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RESEARCH ARTICLE

HEPATITIS B. IN PREGNANCY

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Abstract

Hepatitis B virus (HBV) infection has widespread implications and has already generated 350 million chronic carriers which can further progress to liver cirrhosis & hepatocellular carcinoma[1]. Out of total pool of chronic carriers, half have got infected vertically from their mothers, i.e. through mother - to - child transmission (MTCT). Vertically - acquired HBV infections become chronic in 90% of cases[2].HBV can be transmitted Vertically during pregnancy, delivery or postpartum. HBV has the ability of placental transfer and reach the fetus but the exact impact of this mode is unclear. Transmission during delivery is the most common mode of MTCT, thus, the neonatal administration of HBIG with vaccination is able to prevent newborn HBV infection in more than 85 % of cases. In postpartum period the close contact between mother and baby is responsible for HBV transmission and includes breastfeeding which has potential either through ingestion of the virus or by contact with skin lesions on the mother's breastAll Pregnant women should undergo mandatory screening for Hepatitis B.If HBV viral load or HbeAg is found to be significantly high, then antiviral treatment tenofovir 300 mg should be started. Caesarean section should be performed only for obstetric indications only and not solely due to HBV infection.Every new born of hepatitis B mother should be mandatory given 0.5 ml hepatitis B immunoglobulin, along with zero dose Hepatitis B vaccination within twelve hours of birth and later on full course of HBV should be completed.Breast feeding is allowed for the new born.

Introduction:-

Hepatitis B virus (HBV) infection has widespread implications and has alreadygenerated 350 million chronic carriers which can further progress to liver cirrhosis & hepatocellular carcinoma[1]. Out of total pool of chronic carriers, half have got infected vertically from their mothers, i.e. through mother - to - child transmission (MTCT). Vertically - acquired HBV infections become chronic in 90% of cases[2].The proportion of babies that became HBV chronic carriers is about 10% to 30% for mothers who are HBsAg positive but HbeAg negative but if both are positive than the chances rise to 70% to 90%[3].

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Review Of Literature:-

Chronic HBV infection during pregnancy gives us the chance to interrupt perinatal transmission of HBV.HBV infectionitself does notinfluence fertility, beyond the effects of cirrhosis or liver failure[5].Pregnancy is rare in women with cirrhosis due to impaired fertility. Women with advanced chronic liver disease (CLD)are less fertile due to frequent occurrence of anovulatory cycles and amenorrhoea[6]. The abortion rate is more in cirrhotic women i.e. 30% to 40% vs. 15% to 20% in the normal population[5]. The perinatal complications and pregnancy outcomes like intrauterine growth restriction, intrauterine infection, premature delivery, and intrauterine foetal demise are more commonly seen in cirrhotic women.The availability of latest reproductive technologies and support measures has benefited many women with cirrhosis to deliver at term.[6].The maternal or fetal mortality and morbidity is not influenced by HBV infection. A study compared 824 HbeAg positive mothers to 6,281 HBsAg negative control mothers and concluded that there was no difference in rates of preterm delivery, birth weight, neonatal jaundice, congenital anomalies, or perinatal mortality[7] but a latest study has shown that HBsAg carrier mothers had an increased risk of gestational diabetes mellitus, antepartum haemorrhage, and threatened preterm labour[8].The American Association for the Study of Liver Disease(AASLD) recommends that all pregnant women be screenedfor HBsAg during the first trimester, even if previously vaccinated or tested [9], as it allows Screening for identification ofinfants requiring immunoprophylaxis with HBV vaccine andhepatitis B immune globulin (HBIG), anti-viral treatment ofpregnant carriers if indicated, and counselling of sexual andhousehold contacts[2]. Every HBsAg-positive pregnant womanshould make aware their obstetricians about the same, so thatnew born is given immunoprophylaxis immediately after delivery[9].Women who test negative for HBsAg and are at risk ofacquiring HBV infection should be immunized during pregnancy. The hepatitis B vaccine is given intramuscularlyand is safe duringpregnancy without any side effects.The American Congress of Obstetricians and Gynecologists(ACOG) and AASLD guidelines suggest that HBsAg-positive mothers should be referred to a specialist for further evaluation to assess impact on liver and regular monitoring[9].The definition of "vertical transmission"of an infection the transmission of pathogenfrom mother to child during pregnancy or childbirth, or bybreastfeeding and is themost important cause forendemicity of HBV inAsia because 90 % of children who get HBV infection by vertical route become chronic carrier[6].The most important risk factors for vertical transmission of HBV are maternal HBV viral load and HbeAg status. In the absence of prophylaxis, the risk of verticaltransmission of HBV infection reaches 70 % - 90 %for infants born to HbeAg-positive mothers, and 10 % -40 % forHbeAg-negative mothers[6].Vertical transmission of HBV is defined as positivity at one year of age of the hepatitis B surface antigen or of HBV DNA in an infant born to an HbsAg positive mother. The presence of HBsAg and HBV DNA at birth is temporary and does not necessarily indicate infection transmission.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 placental transfer from mother to the fetus and therefore is unrelated to infection.

Modes of vertical transmission

HBV can be transmitted Vertically during pregnancy, delivery or postpartum.

In-utero Transmission

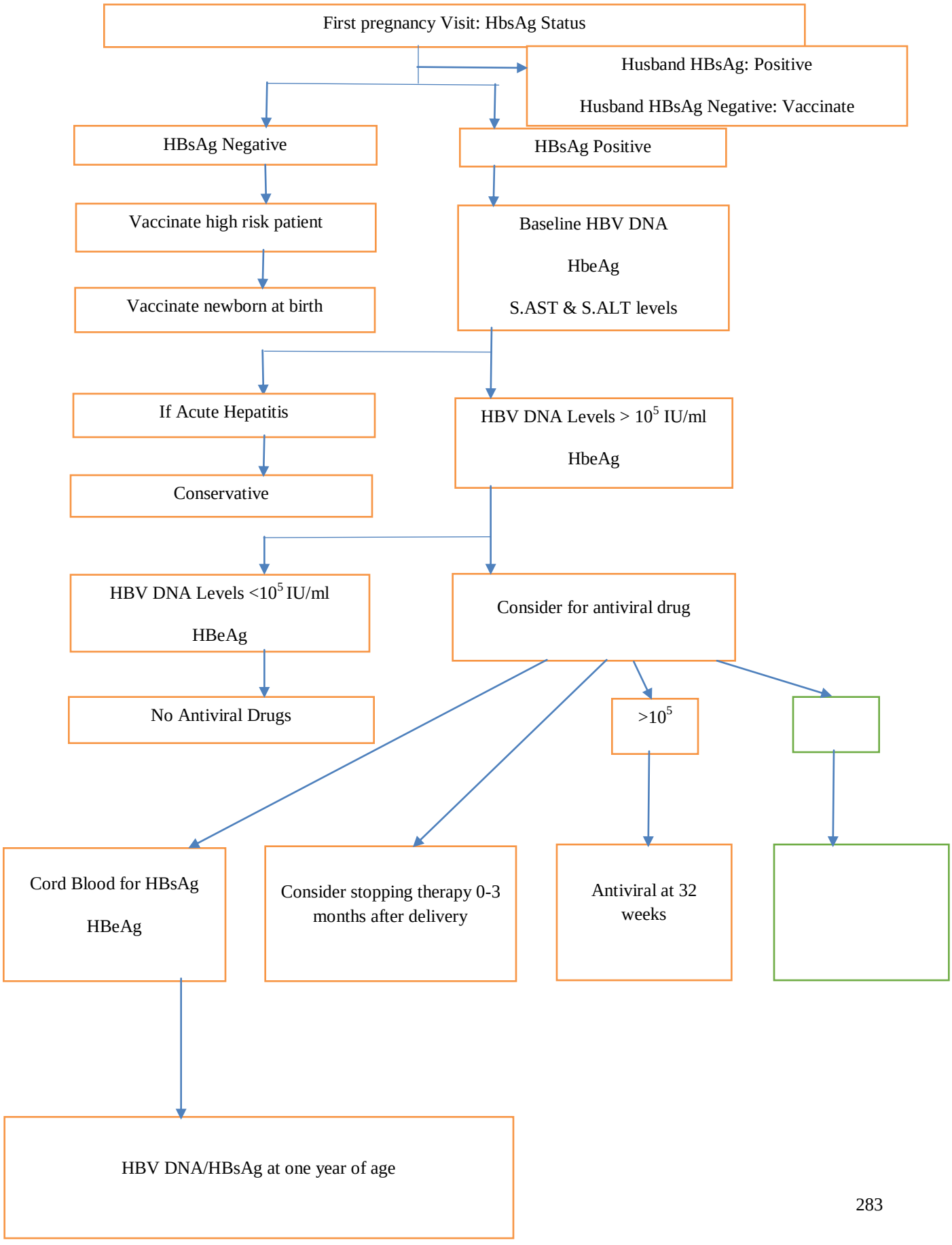
HBV has the ability of placental transfer and reach the fetus but the exact impact of this mode is unclear. In a study conducted on seventy-two pregnancies, 13 (18 %) cord blood samples werepositive for HBsAg[10] but in only 3 patients HBV DNA was detected. In another study, only 3.7 %of babies tested were found to be HBsAg-positive at birth from in-utero infection[11]. Hence it is predicted that in-utero transmission is notthe predominant mode of transmission of HBV. TheHBV vaccine or HBIG given at birth does not prevent In-utero or trans placental HBV infection.Zhang et al did research on fifty-nine HBsAg-positive mothers regarding HbsAg intrauterine transmission. 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 transplacental route was important but other routes of infection may exist[4].The main risk factors for intrauterine HBV infection arematernal serum HbeAg positivity, high maternal viral load,and a history of threatened preterm labor or threatened abortion[6]. Zou et al conducted study on 1043 HbsAg positive mothers and found association between maternal HBV DNA levels and immunoprophylaxis failure that indicatedmaternal pre-delivery HBV DNA level > 6 log copies/ ml are associated with reduced prophylaxis effectiveness. Bai et al findings were also in line with above study and showed 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.

Transmission during delivery

It is the most common mode ofMTCT, thus, the neonatal administrationof HBIG with vaccination is able to prevent newborn HBVinfection in more than 85 % of cases. In one study,duration of labor showed a positive correlation with HBVantigenemia of the cord blood especially when the laborexceeded nine hours[12].An elective cesarean section performed before the onset oflabor and rupture of membranes may effectively reduce the risk of vertical transmission as compared with vaginal delivery or cesarean sectionperformed after the onset of labor or after rupture of membrane[13]but still no guideline has recommended caesarean section solely for HbsAg positivity of pregnant mother.

Postpartum Transmission

In postpartum period the close contact between mother andbaby is responsible for HBV transmission and includes breastfeeding which has potential either throughingestion of the virus or by contact with skin lesions on themother's breast. Many studies have shownthat HBsAg, HbeAg and HBV DNA detection incolostrum, with higher levels in mothers with high serumHBV DNA, highlighting the role of breast milk in transmission of HBV[14] but certainstudies have contradicted the above fact[15]. Asbreast milk may has antiviral properties because it containsimmunoglobulins and other proteins such as lactoferrin, thus even WHO recommends breastfeeding for infants of HBsAg-positive motherseven in endemic areas where HBV vaccination may not bereadily available[14].High maternal HBV DNA load is one of the most important risk factors for vertical transmission of HBV, especially in 10% of babies who develop this infection despite immunoprophylaxis. TheHbeAg-positive mothers are at a higher risk of giving vertical transmission tonewborns than HbeAg-negative mothers, with the risks ofchronic HBV infection by age of 6 months of 70 % - 90 %and 10 % - 40 %, respectively, in the absence of post-exposure immunoprophylaxis.MaternalHbeAg positivity leads to high levels ofmaternal viremia[16]. 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 therapyduring pregnancy provides potent anti-viral suppression, isrelatively safe and well tolerated, and reduces perinatalHBV transmission. There is mild risk of viral drug resistance in the motherand hepatitis flares upon discontinuation [14].The AASLD recommends HBV DNA levels > 2 X 10^5 IU/ml as an indication for initiation of therapy as risk of HBV transmission increases with this level of viremia. Tenofovir, a nucleotide analogue, is currently a preferred oral agent forHBV therapy. It has been used by pregnant women forHIV infection with no increase in congenital malformations. Preliminary data show no evidence of renal impairment, abnormal bone metabolism or impaired growth inchildren exposed to tenofovir in utero[17].There is conflicting evidence surrounding the effect of the mode of delievery on the risk of MTCT. A recent meta-analysis revealed a 17.5% absolute risk reduction with cesarean section compared to immunoprophylaxis alone, suggesting a benefit of elective cesarean section compared to immunoprophylaxis alone. Lee et al investigated 1409 infants over a four-year period who had received appropriate immunoprophylaxis 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 delievery and 4.2% with urgent cesarean section. Another study on 301 newborns in China showed a similar rate of vertical transmission in infants born to HBsAg positive mothersaccording to mode of delievery(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.It is recommended by most guidelines that infants born toHBsAg-positive women should receive both HBIG andhepatitis B vaccine within 12 h of birth, preferably in thedelivery room. This should be followed by at least two moredoses of hepatitis B vaccine within the first 6 months of life.Passive immunoprophylaxis with HBIG at birth followed byat 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 at one year of age. HBsAg-negativeinfants with anti-HBs levels >10 mIU/mL are protected andno further medical management is required. Those with anti-HBs levels <10 mIU/mL are not protected and should berevaccinated with another three-dose series followed byretesting 1 to 2 months after the final dose.With appropriate immunoprophylaxis, including HBIG andhepatitis B vaccine, breastfeeding of infants of chronic HBVcarriers poses no additional risk of transmission of HBV[18].


First pregnancy Visit: HbsAg Status
Husband HBsAg: Positive
Husband HBsAg Negative: Vaccinate
HBsAg Negative
HBsAg Positive
Vaccinate high risk patient
Vaccinate newborn at birth
Baseline HBV DNA
HbeAg
S.AST & S.ALT levels
If Acute Hepatitis
Conservative
HBV DNA Levels > 10^5 IU/ml
HbeAg
HBV DNA Levels <10^5 IU/ml
HBeAg
No Antiviral Drugs
Consider for antiviral drug
>10^5
Cord Blood for HBsAg
HBeAg
Consider stopping therapy 0-3 months after delivery
Antiviral at 32 weeks
HBV DNA/HBsAg at one year of age

Conclusion:-

All Pregnant women should undergo mandatory screening for Hepatitis B. If positive, HBV DNA quantification and HbsAg testing should be done.In addition to liver function test at 28 weeks of pregnancy and if HBV viral load or HbeAg is found to be significantly high, then antiviral treatment tenofovir 300 mg should be started.The safety profile of tenofovir in mother and newborn is adequate.Caesarean section should be performed only for obstetric indications only and not solelydue to HBV infection.Every new born of hepatitis B mother should be mandatory given 0.5 ml hepatitis B immunoglobulin, along with zero dose Hepatitis B vaccination within twelve hours of birth and later on full course of HBV should be completed.Breast feeding is allowed for the new born. The HBV testing in newborn should be done at one year of age for determining vertical transmission.Husband of HBV pregnant patient should be screened for HBV and if found negative should be vaccinated against the same.

Limitations & Future Considerations

Our paper does not discuss potential barriers to HBV screening and vaccination in low resource settings. It could address future research directions such as development of universal immunization programs, use of novel antiviral agents in pregnancy and long term outcomes of infants exposed to HBV during pregnancy.

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