International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622
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www.gynaecologyjournal.com
2019; 3(4): 167-170
Received: 21-05-2019
Accepted: 25-06-2019

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Evaluation of hepatitis B surface antigen positivity in antenatal mothers and the role of anti viral therapy

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DOI: https://doi.org/10.33545/gynae.2019.v3.i4c.309

Abstract
Background: Hepatitis B Virus infection is a serious global public health problem with Prevalence rate of 0.9 to 11.2% among women. Vertical transmission rate of HBsAg Positive mothers who are HBe Antigen Positive is 60-90%. Antiviral therapy with Telbivudine in third trimester of pregnancy in HBeAg Positive mothers with high viral load is required to prevent maternal to child transmission rate.
Objective: To identify HbsAg Positive antenatal women, to evaluate their viraemic status and prevent vertical transmission with anti viral therapy during third trimester of Pregnancy.
Material & Methods: This is a two centers Prospective cohort study conducted in antenatal women attending Government Victoria Hospital & Medical Gastroenterology department, King George Hospital, Andhra Medical College, Visakhapatnam from February 2018 to January 2019.
6500 Antenatal Women attending OPD were screened for HBsAg and evaluation of anti HBeAg, LFT and HBV Viral loads done. In the women with HBV DNA > 10^5 copies Telbivudine therapy was given in third trimester of pregnancy.
The babies were checked for HBsAg & HBV DNA at birth and also for anti HBsAg at 7^{th} month.
Observations & results: Out of the 6,500 women screened, 100 (1.5%) were HBsAg positive. Of these 10% were HBeAg positive and 2% HBV DNA Positive (> 10^5 copies/ml on treatment with Telbivudine in third trimester, the HBV DNA level is below 10^5 Copies /ml.
The babies were negative for HBsAg & HBV DNA at birth and at 7^{th} month and Ab to HBS at 7^{th} Month.
Conclusion: Treatment of the mother with Telbivudine resulted in prevention of almost all cases of vertical transmission and none of the infants were HBsAg Positive.

Keywords: Antenatal women, HBeAg positive, HBV DNA positive, telbivudine, vertical transmission

Introduction
Hepatitis B Virus belongs to the family of Hepadna Virus, also known as Dane Particle. It is 42nm particle with outer envelope HBsAg, Surrounding a nucleocapsid that contains a small DNA genome, which is a circular partially double stranded DNA of approximately 3200 base pairs. The surface (S) gene codes of the small surface protein, HBsAg.
Hepatitis B is a major global health problem with Prevalence rate of 0.9 to 11.2% in antenatal women. India is of intermediate risk group with prevalence rate of 2% - 7%, & life time risk of 20% to 60%. According to World Health Organization statistics 5% of mothers have chronic HBV Infection. Vertical transmission of HBsAg Positive mothers who are HBeAg positive is 60-90%, whereas mothers positive to antibody to HBeAg, transmit the disease less frequently (15%- 20%).
Other less common sources of infection are household contact with HBV carrier, hemodialysis, exposure to infected health care workers, tattooing, body piercing, artificial insemination and receipt of blood products or organs.
HBV is transmitted by percutaneous and mucous membrane exposure to infectious body fluids. The virus is 100 times as infectious as human immune deficiency virus (HIV) and 10 times as infectious as hepatitis C Virus (HCV).
HBV DNA has been detected by sensitive techniques like PCR testing in most body fluids except for stool.
New borns to HBV positive mothers can be effectively protected by passive- Active immunization with >90% protection rate. (Del Canmo 1997, Diestag 2008) Hepatitis B Immunoglobin for passive immunization shall be given as early as possible within 12 hours upto

7 days after birth. Active immunization follows a standard regimen of 3 doses of 10 micrograms at day 0, 1 month and 6th month.

Treatment of HBV DNA positive mothers with nucleoside analogues especially high HBV DNA levels > 10^5 copies level or 2 X105 IU/ml with Telbivudine and Tenofovir are USFDA category B antiviral drugs, which can be used during later half of pregnancy.

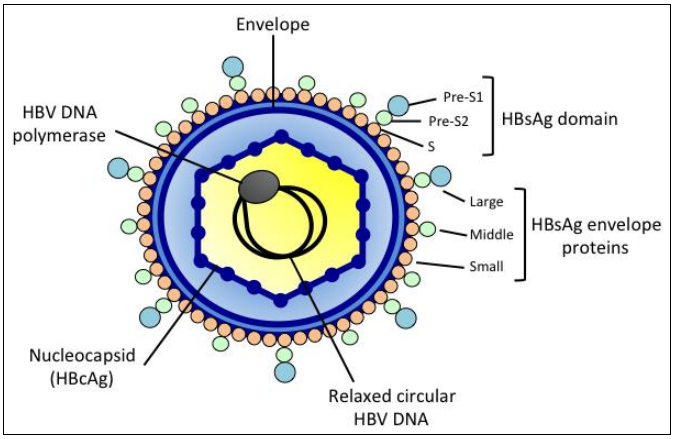

Fig 1: Type of DNA

Aims and Objectives

To identify antenatal women who are HBsAg positive and to evaluate clinically, biochemically and also their viremic status to prevent vertical transmission from mother to fetus and the role of antiviral therapy in pregnancy.

Materials and Methods

This was a two center prospective cohort study. Conducted in antenatal women attending OPD of Government Victoria Hospital, Andhra Medical College, Visakhapatnam for a period of one year from February 2018 to January 2019. Institutional ethical committee approved the study project. Informed and written consent was taken from the antenatal mothers included in the study.

Materials & Methods

HBsAg screening was done using Rapid stick Test to all the pregnant women, attending the OPD in, Government Victoria Hospital, Andhra Medical College, Visakhapatnam. 6500 members were screened.

100 subjects were HBsAg positive and confirmed by using ELISA technique.

Clinical and laboratory evaluation was done to rule out chronic liver disease. Progress of mother and fetus during intra uterine life was followed with standard Antenatal check up.

Evaluation for HBeAg and HBV viral load done in all subjects.

The mother with HBV DNA <5 log copies/ml will be followed up again three months later.

If both or HBV DNA > 5 log copies /ml & ALT >2ULN (upper limit of normal)or HBV DNA alone> 8 log copies/ ml will be offered Telbivudine therapy 600mg orally once a day, after explaining the pros and cons.

The decision to opt for or refuse therapy will lie with the subject.

Irrespective of whether the subject opts for therapy or not all of them will be assessed for HBV DNA & ALT at 7th month, at birth and one month post-partum.

Infants of all HBs Ag+v mothers will receive HBIG at birth and all infants will receive anti HBV Vaccine as per the regular immunization schedule.

Mothers who opted for therapy will be stopped therapy at delivery if the HBV DNA is < 5log copies / ml & will be tested at 1 month, 3 & 7 months.

For those taking therapy, If the HBV DNA remains >5 logs copies/ml at delivery, they will be given the option of continuing or discontinuing therapy, after explaining the pros & cons during the breast feeding.

The decision of continuing or stopping therapy will lie with the patient. Infant will be checked for HBsAg & HBV DNA at birth 1 month & at 7th month and also for anti HBs antibodies at 7th month.

Inclusion criteria

Female >= 18 years of age

Pregnancy conformed by urine pregnancy test or ultra sonography.

Patient has been instructed and is willing to provide written informed consent to participate in the programme

Exclusion criteria

Patient is co infected with HCV, HDV or HIV

Kidney disease patient with GFR<50 ml/min

Patient have received INF (Interferon) or other immuno modulatory treatment in the 12 months before enrolling in this study.

ALF value >50 ug,/ml requires further work up with one imaging technique.

Known sensitivity to study drugs or another class of drugs.

Patient has history of myopathy, myositis or persistent muscle weakness.

Patient has a medical condition requiring the use of potentially hepatotoxic drug or nephro toxic drugs.

Patient has history of clinical pancreatitis.

Patient with severe medical conditions that preclude the investigator prohibiting the participation in the study.

Observation and Results

6500 members were screened, of them 100 (1.5%) were HBs Ag +ve. In this, 10 % were HBeAg +ve & 2% HBV DNA +ve (>10^5 copies/ml).

These patients were treated with Telbivudine drug in their third trimester. The HBV DNA level at the time delivery is below 10^5 copies /ml.

The babies of these patients were checked for HBs antigen and HBV DNA at birth and at 7th month which were negative and also for anti HBs at 7th month.

Table 1: Age wise distribution

Age in years	No. of Patients	Percentage
18-22	50	50%
22-28	44	44%
>28	6	6%

Age distribution

Most of the subjects were between 18 to 28 years.

50% subjects aged between 18 to 22 years.

44% were between 22 to 28 years of age.

6% were > 28 years of age.

All the subjects had normal LFT

- 16% had hemoglobin level < 9gm%.
- 88 patients delivered on the expected date in which 10 were LSCS & 2 were IUDs.
- Antenatal Progress did not show any statistical difference.

Table 2: Hb level in gm%

4b in gm%	No. of subjects	Percentage
<9	17	17%
9-10	71	71%
>10	21	12%

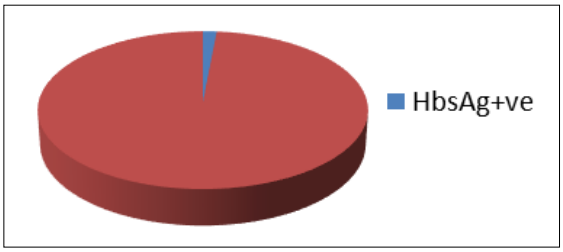

Fig 2: Status of HBsAg+ve in pregnant mother 1.5%

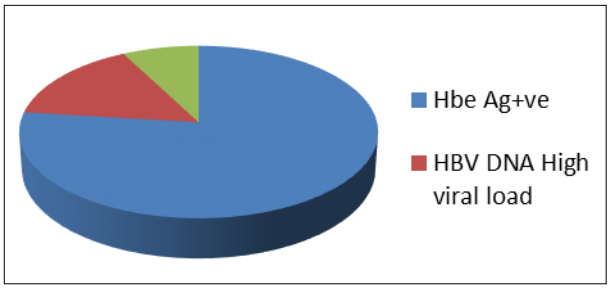

Fig 3: Incidence of HBeAg (10%) & HBV DNA (2%)

Table 3: Prevalence of HBsAg Positivity

Pandey *et al.*	Batham A *et al.*	Lodha *et al.*	Govt. Victoria Hospital
1.1%	2.4%	1-2%	1.53%

Table 4: Prevalence rate in male and female population

Sex	Smitha sood and Shirish Malvankar	Dutta *et al.*	Singh *et al.*
Male	1.04%	35.3%	0.65%
Female	0.58%	19.3%	0.25%

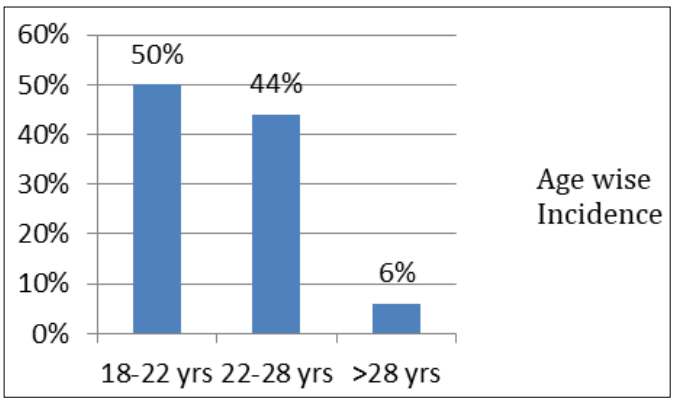

Fig 4: Age wise incidence

Discussion

In our country, 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%.

In our study, prevalence is 1.56 % and high viremia noted in 2% subjects while 10% were HBeAg +ve.

Our study shows they are not more prone to maternal or fetal complications.

There are several studies conducted on seroprevalence of HBsAg in India. Batham A *et al.* in their review of 54 studies on HBsAg prevalence in India have reported that prevalence in non-tribal population is 2.4%, whereas a very high prevalence was observed among tribal population (15.9%) Another review of Hepatitis B prevalence in India by Lodha *et al.* has concluded that it is between 1-2 % [15].

Smita Sood & Shirish Malvankar have reported the prevalence to be 1.04% and 0.58% respectively for males and females [16].

Dutta *et al.* has found it to be 35.3% in males and 19, 3% in females [15]. Singh *et al.* have noticed prevalence to be 0.65 and 0.25 % respectively in males and female subjects. [16] It is hypothesized that females probably clear the HBV more efficiently in comparison to males [16].

Relatively higher percentage of subjects in 6th, 3rd and 2nd decade of life respectively were found with HBsAg in their sera [16]. Similar findings have been noted by Smita Sood and Shirish Malvankar

High prevalence of HBsAg (between 2-7%) has been reported among pregnant women in India in the past but a recent study from Allahabad North India has found the prevalence of 0.9 %. Smita Sood and Shirish Malvankar have noted 0.87% prevalence in a study of HBsAg prevalence in hospital based population similar to ours [16].

A slightly higher prevalence was noticed among rural subjects than their urban counterparts (1.865 versus 1.44%). We hypothesize that this may be due to better awareness of HBV risk factors in the city dwellers.

Sri Krishna *et al.* have reported 1.86 prevalence among blood donors of Bangalore.

A low prevalence of 0.62% has been reported among blood donors from coastal Karnataka.

Hepatitis B virus infection is a serious global public health problem that jeopardizes human life. According to World Health Organization (WHO) statistics, 5% of mothers are estimated to have chronic HBV infection. 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 MTIT, but also an increased chance of liver disease exacerbation during pregnancy, threatening the safety of both mother and infant.

However, the safety of exposure to antiviral drugs in the uterus for infants during the entire pregnancy is of particular concern, especially in early pregnancy, which is a vital time for the development of the fetus. Although LdT (Telbivudine) has been approved as Pregnancy Category B by the FDA, there are very few reports about the safety of LdT treatment in mothers and infants during the entire pregnancy.

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.

Telbivudine or Tenofovir seem to be the treatment of choice. Adefovir and Entecavir are not recommended in pregnancy (Cornberg 2011) [17] as they are USFDA category C drugs.

None of the infants were HBsAge positive, resulting in a 100% success rate of blocking mother to Infant transmission.

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

Acknowledgment

There was no funding for this study

There is no conflict of Interest among the Authors.

Conclusion

HBsAg positivity in antenatal women is a common entity.

Present study shows that they are not more prone to maternal or

fetal complications.

Though 2 cases of IUD reported in the present study. Intrauterine birth defects are not more common than non-infected individuals.

HBeAg positive individuals with high viremia need to be treated with antiviral drugs during that last trimester of pregnancy in order to prevent vertical transmission.

These antenatal women are predominantly negative for envelop Ag (90%)

Summary

- 6500 members were screened, of them 100 (1.5%) were Hbs Ag +ve.
- In this, 10 % were HBeAg +ve & 2% HBV DNA +ve (>10^5 copies/m1).
- These patients were treated with Telbivudine drug in their third trimester.
- The HBV DNA level at the time delivery is below 10^5 copies /ml.
- The babies of these patients were checked for HBs antigen and HBV DNA at birth and at 7th month which were negative and also for anti HBs at 7th month.

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