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Original Research Article

Experience of Hepatitis B e Antigen positive and anti-HBeAg positive pregnancy in hepatitis B virus positive women in a Teaching Hospital: Frequency, viral load association and outcome

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ABSTRACT

Background: Mother to child transmission (MTCT) is the most important mode of acquisition of hepatitis B. MTCT is dependent on HBeAg status and HBV DNA levels. There is lack of information about HBeAg status and HBV DNA levels in HBsAg pregnant women in India.
We aimed to determine the frequency of Hepatitis B infection, HBeAg positive status, its association with HBV viral load and compared the differences in clinical and laboratory characteristics between HBeAg positive and negative cohort.
Materials and Methods: We extracted demographic, laboratory and virological characteristics from case records of pregnant women with HBV seen by department of Obstetrics and Gynaecology and Gastroenterology between January 2011 and December 2018. Patients were stratified into HBeAg positive and negative groups. Descriptive statistics were carried out.
Results: The prevalence of HBsAg positive pregnancy was 0.63% (130/20624 deliveries). Of the 89 patients in whom e antigen results were available, 14 (15.7%) were HBeAg positive and 73 (82%) were HBeAg negative. HBeAg positive women were younger (24y vs 27y), had higher AST (36 vs 18), ALT (56 vs 23) and HBV DNA level ($1.3x10^8$ vs 54 IU/ml) levels compared to HBeAg negative women. 12/14 HBeAg positive women received antivirals to prevent MTCT.
Conclusion: Hepatitis B prevalence in our cohort is 0.63%. HBeAg positive status was seen in 15.7% of pregnant women and was associated with high viral load of $>10^6$/copies/ml. 82% were HBeAg negative and associated with low viral load. HBeAg can be used as a surrogate marker for viral load and has immunoprophylaxis and treatment implications.

1. Introduction

The global burden of Hepatitis B virus is 257 million with India falling in the intermediate endemic category with a prevalence of 2-7%.[1,2] However, there is variation within the country.[3] One of the important modes of transmission of HBV is vertical transmission from mother to child during delivery. Universal immunization of hepatitis B vaccine has had an impact in minimizing transmission of hepatitis B virus (HBV).[4]

Two critical factors are central to mother to child transmission (MTCT). These include maternal hepatitis B e antigen (HBeAg) status and HBV DNA levels. HBeAg positivity is generally associated with high viral load ($>10^6$/copies/ml). This level of viral load is estimated to be associated with high rates of MTCT.[5] Whereas HBeAg is widely available, HBV DNA viral load limited by its availability, has a turnaround time of days to a couple of weeks and is expensive. Given these concerns, the World Health Organization has highlighted the role and importance of HBeAg suggesting that HBeAg status may be used as a surrogate marker of high viral load and be

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considered for administration of HBV antiviral drugs to prevent or minimize MTCT.[1,4] However, there is lack of information about the approximate burden or proportion of pregnant women who are HBsAg positive in India. This is further compounded by paucity of information about HBeAg status and HBV viral load (DNA level) in HBsAg positive pregnant women.

Therefore, the aim of our study was to determine the frequency of HBsAg positive pregnancies amongst all pregnancies seen at our hospital. We also aimed to determine the proportion of women positive for HBeAg and its association with HBV DNA levels. We compared clinical, biochemical and virological characteristics between HBeAg positive versus anti-HBeAg negative pregnant women. We wanted to test the assumption that HBeAg positive status may be used as a surrogate marker for high viral load.

2. Materials and Methods

We extracted demographic, laboratory, serological and virological characteristics from case records of hepatitis B surface antigen (HBsAg) positive pregnant women seen by department of Obstetrics and Gynaecology and Gastroenterology between January 2011 and December 2018. The study was approved by the Institutional Ethics Committee (reference number 154/2012 and 122/2015).

We collected demographic information, liver biochemistry, and about HBeAg and anti HBeAg status as well as HBV. Viral load exemplified by HBV DNA was estimated by PCR. HBsAg, HBeAg and anti HBeAg were carried out by ELISA tests using HBsAg Microwell Elisa kit (manufactured by Avantor Performance Materials). All HBsAg positive pregnant women underwent abdominal ultrasonography to determine liver characteristics including portal hypertension. Women with HBV viral load of $>10^6$ copies/ml were recommended treatment with HBV antiviral drugs as recommended by all liver societies.[6–8] All deliveries in HBV women regardless of the mode of delivery were followed by administration of HBV vaccine and hepatitis B immunoglobulin within 12 hours after birth. Patients were stratified into HBeAg positive and negative groups, and we compared the differences in clinical, biochemical, virological and characteristics between HBeAg positive and negative pregnant women.

Descriptive statistics such as means with standard deviation, median with Inter Quartile Range (IQR) and frequency with percentage distributions were used to describe the cohort. Statistical analysis was carried out with SPSS software version 22.

3. Results

Over an eight-year period (January 2011 to December 2018), 20624 pregnant women delivered in our hospital. There were 130 pregnancies from 117 women who were HBsAg positive, resulting in a prevalence rate of 0.63%.

The mean maternal age was 26 years; 37.7% were primigravida, and 56.9% multigravida. A majority of women (54.1%) were detected to be HBsAg positive for the first time at the current (index) pregnancy. Only 12.8% were found to be HBsAg positive prior to pregnancy and 33% were detected to be HBsAg positive in the previous pregnancy. Among women who were detected to be HBsAg positive for the first time during index pregnancy, detection of HBsAg positive status was 39.7%, 25.9% and 32.8% in the first, second and third trimester respectively and 1.7% during intra or postpartum period.

The mean gestational age at delivery was 37 weeks. The clinical, hematological, biochemical and virological characteristics of the entire patient cohort are shown in Table 1. All babies received hepatitis B immune globulin (HBIG) 0.5ml intramuscularly and hepatitis B vaccine 0.5ml intramuscularly, within 12 hours after birth.

Among the 130 women who were HBsAg positive, HBeAg status data was available in 89 (68.5%) women. Of these, 14 (15.7%) women were HBeAg positive while 73(82%) were HBeAg negative and anti HBe positive. In 2 women (2.3%) both HBeAg and anti HBe were negative. These details are depicted in Figure 1.

The clinical, biochemical, hematological and virological differences between HBeAg positive and anti HBeAg positive pregnant women are shown in Table 2. The women in the HBeAg positive group were younger 23.6 years versus 27 years in the anti HBe positive cohort and this was statistically significant (p = 0.026). The 2 cohorts were comparable in terms of mean gestational age at delivery, complete blood counts and liver function test except for AST, ALT and GGT. The women in the HBeAg positive cohort had a higher AST (36 versus 18.5 IU/ml, p value = 0.042); ALT (56 versus 23 IU/ml, p value = 0.07); GGT (21 versus 18 IU/ml, p value = 0.017); viral load (1.3×10^8 IU/ml versus 54 IU/ml, p value = 0.001) compared to the anti-HBe positive cohort.

12 of the 14 HBeAg positive women were placed on antivirals like tenofovir to prevent MTCT during the last trimester of pregnancy. Of note, pregnant women who were HBeAg negative status, had significantly lower viral load and none fulfilled the threshold criteria for administration of antiviral drugs.

All except one had an uneventful pregnancy; 1 patient had a spontaneous abortion at 7 weeks. 2 women who were HBeAg positive had acute hepatitis as demonstrated by a marked elevation of AST (313,162 IU/ml) & ALT (222,184 IU/ml), suggestive of acute Hepatitis B. This was confirmed with a positive IgM anti HBc result. Another woman who was HBeAg negative had raised AST (458 IU/ml) and ALT (640 IU/ml); this was ascribed to a probable seroconversion. One woman whose HBeAg status was not known also had

Table 1: The clinical, hematological, biochemical and virological characteristics of HBsAg positive women

Variable	HBsAg +
Age (y)	26.18 ± 4.817
Duration of pregnancy(weeks)	37.01 ± 5.006
Hb* (g/dl)	11.85 (10.8 – 12.4)
Total count* (cells/cumm)	9800 (6910 – 11381)
Platelet count* (lakhs/cumm)	2.2 (1.9325 – 2.9425)
Liver Function Test (LFT)	
Total protein* (g/dl)	6.58 (6.15 – 7.07)
Albumin* (g/dl)	2.9 (2.6 – 3.4)
Total bilirubin* (mg/dl)	0.385 (0.2 – 0.515)
Direct bilirubin* (mg/dl)	0.1 (0.08 – 0.1650)
Aspartate aminotransferase (AST)* (U/L)	21 (16 – 28.5)
Alanine transaminase (ALT)* (U/L)	23 (18 – 30.75)
Alkaline phosphatase (ALP)* (U/L)	104 (70 – 179.5)
Gamma glutamyltransferase (GGT)* (U/L)	18 (15 – 22.25)
HBV DNA*	94 (20 – 16368)

*Values are reported as median (Inter Quartile Range) for skewed variables

Table 2: The clinical, biochemical, hematological and virological differences between HBeAg positive and anti-HBeAg positive pregnant women

Variable	HBeAg +	Anti HBe +	p value
Age (y)	23.69 ± 3.301	27.03 ± 5.093	0.026
Duration of pregnancy(weeks)	35.9 ± 6.999	37.48 ± 3.538	0.500
Hb* (g/dl)	12.55 (10.1 – 14.075)	11.7 (10.9750 – 12.4)	0.068
Total count* (cells/cumm)	10105 (6107.5 – 14487.5)	9050 (6500 – 11220)	0.351
Platelet count* (lakhs/cumm)	2.1 (1.915 – 2.3050)	2.4 (2 – 3.03)	0.201
LFT			
Total protein* (g/dl)	6.6 (6.19 – 6.9)	6.63 (6.18 – 7.1150)	0.201
Albumin* (g/dl)	3.02 (2.5 – 3.4)	2.9 (2.6 – 3.45)	0.537
Total bilirubin* (mg/dl)	0.31 (0.19 – 0.5)	0.39 (0.2250 – 0.54)	0.652
Direct bilirubin* (mg/dl)	0.1 (0.06 – 0.13)	0.11 (0.0725 – 0.1650)	0.960
AST* (U/L)	36 (23 – 46)	18.5 (15 – 25)	0.042
ALT* (U/L)	56 (34 – 78)	23 (17.5 – 29)	0.07
ALP* (U/L)	104 (79 – 245)	98 (69.5 – 154.5)	0.261
HBV DNA*	138270531(28090510.5-172503805.5)	54 (20 – 302.5)	0.000

*IQR

Table 3: Seroprevalence of HBsAg in pregnancy in Indian studies

Study (reference)	Year	Sample size	HBsAg prevalence rate	HBeAg prevalence rate	HBV viral load Vertical transmission	Place
Dwivedi et al [9]	2011	37 / 4000	0.9%	56.8% 21 / 37	65% 13/20	Allahabad
Katke RD [10]	2015	47 / 8467	0.5%			Mumbai
Sibia P et al [11]	2016	41 / 3686	1.11%			Punjab
Sathiyakala R et al [3]	2016	13 / 1282	1.01%			Tamil Nadu
Garg R et al [12]	2017	420 / 2058	2.07%	4/420		Agra
Our study	2011-2018	130/20624	0.63%	14/89		Bengaluru

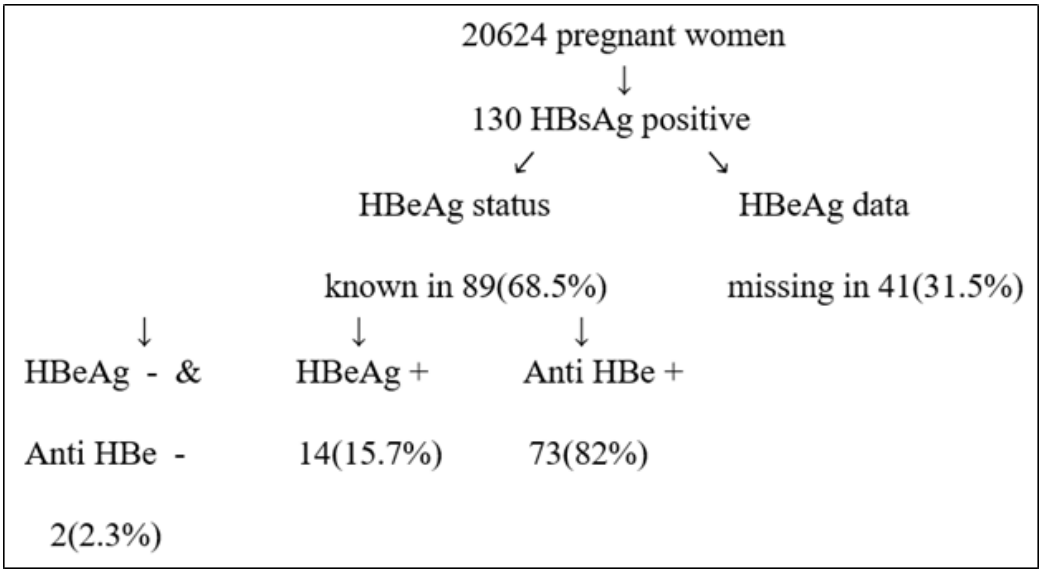

Fig. 1: Flow-chart depicting HBeAg/anti-HBeAg status in pregnant women

elevated AST (139 IU/ml) and ALT (154 IU/ml) and was on antiviral drugs as viral load was 78000 copies/ml. None of the women in either group had cirrhosis either clinically, biochemically or radiologically.

4. Discussion

It is estimated that 17 million of the 257 million Hepatitis B chronic carriers worldwide are in India.[1,4] Although the national carrier rate of Hepatitis B in India is reported as 4%, there is considerable variability within different areas of the country with a lower prevalence in Southern part of India compared to the rest of the country.[3,11] The seroprevalence of HBV in pregnancy in our study was 0.63% which is similar to 2 other studies from India carried out from Allahabad and Mumbai.[9,10] The0.63% prevalence is much lower than the national average of 4% and highlights the heterogeneity of HBV status in our country. Further, only 15% of these HBV infected women were HBeAg positive in our study. This low proportion of HBeAg positive women is striking and contrasts with the 56.8% reported by Dwivedi et al which attests to the considerable heterogeneity of the HBsAg positive population.[9] (Table 3)

Most of the HBsAg positive women were asymptomatic and were first detected during pregnancy. HBeAg status is an indicator of infectivity. Our study identified a higher aminotransferase levels in HBeAg positive women together with high viral load. This fact highlights the statement by World Health Organization that HBeAg positive status could be considered a surrogate marker for high infectivity. Such women may be specifically targeted for primary prophylaxis with antiviral drugs during last trimester of pregnancy particularly in areas where HBV DNA levels may not be easily available. This should be followed by routine primary and secondary prophylaxis with HBIG and HBV vaccine to babies born to these mothers.

The current recommendations of treatment lay significant emphasis on HBV DNA viral load levels and also HBeAg positivity which is considered a surrogate marker of high viral load and infectivity.[2,5–8] Hence it is important to identify the burden of HBeAg positive pregnant women, so that these can be targeted for both active and passive immunization to limit MTCT.[2,5–8]

In our study, we found only 15% of HBsAg positive pregnant women to be HBeAg positive. Further HBV DNA levels were significantly elevated only in HBeAg positive women. Indeed 100% of HBeAg negative women had very low viral load, well below the thresholds identified as significant for MTCT.

The World Health Organization states that "HBIG prophylaxis in conjunction with hepatitis B vaccination may be of additional benefit in newborn infants whose mothers are HBsAg-positive, particularly if they are also HBeAg-positive".[13] Further it states "In full-term neonates born to mothers who are HBsAg-positive and HBeAg-negative, protection against perinatally acquired HBV infection may not be significantly improved by the addition of HBIG to hepatitis B vaccine".[13] Further, there are concerns related to supply, safety and cost of the use of HBIG especially in rural settings.[1,13] Therefore, our study findings of HBeAg positivity in only 15% of pregnant women, and the corresponding high DNA levels suggests that passive immunization may perhaps be targeted in this subgroup only, thereby excluding 85% of pregnant women from taking HBIG. This kind of strategy has been identified as being useful as shown in one study, where MTCT was 0% in HBeAg negative pregnant women.[14]

Our study has limitations. Although the study was retrospective much of the data was prospectively collected. Further our study was limited to the duration of pregnancy and the few weeks post partum. The strength of our study is the large number of women who were screened for HBsAg following which a detailed analysis could identify only 15% who were HBeAg positive highlighting the fact that a very large proportion of HBsAg positive pregnant women were indeed HBeAg negative.

5. Conclusion

We found that a majority of pregnant women are detected to be HBsAg positive during pregnancy. Only a sixth of HBsAg positive pregnant women are HBeAg positive. A high viral load is confined to this subgroup. Almost all of the HBeAg negative pregnant women have very low viral load, below the levels identified as promoting MTCT. In a middle income country like India, this information is important and suggests that a targeted approach at identifying HBeAg positive women, may help optimize administration of HBIG to HBeAg positive women. Further, HBeAg positivity may be considered a surrogate marker of high viral load, particularly when this test is not available or affordable.

6. Source of Funding

None.

7. Conflict of Interest

None.

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