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ORIGINAL ARTICLE

EVALUATION OF HEPATITIS B SURFACE ANTIGEN POSITIVITY IN ANTENATAL WOMEN AND ROLE OF ANTIVIRAL THERAPY

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ABSTRACT: BACKGROUND: Hepatitis B infection is a major global health problem**. AIM:** of the study is to identify the antenatal women who are HBsAg positive and to evaluate their viremic status to prevent vertical transmission from mother to foetus and role of antiviral therapy in pregnancy. **STUDY DESIGN:** Is two centres prospective cohort study. All the pregnant women who attended the antenatal OPD in Government Victoria hospital/ Andhra Medical College, Visakhapatnam between February 2013 and September 2014 were evaluated. **METHODS AND MATERIAL**: HBs Ag screening was done using Rapid Stick test to all the pregnant women attending the OPD. 6400 members were screened. 100 subjects were HBsAg positive and confirmed by using ELISA technique. Evaluation for HBeAg and HBV viral load is done in all subjects. If HBV DNA is > 10^5 log copies/ml and Alanine transaminase (ALT) is > 2 ULN or HBV DNA is >10^8 log copies/ml will be offered telbivudine therapy. **RESULTS:** Of the 6400 members screened, 100(1.5%) were HBsAg positive. Of them, 10% were HBe Ag positive and 2% had HBV DNA > 10^5 log copies/ml. These patients were treated with drug, telbivudine in their third trimester. The HBV DNA level at the time of delivery is below 10^5 log copies/ml. The babies of these patients were checked for HBsAg and HBV DNA at birth and at 7th month which were negative and also for anti HBS at 7th month. **CONCLUSIONS**: The present study shows that HBsAg positive antenatal women are not prone for maternal and foetal complications. HBeAg positive individuals with high viremia need to be treated with antiviral drugs during the last trimester of pregnancy in order to prevent vertical transmission.

KEYWORDS: Hepatitis B surface antigen, Hepatitis e antigen, telbivudine, tenofovir, viral load, hepatitis B vaccine, mother to infant transmission, active and passive immunization.

INTRODUCTION: Hepatitis B infection is a major global health problem. According to WHO survey in 2008, endemicity is divided into zones depending on the prevalence rate.

1. High > 8%.
2. Intermediate 2-7%.
3. Low < 2%.

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Figure 1: Prevalence of Hepatitis B infection in various parts of world.

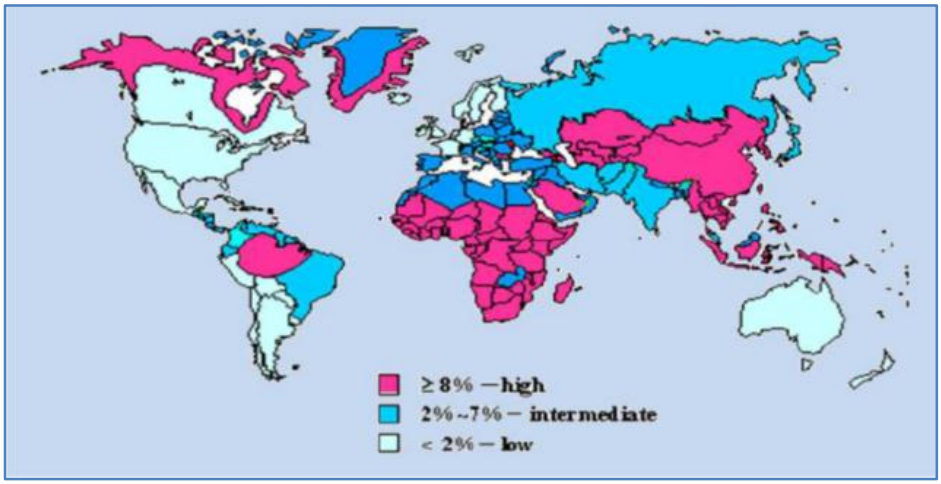

Fig. 1

According to various Indian studies by Tandon et al (1996), Dewedi et al (2011), Pandey et al (2011), HBsAg prevalence rate among pregnant women varies from 0.9% to 7%. Transmission of infection from a HBV carrier mother to her neonate accounts for the majority of new infections in the world today. 60-90% of hepatitis B surface antigen positive mothers who are hepatitis e antigen positive transmit the disease to their offspring.(1) So the aim of the study is to identify antenatal women who are HBsAg positive and also their viremic status and role of antiviral therapy during pregnancy to prevent vertical transmission from mother to foetus.

METHODS: This is a two centres prospective cohort study. All the pregnant women who attended the antenatal outpatient department in Govt. Victoria hospital/ Andhra medical college, Visakhapatnam between February 2013 to September 2014 were evaluated.

HBsAg screening was done using rapid stick test to all the pregnant women attending the O.P.D in Govt. Victoria hospital, Visakhapatnam. 6400 members were screened. 100 subjects were HBsAg positive and were confirmed by using ELISA technique. Clinical and laboratory evaluation was done to rule out chronic liver disease. Progress of mother and foetus during intrauterine life was followed with standard antenatal check-ups. The patients with HBV DNA less than 10^5 log copies/ml were followed up again three months later.

If the HBV DNA is more than 10^5 log copies/ ml and alanine transaminase (ALT) >2 ULN or HBV DNA > log 10^8 copies/ml, they were offered Telbivudine therapy after explaining the pros & cons. The decision to opt for or to refuse therapy will lie with the patient. Irrespective of whether the patient opts for therapy or not, all of them were assessed for HBV DNA and ALT at seventh month of gestation, at delivery time and 1 month postpartum. Infants of all HBsAg positive mothers received Hepatitis B immunoglobulin at birth and anti-hepatitis B vaccine as per the regular immunization schedule.

We stopped therapy at delivery if the HBV DNA was < 10^5 log copies/ml and were tested at 1 month, 3 and 7 months. If the HBV DNA remains > 10^5 log copies/ml at delivery, they were given the option of continuing or discontinuing therapy, after explaining the pros and cons during the breast feeding. The decision of continuing or stopping therapy lies with patient.

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Infants were checked for HBsAg and HBV DNA at birth and 7th month and also for anti HBs antibodies at 7th month.

Inclusion Criteria:

1. Female >= 18 years of age.
2. Pregnancy confirmed by urine pregnancy test or ultrasonography.
3. The woman has been instructed and is willing to provide written informed consent to participate in the programme.

Exclusion Criteria:

1. Patient is co- infected with HCV, HDV or HIV.
2. Patient with kidney disease with GFR <50ml/min.
3. Patient have received interferons or other immuno modulatory treatment in the 12 months before enrolling in the this study.
4. ALT value > 50 mcg/ ml requires further work up.
5. Known sensitivity to study drugs or another class of drugs.
6. Patient has history of myopathy, myositis or persistent muscle weakness.
7. Patient has a medical condition requiring the use of potentially hepatotoxic or nephrotoxic drugs.
8. Patient has history of clinical pancreatitis.

Ethics: We have taken permission from the ethical committee of our institute and followed the ethical standards. We have taken written informed consent from all the women enrolled in the study.

Statistics and Results: Of the 6400 members screened, 100 (1.5%) were HBsAg positive. So the prevalence rate of hepatitis B surface antigen positivity in our institute is 1.5%.

Figure 2: Status of HBs Ag positivity in pregnant women (1.5%).

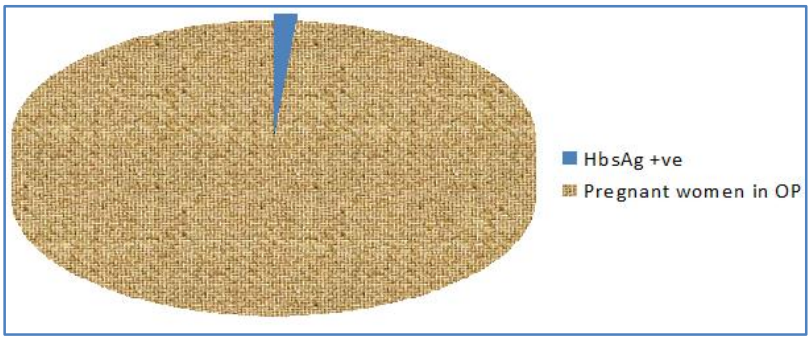

Fig. 2

Of them, 10% were HBeAg positive and 2% had HBV DNA more than 10^5 log copies/ml.

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Figure 3: Incidence of HBe Ag (10%) and HBV DNA (2%).

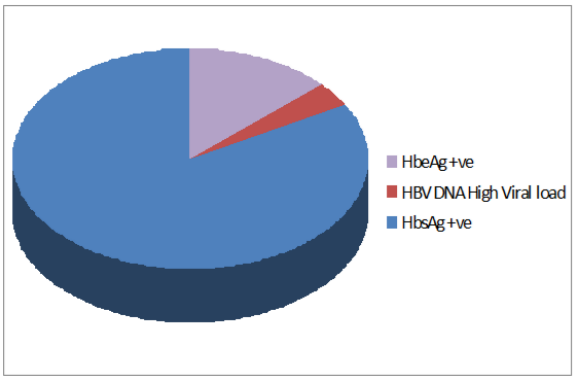

Fig. 3

Age Distribution:

50% subjects were aged between 18 to 22 years.
44% were between 22 to 28 years of age.
6% were more than 28 years of age.

Figure 4: Age wise Incidence

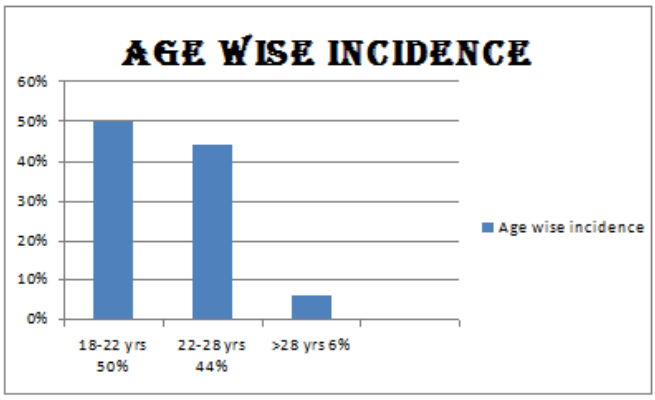

Fig. 4

Parity:

65% were primigravidas.
33% were second gravidas.
2% were multi gravidas.
All the subjects had normal LFT.
16% had haemoglobin level < 9 g%.

RESULTS: Of the 6400 members screened, 100 (1.5%) were HBsAg positive. So the prevalence rate of hepatitis B surface antigen positivity in our institute is 1.5%.

Of them, 10% were HBeAg positive and 2% had HBV DNA more than 10^5 log copies/ml.

These patients were treated with drug, telbivudine in their third trimester. We have observed that the HBV DNA level at the time of delivery dropped to below 10^5 log copies/ml.

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The babies of these patients were checked for HBs antigen and HBV DNA at birth, first and seventh month which were negative and also for anti HBs antibodies at seventh month.

92 HBsAg positive patients delivered so far, of which 6 were caesarean sections and 86 were normal deliveries 2 were intrauterine deaths which were not related to HBs Ag positivity Antenatal and intrapartum progress did not show any statistical difference.

DISCUSSION: Hepatitis B virus infection is a serious health problem that jeopardizes human life. In our country, Manish Dwivedi, Pandey et al published an article in 2011 according to which the prevalence of HBsAg positivity among asymptomatic pregnant mothers in North India is 1.1%. Another review of Hepatitis B prevalence in India by Lodha et al has concluded that it is 1-2 %.[2] In our study, prevalence is 1.56% and high viremia noted in 2% subjects while 10% were HBeAg positive. Our study shows that they are not prone to maternal or fetal complications. Smitha Sood and Shirish Malvankar[3] have noted 0.87% prevalence in a study of HBsAg prevalence in hospital based population similar to ours.

According to World Health Organization (WHO) statistics, 5% of the mothers are estimated to have chronic HBV infection, and the HBsAg positivity rate among fertile women in some high endemic areas such as Africa and South Asia, can reach as high as 9.2- 15.5%. Nearly one-third of HBV infected women enter immune clearance phase before or during pregnancy, with high HBV DNA load and abnormal ALT levels. They are faced not only with a high risk of mother to infant transmission (MTIT), but also an increased chance of liver disease exacerbation during pregnancy, threatening the safety of both mother and infant.[4]

If the infant acquires hepatitis B infection from mother by vertical transmission, the infant becomes a chronic carrier for hepatitis B infection throughout the life and chances of cirrhosis of liver and hepatocellular carcinoma are high. Hence all antenatal women with high viral load should be given antiviral therapy to prevent mother to infant transmission.

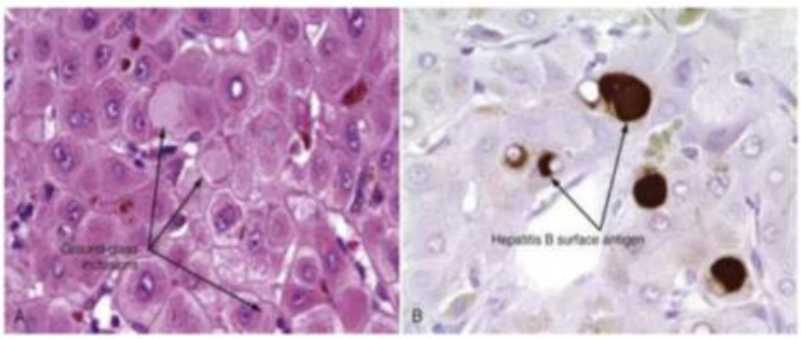

Figure - 5. *A*, Liver biopsy specimen showing ground-glass inclusions in hepatocytes. These inclusions represent large amounts of hepatitis B surface antigen (HBsAg) in the endoplasmic reticulum of infected hepatocytes (Hematoxylin and eosin, ?630.) *B*, Immunohistochemical stain for HBsAg. Note that the brownish inclusions correspond to the ground-glass inclusions seen in *A* (?630).

The antiviral drugs that are used during pregnancy for hepatitis B infection are nucleoside and nucleotide analogs. Nucleoside analogs have excellent oral bioavailability, good safety record and antiviral efficacy when compared with interferon alfa-2b. Nucleoside and nucleotide analogs replace natural nucleosides during the synthesis of the first or second strand or both of HBV DNA. They thus

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serve as competitive inhibitors of the viral reverse transcriptase and DNA polymerase and partially suppress viral replication.

Nucleoside analogs like lamivudine, telbivudine and tenofovir can be used during pregnancy.[5] The approval of lamivudine in 1998 was a major breakthrough in the treatment of hepatitis B infection. But it has high drug resistance, hence it is not used.[6]

In our randomised, prospective study, treatment of the mother with telbivudine resulted in prevention of almost all cases of vertical transmission compared to a vertical transmission rate of about 10% in the arm receiving only active and passive immunization. Telbivudine and tenofovir seem to be the treatment of choice.[7] Adefovir and entecavir are not recommended in pregnancy (Cornberg 2011). All the HBV antiviral drugs are category C, except for tenofovir and telbivudine, which are category B drugs.[8]

Table 1

FDA pregnancy categories and HBV antiviral therapy

Category	FDA description	HBV therapy
A	Adequate andwell-controlled studies have failed to demonstrate a risk to thefetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).	
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women or animal studies, which have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.	Telbivudine Tenofovir
C	Animal reproduction studies have shown an adverse effect on the fetus and there arenoadequateandwell-controlledstudiesinhumans,butpotentialbenefitsmay warrant use of the drug in pregnant women despite potential risks.	Lamivudine Entecavir Adefovir
D	There is positive evidence of human fetal risk based on adverse-reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.	
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse-reaction data from investigational or marketing experience and the risks involved In use of the drug in pregnant women clearly outweigh potential benefits.	Interferon

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As per current standard of care, patients in the immune tolerance phase should be monitored without treatment. However, they may receive antiviral therapy for the prevention of MTIT during the third trimester or rarely, for the management of maternal disease due to chronic hepatitis B activation in pregnancy.

The safety of exposure to antiviral drugs in the uterus for infants during the entire pregnancy is of particular concern, especially in early pregnancy (Ref. 8). Although telbivudine has been approved as pregnancy category B by the FDA, there are very few reports about safety of telbivudine treatment in mothers and infants during entire pregnancy.

HbeAg positive individuals with high viraemia need to be treated with antiviral drugs during the last trimester of pregnancy in order to prevent vertical transmission.

600mg of Telbivudine was administered per day at the gestational age of 20 to 32 weeks in women with HBV DNA > 10^5 log copies/ml. All infants received appropriate immunoprophylaxis. At age of 7 months, none of the infants in the treatment group had positive HBsAg or detectable HBV DNA. There was no significant difference in foetal development or infant outcomes, in terms of body weight, height or APGAR score.

Resistance and Hepatitis flare from antiviral therapy: Current available data have shown that antiviral resistance to lamivudine or telbivudine therapy in treatment of pregnant mothers are very uncommon due to short duration (8-12 weeks) of therapy during the third trimester of pregnancy. For treatment experienced patients when indicated, initiating tenofovir is recommended because of its favourable resistance profile and high potency in viral suppression. As per the European Association for the Study of the Liver and the American Association for the Study of Liver diseases, telbivudine and tenofovir are considered as one of the first line therapies in standard treatment. When pregnant women experience an acute hepatitis flare or have preexisting severe or advanced liver disease such as cirrhosis, antiviral therapy may be initiated during pregnancy or continued if antiviral drug has been started prior to pregnancy.[9]

In recent years, there have been gradually increasing reports on the safety of telbivudine treatment for chronic hepatitis B infection in the third trimester of pregnancy to block mother to infant transmission.

Caesarean section should not be performed routinely except in cases of high viral load. If the infant is vaccinated, he/she may be breastfed. The infant should be given both active and passive immunization. The schedule is given in table 2

Table 2: Hepatitis B prophylaxis of infants born to hepatitis B surface antigen positive mothers.

AGE OF THE INFANT	HBIG	VACCINATION
Within 12 hours of birth	0.5 mL IM*	First dose
1 month	None	Second dose
6 months[†]	None	Third dose[†]

If four doses of vaccine are administered, the third dose is given at 2 months and fourth dose is given at 12- 18 months.[10] Hepatitis B immunoglobulins should be administered at a site different from that used for the vaccine.

The aim of the study is to evaluate the safety of telbivudine treatment for chronic HBV infection during the pregnancy and provide a reference for HBV infected fertile women on how to block the mother to infant transmission of HBV.

In our study, the cases who were on treatment showed no transmission from mother to foetus and none of the infants were HBsAg positive, showing 100% success rate.

CONCLUSION: HBsAg positivity in antenatal women is a common entity. 6400 members were screened, of them 100(1.5%) were HBsAg positive. In this, 10% were HBeAg positive and 2% had HBV DNA >10^5 log copies/ml. These were treated with telbivudine in their third trimester. The HBV DNA level at the time of delivery was below 10^5 log copies/ml in these patients. The babies of these patients were checked for HBs antigen and HBV DNA at birth and 7th month which were negative and also for anti HBs antibodies at age of 7 months. If the infant acquires hepatitis B infection from mother by vertical transmission, the infant becomes a chronic carrier for hepatitis B infection throughout the life and chances of cirrhosis of liver and hepatocellular carcinoma are high. Hence all the antenatal women with high viral load should be offered antiviral therapy to prevent mother to infant transmission and infants should be immunized by giving both active and passive immunization.

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REFERENCES:

1. Han GR, Cao MK, Zhao W et al. An algorithm for risk assessment and intervention of mother to child transmission of hepatitis B virus. Clin Gastroenterol Hepatol 2012; 10(5): 452-459 29
2. Lodha R, Jain Y, Anand K, Kabra SK, Pandava CS. Hepatitis B in India: A review of disease epidemiology. Indian Pediatric journal 2001; 38: 1318- 22.
3. Sood S and Malvankar S. Seroprevalence of Hepatitis B surface antigen, Antibodies to Hepatitis C virus and Human immunodeficiency virus in a Hospital Based Population in Jaipur, Rajasthan. Indian J Community Med 2010; 35(1): 165- 169. 10.
4. EASL clinical practice guidelines: management of chronic hepatitis B virus infection Dienstag JL, Goldin RD, Healthcote EJ, et al: Histological outcome during long term lamivudine therapy. Gastroenterology 2003; 124: 105-17.
5. Vigano A, Mora S, Giacomet V et al. Seminars in Liver disease Vol. 33 No. 2/2013 Antiviral Therapy for Chronic HBV in Pregnancy Pan, Lee 145 Downloaded by: WHO. Copyrighted material. 37.
6. Dienstag JL, Goldin RD, Healthcote EJ, et al: Histological outcome during long term lamivudine therapy. Gastroenterology 2003; 124: 105-17.
7. Safety of telbivudine treatment for chronic hepatitis B for the entire pregnancy M. Liu, 1 H. Cai2 and W. Yil Department of Obstetrics and Gynaecology, Beijing Ditan Hospital affiliated to Capital Medical University, Beijing, China; and Department of Hepatology, Beijing Ditan Hospital affiliated to Capital Medical University, Beijing.

8. Pan C, Zhang H, Pang Q et al. FDA's proposed rule for pregnancy and lactation labelling: improving maternal child health through well-informed medicine use. J Med Toxicol 2008; 4(4): 284-288 32 Antiviral pregnancy registry. Antiviral pregnancy registry interim report 1, January 1989 through 31 January 2012. Available at: http://APregistry.com 2012. Accessed November 1, 2012 33.
9. Perrillo RP: Acute flares in chronic hepatitis B. The natural and unnatural history of an immunologically mediated liver disease. Gastroenterology 2001; 120: 1009-22.
10. Shepard CW, Simard EP, Finelli L, et al: Hepatitis B virus infection: Epidemiology and vaccination. Epidemiol Rev 2006; 28: 112-25.

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