EFFECT OF LAMIVUDINE TREATMENT IN THE THIRD TRIMESTER IN HEPATITIS B POSITIVE PREGNANT WOMEN IN DECREASING THE VIRAL LOAD AND SUBSEQUENT FOETAL TRANSMISSION

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ABSTRACT

BACKGROUND

Hepatitis B infection is most commonly acquired through perinatal or horizontal transmission. The combined immunity of hepatitis B vaccine and high-titre hepatitis B immunoglobulin HBIG has excellent efficacies in blocking the maternal-foetal transmission of hepatitis B virus. This study was aimed to stop such transmission from mothers with high hepatitis B virus DNA viral loads by giving them lamivudine antenatally.

The aim of the study is to study the effect of lamivudine treatment to decrease hepatitis B virus DNA viral load in the third trimester in hepatitis B surface antigen pregnant positive women and its effect on vertical transmission of hepatitis B.

MATERIALS AND METHODS

The hepatitis B surface antigen positive pregnant women attending the department who satisfied the inclusion criteria were selected for this prospective case-control study of 30 in each group. Hepatitis B viral DNA load was seen at 28 weeks in both groups and lamivudine started at 32 weeks in the case group. Both groups were followed up antenatally, intrapartum and postpartum till 1 month and babies till 6 months. DNA viral load 1 month postpartum for the mother and hepatitis B surface antigen positivity observed in the babies till the age of 6months.

RESULTS

The prevalence of hepatitis B infection was more in the age group of 25-30 years. A high transmission rate of 36.1% was observed in hepatitis B envelope antigen positive mothers. There was a significant fall in the DNA viral load in the range of 10 log 4 to 10 log 6 in the case group, p value 0.000. 48.3% hepatitis B envelope antigen positive mothers in the case group became hepatitis B envelope antigen negative at the end of the study. 46.7% babies in the control group versus only 16.7% in the case group were hepatitis B surface antigen positive at the end.

CONCLUSION

Lamivudine treatment of highly viraemic hepatitis B surface antigen positive women during the final months of pregnancy has reduced the risk of perinatal transmission of hepatitis B virus combined with hepatitis B virus vaccination plus hepatitis B immunoglobulin. Hepatitis B envelope antigen positivity, a condition which is an independent predictor of foetal transmission, seroconverted to a negative status with lamivudine treatment, foetal transmission also decreased appreciably.

KEYWORDS

Lamivudine, Hepatitis B Positive Pregnancy, Viral Load.

HOW TO CITE THIS ARTICLE: Guhan B, Sadananda SD. Effect of lamivudine treatment in the third trimester in hepatitis B positive pregnant women in decreasing the viral load and subsequent foetal transmission. J. Evid. Based Med. Healthc. 2017; 4(25), 1476-1481. DOI: 10.18410/jebmh/2017/286

BACKGROUND

In regions with high prevalence, hepatitis B infection is most commonly acquired through either perinatal or horizontal transmission. The risk of progression to chronic infection is inversely proportional to the age at which it was acquired. Without immunoprophylaxis, up to 90% of infants born to HBeAg positive mothers become infected. Though the combined immunity of hepatitis B vaccine and high-titre hepatitis B immunoglobulin, HBIG is highly effective in blocking the maternal-foetal transmission of HBV in around 10% of the mothers with positive HBV serum marker, neonates later became chronically infected with HBV. The risk of perinatal transmission of HBV increases as the mother's viral load increases as high as 28% in a series. Lamivudine treatment of highly viraemic HBsAg positive women during the final months of pregnancy appears safe and may effectively reduce the risk of perinatal transmission of HBV even in the setting of HBV vaccination plus HBIG. Without intervention, a mother who is positive for HBsAg confers a 20% risk of passing the infection to her offspring at the time of birth. Perinatal HBV transmission can be prevented by identifying HBV-infected pregnant women and

Financial or Other, Competing Interest: None.
Submission 21-02-2017, Peer Review 28-02-2017,
Acceptance 04-03-2017, Published 25-03-2017.
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DOI: 10.18410/jebmh/2017/286

providing HBIG and hepatitis B vaccine to their infants within 12 hours of birth.

National guidelines call for universal screening of pregnant women for HBsAg during each pregnancy, case management of HbsAg positive mothers and their infants, provision of immunoprophylaxis for infants born to infected mothers including hepatitis B vaccine and HBIG and routine vaccination of all infants with the hepatitis B vaccine series with the first dose administered at birth.

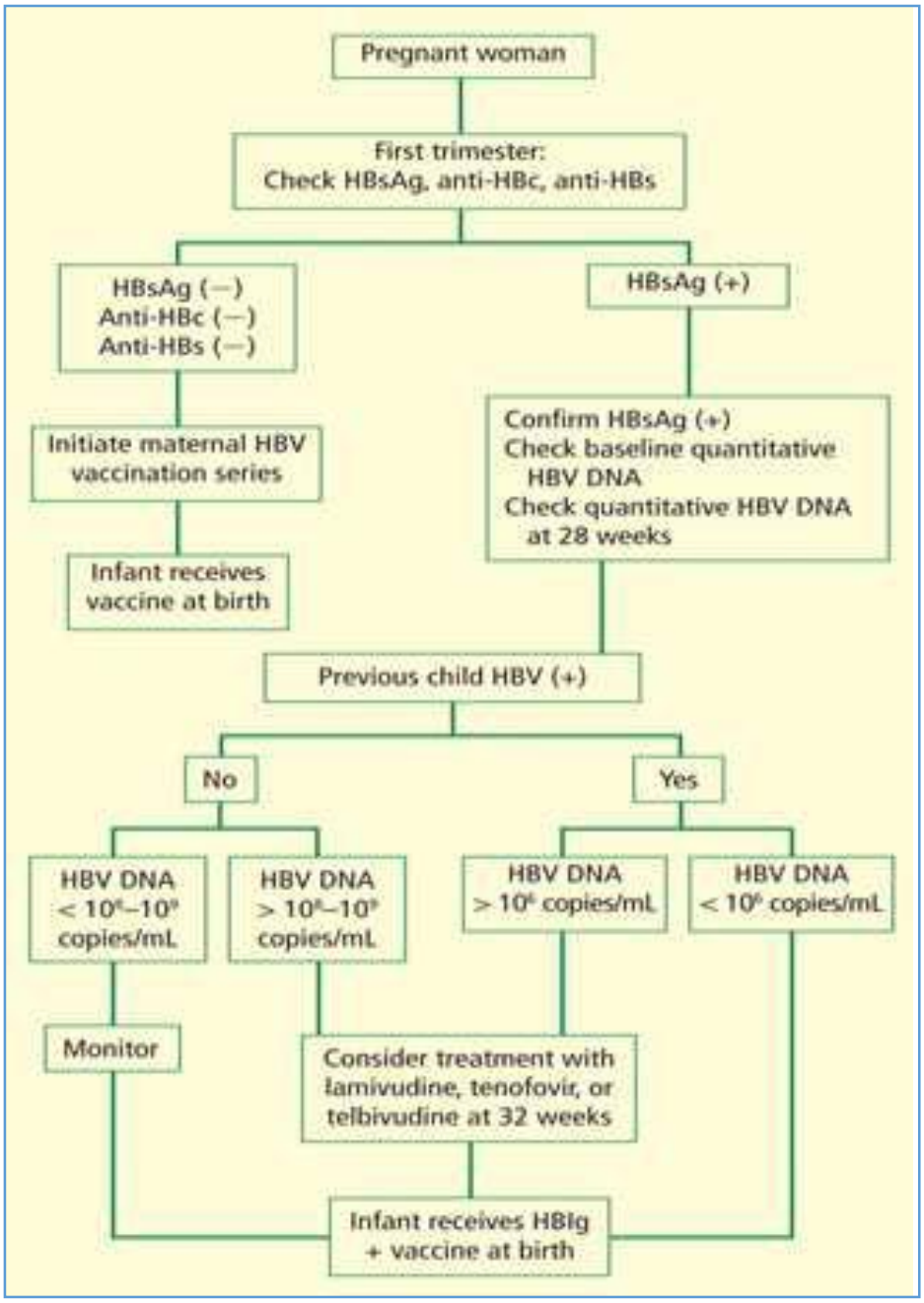
The chance of infection depends on timing of infection, viral load, other antigen markers and treatment. If infection occurs early in pregnancy, the chances are less than 10% that the baby is affected and is up to 90% if late. Treatment is initiated in the third trimester after a high viral load is documented in the latter part of the second trimester. The two most commonly used agents in pregnancy are lamivudine and tenofovir. Lamivudine is a potent Nucleoside (analogue) Reverse Transcriptase Inhibitor (NRTI). It improves the seroconversion of e-antigen positive hepatitis B and also improves histology staging of the liver. Even though categorised as a class C agent by the FDA being the first oral agent approved for the treatment of HBV, lamivudine has extensive clinical experience and is considered safe by the APR (Antiretroviral Pregnancy Registry). Although, there is less clinical experience with tenofovir, it is categorised as a class B agent by the FDA. Lamivudine and Tenofovir Disoproxil Fumarate (TDF) are both active against Hepatitis B Virus (HBV). Due to its potency, high genetic barrier to resistance and safety during pregnancy, TDF may be useful to prevent HBV transmission from mother to child, which is the leading cause of transmission globally.[1] The benefits of treatment of hepatitis B in pregnancy appear to be most pronounced in cases with high maternal viraemia. Although, none of the available drugs can clear the infection, they can stop the virus from replicating, thus minimising liver damage. Lamivudine is associated with a risk of birth defects (2.2% to 2.4%) that is no higher than the baseline birth defect rate and its long-term use leads to emergence of a resistant hepatitis B virus YMDD mutant. Despite this, lamivudine is still used widely at a dose of 100 mg daily as it is well tolerated. No antiviral agent has been approved by the FDA for use in early pregnancy. The majority of perinatal transmission is thought to occur at delivery, because a combination of passive immunisation with HBIG given within 12 hrs. of birth and active immunisation with three doses of the hepatitis B vaccine in the first 6 months of life results in preventing most infections. Although, highly effective in preventing MTCT, standard passive-active immunoprophylaxis with hepatitis B immunoglobulin and the hepatitis B vaccine may have a failure rate as high as 10% to 15%. Antiviral treatment has been used during pregnancy and may decrease MTCT.[1]

Beasley et al[2] showed that HBIG administration could reduce the rate of HBV transmission from more than 90% from HBeAg-positive mothers down to about 26%. When combined with the vaccine, the rates of transmission fell from 7% to 3%.

Besides the WHO recommended joint immunoprophylaxis starting from the newborn, multiple injections of small doses of HBIG or oral lamivudine in HBV carrier mothers with a high degree of infectiousness >106 copies/mL in late pregnancy, the last three months of pregnancy, effectively and safely prevent HBV intrauterine transmission.

Van Zonneveld M et al treated eight highly viraemic HBV-DNA ≥1.2×109 geq/mL mothers with 150 mg of lamivudine daily during the last month of pregnancy and concluded that in highly viraemic HbsAg positive mothers, reduction of viraemia by lamivudine therapy in the last month of pregnancy maybe an effective and safe measure to reduce the risk of child vaccination breakthrough. This finding led to a randomised, double-blind, placebo-controlled trial of lamivudine to prevent transmission in highly viraemic HBeAg-positive women. At 1 year of age, 18% of babies of lamivudine-treated mothers were HBsAg positive compared to 39% in the placebo-treated arm. Both groups received vaccination and HBIG. Based on these results, the authors recommended treatment in the third trimester for women with high viral loads.

Another meta-analysis of 10 randomised-controlled trials, RCTs including 951 patients was reported to evaluate the efficacy of lamivudine in reducing in utero transmission of HBV.[3] Newborns in the lamivudine group had a 13% to 24% significantly lower incidence of intrauterine exposure indicated by newborn HBsAg (P=0.04) and HBV-DNA newborns in the lamivudine-treated group had a 1.4% to 2% lower perinatal infection rate at 9 to 12 months as indicated by HbsAg P<0.001 seropositivity. Sukran Kose et al studied the efficacy and safety of lamivudine treatment in pregnant women with chronic hepatitis B and a high viral load and showed that HBV viral load decreased in five of the seven patients (71%) and in three patients (43%), HBV-DNA was found to be completely negative after labour. They suggested that lamivudine therapy in highly viraemic HbsAg positive-pregnant women could decrease perinatal transmission rates of HBV and can lower the HBV viral load during labour.



Algorithm for Management of HBV in the Pregnant Patient

Transmission of HBV Infection in Breastfed Babies

Although, early studies claimed that HBV transmission could occur through breast milk, more recent studies Hill et al found a similar rate of infection in breastfed and formula fed infants (0% and 3%). Thus, current guidelines state that breastfeeding is not contraindicated in HBV-infected mothers who are not on antiviral therapy whose infants receive immunoprophylaxis.

Although, it is known that lamivudine and tenofovir are both excreted into human breast milk, little is known about the extent of exposure of antiviral agents during breastfeeding.

MATERIALS AND METHODS

Ours was a prospective study over 18 months March 2012-September 2013 with a sample size of 30 cases and 30 controls. All HBsAg positive-pregnant women detected during antenatal period with HBV DNA >108 in primigravida/multigravida with previous child HBV negative; HBV DNA >106 in multigravida with previous child HBV positive and patients who are willing to continue the drug after the study period if indicated were included in the study population. Those taken treatment for hepatitis B previously, patients with concomitant HCV/HIV infection or developing PIH/AFLP/pregnancy-related complications or those not willing for the study were excluded. The study was conducted at the Department of Obstetrics and Gynaecology, IMCH, Government Medical College, Kozhikode. The HbsAg positive pregnant women attending

the OP for their antenatal checkups and those fulfilling the inclusion criteria were selected for this study. An informed written consent was taken. Patient's details recorded as per proforma. Patients were alternately assigned to case and control group. HBV DNA was assessed at 28 weeks and lamivudine prophylaxis 100 mg OD was started from 32 weeks of gestation in the case group. Both groups were followed up during their delivery for any complications. Their babies were evaluated for any congenital anomalies and routinely immunised with the appropriate HbsAg vaccine and HBIG as per schedule. One month after delivery, HBeAg, HBV DNA and LFT were repeated. Babies were followed up to check for HbsAg positivity till the age of 6 months. Both groups were compared to evaluate the efficacy of treatment.

RESULTS

Data analysis was done by using SPSS software by applying appropriate tests of Chi-square, t-test or Mann-Whitney test wherever required.

The case and the control group were divided into 3 groups depending on the age and compared. The mean age in both groups being 27 years, they were statistically comparable. It was observed that the maximum number (45) of patients was in the age group of 25-30 years, which depicted the peak time in the reproductive life of a woman (Table 1).

There were primigravida, 2nd gravida with 1 living child and 3rd gravida with 2 living children who were included in this study (Table 2).

Gestational age at detection of HBsAg positivity- The number of cases that were detected to be HBsAg positive in their present pregnancies was 47. This shows that they were all acute infections. On account of which, there were 15 babies who turned HbsAg positive during this acute infectious period compared to only 4 babies who turned HBsAg positive whose mothers had a chronic infection, which was procured preconceptionally (Table 3).

HBsAg status of the previous child (Table 4)- This table tries to decipher if there was any relation with the HBsAg positivity of the previous baby to the HBsAg positivity of the baby of this pregnancy. Mothers in the case group who had their previous babies HBsAg positive and negative were 7 and 8 respectively and it was 7 and 9 in the control group.

Table 5 compares the HBeAg status of the mother and the subsequent effect on the transmission of HBsAg to the baby. HBeAg depicts an acute state of infection. Transmission rate would be higher in the acute period. Of the total 36 HBeAg positive mothers, 13 babies became HBsAg positive, 23 babies became negative, majority of which were in the case group treated with lamivudine. When the HBeAg status of the mother was negative, there were only 6 babies who got the infection.

The overall descriptive data is as shown in Table 6. To note the important relation in the below table is that in a range of pretreatment, HBV DNA viral load of 10^{10} babies had become HBsAg positive and if the load was in the range of 10^{8} or less, babies could be saved from procuring the infection.

The table 7 has been put up to draw the relation regarding the pattern of HBeAg status change in the case and the control group. In the case group, though a small number of patients (5) maintained the positivity of the HBeAg status even after treatment, a good number of patients (14) were taken back to their HBeAg negative status with lamivudine treatment. By contrast in the control group, 15 cases maintained their HBeAg positivity and only 1 case had become HBeAg negative (Table 7). A significant p value 0.001 and df 3 was observed.

The descriptive statistics of the mode of delivery whether it was a normal vaginal delivery or a caesarean delivery is depicted as 1 and 2 has been shown in Table 8. The vaginal delivery rate was 73% in the case group slightly higher than the control group. The caesarean delivery rate was higher in the control group probably owing to the higher rate of complications observed during the progress of labour.

To have a look into the data that gives the most rewarding results (Table 9), our study had only 16.7% babies, which became HBsAg positive in the case group compared to a 46.7% in the control group. Again comparing the babies, which turned out to be HBsAg negative at the end of the study, a whopping 83.3% babies in the treated group were negative versus 53.3% in the control group. The p value was significant (0.012), df-1.

Age	Cases	Controls	Total
20-24	3	2	5
25-30	21	24	45
31-35	6	4	10
Total	**30**	**30**	**60**

Table 1. Age Distribution

	Primi	2nd Gravida	3rd Gravida	Total
Cases	15	11	4	30
Controls	14	12	4	30
Total	**29**	**23**	**8**	**60**

Table 2. Obstetric Score

	Baby HBsAG Positive	Baby HBsAG Negative	Total
Post conception	15	32	47
Preconception	4	9	13
	19	**41**	**60**

Table 3. Gestational Age

	Previous Baby HBsAG Positive	Previous Baby HBsAG Negative	Total
Cases	7	8	15
Control	7	9	16
Total	**14**	**17**	**31**

Table 4. HBsAG Status of Previous Child

	Baby HBsAG Positive	Baby HBsAg Negative	Total
HBeAg positive	13	23	36
HBeAg negative	6	18	24
Total	**19**	**41**	**60**

Table 5. Pretreatment HBeAg Status

Descriptives

	baby positivity		Statistic
obs score	1	Median	2.00
		Interquartile Range	0
	2	Median	2.00
		Interquartile Range	1
lcb	1	Median	2.00
		Interquartile Range	2
	2	Median	1.70
		Interquartile Range	1
pre sgpt	1	Median	65.00
		Interquartile Range	21
	2	Median	63.50
		Interquartile Range	19
pretreatmentdna	1	Median	2800000.00
		Interquartile Range	27760000
	2	Median	290000.00
		Interquartile Range	17939250

Baby HBsAg positive-1, Baby HBsAg negative-2.

Table 6. Overall Descriptive Data

	Change IN HBeAg Status				**Total**
	Positive to Positive	**Positive to Negative**	**Negative to Positive**	**Negative to Negative**	
Case	5	14	0	10	29
Control	15	1	1	13	30
Total	**20**	**15**	**1**	**23**	**59**

Table 7. Change in HBeAg status

	Mode of Delivery		**Total**
	Vaginal Delivery	**Caesarean Delivery**	
Case	22	8	30
Control	21	9	30
Total	**43**	**17**	**60**

Table 8. Mode of Delivery

	Baby HBsAG Positive	**Baby HBsAG Negative**	**Total**
Case	5	25	30
Control	14	16	30
Total	**19**	**41**	**60**

Table 9. HBsAg Status of Baby

ACKNOWLEDGEMENT

I express my sincere gratitude to Dr. Varghese Thomas, Head of the Department of Gastroenterology and Dr. Rajani Antony for their continuous guidance, Dr. Biju George, Assistant Professor, Department of Community Medicine for teaching me statistics and analysing the data. I am extremely thankful to the Government of Kerala for supplying the medicines and investigations free of cost to my patients through JSSK. I am greatly indebted to Head of the Department, all unit chiefs, teaching faculties and residents, Department of Obstetrics and Gynaecology, Government Medical College, Kozhikode, for their encouragement and help throughout the study.

DISCUSSION

Table 2 shows that the 2 groups were comparable with respect to the obstetric scores. It shows an almost equal distribution of the 3 obstetric score groups. Obstetric score in relation to the fall of DNA load and baby positivity was not statistically significant.

Table 4 shows a comparable data between the cases and controls. According to this study, the HBsAg status of the previous child did not significantly affect the positivity of the child born by the present pregnancy.

Table 5 wants to highlight the fact that HBeAg could act as an independent predictor for perinatal transmission of HBsAg. In a study conducted by Wiseman et al in 313 HBsAg positive women, transmission rates were 4/138 (3%) from HBV DNA positive mothers, overall 4/61 (7%) from HBeAg-positive mothers and 4/47 (9%) from mothers with very high HBV DNA levels. They had concluded that HBV perinatal transmission was restricted to HBeAg-positive mothers with very high viral loads.

Table 6 shows that if the initial viral loads were high, there was a high likely chance for the babies to become HBsAg positive. As previously mentioned by the Wiseman et al study, HBV perinatal transmission was restricted to HBeAg-positive mothers with very high viral loads. All mothers who had very high HBV DNA levels >10 log 8 copies/mL and were HBeAg-positive acted as factors to determine the acquisition of the infection by the baby. No transmission was seen in 91 babies of mothers with HBV DNA levels <108 copies/mL.[4] In a study conducted by Xu et al, the intrauterine infection rate increased linearly and significantly with maternal serum HBsAg titres trend test P value 0.0117 and HBV DNA concentration trend test P <0.01.[5] There was a significant decline in the range of 6 log 10 in the viral load in the case group, whereas there was a significant rise or same value maintained in the control group. Only a meagre number had their viral load fall in the control group. A similar trend was seen in the SGPT values too. The negative sign depicts that the initial viral load and SGPT values were lesser at the beginning of the study, which increased with gestational age in the control group. This was shown by a significant (p value 0.000). P value being highly significant, the fall of HBV DNA load and SGPT was appreciable.

A study conducted by Sukran Kose et al at the Tepecik Training Institute involved lamivudine treatment to HBsAg pregnant women. They found that after 8 weeks of lamivudine treatment, HBV viral load decreased to levels ≤10,000 copies/mL in five of the seven patients (71%) and in three patients (43%), HBV DNA was found to be completely negative after labour.[6]

Table 9 shows that a whopping 83.3% babies in the treated group were negative versus 53.3% in the control group. There was a similar study conducted by Van Zonnevald et al[7] where only one of the eight children in the lamivudine group (12.5%) was HBsAg and HBV-DNA positive at the age of 12 months. All other children seroconverted to anti-HBs and maintained seroprotection. In the untreated historical control group, perinatal transmission occurred in seven of 25 children (28%). In a study by Canho R et al, the vaccine and HBIG failures almost all had occurred in HBeAg-positive women with very high viral loads generally above 108 copies/mL. Another similar study by Shi et al[8] showed that oral lamivudine in HBV carrier mothers with a high degree of infectiousness (>106 copies/mL) in late pregnancy the last three months of pregnancy, effectively and safely prevent HBV intrauterine transmission.

CONCLUSION

Treatment of HBsAg positive women above an indicated viral load level in the third trimester of pregnancy significantly reduces the viral load of the mother and perinatal transmission to the baby. It increases the seroconversion to HBeAg negativity of the mother.

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