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Original Article

Obstetrics and Gynaecology Section

A Prospective Study on Fetomaternal Outcomes in Asymptomatic Chronic Hepatitis B Pregnant Women in a Tertiary Level Hospital

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ABSTRACT

Introduction: Hepatitis B surface Antigen (HBsAGg) prevalence among pregnant women in India is between 0.9-3.1%. The most important factor in determining the prevalence is transmission from asymptomatic chronic Hepatitis B Virus (HBV) mother to newborn. The present study was done to observe antiviral treatment and fetomaternal outcome in asymptomatic HBV mothers.

Aim: To study fetomaternal outcomes in asymptomatic chronic hepatitis B pregnant women.

Materials and Methods: This prospective cohort study enrolled 125 HBsAg seropositive singleton pregnancy over a period of 18 months from October 2020 to March 2022 in Department of Obstetrics and Gynaecology and VMMC and Safdarjung Hospital, New Delhi, India. Chronic Hepatitis B (CHB) was diagnosed when HBsAg, HBeAg or HBV DNA was present and IgM anti-HBc was absent. Tenofovir was started in consultation with the gastroenterologist in women with HBeAg positivity or with high HBV DNA titre ≥200,000 IU/mL or Alanine Transaminase (ALT)> two times the Upper Normal Limit (UNL). All women were followed with Liver Function Test (LFT) till delivery and six weeks postpartum and their fetomaternal outcome were noted. The p-value <0.05 was taken as significant. Descriptive statistics was analysed with Statistical Package for the Social Sciences (SPSS) software version 17.0.

Results: Tenofovir was started in 26 (20.8%) women. LFT flare was seen in 15.15% (15/99) women who were not on treatment and 0% in women on treatment. In women without treatment, log HBV DNA level was significantly increased while it was reduced in the women who received tenofovir and the reduction was significant (p-value <0.05). HBeAg was positive in 61.5% women on treatment and 0% in untreated women. No significant association was found in maternal outcomes i.e., Gestational Diabetes Mellitus (GDM), Antepartum Haemorrhage (APH), Preeclampsia, Premature Rupture Of Membrane (PROM), Preterm labour, Postpartum Haemorrhage (PPH) and High Dependency Unit (HDU) stay, in treated and untreated women. Foetal outcomes such as birth weight, APGAR score, Neonatal Intensive Care Unit (NICU) admission, prematurity, Foetal Growth Restriction (FGR) and neonatal jaundice also showed no significant association between antiviral treated and untreated women.

Conclusion: There was no significant association of antiviral treatment with maternal and foetal outcome. Tenofovir is safe and reduces the LFT flare in CHB mothers. HBV DNA levels were reduced in treated women which may have reduced the incidence of Mother To Child Transmission (MTCT), which was not studied in the present study. HBeAg seropositivity and ALT >2 times the ULN can replace the need of HBV DNA titres for initiation of antiviral therapy in India.

Keywords: Antiviral, Hepatitis B virus, Mother to child transmission

INRODUCTION

The HBV infection in pregnancy and its fetomaternal complications are health problems that have been rarely addressed. There are approximately 257 million people who are chronically infected with Hepatitis B, which is around 3.5% of the world's population [1,2]. Different parts of India have put the HBsAg prevalence rate among pregnant women between 0.9-3.1% and transmission of HBV from asymptomatic chronic carrier mothers to their babies is an important factor in determining the prevalence of this disease [3].

CHB infection is diagnosed when HBsAg, HBeAg, HBV DNA are present or IgM anti-HBc is absent, as it is present only in acute infection [4]. The natural history of CHB infection is complex. It comprises the immune-tolerant phase, immune-active chronic phase, inactive HBsAg phase and reactivation. The four phases differ from each other in certain parameters such as serum Alanine Transaminase (ALT) level, HBeAg status and viral load. In the immune-tolerant phase, the host immunity against HBV is weak so the viral load is high Aspartate Transaminase (AST) (AST/ALT) is low because there is no attack on the infected hepatocytes by the weak host immune system. In the immune-active phase, host immunity become strong and infected hepatocytes are attacked and AST/ALT increases leading to decrease in viral load. The host immunity is stronger in the immune-control phase and the viral load is under control whereas in the reactivation phase, host immunity is weakened due to immunosuppressive agents leading to high ALT levels with increased viral load [5,6].

The wide variation in the global distribution of CHB infection largely depends on the age at which infection is acquired. In endemic regions, HBV infection is acquired predominantly during the perinatal period or in early childhood [7]. The long-term effects of CHB are cirrhosis, fulminant hepatitis and hepatocellular carcinoma [2].

Prevention of MTCT via concurrent use of Hepatitis B Immune Gl obulin (HBIG) and birth dose vaccination followed by completion of total 3-dose Hepatitis B vaccine along with antiviral therapy can reduce the risk of perinatal HBV transmission [4]. Tenofovir monotherapy is preferred in antenatal HbsAg positive women is a nucleotide inhibitor of HBV polymerase, classified as a category B drug in pregnancy. It is safer and more effective as compared to lamivudine in antenatal women and in breast-feeding mothers hence can also be continued in the postpartum period [8,9]. About 1.3%

children under the age of five years were estimated to be have HBV infection as compared to prevaccination era when it was 4.7% [2]. A meta-analysis indicated that maternal viral load was an important risk factor for MTCT in HBeAg positive mothers [10,11].

WHO in 2016, issued first ever global health sector strategy on viral hepatitis, called elimination of HBV and HCV by 2030, meaning 90% reduction in new cases and 65% reduction in mortality. For hepatitis B this means reducing new cases from 4.7 million in 2015 to 4.7 lac by 2030 and reduction in deaths from 88,400 to 30,900 by 2030. Prevention of MTCT of HBV is one of the five core strategies of global HBV elimination by 2030 [12].

At present there are studies about the fetomaternal outcomes including GDM, APH, PE, PROM, Preterm labour, PPH, Prematurity, Low Birth Weight (LBW), NICU stay, stillbirth, neonatal jaundice, in asymptomatic pregnant women with CHB infection [13-17]. However, there are limited studies about indication for starting maternal antiviral therapy and its effect on viral load and MTCT [5,8,9].

So, the aim of the present study was to ascertain indications for initiation of maternal antiviral therapy and its effect on fetomaternal outcome in CHB mothers.

MATERIALS AND METHODS

This prospective cohort study was conducted at the Department of Obstetrics and Gynaecology at Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India in collaboration with the Department of Gastromedicine and Microbiology. The study was conducted over a duration of 18 months, from October 2020 to March 2022, after Institutional Ethics Committee (IEC) approval (S. No. IEC/VMMC/SJH/Thesis/2020-11/CC-163).

Inclusion criteria: HBsAg seropositive women, with singleton pregnancy, attending antenatal clinic in any trimester at Safdarjung Hospital, New Delhi were enrolled in the study, with prior informed consent.

Exclusion criteria: Women co-infected with HIV and HCV, syphilis, type 2 DM, Intra Hepatic Cholestatis of Pregnancy (IHCP), congenital anomalies in the baby were excluded from the study.

Sample size calculation: Sample size was calculated using a study reported by Tse K et al., [6]. Adverse fetomaternal outcome was found in 10-30% of pregnant women. Therefore, assuming (p)=20% with 7% margin of error, the minimum required sample size at 5% level of significance was of 125 patients.

Formula used:

$$n=\frac{Z^2_{\alpha/2}pq}{d^2}$$
$$=\frac{1.96*1.96*0.20*0.80}{(0.07*0.07)}$$
$$=125.44$$

where 'p' is the observed adverse fetomaternal outcome in women with CHB infection, q=1-p, d is the margin of error, $Z_{\alpha/2}$ is the ordinate of standard normal distribution at α% level of significance

Demographic characteristics of pregnant women with CHB infection were studied in the present study. Age, Body Mass Index (BMI), education, occupation, husband's occupation, high risk behaviour (history of piercing, tattooing, blood transfusion, invasive procedure), parity were included.

Fetomaternal outcomes GDM, APH, PE, PROM, labour before 37 weeks of gestation (preterm labour), PPH, prematurity, LBW weighing less than 2500 g, NICU stay, stillbirth, neonatal jaundice and newborn immunoprophylaxsis within 12 hours, in women with CHB infection, were recorded. Premature infants were those who were born before 37 weeks. The birth weight of the newborns were compared under categories of Normal Birth Weight (NBW) 2500-4500, LBW 1500-2500 g and Very Low Birth Weight (VLBW) <1500 grams. The Apgar score comprises of appearance, pulse, grimace, activity, respiration, each of which is given a score and this score is reported at one minute and five minutes after birth and a score of 7-10 is reassuring [18-20].

In the present study, total of 125 women, found to be HbsAg positive in first antenatal visit, satisfying the inclusion criteria were enrolled with prior informed consent. HbsAg positive women were investigated further with Complete Blood Count (CBC), Prothrombin Time (PT), International Normalised Ratio (INR), LFT, HBV, Deoxyribonucleic Acid (DNA) levels, Hepatitis B Envelope Antigen (HBeAg), Hepatitis B Envelope antibody (anti-HBe), IgM antibody to Hepatitis B core antigen (HBc IgM), Hepatitis B core antibody- total (HBc total) (IgM+IgG) and a fasting upper abdominal ultrasound.

All women were referred to a gastroenterologist to ascertain the need for antiviral therapy at first visit and at 28 weeks period of gestation. HBV DNA levels were ascertained at the end of second trimester (26-28 weeks). In consultation with the gastroenterologist antiviral Tenofovir was started in women with HBeAg seropositive status or with high HBV DNA titre ≥200,000 IU/mL or ALT >2 times the ULN. The normal level of ALT was taken as (0-25) IU/mL [5,21]. Tenofovir was started in a dose of 300 mg BD and was continued till six weeks postpartum. LFT flare was reported when ALT levels were >2 times the ULN [5]. The women with HBV DNA levels ≤200,000 IU/mL were not given antiviral therapy. All women were followed-up antenatally with three monthly LFTs and fetomaternal outcomes were noted at delivery. The women were further followed at six weeks postpartum with LFT. The infants of HbsAg positive women were immunised within 12 hours of delivery with hepatitis B vaccine and HBIG.

STATISTICAL ANALYSIS

The results were analysed using descriptive statistics and making comparisons among various groups. Categorical data were summarised as proportions and percentages (%) and quantitative data were summarised as mean±SD. The p-value <0.05 was taken as significant and data were analysed by Chi-square test, arithmetic mean, standard deviation, paired and unpaired t-tests. Descriptive statistics was analysed with SPSS software version 17.0.

RESULTS

The mean age of the women was 26.02±4.5 years and majority (72.8%) were multiparous with BMI ranging from 18.6-28.5 Kg/m^2. Majority (87.2%) were housewives, 86.4% had some level of education and 38.4% of their husbands were unskilled worker. History of piercing, tattooing and invasive procedure was present in 100%, 12.8%, 26.4% women, respectively [Table/Fig-1].

Variables	Mean	Median	Range
Age distribution (years)	26.02±4.5	25	18-38
BMI (kg/m^2)	22.23	21.8	18.6-28.5
N (%)			
Education	86.4 % (literate)	13.6% (Illiterate)	
Occupation	87.2% (Housewife)	9.6% (Unskilled worker)	3.2% (Skilled worker)
Husband's occupation	4% (Unemployed)	38.4% (Unskilled worker)	57.6% (Skilled worker)
High-risk behaviour	100% (history of piercing/ tattoing 12.8%/blood transfusion/invasive procedure 26.4%)	4.8% (history of HBV in husband)	0% (history of immunisation not known)
Parity	27.2% (Primigravida)	72.8% (Multiparous)	

[Table/Fig-1]: Demographic characteristics of women with chronic Hepatitis B infection in pregnancy.

Overall positive HBeAg was observed in 12.8% (16/125) women and amongst those receiving treatment it was 61.5% (16/26) women. Significant difference was found in HBeAg positivity between women

with and without treatment (p-value <0.001). Overall positive HBeAb was observed in 67.2% women (84/125). The anti-HBe was found to be positive in 84.8% (84/99) women without treatment. Total HBc seropositivity was found in all the 100.0% women [Table/Fig-2].

LFT flare was observed in 15.15% (15/99) women who were not on treatment and 0% in women on treatment. Baseline ALT was found to be raised in 16.2% (16/99) women without treatment versus 61.5% (16/26) women with treatment which was significant (p-value <0.001). Overall raised ALT at 26-28 weeks was observed in 24.8% (31/125) women [Table/Fig-3].

A highly significant difference was observed in log HBV DNA level between women with and without treatment (p-value <0.001). In women who did not receive treatment, log HBV DNA level was significantly increased (p-value=0.019) while in the women on treatment, log HBV DNA level was significantly reduced (p-value <0.001) [Table/Fig-4]. ALT levels were reduced at six weeks postpartum in women with treatment whereas ALT levels remained raised in women without treatment.

Foetal outcomes such as birth weight, APGAR score, NICU admission, prematurity, FGR and neonatal jaundice also showed no significant association (p-value >0.05) between treated and untreated women [Table/Fig-5].

No significant association was found in maternal outcomes i.e., GDM, APH, PE, PROM, preterm labour, PPH and HDU stay, in treated and untreated women (p-value >0.05) [Table/Fig-6].

There was no significant association of treatment with maternal and foetal outcome (p-value >0.05), the reason being that the treatment was provided only those who had high ALT and HBV DNA level and after the treatment their level declined and were found similar to those without treatment. So, the outcomes were similar in both antiviral treated and untreated women.

DISCUSSION

In the present study, the mean age of pregnant women with CHB was 26.02 years and majority of them were multiparous, similar results were observed in a previous study [3]. When the mean log

Parameters	Negative/positive	Not on treatment n=99, n (%)	On treatment n=26, n (%)	Total	χ^2	p-value
		n (%)	n (%)	n (%)		
HBeAg	Negative	99 (100.0)	10 (38.5)	109 (87.2)	69.87	<0.001**
	Positive	0	16 (61.5)	16 (12.8)		
HBeAb	Negative	15 (15.2)	26 (100.0)	41 (32.8)	67.26	<0.001**
	Positive	84 (84.8)	0	84 (67.2)		
Total HBc	Positive	99 (100.0)	26 (100.0)	125 (100.0)	NA	NA

[Table/Fig-2]: Distribution of women with Chronic HBV (CHB) infection according to HBeAg, HBeAb and HBcAg.
**p-value <0.001 is considered to be highly statistically significant

ALT		Not on treatment n=99, n (%)	On treatment n=26, n (%)	Total	χ^2	p-value
		n (%)	n (%)	n (%)		
Baseline (1st visit)	Normal	83 (83.8)	10 (38.5)	93 (74.4)	22.26	<0.001**
	Raised	16 (16.2)	16 (61.5)	32 (25.6)		
Repeat 26-28 week	Normal	84 (84.8)	10 (38.5)	94 (75.2)	23.76	<0.001**
	Raised	15 (15.2)	16 (61.5)	31 (24.8)		
Postpartum 6 week	Normal	83 (83.8)	11 (42.3)	94 (75.2)	19.04	<0.001**
	Raised	16 (16.2)	15 (57.7)	31 (24.8)		

[Table/Fig-3]: Comparison of ALT level between women with and without tenofovir treatment (normal range-0-25 IU/mL) [5,21].
**p-value <0.001 is considered to be highly statistically significant; N=125

Log HBV DNA (U/mL)	Antiviral treatment		Intergroup	
	No (n=26)	Yes (n=99)		
	Mean±SD	Mean±SD	t-value	p-value
First visit	1.84±0.37	3.94±0.76	20.00	<0.001**
26-28 weeks	1.97±0.53	2.51±0.79	4.14	<0.001**
Intragroup	t=2.40, p=0.019*	t=12.56, p<0.001**		

[Table/Fig-4]: Intergroup and intragroup comparison of log HBV DNA level between women with and without antiviral treatment.
*p-value <0.051 is considered to be statistically significant, **p-value <0.001 is considered to be highly statistically significant; N=125

HBV DNA of women on treatment was compared with the women not on treatment, it was observed that in women who didn't receive treatment, had significantly higher log HBV DNA levels (p-value=0.019) while women who were treated had significantly reduced log HBV DNA levels (p-value <0.001). In the present study it was observed that ALT levels were reduced at six weeks postpartum in women on treatment whereas ALT levels remained raised in women without treatment. An earlier study by Taiwanese group reported that treatment in highly viraemic mothers improved maternal ALT levels, decrease HBV DNA of infant at birth and

Variable		Treatment with tenofovir		Total	χ^2	p-value
		Received	Not received			
		n (%)	n (%)	n (%)		
Birth weight	NBW	67 (67.7)	18 (69.2)	85 (68.0)	0.09	0.956
	LBW	29 (29.3)	7 (27)	36 (28.8)		
	VLBW	3 (3.0)	1 (3.8)	4 (3.2)		
APGAR 1 min	< 7	11 (11.1)	2 (8.0)	13 (10.5)	0.21	0.650
	>=7	88 (88.9)	23 (92.0)	111 (89.5)		
APGAR 5 min	< 7	3 (3.0)	1 (4.0)	4 (3.2)	0.06	0.806
	>=7	96 (97.0)	24 (96.0)	120 (96.8)		

NICU admission	Done	4 (4.0)	0	4 (3.2%)	1.04	0.307
	Not done	95 (96.0)	25 (100.0)	120 (96.8)		
Prematurity	Absent	84 (84.8)	22 (84.6)	106 (84.8)	0.00	0.976
	Present	15 (15.2)	4 (15.4)	19 (15.2)		
FGR	Absent	94 (94.9)	25 (96.2)	119 (95.2)	0.07	0.798
	Present	5 (5.1)	1 (3.8)	6 (4.8)		
Neonatal jaundice	Absent	95 (96.0)	23 (88.5)	118 (94.4)	2.19	0.139
	Present	4 (4.0)	3 (11.5)	7 (5.6)		
Received immunoprophylaxis	Given	99 (100.0)	26 (100.0)	125 (100.0)	NA	NA

[Table/Fig-5]: Association of Tenofovir treatment with foetal outcomes.
NBW: Normal birth weight; LBW: Low birth weight; VLBW: Very low birth weight; APGAR: Appearance, pulse, grimace, activity, respiration; NICU: Neonatal intensive care unit; FGR: Foetal growth restriction

Variables		Treatment with tenofovir		Total	χ^2	p-value
		Received	Not received			
		n (%)	n (%)	n (%)		
GDM	Absent	87 (87.9)	21 (80.8)	108 (86.4)	0.89	0.347
	Present	12 (12.1)	5 (19.2)	17 (13.6)		
APH	Absent	94 (94.9)	24 (92.3)	118 (94.4)	0.27	0.602
	Present	5 (5.1)	2 (7.7)	7 (5.6)		
Pre-eclampsia	Absent	90 (90.9)	24 (92.3)	114 (91.2)	0.05	0.823
	Present	9 (9.1)	2 (7.7)	11 (8.8)		
PROM	Absent	89 (89.9)	20 76.9)	109 (87.2)	3.11	0.078
	Present	10 (10.1)	6 (23.1)	16 (12.8)		
Preterm labour	Absent	87 (87.9)	22 (84.6)	109 (87.2)	0.20	0.658
	Present	12 (12.1)	4 (15.4)	16 (12.8)		
Mode of delivery	NVD	80 (80.8)	16 (61.5)	96 (76.8)	5.75	0.056
	IVD	5 (5.1)	1 (3.9)	6 (4.8)		
	LSCS	14 (14.1)	9 (34.6)	23 (18.4)		
PPH	Absent	94 (94.9)	26 (100.0)	120 (96.0)	1.37	0.242
	Present	5 (5.1)	0	5 (4.0)		
HDU admission	Not done	91 (91.9)	21 (80.8)	112 (89.6)	2.75	0.097
	Done	8 (8.1)	5 (19.2)	13 (10.4)		

[Table/Fig-6]: Association of Tenofovir treatment with maternal outcomes.
GDM: Gestational diabetes mellitus; APH: Antepartum haemorrhage; PPH: Postpartum haemorrhage; HDU: High dependency unit

decreased HBsAg positivity of infant at six months [22]. Similarly in present study, HBV DNA levels were reduced in treated women, which may have reduced the incidence of MTCT, which was not studied, as they were followed for six weeks postpartum.

Similar to the present study, some previous studies also showed no significant association in the fetomaternal outcomes like preterm births, GDM and preeclampsia between antiviral treated and untreated women [13,23]. In a previous study a higher odd ratio of 1.13 and 1.12 was found for GDM and caesarean delivery respectively, in HbsAg positive women [15]. This was in contrast to present study, as no significant association was observed in fetomaternal outcomes between antiviral treated and untreated women. This could be because Tenofovir was given only to women with high, ALT levels and log HBV DNA load, resulting in improved outcome in them making it similar to women with low viral load who didn't receive it.

Comparison of fetomaternal outcomes in HBV positive women in the present study versus previous studies shown in [Table/Fig-7] [13-15].

Another study by Sirilert S et al., concluded that HbsAg infection along with pregnancy hormones caused increased risk of preeclampsia, GDM and preterm births in pregnant women especially those who were not on antiviral treatment and HBeAg positive, which was discordant to findings in the present study [9].

No statistical significant association was observed in foetal outcomes like birth weight, APGAR score and gestational age in the antiviral treated and untreated women, in present study, which was in concordance with a previous study conducted in 2020 [16]. One recent study revealed that HbsAg positive antenatal women were more prone to have preterm births which were in discordance with present study, as no significant association was observed between preterm births and HBsAg positive status [14].

Outcomes	Study period	Maternal outcome	Foetal outcome
Bajema KL et al., [13] (2018)	1992-2014	No significant difference between HBV infected and non infected group (GDM, preeclampsia, eclampsia, placenta previa, preterm delivery).	No significant difference in Low Birth Weight (LBW), large for gestational age.
Zhao Y et al., [15] (2020)	2011-2018	HBsAg positive group had Odds Ratio (OR) of 1.13 for GDM and OR of 1.12 for caesarean delivery.	No significant difference between HBsAg positive or negative group.
Zhang Y et al., [14] (2020)	2016 to 2018	-	Preterm births were significantly more (OR 1.44) among HBV positive cases.
Present study (2023)	October 2020-March 2022	No statistical significance between antiviral treated and untreated women in maternal outcomes.	No statistical significance between antiviral treated and untreated women in foetal outcomes.

[Table/Fig-7]: Showing comparison of present study with other studies [13-15].

Limitation(s)

The limitations of present study was that women enrolled in the study were limited to those coming to Safdarjung Hospital which is

a tertiary care centre leading to selection bias and long-term follow-up of the baby was not done to look for seropositivity of the baby.

CONCLUSION(S)

In current study, tenofovir was well tolerated and reduced the LFT flare and log HBV DNA level in CHB mothers. There was no significant association of antiviral treatment with maternal and foetal outcome because it was given only to women with higher, ALT levels and log HBV DNA, resulting in improved outcome in them making it similar to women with low ALT and viral load, who didn't receive it. Reduced HBV DNA levels after tenofovir might have reduced the incidence of MTCT, which was not studied in the present study. Hence, there is need for further studies with large sample size and follow-up of newborn for atleast six-nine months. As majority women needing treatment were HbeAg positive or with ALT >2 times ULN. Hence, in low resource country like India, HBeAg seropositivity and ALT >2 times ULN can replace HBV DNA titres for initiation of antiviral therapy. By reducing MTCT with tenofovir, both prevalence and also long-term effects of CHB can be reduced on the population.

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