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Effective Strategies for Preventing Vertical Transmission in Hepatitis B

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1. Abstract

1.1. Introduction: Hepatitis B Virus (HBV) infection is a global problem with nearly 350 million chronic carriers, who are at risk of liver cirrhosis & hepatocellular carcinoma. Over 50% of these carriers are believed to have acquired their infection vertically from their mothers, i.e. through mother - to - Child Transmission (MTCT). Vertically - acquired HBV infections frequently (>90%) become chronic. The proportion of babies that became HBV chronic carriers is about 10% to 30% for mothers who are HbsAg positive but HbeAg negative. However, the incidence of perinatal infections is higher, i.e. 70% to 90%, when the mother is also HbeAg positive.

1.2. Aims and objectives: 1) To prevent Mother to Child Transmission (MTCT) of HBV by administrating antiviral drugs, as per indication to Hepatitis B positive pregnant mothers and mandatory HBV Vaccine and Hepatitis B immunoglobulin (HBIG) to newborn. 2) To evaluate vertical transmission to neonate

1.3. Materials & Methods: It was an prospective study conducted at Medical Gastroenterology in collaboration with Obstetrics & Gynecology and Microbiology Department, PGIMS, Rohtak over a period of four years. Two hundred and fifty eight (258) pregnant patients who were confirmed to be positive for HbsAg on Enzyme linked Immunoassay test (ELISA) and HBV DNA on PCR testing were enrolled in the study and followed. Out of these 258 patients, six patients had miscarriage and were excluded from the study. Out of remaining 252 patients, sixty (23.80%) were found to be having high HBV DNA and/or HbeAg positivity, hence were started on tablet Tenofovir 300 mg from 28 weeks of pregnancy. All the newborns were given zero dose of HBV vaccine and HBIG (0.5 ml) within few hours of birth and next three doses of HBV at 6, 10 &14 weeks of life. All the newborns were followed till 12 months of age and HbsAg was done at one year of age. Out of these 252 patients, data of 100 newborn who attained one year of age and were tested for HbsAg positivity was collected and analyzed.

1.4. Results: Out of 252 patients who were followed, 175 delivered in Government hospitals (145 normal delivery and 30 were caesarean section). Seventy five patients delivered in private hospitals (55 had normal deliveries and 20 had caesarean section). Two patients got delivered at home. Till date 100 newborns who have attained one year of age and got tested for HbsAg were found to be HbsAg negative i.e. zero percent vertical transmission.

1.5. Conclusion: Our study clearly highlights the success associated with timely intervention at different stage of pregnancy in HbsAg positive mother which includes mandatory screening of every pregnant mother, and if indicated ,then starting of antiviral treatment at 28 weeks of pregnancy, followed by mandatory HBIG, complete course of hepatitis B vaccination, including zero dose vaccination to new born and thus leading to complete prevention of vertical transmission.

2. Introduction

Hepatitis B virus (HBV) infection is a global problem with nearly 350 million chronic carriers, who are at risk of liver cirrhosis & hepatocellular carcinoma [1]. Over 50% of these carriers are believed to have acquired their infection vertically from their mothers, i.e. through mother - to - child transmission (MTCT). Vertically - acquired HBV infections frequently (>90%) become chronic [2]. The proportion of babies that became HBV chronic carriers is about 10% to 30% for

mothers who are HBsAg positive but HbeAg negative. However, the incidence of perinatal infections is higher, i.e. 70% to 90%, when the mother is also HbeAg positive [3]. There are three possible routes of transmission of HBV from infected mothers to infants: transplacental transmission of HBV in utero, natal transmission during delivery or post-natal transmission during care of infant or through breast milk [4]. Chronic HBV infection during pregnancy is an important opportunity to interrupt perinatal transmission of HBV. The HBV infection does not appear to influence fertility or conception per se, beyond the effects of cirrhosis or liver failure [5]. If cirrhosis has set in, then pregnancy may be a rare event. The rate of spontaneous abortion is also significantly higher in women with cirrhosis, reaching 30% to 40% vs. 15% to 20% in the general population [5]. Women with advanced chronic liver disease, regardless of cause, have decreased fertility due to anovulatory cycles and amenorrhoea [6]. The medical dictionary defines the phrase "vertical transmission" of an infection as the transmission of pathogen from mother to child during pregnancy or childbirth, or by breastfeeding. In case of HBV it is defined as positivity at 6-12 months of life of the hepatitis B surface antigen (HBsAg) or of HBV-DNA in an infant born to an infected mother [7, 8]. Vertical transmission of HBV infection is the main reason for the continued endemic infection of HBV in Asia. Approximately 90 % of children who get HBV infection vertically from their mothers fail to clear the infection and develop chronic infection [6]. The risk of vertical transmission of HBV predominantly depends on the maternal HBV viral load and HbeAg status. In the absence of prophylaxis, the risk of vertical transmission of HBV infection is as high as 70 % to 90 % for infants born to HbeAg-positive mothers, and 10 % to 40 % for infants born to HbeAg-negative mothers [6]. The presence of both HBsAg and HBV DNA at birth are transitory events and do not imply transmission of the infection. Similarly the presence of antibodies against hepatitis B e antigen or antibodies against Hepatitis b core antigen at birth or upto two years of age is simply due to crossing the placenta from mother to the fetus and therefore is unrelated to infection. Though several epidemiological studies on viral hepatitis in pregnancy are available, there is paucity of data on maternal to perinatal transmission of HBV during pregnancy. The goal of this study was to determine risk of vertical transmission on treatment with antiviral drugs where indicated and administration of HBIG and complete course of HBV vaccine, including zero dose vaccination to neonate and to follow these infants uptill one year of age.

3. Aims and Objectives

1) To prevent Mother to Child Transmission (MTCT) of HBV by administrating antiviral drugs, as per indication to HbsAg positive pregnant mothers and mandatory HBV Vaccine and HBIG to newborn.

2) To evaluate vertical transmission to neonate.

4. Material and Methods

It was a prospective study done over a period of four years i.e. 01.03.2018 to 28.02.2022 in Department of Medical Gastroenterology in collaboration with Obstetrics and Gynaecology, & Microbiology Department, PGIMS, Rohtak. All the antenatal women who tested positive for HbsAg and HBV DNA quantitative were enrolled in the study after an informed consent. The enrolled candidates were encouraged to have institutional delivery and immunisation of newborn during its first hours of life. Detailed history and general, systemic and obstetric examination was carried out. Personal history and history of risk factors like tattooing, previous blood transfusions or operative procedures were taken. All the women were followed during pregnancy, delivery, post-partum, breast feeding and also later on. All newborn were followed till one year of age. At their first antenatal visit, sample was taken for HBV DNA levels, HbeAg status and activity of liver. Women who were chronic carriers and with high HBV DNA load (> 2 x 107 I.U.) or HbeAg positive or both were treated with tablet Tenofovir 300 mg once a day from 28 weeks of gestation. All the women were followed during whole duration of pregnancy. All the newborns were given zero dose of HBV vaccine and HBIG (0.5 ml) intramuscularly within twenty four hours of birth and next three doses of HBV at 6, 10 &14 weeks of life. All the newborns were followed till 12 months of age and HbsAg was done at one year of age.

5. Statistical Analysis

All the data was entered in Microsoft Excel Data and analysed using SPSS 15.0 version.

6. Observation and Results

Two hundred and fifty eight (258) patients who were confirmed to be positive for HbsAg on Enzyme linked Immunoassay test (ELISA) and HBV DNA on PCR testing were enrolled in the study and followed. Out of these 258 patients, six patients had miscarriage and were excluded from the study. In the study pool of 252 HBsAg pregnant patients, majority belonged to rural areas (72.22%) & were in 21-30 yrs of age group (75.79%), sixty (23.80%) were found to be having high HBV DNA and/or HbeAg positivity, hence were started on tablet Tenofovir 300 mg from 28 weeks of pregnancy. The rest 192 pregnant patients (66.20%) were inactive carrier, hence were not started on oral antiviral. Out of these 252 patients, 175 delivered in Government hospital, 75 patients delivered in private hospital and 2 patients had home delivery. On analysis of 175 delivery in Government hospital, 145 patients had normal vaginal delivery and 30 patients underwent caesarean section. On analysis of 75 delivery in Private hospital, 55 patients had normal vaginal delivery and 20 patients underwent caesarean section. The two home delivered patients as expected had normal vaginal delivery. One patient had premature delivery who survived and two babies died after few months of birth due to cardiac ailment and sepsis i.e. both deaths were not related to hepatitis B. Out of sixty patients who were started on antiviral treatment, 15 patients had raised transaminases, in addition to high viral load and HbeAg positivity and would have merit treatment, even if they were non pregnant. In rest 45 patients, they were started on oral antiviral treatment with sole purpose of preventing vertical transmis-

sion because their transaminases were normal but HBV DNA were high along with HbeAg positivity in majority of cases i.e. they were in immunotolerant phase. All the newborns were given zero dose of HBV vaccine and HBIG (0.5 ml) intramuscularly within few hours of birth and next three doses of HBV at 6,10 &14 weeks of life. All the newborns were followed till 12 months of age and HbsAg was done at one year of age. Out of total 252 deliveries, 2 deaths were excluded, thus 250 neonates were followed. At the time of writing this paper, data pertaining to 100 neonate who have reached one year of age and got tested for HbsAg was analyzed. All the 100 infant at one year of age were found to be HbsAg negative, thus signifying zero percent vertical transmission after adopting above method of oral antiviral treatment wherever indicated and mandatory use of HBIG 0.5 ml intramuscular and zero dose hepatitis B vaccination to newborn within 24 hours of birth, followed strictly by completion of full course of hepatitis B vaccination. All the newborns were breast fed for 6-9 months with mean of 7 months (Table 1-6).

Table 1: Showing Age Group Distribution of Patients

Age Distribution	10-20 yrs	21-30 yrs	31-40 yrs	41-50 yrs
252 Patients	30 (11.90%)	191 (75.79%)	28 (11.12%)	3 (1.19%)

Table 2: Showing Rural/Urban Distribution of Patients

Residential Area	Rural	URBAN
252 Patients	182 (72.22%)	70 (27.88%)

Table 3: Showing Distribution Pattern of Deliveries and Miscarriage

Total Patients	Term Delivery	Premature Delivery	Miscarriage	Death of Newborn
258	251	1	6	2

Table 4: Showing Distribution Pattern of Deliveries On Basis of Place of Delivery

Total Deliveries	Government Hospital	Private Hospital	Home Delivery
252	175 (Normal-145, C.S.-30)	75 (Normal-55,C.S.-20)	2

Table 5: Showing Distribution of Patients Requiring Treatment

Total Number Of Patients	On Treatment	Inactive Carrier
252 Patients	60 (23.80%)	192 (66.20%)

Table 6: Showing Distribution of HbsAg Positivity and Breastfed Newborn

Total Newborns	Breast Fed	HbsAg Positive	HbsAg Negative
100	100 (100%)	0 (0%)	100 (100%)

7. Discussion

HBV infection during pregnancy does not appear to increase maternal or fetal mortality and morbidity. A large study that compared 824 HbeAg positive mothers to 6, 281 HBsAg negative control mothers found no difference in rates of preterm delivery, birth weight, neonatal jaundice, congenital anomalies or perinatal mortality [9]. Our study is also in line with above study, as in total six miscarriages occurred which is comparable to miscarriages in HbsAg negative pregnant patients. There were only two newborn deaths and those were due to cardiac problem & sepsis and were unrelated to HbsAg positivity of mother. However, a recent study showed that HBsAg carrier mothers had an increased risk of gestational diabetes mellitus, antepartum haemorrhage, and threatened preterm labour [10]. Our study is not in alignment with above study, as no patient developed diabetes mellitus or antepartum haemorrhage and only one patient had premature delivery which is comparable to other HbsAg negative pregnant patients.

The American Association for the Study of Liver Disease (AASLD) recommends that all pregnant women be screened for HBsAg during the first trimester, even if previously

Vaccinated or tested [11]. Screening allows for identification of infants requiring immuno-prophylaxis with HBV vaccine and HBIG, anti-viral treatment of pregnant carriers if indicated, and counselling of sexual and household contacts [2]. The HBsAg-positive pregnant woman should be counseled to inform their obstetricians so that immuno-prophylaxis can be administered to the newborn immediately after delivery [11]. At our centre also, all pregnant mother are screened for HbsAg, HCV and syphilis infection. The pregnant patients who turn out to be HbsAg positive are counseled on every visit for hospital based delivery, need of zero dose hepatitis B vaccination and HBIG to new born within 24 hours of birth. The husband and other household contacts are screened for HbsAg and if negative are vaccinated against hepatitis B. In our study group of 252 patients, counseling worked and 250 patients i.e. 99.20%, had hospital based delivery (175 Government and 75 Private) and only two patients (0.80%) had home based delivery. Out of total 252 de-

livered patients, 226 newborn (89.68%) received HBIG and 26 newborn (10.32%), who got delivered in private hospital, did not receive HBIG immunoglobulin. This emphasizes the need of more spread of knowledge among treating Gynecologist, especially private practitioners, for need of mandatory HBIG to all newborn delivered to HbsAg pregnant mother, within 24 hours of birth. The American Congress of Obstetricians and Gynecologists (ACOG) and AASLD guidelines suggest that HBsAg-positive mothers be referred for further medical evaluation so that those with liver disease can be identified and monitored frequently by a team of specialists. This should not be deferred to the postpartum period [11].

The vertical transmission can occur in-utero, during delivery, or after delivery.

7.1. In-utero Transmission

HBV can cross the placental barrier and reach the fetus, however the impact of this mode is not clear. In a study from the United States, of 72 pregnancies,13 (18 %) cord blood samples were positive for HBsAg [12]; however, HBV DNA was detected in only three (23 %) of these. In a Chinese study, only 3.7 % of babies tested HBsAg-positive at birth from in-utero infection [13]. Hence it is suggested that in-utero transmission may not be the predominant mode of transmission of HBV in-utero or trans placental HBV infection cannot be blocked by HBV vaccine or HBIG given at birth, and is an important reason for immunoprophylaxis failure. The mechanism of intrauterine transmission of Hepatitis B was studied by Zhang et al on 59 HBsAg-positive mothers. Both HBsAg and HBcAg were detected in the placenta from HBsAg-positive mothers. The concentration of two antigens decreased from mother's side to fetal side but in four patients, the concentration was in reverse order. The authors concluded that although the predominant rout of transmission was transplacental, other routes of infection may exist [4]. The main risk factors for intrauterine HBV infection are maternal serum HbeAg positivity, high maternal viral load, and a history of threatened preterm labor or threatened abortion [6]. Zou et al studied a large cohort of 1043 mothers and found a correlation between maternal HBV DNA levels and immunoprophylaxis failure that indicated maternal pre-delivery HBV DNA level > 6 log copies/ ml are associated with reduced prophylaxis effectiveness. Bai et al corroborated this finding by showing that intrauterine transmission may be due to HBV crossing the placental barrier, according to positive HBV staining of placental tissue in mothers with high viral loads. High maternal HBV DNA titer is probably one of the most important risk factor for vertical transmission of HBV. HBV infection was found to occur in upto 10% of babies despite immunoprophylaxis and high maternal HBV DNA level was one of the most important risk factor for this. Traditionally HbeAg-positive mothers were considered to be at a higher risk of transmitting HBV infection to newborns than HbeAg-negative mothers, with the risks of chronic HBV infection by age of 6 months of 70 % to 90 %and 10 % to 40 %, respectively, in the absence of post-exposure immunoprophylaxis. The mechanisms for high rate of infection in infants born to HbeAg-positive mothers remain unclear. Maternal HbeAg positivity is strongly correlated with high levels of maternal viremia [14]. The American College of Gastroenterology (ACG) and AASLD guidelines both strongly recommend initiation of antiviral drugs in highly viremic patients at 28-32 weeks of gestation in order to reduce MTCT. Anti-viral therapy during pregnancy provides potent anti-viral suppression, is relatively safe and well tolerated, and reduces perinatal HBV transmission. Problems associated with such treatment include the risk of viral drug resistance in the mother depending on the antiviral agent used, contraindication to breastfeeding, and the risk of hepatitis flares upon discontinuation [15].Current recommendations by the AASLD cite HBV DNA levels > 2 X 107 IU/ml as an indication for initiation of therapy as risk of HBV transmission increases with level of viremia. Tenofovir, a nucleotide analogue with activity against HBV polymerase, is currently a preferred oral agent for HBV therapy. It has been used by pregnant women for HIV infection with no increase in congenital malformations. Preliminary data show no evidence of renal impairment, abnormal bone metabolism or impaired growth in children exposed to tenofovir in utero [16].

In our study pool of 252 patients, we were able to collect data of 100 newborn all of whom delivered in hospital set up and received zero dose vaccination and HBIG against hepatitis B within 24 hours of birth. Out of these 100, 25 newborn delivered to pregnant mother who were on treatment with tenofovir 300 mg, in view of high viral load and/or HbeAg positivity and rest 75 pregnant patients were inactive carrier. The safety profile of Tenofovir in pregnant females and newborns have already been highlighted in study done by Malhotra etal [15] and same was confirmed in the present study in which no side effects occurred in 25 pregnant patients and their newborns in which Tenofovir was used.

7.2. Transmission during delivery

This is widely believed to be the most frequent mode of MTCT. This is the reason why the neonatal administration of HBIG with vaccination is able to prevent newborn HBV

infection in more than 85 % of cases. Most guidelines now recommend that infants born to HBsAg-positive women should receive both HBIG and hepatitis B vaccine within 12 h of birth, preferably in the delivery room. This should be followed by at least two more doses of hepatitis B vaccine within the first 6 months of life. Passive immunoprophylaxis with HBIG at birth followed by at least 3 doses of the vaccine provides 90 % to 95 %protection from perinatal infection, and is superior in reducing MTCT than HBIG or vaccine alone (RR 0.08, 95 % CI0.03–0.17) [18]. After completion of the vaccine series, HBsAg and anti-HBs should be tested by 9-12 months of age. HBsAg-negative infants with anti-HBs levels >10 mIU/mL are protected and no further medical management is required. Those with anti-HBs levels <10 mIU/mL are not protected and should be revaccinated with another three-dose series followed by retesting 1 to 2 months after the final dose. In one study, duration

of labor showed a positive correlation with HBVantigenemia of the cord blood especially when the labor exceeded nine hours [19]. Our study clearly proves effectivity of HBIG and vaccination as none out 100 patients were HbsAg positive at one year of age. An elective cesarean section performed before the onset of labor and rupture of membranes may effectively interrupt such transmission and reduce the risk of vertical transmission as compared with vaginal delivery or cesarean section performed after the onset of labor or after rupture of membrane [20]. However, there is lack of agreement on this issue. There is conflicting evidence surrounding the effect of the mode of delivery on the risk of MTCT. A more recent meta-analysis revealed a 17.5% absolute risk reduction with cesarean section compared to immuno prophylaxis alone, suggesting a benefit of elective cesarean section compared to immuno prophylaxis alone, suggesting a benefit of elective cesarean section to reduce MTCT. Lee et al investigated 1409 infants over a four-year period who had received appropriate immuno prophylaxis at birth and who had been born to HBsAg-positive mothers. They reported MTCT rates of 1.4% with elective cesarean section compared to 3.4% with vaginal delivery and 4.2% with urgent cesarean section. An observational study on 301 newborns in China showed a similar rate of vertical transmission (defined as HBsAg positivity at one year) in infants born to HBsAg positive mothers according to mode of delivery (3%, 7.7% and 6.8% in the vaginal, forceps and cesarean groups respectively). The society for Maternal Fetal Medicine states that cesarean section should not be performed for sole indication of reducing vertical transmission.

Our study results do not agree for elective caesarean section for HbsAg mothers, as out of 100 newborns who were HbsAg negative at one year of age, 81 (81%) were delivered vaginally and rest 19 (19%) were born by caesarean section but all were HbsAg negative, irrespective of mode of delivery. The reason behind it was timely starting of antiviral treatment of pregnant mother wherever indicated and mandatory giving of zero dose vaccination and HBIG within 24 hours of birth to all new born.

7.3. Postpartum Transmission

In the immediate postpartum period, transmission results from close contact between mother and baby. Transmission of HBV by breastfeeding, either through ingestion of the virus or by contact with skin lesions on the mother's breast, is another potential mechanism. Early studies reported HBsAg, HbeAg and HBV DNA detection in colostrum, with higher levels in mothers with high serum HBV DNA, suggesting that breast milk may be an important vehicle for transmission of HBV [15]. However, several studies have reported that breastfeeding carries no additional risk of transmission [21]. It has also been suggested that breast milk may have antiviral properties since it contains immunoglobulins and other proteins such as lactoferrin. In view of several benefits of breast feeding, WHO recommends breastfeeding for infants of HBsAg-positive, mother seven in endemic areas where HBV vaccination may not be readily available [15]. With appropriate immunoprophylaxis, including HBIG and hepatitis B vaccine, breastfeeding of infants of chronic HBV carriers poses no additional risk of transmission of HBV [15]. In view of several benefits of breastfeeding, WHO recommends breastfeeding even for infants of HBsAg-positive mothers in endemic areas where HBV vaccination may not be readily available [15].

Our study is also in agreement with WHO guidelines, as all 100 newborns that were HbsAg negative at one year of age, were breastfed for 6-9 months (mean 7 months). The reason behind for no added risk of transmission through breast milk can be timely starting of antiviral treatment of pregnant mother wherever indicated and mandatory giving of zero dose vaccination and HBIG within 24 hours of birth to all new born.

8. Limitation of Study

The limitation of study is small data of 100 newborn and all of them received HBIG and full course of Hepatitis B vaccination. Hence no comparison was made with those newborn who did not receive HBIG and vaccination or those pregnant females who did not receive antiviral treatment, despite being high HBV DNA viral load. This second part of comparison is under research at present and findings of the same will definitely clear the role of antiviral treatment, HBIG and Hepatitis B vaccination in preventing vertical transmission of hepatitis B.

9. Ethical Clearence

The study was approved by Ethical committee of University of Health Sciences, Rohtak.

10. Conclusion

Our study clearly highlights the success associated with timely intervention at different stage of pregnancy in HbsAg positive mother which is not only helpful in preventing vertical transmission but also decreases morbidity and mortality in both mother and newborn. Hence every pregnant mother should be screened for hepatitis B and if indicated then antiviral treatment should be started at 28 weeks of pregnancy, followed by mandatory HBIG, complete course of hepatitis B vaccination, including zero dose vaccination to new born and thus vertical transmission can be completely prevented as shown in our study. There is no indication of doing elective caesarean section for preventing vertical transmission. The breast feeding should be allowed as it has no added risk of transmission to newborn from mother.

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