lert-amorpong et al with 82.9% normal delivery and 16.5% cesarean section [10]. The use of antiviral during pregnancy is done with aim for decreasing Mother to Child Transmission (MTCT) of HBV, particularly among women with high HBV DNA loads and HbeAg positivity, in whom rates of breakthrough HBV transmission to the infant despite immunization can be high [11,12]. In our study group of 32 patients were started on Tenofovir 300 mg daily once, in view of high viral load, at seventh month of pregnancy, in addition every new born was given single dose of 0.5 ml hepatitis B immunoglobulin intramuscularly and zero dose hepatitis B vaccination at time of birth and later full vaccination schedule was completed. At one year of age, no infant was found to be HbsAg positive. Lamivudine and telbivudine have been evaluated in late pregnancy among HBV-infected women to prevent vertical transmission in a few studies [12-

16], but Tenofovir has not yet been evaluated. A small cohort of 11 Asian HBV-monoinfected, HbeAg-positive pregnant women were treated with TDF in the third trimester [17]. After a median duration of 10 weeks' exposure, a significant reduction in serum HBV DNA was achieved at delivery. No HBV MTCT occurred, and no obstetric complications or congenital anomalies were observed. The results of our study are totally in line with the above study, as no MTCT, obstetric complications or congenital anomalies were observed in our group. In HIV-1/HBV coinfected individuals, liver enzymes can get elevated after initiation of antiretroviral drugs, particularly in presence of low CD4+ T-cell counts and advanced immuno suppression, as a result of immune reconstitution [18]. Such immune-mediated flares can also occur postpartum in HBV monoinfected women, even in the absence of therapy [19,20]. In our study group, there were no side effects noted in 32 pregnant patients who were started on Tenofovir. Pregnant women who are started on TDF-based regimens should be counseled about signs and symptoms of liver toxicity, and liver enzymes should be assessed regularly after antiretroviral drug initiation.

Conclusion- Tenofovir is safe for use in pregnancy and should be used in last trimester of pregnancy on scientific rationale in patients who have high HBV DNA viral load with or without HbeAg positivity. Every new born of hepatitis B pregnant mother should always receive hepatitis B immunoglobulin and vaccination at time of birth, followed by completion of vaccination schedule. All these efforts will lead to decrease of MTCT to great extent which will further significantly minimize overall burden of this deadly disease.

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