International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 01 Issue 10 December 2016, ISSN No. – 2455-8737
Available online at - www.ijirms.in

Open Access Journal | Research Article | ISSN - 2455-8737

Maternal and Fetal Outcomes of Hepatitis B Infection in Pregnant Women

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Abstract:

Background: *Little is known about the natural progression of the disease during pregnancy or its impact on pregnancy outcomes in women with hepatitis B virus (HBV) infection.*

Objective: *To provide comprehensive details about the natural progression of HBV infection during pregnancy or its impact on pregnancy outcomes based on recent clinical reports.*

Search method: *We searched from the Cochrane, Google scholar and PubMed by putting search item "maternal and fetal outcomes of hepatitis B infection in pregnant women". We also searched the references list of relevant articles and contacted authors of retrieved studies.*

Data collection and analysis: *Data were collected from the Medline and PubMed websites and analyzed by the expert gastroeneterologists and biologists.*

Keyword: - Hepatitis B virus, pregnancy, maternal and fetal prognosis, hepatocellular carcinoma.

Introduction:

Chronic hepatitis B virus (HBV) is an infectious disease which can lead to serious liver disease, including cirrhosis, hepatocellular carcinoma (HCC) and end stage liver disease[1-2]. Worldwide, about 350 million people are chronically infected with HBV and in regions where HBV is endemic, China and south Asian countries, such as India and Pakistan. About 10-20% pregnant women have the confirmed of HBV infection [3]. In India viral hepatitis is the most common cause of jaundice in pregnancy, which complicates 1 in every 1000 pregnancies. Most studies, demonstrated that it is associated with adverse maternal and fetal prognosis [4]. So that hepatitis in pregnancy has become a challenging disease to the obstetrician. Vertical transmission taking place in the pregnant women who are HBV carriers, is of particular concern from an infected mother to her newborn child. It remains the predominant mode of infection in such areas. For prompt public awareness about the various routes of transmission of viral hepatitis, improving sanitary conditions & habits, imparting health education and knowledge of preventive measures, routine and regular antenatal checkups and viral markers as a part of routine antenatal screening can help in reducing the burden of jaundice in pregnancy.

In the developing countries such as India, HBV infection is most commonly transmitted by perinatal means from mother to child. In the developed countries, the transmission of infection via unprotected sexual contact, blood transfusion and injectable drug use. HBV infection occurs in phases that can move in the gamut from a silent, acute phase that is resolved by the immune system to a persistent chronic stage of infection that often requires life-long therapy. HBV infection occurs primarily in hepatocytes and is non-cytopathic. In chronic hepatitis B, hepatic liver inflammation is the long-term infection which leads to acute and chronic hepatic d ysfunction includes acute hepatic failure, cirrhosis and hepatocellular carcinoma. If the virus is acquired at the time of infancy then the probability of becoming chronically infected is highest. The various HBV genotypes also appear to have differing impacts on the natural course of HBV infection and the development of negative squeal [5].

HBV Genome:

HBV is a small enveloped DNA virus which replicates its genome in the cytoplasm via reverse transcription of the encapsidated pregenomic RNA (pgRNA) into a circular partially double stranded DNA (RC-DNA). Upon infection, encapsidated RC-DNA is imported into the nucleus where is converted into covalently closed circular DNA (cccDNA) that serve as a template for the transcription of all viral RNAs. Antiviral treatment of chronic HBV carriers leads to successful viral suppression but can't clear the viral

cccDNA from infected hepatocyte so it constitute a viral reservoir liable for viral rebound at the end of antiviral treatment (47).

Factors Associated with Risks of Chronic hepatitis B in pregnant women:

HBeAg status has the highest impact on the vertical transmission of hepatitis B. Without prophylaxis, less than 10% of the HBeAg negative mother has the risk of transmission of perinatal HBV infection in an infant, but it is 70 to 90 % if her HBeAg status is positive [6]. 90% has the chances of becoming a chronic HBV carrier if infected at birth and, when chronically infected, has a 15 to 25 % risk of dying in adulthood from cirrhosis or liver cancer [7]. However, 85-95% effectively reducing HBV infection from vertical transmission by giving the combination of hepatitis B vaccine and hepatitis B immune when given within 12 hours of birth [6].Dental procedures and surgical operations are other important sources of infection as 37.2% and 35.6% of the patients are probably infected through this route. A blood transfusion is considered to be the source of infection for about 24.6% of the infected individuals.

Effect of hepatitis B on pregnancy:

Pregnant women with acute hepatitis B during pregnancy are indistinguishable from that in the general population. Acute HBV infection must be differentiated from other acute liver diseases that occur during pregnancy such as intrahepatic cholestasis or acute fatty liver of pregnancy if jaundice is present, or haemolysis, elevated liver enzymes and low platelets syndrome if jaundice is absent. Acute HBV infection does not increases the mortality rate during pregnancy, or that it has teratogenic effects. However, a low birth weight and prematurity has been reported the higher incidence rate. In addition, 10% perinatal transmission rate is associated with early pregnancy and the rate increases substantially with HBV infection in the third trimester.

The effects of chronic HBV infection on pregnancy outcomes have not been clearly defined. One large study demonstrated no differences in gestational age at delivery, birth weight, and incidence of prematurity, neonatal jaundice, congenital anomalies or perinatal mortality comparing HBsAg positive women with controls (10). However, a relatively recent study described an association of maternal HBV infection (HBsAg positive) with gestational diabetes mellitus and antepartum haemorrhage (11). There was a suggested association with preterm delivery.

In a study, 21 mother–infant pairsin which the mothers were HBsAg positive (but only one HBeAg positive) who have active HBV infection during pregnancy, and underwent amniocentesis for accepted indications at a mean of 19.5 weeks gestation, none of the infants were HBsAg positive at 1 or 12 months of age (12).They had received the HBIG and HBV vaccine as recommended. In another prospective longitudinal analysis of outcomes in 47 HBsAg positive women who presented foramniocentesis (13), all the amniotic fluid samples and cord blood samples from the infants were analyzed for HBsAg and HBV DNA. In this cohort, 32% of the amniotic fluid samples were HBsAg positive, but HBV DNA was undetectable in all. Although cord blood from 27% of the infants contained HBsAg, none contained HBV DNA. As a control, cord blood was sampled from 72 infants delivered from HBsAg positive women who did not undergo amniocentesis. Of these, 18% contained HBsAg and 4% contained HBV DNA. Both studies concluded that the risk of HBsAg transmission by amniocentesis is low.

Mother to child transmission (MTCT)

The transmission of infections from mother to offspring is traditionally known as perinatal infection. The period that begins from 28 weeks of gestation and end with 28 days after delivery is known as perinatal transmission. It does not actually includes infections that occur before or after this time period therefore it can be replaced by the suitable term “mother to child transmission (MTCT)” which takes account of all HBV infections contracted before birth, during birth and in early childhood. The importance of which as a group is their remarkably greater risk of chronicity compared to infections acquired later in life [14].60% of unborn children acquire vertically transmitted Hepatitis B infection at or near delivery. This has deleterious outcome for the child as nearly 90% of these infections shall become chronic and translate into liver cirrhosis, portal hypertension or hepatocellular carcinoma in the child. Theoretically, there are three possible routes for transmission of HBV from an infected mother to her infant [15].

1. Prenatal transmission (trans placental transmission of HBV in utero)
2. Natal transmission during delivery
3. Postnatal transmission during care or through breast milk.

Prenatal transmission

In spite of the relatively excellent effectiveness of high titer HBIG and HBV vaccination as post exposure prophylaxis (PEP) in newborns, in 3% to 9% of children born to mothers with positive HBV serum markers, this strategy fails to block MTCT of the virus [16-17]. In general the PEP failure rate is 3% and 9% from mothers with very high levels of HBV-DNA [17].The failure of HBV transmission is the prenatal route and is currently considered the chief culprit behind this failure. The exact mechanism for prenatal

transmission of HBV is not fully elucidated yet, however various possibilities are hypothesized including:

1. A breach in the placental barrier: The main route of intrauterine infection during pregnancy is the trans placental leakage of HBeAg positive maternal blood, which is induced by uterine contractions during pregnancy and the disruption of placental barriers (such as threatened preterm labor or spontaneous abortion) [16]. It has been shown that amniocentesis inoculates the intrauterine cavity with maternal blood because the needle traverses the abdominal and uterine wall. However, HBV transmission during amniocentesis appears to be rare, particularly in mothers who are HBeAg negative and when the procedure is done using a 22 gauge needle under continuous guidance [18].
2. Placental infection and Trans placenta transmission of HBV: Primary route for transmission of HBV from the mother to the fetus is the Placental infection in a fetus with intrauterine HBV infection or secondary to fetal infection by another route. To distinguish between these two possibilities, researchers have measured the gradient of placental infection between the maternal side and the fetal side of the placenta and concluded that in the majority of cases, trans placental infection is the mechanism for HBV intrauterine infection [16-19].
3. Studies have also demonstrated that HBV-DNA exists in oocytes of infected females and sperms of HBV infected males. Therefore, it is possible for the fetus to become infected with HBV at conception [20].
4. Another possibility is the intrauterine transmission of HBV to the fetus, not from maternal blood but ascending from vaginal secretions of the mother that contain the virus [20].

Natal transmission

The result revealed that transmission of HBV to the infant is at the time of birth is believed by the exposure to maternal cervical secretions and maternal blood that contain the virus [21]. Many controversies are still there regarding the effect of delivery mode on MTCT. In current obstetrical guidelines, the mother's HBsAg positivity does not affect the planned mode of delivery irrespective of her HBeAg status or level of viremia. Few articles recommend cesarean section in case of high maternal HBV-DNA levels [22], whereas others believe that mode of delivery does not influence the rate of HBV transmission provided that all infants receive HBIG and HBV vaccine at the recommended schedule [23]. A recent systematic review in 2008 on four randomized controlled trials (RCTs) involving 789 people concluded that cesarean section before labor or before ruptured membranes (elective cesarean section or ECS) appears to be effective in preventing MTCT of HBV. RCTs of higher quality are required for assessing the effects of ECS in comparison to vaginal delivery for preventing MTCT of HBV.

Postnatal transmission

Infected mother having a HBV-DNA in their milk but in infant it poses no additional risk for transmission of HBV by providing appropriate immune prophylaxis at birth and continued as scheduled. Until the child has received all doses of HBV vaccine and there is no need to delay breastfeeding [24]. Breastfeeding does not have a negative influence on the immune response to the HBV vaccine and does not increase its failure rate [25]. For awareness, it is need to explain to mothers that they should take good care of their nipples while breastfeeding, ensuring proper latch on and allowing the nipples to dry before covering to avoid cracking or bleeding, having in mind that HBV is commonly passed by blood to blood routes [26].

Difference between Acute and Chronic HBV Infection in Pregnancy:

Acute HBV: Acute HBV infection is not a severe infection during pregnancy and is not associated with increased mortality or teratogenicity [27, 28]. Thus, infection during gestation should not prompt consideration of termination of the pregnancy. However, the study revealed that the mothers with acute HBV infection had increased incidence of low birth weight and prematurity in infants [29, 30]. Furthermore, 10 % perinatal transmission rate occurring early in the pregnancy has been associated with acute HBV infection [30]. Transmission rates significantly increase if acute infection occurs at or near the time of delivery, with rates reported as high as 60 % [27].

Chronic HBV: Pregnancy is generally well tolerated by women with chronic hepatitis B infection who do not have advanced liver disease. However, some patients show hepatitis signaling, HBsAg positive mothers should be monitored closely. Every three months we obtain liver biochemical tests during pregnancy and for six months postpartum. HBV-DNA should be tested concurrently or when there is ALT elevation. There are no linked between chronic HBV and the development of other diseases during pregnancy. Chronic HBV and gestational diabetes mellitus have the possibility of their associations [30, 31] However, data are mixed and conflicting [32, 33] and the strength of these associations is unclear. Pregnancy is considered to be an immune tolerant state and is associated with high levels of adrenal corticosteroids with modulation of cytokines involving the immune response. This has the potential to increase HBV viremia, although most studies have found

that HBV DNA levels remain stable during pregnancy [34, 35]. ALT levels tend to increase late in pregnancy and in the postpartum period in women with chronic HBV infection.

The hepatitis shows signaling (including hepatic decomposition) when immunological changes during pregnancy and postpartum have been associated although flares (particularly those with serious clinical squeale) appear to be uncommon [35].In the postpartum period, this signaling may be related to immune reconstitution, a situation immunologically analogous to flares that have been described following the withdrawal of corticosteroids in non-pregnant patients with chronic HBV [35, 36]. Prognosticators of HBV signaling during pregnancy have not been established. Approximately 12 to 17 % of patients show signaling associated with HBeAg seroconversion[34], a rate similar to what has been described in patients who are not pregnant. The patients who develop a signaling associated with HBeAg seroconversion remain uncertain. Limited evidence suggests that seroconversion is unrelated to maternal age, parity, or the presence of precore or basal core promoter mutations [34, 39].

Phases of Disease of CHB:

"Immune Tolerant" Phase: This first phase is more frequent and prolonged inperinatally infected patients or those infected in the early years of life. It is characterized by HBeAg positivity, high levels of HBV replication, normal or low levels of aminotransferases, and mild or no liver involvement. Patients in this stage are highly contagious because of the high levels of viremia [40].

"Immune Reactive" Phase: This phase may occur after several years of immune tolerance and is more frequently observed in patients infected during adulthood. It is characterized by HBeAg positivity, a lower level of HBV replication, increased or fluctuating levels of aminotransferases, and a greater degree of liver involvement than in the Immune Tolerant phase [40].

"Inactive HBV Carrier State": This phase may follow seroconversion from HBeAg positive to anti-HBe antibody positive. It is characterized by very low or undetectable serum HBV-DNA levels and normal aminotransferases. This state is associated with a favorable long-term outcome with a very low risk of cirrhosis or hepatocellular carcinomain the majority of patients [42].

"HBeAg-negative Chronic Hepatitis B" – This phase may follow HBeAg seroconversion during the immune reactive phase and represents a later stage in the natural history ofchronic hepatitis B. It is characterized by periodic reactivation with pattern offfluctuating levels of HBV DNA and aminotransferases and active hepatitis. Although patients in this phase are HBeAg negative, they harbor HBV variants with mutations inthe precore and/or basal core promoter regions and so are unable to express or expressonly low levels of HBeAg. In contrast to patients who have truly seroconverted from HBeAg to anti-HBe antibodies and who have a good prognosis, these patients have active liver disease, with a high risk of progression to advanced hepatic fibrosis, cirrhosisand subsequent complications such as decompensated cirrhosis and hepato-cellularcarcinoma (HCC) [43].

"Hepatitis B surface antigen (HBsAg)-negative Phase" – Low levels of HBV replication may still occur in the liver after loss of HBsAg [44]. HBsAg loss is associated with improvement in outcome with a lowered risk of cirrhosis, decompensation and hepatocellular carcinoma. Immunosuppression can lead to reactivation in these patients [45, 46].

Caring for Pregnant Women and Newborns with Viral Hepatitis:

The care of the pregnant women is more important than the other thing. HBV infected mother should go for regular checkups and routine test. They should go for biometry test after every three month or trimester. Many study revealed that the fetus infected through the perinatal route and not from the blood so they are not suggested for normal delivery and recommended for cesarean. One of the study revealed that care of newborn based on Maternal HBsAg status. If maternal HBsAg status is negative then give a hepatitis B vaccine to newborn before discharge, preferably within 12 hours of birth and if the birth weight is less than 4 lb, 6 oz (2,000 g), postpone first dose of vaccine until one month of age and when the newborn is HBV positive then give hepatitis B immune globulin and hepatitis B within 12 hours of birth and complete vaccine series by six months of age. Obtain follow-up serology (HBsAg and hepatitis B surface antibody) between nine and 18 months of age. If birth weight is less than 4 lb, 6 oz: give birth dose and do not count as part of the three dose series, but give next dose at one month of age (will receive four total doses).

Conclusions

The Hepatitis B is not an uncommon infection encountered during pregnancy. Hepatitis B viral load and envelope antigen status are the two major viral determinants for mother to child transmission beyond many gynecological and obstetrical factors. There is controversy regarding effect of hepatitis B on pregnancy, only few studies have shown adverse outcome. Pregnancy itself has no effect on the natural course of hepatitis B infection. Hepatitis B immunoglobulin and vaccination are two major preventive measures for mother to child transmission.

Acknowledgement:

I am deeply grateful to UGC for providing me UGC-BSR fellowship which help me conducting the experimental work smoothly and to the Dr. OMKAR, HOD of Zoology Department, University of Lucknow for all sources and materials used for reviewed this manuscript, for his valuable support and guidance.

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