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Study of Hepatitis B Virus Infection in Pregnant women And Their Outcome

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Abstract
Aim: *to determine seroprevalence of hepatitis b viral infection in pregnant women and its effect on pregnancy and perinatal outcome.*
Material and Methods: *This study was conducted at Gandhi Hospital, Secunderabad during December 2009-October 2011. women attending our antenatal clinic were screened for HbsAg and seropositive women were studied with respect to maternal and perinatal outcome.*
Results: *of the 11,650 pregnant women studied, 126 (4.11%) were found to be seropositive for HbsAg with highest prevalence in the age group 21-30 years.(1.12%). seropositivity is more common with multipara than primi.(2.18%vs0.49%). majority are seropositive women give history of blood transfusions and injection with glass syringes with unauthorized ddoctors(49.2%). Chronic inactive carriers(89.7%) are more prevalent than those with acute hepatitis(8.7%) or chronic active hepatitis(1.58%). The study also showed increased incidence of maternal (GDM, PROM, Preterm labour) and perinatal(IUD, still birth, NICU admission) in the affected women.*
Conclusion: *Although a low prevalence of HbsAg is reported among pregnant women a significant increase in maternal and perinatal morbidity and mortality were identified. It emphasizes the importance of screening of all pregnant women for HbsAg as a part of routine antenatal care. HBV vaccine is recommended for non immunized pregnant women from first trimester.*
Keywords:- *Hepatitis B Virus, Prenatal HBsAg screening, Seropositive women.*

I. Introduction

Hepatitis B virus (HBV) infection is a major global public health problem. Of the approximately 2 billion people who have been infected worldwide, more than 350 million are chronic carriers of HBV.[1] Approximately 15-40% of infected patients will develop cirrhosis, liver failure, or hepatocellular carcinoma (HCC). [2] HBV infection accounts for 500 000 to 1.2 million deaths each year [3, 4] and is the 10th leading cause of death worldwide. Hepatocellular carcinoma incidence has Increased worldwide and the disease is now the 5th most frequent cancer, killing 300 000-500 000 people each year. In India, HBsAg prevalence among general population ranges from 2% to 8%, placing India in intermediate HBV endemicity zone and the number of HBV carriers is estimated to be 50 million, forming the second largest global pool of chronic HBV infections. India is a vast country, comprised of multiracial communities with wide variations in ethnicity and cultural patterns, which is attributable to its geographical location, gene influx due to invasion and/or anthropological migrations in the past. Moreover, recent increase in trade, trafficking and use of illicit drugs has also considerably influenced the epidemiology of HBV, specifically in the eastern and north eastern parts of India. However, data on the molecular epidemiology of HBV in India is scanty. HBV genotypes A and D have been well documented from different parts of mainland India. Interestingly, in addition to genotypes A and D, genotype C having high nucleotide similarity with south East Asian subgenotype Cs/C1 strain, have been detected exclusively from eastern Indian HBV carriers, suggesting a recent introduction. Thus, compared to other parts of India, the molecular epidemiology of HBV is naturally distinct in eastern India.

Serologic And Virologic Markers:

- After a person is infected with HBV the first marker detectable in serum is HBsAg, it precedes elevations of serum amino transferase activity and clinical symptoms and remains detectable during the entire icteric or symptomatic phase of acute hepatitis B and beyond.
- HBsAg becomes undetectable one to two months after the onset of jaundice and rarely persists beyond six months.

- After HBsAg disappears, antibody to HBsAg becomes detectable in serum and remains detectable indefinitely thereafter.
- HbcAg is sequested within an HBsAg coat, because of which it is not detectable routinely in the serum of patients with HBV infection.
- By contrast, anti-HBc is readily demonstrable in serum, beginning within the first one to two weeks after the appearance of HBsAg and preceding detectable levels of anti-HBs by weeks to months. Because of variability exist in the time of appearance of anti-HBs after HBV infection, occasionally a gap of several weeks or longer may separate the disappearance of HBsAg and appearance of anti-HBS. During this "window" period anti-HBc may represent serologic evidence of current or recent HBV infection.
- Blood containing anti-HBc in the absence of HBsAg and anti-HBs has been implicated in the development of transfusion associated hepatitis B.
- Recent and remote HBV infections can be distinguished by determination of immunoglobulin class of anti-HBc. IgM anti-HBc predominates during the first six months after acute infection, where as IgG anti-HBc is the predominant class of anti HBc beyond six months. Therefore, patients with current or recent acute Hepatitis B, including those in the anti-HBc window, have IgM anti-HBc in their serum.
- In patients who have recoveredfrom hepatitis B in the remote past as well as those with chronic infection, anti- HBc predominately of IgG classInfrequently in 1-5% of the cases with acute Hepatitis B infection, levels of HBsAg are too low to be detected; In such cases, the presence of Ig M anti-HBc establishes the diagnosis of acute hepatitis B.

Hepatitis B Virus Infection In Pregnancy:

India falls into the intermediate endemicity area as regards the prevalence of HBV infection, which is 4%.[5]Vertical and horizontal transmission in the perinatal period and early childhood are the major ways of propagation of this infection in India. To have control over these modes of transmission we need to have proper idea of HBV infection in pregnancy.

Thus, knowledge of HBV infection in pregnancy is important to us in view of:

a) the morbidity and mortality of the host (pregnant woman).

b) Its effect on the process of parturition.

c) Its capability to transmit the infection to an altogether new generation (foetus) and thereby increase the pool size.

Prevalence Of Hbv Infection In Pregnancy:

There are a large number of studies from India showing the seroprevalence of HBV infection in pregnancy by testing for the presence of HBsAg. The presence of HBeAg in the HBsAg positives has also been looked into to know the replicative status (highly infective). The overall seropre-valence of HBV infection in pregnancy is not significantly different from the general population. [6]

Different measures have be a adopted to modify (interrupt) the vertical transmission of HBV infection:

Hbig- Administration of HBIG in a dose of 200 IU i.e. every week from 28th week of gestation reduces the intrauterine infection to 16.1% against 32.7%(in controls).[7]

Lamivudine - It has been used with good safety and efficacy in the last four weeks of pregnancy to decrease the risks of vertical transmission.[8] Li et al[7] in 2003 showed that the intrauterine infection was reduced to 16.3% against 32.7% (controls) with its use from 28th week of gestation in a dose of 100mg/day. There are other studies too to substantiate this. However, there is a report of failure of vertical transmission of hepatitis B virus despite antenatal lamivudine therapy. [9] Of course, in this case the authors detected precore mutant in both the mother and the child and this is to be interpreted appropriately without undermining the vertical transmission lowering effect of lamivudine.

Caesarean-section-does not show any extra reduction in the incidence of immunoprophylaxis failure in comparison to vaginal delivery.

Other influences on the fetus:

Apart from vertical transmission, the maternal HBV infection does not have any effect on the fetal outcome. Although there was an increase in incidence of prematurity, it had no effect on congenital malformations, stillbirths, abortions or intrauterine malnutrition in comparison to the controls.

Breastfeeding:

Breast feeding is an important outcome of pregnancy and successful delivery. So, once the HBV infected mother with all possible precautions delivers a baby without any evidence of infection at birth, the next

question about comes to mind is: whether breast feeding can be done safely? Even though, breast milk of infected mother contains HBV DNA, with appropriate immunoprophylaxis, including hepatitis B immunoglobulin and hepatitis B vaccine, breast feeding of infants of chronic HBV carriers (irrespective of replicative status) poses no additional risk for the transmission of the hepatitis B virus.[10]

Prevention:

Three main strategies are available for the prevention of HBV infection: (1) behavior modification to prevent disease transmission, (2) passive immunoprophylaxis, and (3) active immunization.

Behavior Modification:

Changes in sexual practice and improved screening measures of blood products have reduced the risk of transfusion-associated hepatitis. Behavior modification is thought be more beneficial in developed countries than in developing countries, where neonates and children in early childhood are at the greatest risk of acquiring infection. In these group, immunoprophylaxis, both passive and active, will be more effective.

Passive Immunoprophylaxis:

Hepatitis B Immune Globulin (HBIG) is a sterile solution of ready-made antibodies against hepatitis B. HBIG is prepared from human blood from selected donors who already have a high level of antibodies to hepatitis B and used in passive immunoprophylaxis. Passive immunoprophylaxis is used in four situations (1) newborns of mothers infected with hepatitis B; (2) after needlestick exposure, (3) after sexual exposure, and (4) after liver transplantation. Immunoprophylaxis is recommended for all infants born to HBsAg positive mothers. Current dosing recommendations are 0.13ml/kg HBIG immediately after delivery or within 12 hours after birth in combination with recombinant vaccine. The combination results in a higher-than-90% level of protection against perinatal acquisition of HBV. Between 3.7% to 9.9% of infants still acquire HBV infection perinatally from HBV-infection mothers, despite immunoprophylaxis. Failure of passive and active immunoprophyxis in this setting may be the result of in utero transmission of HBV infection, perinatal transmission related to a high inoculum, and/or the presence of surface gene escape mutants. To study the interruptive effect of HBIG before delivery in attempt to prevent intrauterine transmission of HBV, a large-scale, random-control study was conducted in China. In this study, nine hundred and eighty HBsAg carrier pregnant women were randomly divided into HBIG group and control group. Each subject in the HBIG group received 200 IU or 400 IU of HBIG intramuscularly at 3, 2 and 1 month before delivery, in addition to newborns receiving HBIG intramuscularly. By this way, the rate of intrauterine transmission in this group fall to 5.7%, compared to 14.3% in control group. ($P < 0.001$). However, the preventive effect of HBIG administration before delivery needs to be confirmed by more study in the future.

Active Immunization:

Prevention of primary infection by vaccination is an important strategy to decrease the risk of chronic HBV infection and its subsequent complications. The first-generation hepatitis B vaccine, an inactive plasma-derived vaccine, became available in 1982. Consequently, the second generation of HB vaccine, a DNA recombinant HB vaccine was also available for general use in 1986. Both of the vaccines were proven to be safe and efficacious in preventing HBV infection. In 1991, the World Health Organization (WHO) recommended that hepatitis B vaccination should be included in national immunization system in all countries with a hepatitis B carrier prevalence (HBsAg) of 8% or greater by 1995 and in all countries by 1997.

The Hepatitis B Project was initiated in India in the year 2002 with support of Global Fund for vaccines & Immunization (GAVI). An agreement was signed by Govt. of India, Inter Agency Cooperation Committee (IAC) & the GAVI for this project. The partners from IAC for this initiative include W.H.O., Unicef, Usaid, Path, World Bank, Difid & European Commission.

Aim:

To determine sero prevalence of hepatitis B virus infection in pregnant women and its effect on pregnancy and perinatal outcome.

Objectives:

- To study the sero prevalence of hepatitis B virus infection in pregnant women.
- To determine mode of infection and stage of infection in pregnant women infected with hepatitis B.
- To study the effect of hepatitis B virus infection on pregnancy and perinatal outcome in comparison to the normal (HBsAg negative) controls.

Study Design:

This was a hospital based study conducted in Gandhi Hospital, Secunderabad for the duration of women attending the antenatal outpatient clinics for the antenatal check up were selected at their first visit irrespective of parity these women were screened for HBsAg. All seropositive women were further enquired to determine social characteristics and mode of acquiring infection by serial questionnaire, family history and history of childhood immunization for Hepatitis B virus. These women were further investigated for Liver function test, HBeAg, anti HBe anti body, anti HBc and ultra sonogram. There were followed until delivery to note the pregnancy and perinatal outcome and complications during postnatal period. These seropositive women were compared with normal controls (HBsAg negative) retrospectively. Both groups were matched for age, parity and BMI. Maternal and perinatal outcome noted in comparison to the normal controls. Adverse maternal outcomes included are pregnancy induced hypertension, gestational diabetes mellitus, pre term labor, pre term rupture of membranes, post partum hemorrhage, prolonged hospital stay. Perinatal outcomes evaluated for NACU admissions, birth weights, still births and intra uterine deaths.

We hence screened 11650 antenatal women after informed consent.

II. Results

In The Present Study Following Observations Were Made:

- The total number of pregnant women screened was 11650.
- Numbers of Seropositive women (HBsag +ve) were 126

Demographic Data

Table 1: Maternal Age- Sero Positivity

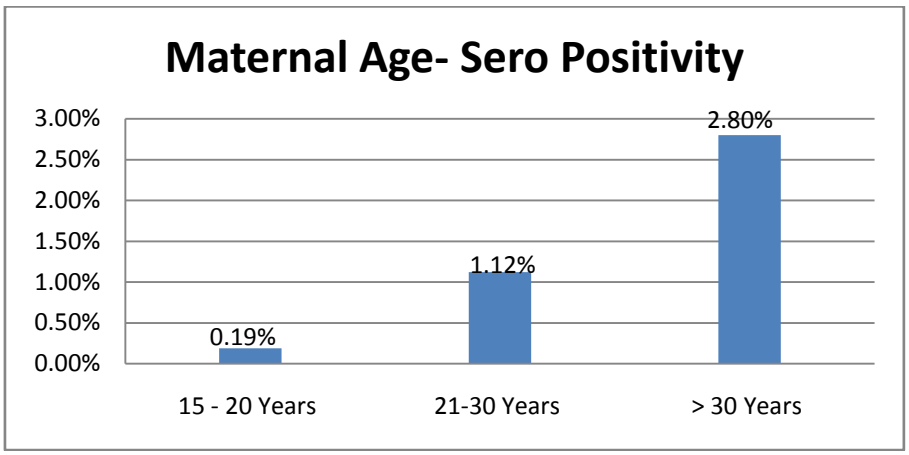
Maternal Age	Number of pregnant women Screened	Number of women with Surface Antigen Positive.	% of HBSag positive.
15 - 20 Years	1510	3	0.19%
21-30 Years	9620	108	1.12%
> 30 Years	520	15	2.8%
Total	11650	126	4.11%

In the present study highest prevalence observed in the age group of 21-30 years. The minimum age of the subject is 16 and maximum age is 36 years.

For the calculations of P value and OR seropositive women grossly divided into 2 groups (< 30 years and > 30 years) according to that

Table 2:

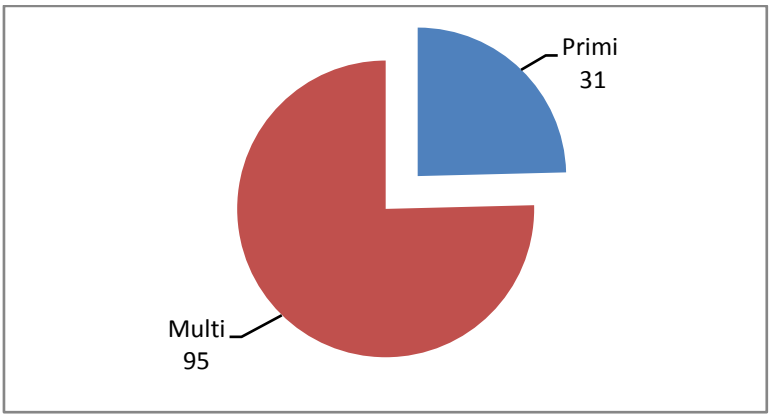
Maternal Age	Number of pregnant women Screened	Number of women with Surface Antigen Positive.	% of HBSag positive.
< 30 years	11130	111	0.99%
> 30 Years	520	15	2.88%
P value Highly significant (<0.001) OR - 2.89			



In our study as the age increases Sero Positivity increased. (0.99% in less than 30 years, 2.88% in more than 30 years age group).

Table-3: Parity - Sero Positivity

	Number of women screened	% of HBsAg positive.
Primi	4022	0.70 (31)
Multi	7628	1.24 (95)
P Value Highly significant (<0.001) OR – 2.89		

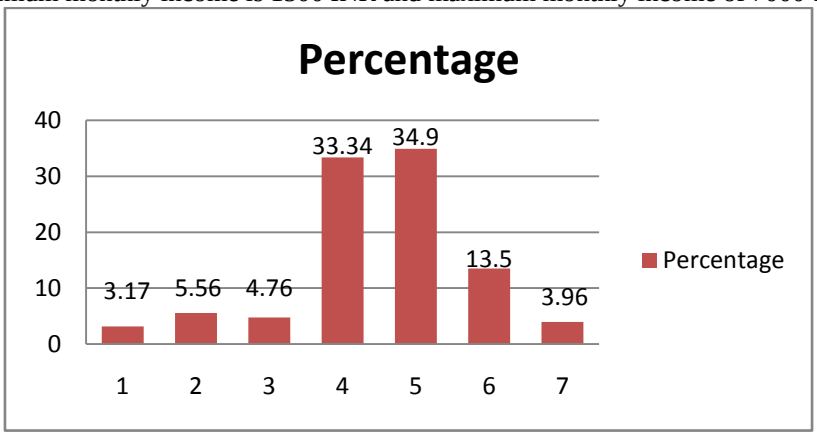


In the present study, with the increase in the parity there was an increase in the seropositivity also (multi-2.18%) Vs (Primi- 0.49%).

Table-4: Socio Economic Status (As per the Modified Kuppu Swamy Classification of 2007)

Income Per Month (In Rupee) □	Number of Seropositive Cases	Percentage
Class I: ≥ 19575	4	3.17 %
Class II: 9788 to 19574	7	5.56 %
Class III: 7323 to 9787	6	4.76 %
Class IV: 4894 to 7322	42	33.34 %
Class V: 2936 to 4893	44	34.9 %
Class VI: 980 to 2935	17	13.5 %
Class VII: ≤ 979	6	3.96 %

Minimum monthly income is 1500 INR and maximum monthly income of 7000 INR.



In the present study majority of the women belongs to class IV and V Socio Economic Status.

Table -5 Risk Factors for HBV infection in seropositive women

	Number of Seropositive Cases	Percentage
History of Blood Transfusions and injections with glass syringes.	62	49.2%
History of Surgeries	12	9.52%
Probable Sexual Route (Husband – HBsAg positive)	38	30%
History of Drug Abuse	0	0
Family History	2	1.58%
Tattooing	12	9.52%

In the present study majority women gave the history of blood transfusions and injections with glass syringes by Un authorized doctors in their villages (total accounting for 49.2%). Small percentage of seropositive women gave the positive history (1.58%).

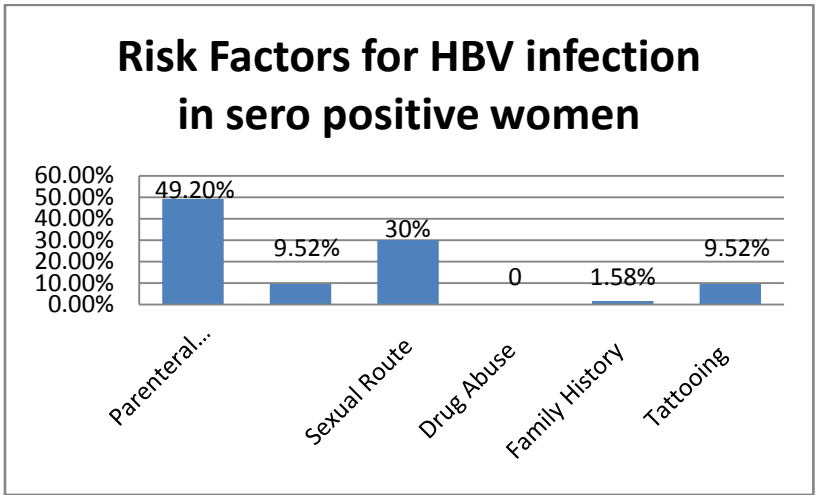
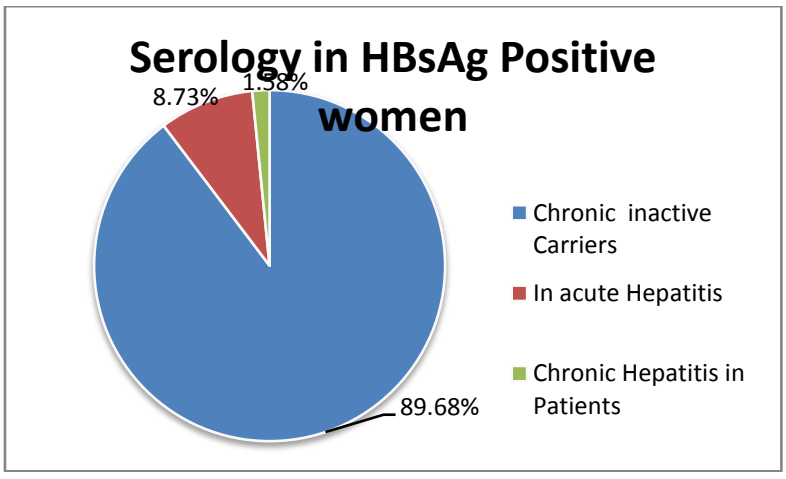


Table – 6 Serology in HBsAg Positive women

Seropositive Women	**Number**	**Percentage**
Chronic inactive Carriers	113	89.68%
In acute Hepatitis	11	8.73%
Chronic Hepatitis in Patients	2	1.58%

Table -7 – Parity – Sero positivity

	HBeAg	**Anti HBeAb**	**Anti HB-c Antibody**	**LFT**	**USG**
Chronic in active Carriers	Negative	Positive	IgG Anti HBc positive	Normal Study	Normal Study
Acute HBV Infection	Positive	Negative	IgM Anti HBc Positive	Raised ALT	Abnormal Study
Chronic Hepatitis	Negative	Positive	IgG Anti HBc positive	Normal / Increased	Cirrhotic changes



In the present study 89.68% were Chronic Inactive carriers and 8.7% women presented with Acute Hepatitis and 1.58% women presented with Chronic Active Hepatitis (cirrhosis).

Maternal Outcome and Perinatal outcome:
Maternal and Perinatal outcome compared with controls of same number (controls are matched for age, parity)

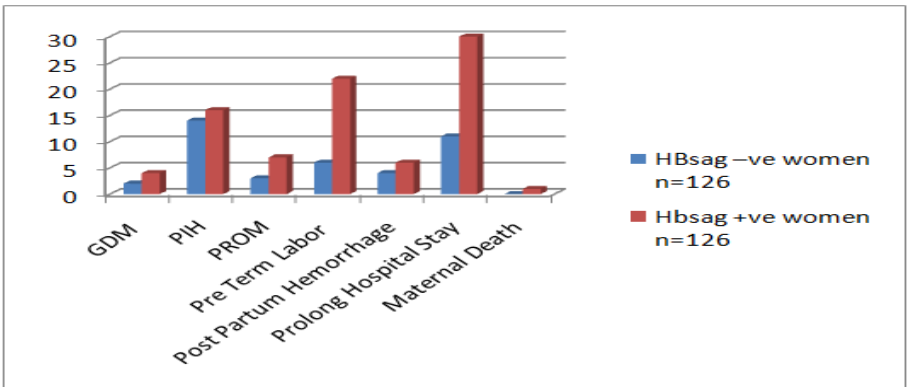
Table- 8 Demographic factors with respective to HBsAg Status

	Hbsag +ve women n=126	**HBsag –ve women n=126**
Primi	31	34
Multi	95	92
Age	25.49	26.39

There was no difference in the mean age, parity, BMI between the Seropositive and Sero Negative pregnant women.

Table -9: Maternalcomplications with respect to HBsAg Status

	HBsAg +ve women n=126	**HBsAg –ve women n=126**
GDM	4 (3.17%)	2 (1.58%)
PIH	16 (12.6%)	14 (11.11%)
PROM	7 (5.56%)	3 (2.38%)
Pre Term Labor	22 (17%)	6 (4.76%)
Post Partum Hemorrhage	6 (4.76%)	4 (3.17%)
Prolong Hospital Stay	30 (23.8%)	11 (8.7%)
Maternal Death	1 (0.79%)	0

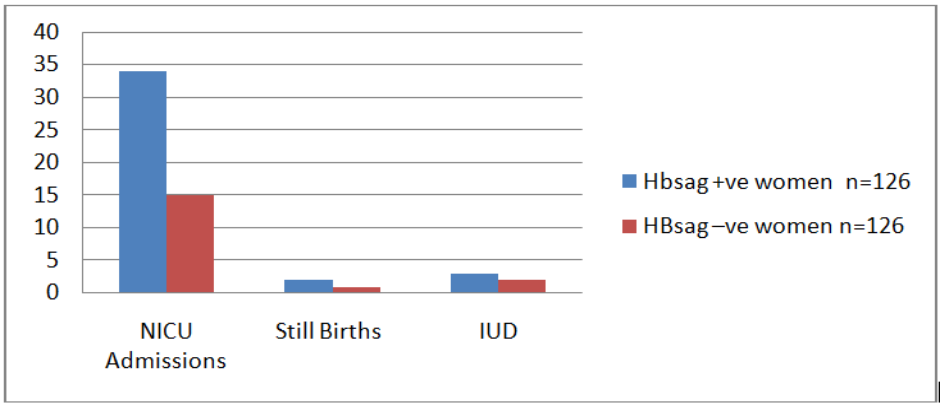


In our study there I two fold increase in the incidence of gestational diabetes (3.17%) Vs (5.18%) and PROM (5.56%) Vs (2.38%) in seropositive women when compared to matched controls. There is no significance difference in the pre eclampsia (12.6%) Vs (11.11%) and Post Partum Hemorrhage (4.76%) Vs (3.17%) between seropositive women and sero negative controls.

There is a significance difference in the incidence of pre term labor (17%) Vs (4.76%) and prolonged hospital stay after delivery (23.8%) Vs (8.7%) between seropositive women and sero negative controls.

Table -10: Perinatal outcome with respect to HBsAg Status

	Hbsag +ve women n=126	**HBsag –ve women n=126**
NICU Admissions	34 (26.98%)	15 (10.3%)
Still Births	2 (1.58%)	1 (0.7%)
IUD	3 (2.38%)	2 (1.58%)



In the present study 26.98% babies of seropositive mothers were admitted in NICU when compared to 10.3% babies of sero negative women. Low birth weight, pre term labor are common causes for NICU admission in both groups.

To calculate the P Value and ODD's ratio perinatal outcome is divided into two groups. Those with NICU admissions, still births, IUD categorized into abnormal perinatal outcome. Those with healthy babies categorized into normal perinatal outcome.

Table -11:

	HbsAg +ve women n=126	**HBsAg –ve women n=126**
Abnormal Perinatal outcome	39 (30.95%)	18 (14.28%)
Normal Perinatal outcome	87 (69.04%)	108 (85.71%)
P Value is < 0.05 which is significant. OR=2.69%.		

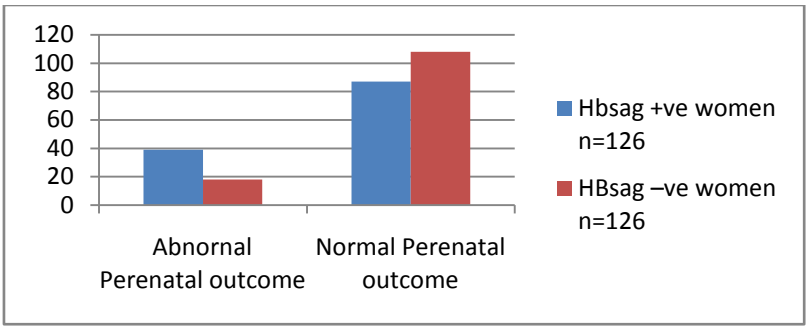
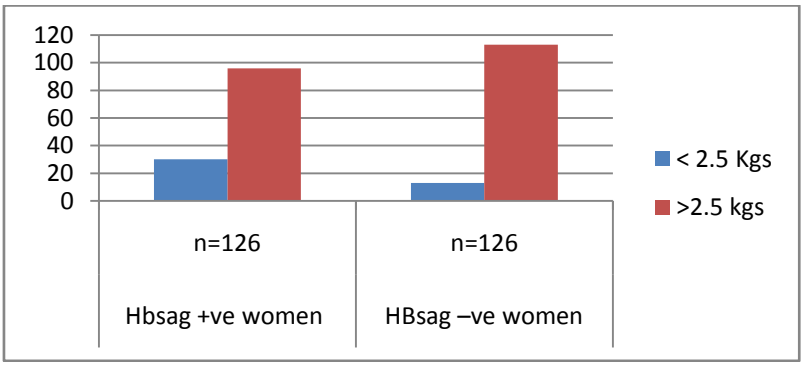


Table- 12: Perinatal outcome according to the birth weight

Birth Weight	**Hbsag +ve women n=126**	**HBsag –ve women n=126**
< 2.5 Kgs	30 (43.8%)	13 (10.3%)
>2.5 kgs	96 (76.19%)	113 (89.7%)
P Value is < 0.05% which is significant. OR=2.72.		



In our study there is significant increase in incidence of low birth weight in seropositive women when compared to sero negative controls (23.8%) Vs (10.3%)

III. Discussion

In the present study, seroprevalance of HBsAg among pregnant women was found to be 1.08%. This prevalence of HBsAg correlates with studies conducted in Saudi Arabia (Mohammed et al. 2008)[11] and in Qatar (Al Awaidy et al. 2006)[12]sero positive and in MLN medical college, Allahabad 2008.[13]Sero epidemiological study of different population shows variations and differences. These differences may be because of the type of the population studied, different geographical regions, genetic factors and socio economic factors.

We observed the significant increase in HbsAg positivity rate with increase in age. It was 0.99% for less than 30 years of age group and 2.88% in the age group of more than 30 years. This finding correlated with studies conducted in Saudi Arabia, Mohammed et al. 2008, bertoli et al. 2006 in Brazil.[14] We also found significantly higher frequency of HbsAg positivity in multi gravida (75.39%) when compared to prim

gravida(24.6%). These findings are correlated with study conducted in Allahabad, 2008. In the present study, majority of the women belongs to class IV and class V socio economic status.

In the present study most significant risk factor for HBV infection was parenteral route (49.2%). In our study sero positivity of husband is low (30%). None of the studies studied sero positivity of husbands of all HbsAg positive women. HBeAg positivity rate among antenatal women have been shown to vary widely in different geographic regions around the world. HBeAg positivity in our study (8.73%) was closely related to previous reported studies by okoth et al 2006 from Kenya, makuwa et al 2008 from Gabon and nayak et al from Northern India 1987[15].

Out of 126 seropositive women 11 cases were present with acute hepatitis like illness. In 6 out of 11 cases in second trimester and 5 out of 11 cases in third trimester. On follow up of these cases 8 cases recovered from illness in 6 months and they became sero negative. 3 cases became chronic inactive carriers. Out of 2 cases with chronic hepatitis first case was multi gravid with bad obstetric history presented with decompensate cirrhosis at 20 weeks of gestation, pregnancy was terminated and the second case was asymptomatic with compensated cirrhosis. Rest of the women (113) were chronic inactive carries and they were asymptomatic.

Maternal outcome was compared with seronagative matched controls.Based on the results seropositive mothers had a significantly higher prevalence ofpreterm labor (17%Vs4.76%) and prolonged hospitals stay after delivery (23.8%Vs 8.7%). These findings correlated with studies conducted in Tehran. In this study we found no significant differences in the prevalence of preeclampsia (12.6%) Vs (11.11%) and post partum hemorrhage (4.76%) Vs (3.17%) between seropositive women and seronagative controls. We found a positive association between HBsAg positivity and poor perinatal outcome. The incidence of NICU admissions (26.98%) Vs (10.35%) and low birth weight (23.8%) Vs (10.3%) is significantly increased in the seropositive women.

The reports of hepatitis B-related adult-onset Still's disease, polyarteritis nodosa, glomerulonephritis and vasculitis (Gambichler *et al.,* 2003), indicate that chronic HBV infection may be associated with a systemic inflammatory state that plays a causative role in these autoimmune diseases. Chronic HBV infection is associated with increased levels of pro-inflammatory cytokines such as IL-2, IL-6, IL-10, macrophage migration inhibitory factor, and tumour necrosis factor-alpha (TNF-α), which are more pronounced during active hepatitis.

(Sheron *et al.,* 1991) Similarly, many studies have shown that increased serum concentrations of proinflammatory cytokines that include IL 2 receptors, IL-6, IL-8, TNF- α and thrombin play an important role in premature labor. (Gucer *et al.,* 2001) Therefore, the additional systemic inflammatory response induced by chronic HBV infection could be the central explanation of the findings in our study. But in order to come to a definite conclusion for explaining the potential role of chronic HBV infection in pregnancy complications, more investigation with more data must be carried out in a prospective manner.

IV. Conclusion

1. Present study reported low prevalence of HBsAg in pregnant women; however the cases studied showed significantly increased Maternal and perinatal morbidity and mortality in the seropositive women.
2. At present in India, majority of the women in the reproductive age group are not immunized against Hepatitis B infection, because, Hepatitis B vaccination project was initiated in India in the year 2002.
3. Screening all the pregnant women for HBsAg, should be made a part of routine antenatal care, irrespective of the risk factors.
4. Prenatal HBsAg screening would identify infected mothers and allow immunization of their new borns with HBV IG and HBV vaccine, which is effective in preventing 85 – 95% development of HBV carrier state in children. HBV carrier state in children has approximate life time risk of 25% of dying due to primary hepatocellular carcinoma and cirrhosis. Deaths usually occur during adulthood when familial and financial responsibilities are maximum. In addition, these carriers serve as a source of infection to their families and communities.
5. Antenatal HBsAg screening also identifies HBsAg negative and non immunized mothers, so that, they can be recommended HBV vaccine, starting the first dose in first trimester.
6. Ours is a tertiary government referral centre, most of the cases are unbooked, admitted late in the gestation without immunization. So these women can be recommended, HBV vaccine, giving the first dose immediately on the first postnatal day before discharge and the second dose to coincide with her child's first vaccine at the age of two months and third dose at 6 months of age. However further studies to assess the feasibility as well as effectiveness of such a programme is necessary.

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