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THE COURSE OF PREGNANCY IN WOMEN WITH CHRONIC HEPATITIS B AND C

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ABSTRACT

The global prevalence of viral hepatitis is very high and seems to be rising over the years. The infection can profoundly affect pregnant women causing significant maternal and perinatal morbidity and mortality with some strains much worse than others.

Hepatitis B is the most prevalent form and is part of the ante-natal screening program. The presence of HBeAg is associated with high viral loads and infectivity. Antiviral therapy, preferably tenofovir (TDF), is recommended for mothers with viral load 200,000 IU/mL2), with the neonates receiving both active and passive immunisations. Hepatitis C and D are usually found as chronic infections in the pregnant and non-pregnant populations. Screening for hepatitis C during pregnancy and its subsequent management is still unsettled, but the introduction of direct-acting antiviral (DAA) drugs will change the picture if their safety is established in pregnancy. HDV is an incomplete virus linked to HBV and cannot establish an infection on its own. Controlling HBV is paramount to controlling HDV. HEV is quite prevalent and looked upon as hepatotropic. It seems to be quite prevalent in some blood donor populations and has a high co infection rate with HCV. It has a high Mother-to-Child-Transmission (MTCT) but causes little or no illness in infected infants, and antenatal screening is not justified.

This review summarises the prevalence, clinical picture, maternal, perinatal effects, and the management and prevention of hepatitis B and C viral infections during pregnancy.

Introduction. Viral hepatitis is a widespread infection affecting both the pregnant and the non-pregnant population. In 2015 alone, there were more than 10 million new infections and 1.34 million deaths due to viral hepatitis [1]. This represents an increase of 22 % in the number of deaths from 2000 [1] and may be associated with rising cases of Hepatitis C in young intravenous drug users [2], but more so from poor detection of disease and treatment [1]. The global prevalence of Hepatitis C Virus (HCV) in 2015 was 71 million, and that of Hepatitis B Virus (HBV) in 2016 was 257 million [1] when compared with a prevalence of about 38 million living with HIV [3]. Hepatitis B and C are responsible for 96 % of all deaths from hepatitis [1]. Viral hepatitis is caused by a diverse collection of viruses with differing structural biology, transmission, endemic patterns, and chronicity that share a common propensity to infect and replicate in human hepatocytes. These are referred to as hepatotropic viruses, and cause most hepatitis in the pregnant and non-pregnant populations.

Hepatitis B (HBV) Hepatitis B virus (HBV) infection is the most common form of chronic hepatitis worldwide [5], and carriers can continue to transmit the disease for many years before becoming symptomatic [6]. Chronic HBV infection is a major risk factor for chronic hepatic insufficiency, cirrhosis, and hepatocellular carcinoma [3]. In the Eastern Mediterranean Region, South East Asia Region and European Regions, an estimated 3.3 %, 2.0 % and 1.6 % of the general population are infected respectively. In contrast, in the Americas, only 0.7 % of the population are infected [5]. HBV is an enveloped virus containing a partially double stranded, circular DNA genome and classified within the family hepadnavirus [6,7]. The nucleocapsid core measures 27 nm in diameter, and the hepatitis B core antigen (HbcAg) is derived from it. The core is surrounded by a lipoprotein coat or envelope, which is the HbsAg [7,8]. The envelope lipoprotein is produced in excessive amounts and released into the circulation as HBsAg [7]. Infectivity is determined by HBeAg-positive specimens as they tend to contain high concentrations of infectious virions and HBV DNA, in contrast to anti-HBe positive samples, in which the number of hepatitis B virions is much lower [9]. The concentra tion of HBV is highest in blood serum and wound exudates. A moderate concentration is found in semen, vaginal fluid, and saliva, and low or undetectable levels are found in urine, faeces, sweat, tears, and breast milk [10]. It is good practice to test all patients with hepatitis B for hepatitis D virus (HDV) as well as for HCV and HIV infections [9]. Investigations should include the assessment of liver functions as described above. The hallmark of infection is that of an elevated ALT which may be elevated 2–100 fold [8]. An elevated ALT suggests active disease with progression, although the elevation may reduce when liver cirrhosis sets in [8].

Specific tests evaluate specific HBV antigens and antibodies. HBV antigen and antibodies have been classified into three clinically useful groups: 1 Surface antigen (HbsAg) and antibodies (anti-HBs): HbsAg tends to appear in serum several weeks before the onset of symptoms and persist for months in chronic infections. It indicates that the patient is potentially infectious. On the other hand, anti-HBs appears during recovery from the acute phase and is evidence of resolution of the disease. It remains positive for lifetime in 80 % of patients [4,10]. 2 Core antigen (HbcAg) and antibodies (anti-HBc)

HbcAg is not found in the bloodstream, whereas Anti-HBc is the first antibody to appear and can reliably diagnose acute infection. The IgM appears early in the disease process and disappears in 6 months while the IgG appears in convalescence and stays for life. 3 "e" or precore antigen (HBeAg) and antibodies (anti-HBe). HBeAg is indicative of infectivity and disease severity. Chronicity is likely if HBeAg remains positive for 2–3 months after the acute phase. The presence of this antigen correlates with elevated levels of HBV DNA Testing for entire viral particles or virions and HBV DNA is also available and has become the best monitor of infectivity and a guide to therapy [4]. Viral loads less than 200,000IU/mL are associated with lower chances of Mother-to-Child Transmission (MTCT) [4]. Other antigens present during the acute phase include virions, HBV DNA, HBV DNA polymerase and HBeAg. HbsAg, HBeAg, and viral DNA are present for approximately six months before clearing and thereafter are replaced by anti-HBs and anti HBe. Perinatal transmission from the mother to her new-born baby is the commonest mode of transmission [11]. HBV, however, does not cross the placenta because of its size, and intra-uterine infection can therefore only happen if there have been breaks in the maternal-fetal barrier as occurs during amniocentesis. Vertical transmission, therefore, occurs primarily at birth with the new borns at high risk of developing chronic HBV infection [7]. If an HBV carrier mother is also positive for hepatitis B "e" antigen (HBeAg), her new-born has a 53 % likelihood of becoming infected if immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and HBV vaccination is not administered to the infant within 12 h of birth [12,13]. Acute HBV occurring early in pregnancy has been associated with a 10 % risk of perinatal transmission rate [14]. On the other hand, if an acute infection occurs at or near the time of delivery, the transmission rate could be as high as 60 % [15]. Approximately 25 % of infected infants will become chronic carriers [8,10]. Most of HbsAg carriers are asymptomatic, potentially infectious, and a constant source of new infections [8]. Infection can also occur through percutaneous or parenteral contact with infected blood, body fluids, and by sexual intercourse through a break in the skin or mucosal barrier [8,10]. HBV infection is transient in about 53 % of adults and 10 % of new-borns. In the rest, it becomes persistent and about 5–10 % of adults progress to become asymptomatic carriers and develop chronic hepatitis which can lead to cirrhosis and hepatocellular carcinoma [10]. About a third of chronic HBV infections are associated with liver cirrhosis and hepatocellular carcinoma [10], with the condition affecting 40–50 % of chronically infected men and 15 % of women. Men who acquired the infection in childhood are the most likely to develop hepatocellular carcinoma [5]. The strongest predictor of progression to cirrhosis is the presence in serum of HBV DNA regardless of ALT and HBeAg status [4]. The average duration of HBV disease before the development of hepatocellular carcinoma is about 35 years [10]. The effect of pregnancy on the course of HBV if any is minimal. The presentation of acute HBV infection might differ in pregnant women when compared with non-pregnant women [16]. A recent study of 22 pregnant women with acute HBV infection was compared with 50 matched non-pregnant controls showed fewer typical clinical symptoms and delayed HBsAg loss and serocon version in the pregnant group than in the non-pregnant group of women [17]. In rare cases, acute infections can progress to acute liver failure necessitating liver transplantation [18]. Liver

trans plant can be life-saving but is associated with a high perinatal mortality rate [18]. Acute HBV infection does not seem to affect the course of pregnancy or perinatal outcome apart from increased risk of prematurity by forced interventions in severe maternal illness [4]. In chronic disease which is the prevalent pathway, altered immunity in the state of pregnancy can increase the risk of HBV flares which is reported to be about 6%–14% in women during pregnancy, and between 10 % and 50 % during the postpartum period, depending on the population studied [19]. Most flares are, however, mild and self-limiting, and in the absence of advanced fibrosis or Hepatitis D co-infection, only a few cases will progress to hepatic decompensation or jaundice [20]. It is, therefore, reasonable to monitor ALT levels during the first six months after delivery or within the first six months after the discontinuation of antivirals for mothers receiving third-trimester antiviral treat ment [4]. It is not clear if HBV infection affects pregnancy outcomes. There have been vague associations of chronic HBV with gestational diabetes, antepartum haemorrhage, and threatened preterm labour [21] but these data have not been substantiated with good quality studies. There is, however, no doubt that women with HBV cirrhosis (as in other severe liver diseases) have an increased risk for maternal and fetal mortality [22].

There is currently no definitive cure for HBV, so the mainstay of treatment remains viral suppression and immunisation. Despite the administration of passive and active vaccination, HBV transmission occurs in up to 25 % of infants born to mothers with HBV DNA levels greater than 200,000 IU/ mL [23][24]. Most guidelines, therefore advise initiation of antivirals during the third trimester of pregnancy, and this appears to be safe and effective in decreasing MTCT [13,4,11]. The World Health Organisation recommends that pregnant women testing positive for HBV infection (HBsAg positive) with an HBV DNA 5.3log10IU/mL (200,000 IU/mL2) receive tenofovir (TDF) prophylaxis from the 28th week of pregnancy until at least birth, to prevent MTCT of HBV [11]. This is in addition to three-doses of hepatitis B vaccination to all infants, including timely birth dose [11]. The other antivirals considered safe and effective in pregnancy are lamivudine (LAM), and telbivudine (TBV). Lamivudine has a lower barrier of resistance and seems to be associated with slower decline in HBV DNA levels when compared with TDF [25]. TBV is effective at preventing MTCT [24] and may be associated with increased creatinine kinase levels, and seem to have limited safety data in breastfeeding mothers [26]. TDF is the preferred agent for treating HBV in pregnancy, given its high barrier to resistance, favourable safety profile, and efficacy [13,11,26]. It is recom mended that treatment if started during pregnancy for high viral load, is continued for 6–12 weeks to prevent postpartum flares of HBV and possible disease progression and cirrhosis [27]. The prevention of MTCT by timely active and passive immunisation of the new-born is discussed in detail in another section of this series. It is, however, important to mention that breastfeeding has substantial benefits to both the mother and child, and does not appear to increase the risk of HBV transmission to the new-born.

Hepatitis C. virus (HCV) is a bloodborne virus that belongs to the Flaviviridae family. It is a partially double-stranded RNA virus, which frequently mutates secondary to changes in the structural proteins of the viral envelope. There are 11 major genotypes

of HCV, with 15 different subtypes. These serotypes vary in prevalence in different regions of the world. Each of the major genotypes can differ significantly in their biologic effects including replication and mutation rates, and also in the severity of the damage that they can cause, and most importantly in their response to currently available therapies [28,29]. The development of antibodies against HCV does not produce immunity against the disease the way it does in most other infections [5]. Unsafe health-care procedures and injection drug use are the leading routes of new HCV infections accounting for most of the 1.75 million new infections in 2015 [1]. Globally, 8.5 % of all HCV infections occur among persons aged 15–64 years who injected drugs within the last 12 months [30]. The WHO estimates that 71 million people have chronic HCV infection, and 399,000 people died from Hepatitis C in 2016, mainly from cirrhosis and hepatocellular carcinoma [1]. Co-infection with human immuno deficiency virus (HIV) or hepatitis B virus (HBV) is common [1,31]. HCV infection is a major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) worldwide [1,30]. It has a slow onset with symptoms in only about 25 % of patients, and approximately 75 % of patients chronically infected may not be aware of their infection [32]. These individuals serve as a reservoir of infection for others and are at risk of chronic liver disease. Approximately 40 % of infected patients recover completely, and the remainder become chronic carriers; 20 % of the carriers develop cirrhosis, and in these, about 20 % will develop liver cancer [31,32].

Unlike HBV, there is no universal antenatal screening for HCV. However, screening is recommended in those with risk factors (e.g. women with a history of illegal injection drug-use, long-term haemodialysis, blood product recipients, affected partners, people with sexually transmitted disease or with unexplained chronic liver disease) [31]. This approach will miss HCV carriers in women without risk factors. In a retrospective cohort study of more than 57,000 women between 2007 and 2013 in Brisbane, Australia, 2.5 % of HCV-positive women had no identifiable risk factors [33]. Where feasible, universal screening seems to be relatively cost-effective; hence both the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America recommend universal screening for HCV in pregnancy [34]. Due to the absence of universal screening, it is difficult to estimate its prevalence in the pregnant population. The WHO global estimate of 71million people living with HCV in 2015 corresponded to 1% of the world population, and this estimate mirrors its prevalence in the pregnant population [30]. It is noteworthy that mortality from viral hepatitis has increased by 22 % since 2000 [1]. This increase in mortality reflects the increasing numbers of new infections associated with rising rates of injection-drug use among young, white persons who live in non urban areas [35,36]. The prevalence of maternal HCV infection in the United States rose significantly from 1.8 to 3.4 per 1000 live births from 2009 to 2014 ($p < 0.001$) [37]. The incidence of acute HCV is low in pregnancy, and the development of fulminant hepatitis C is rare [38]. Both acute and chronic infections of HCV are mostly asymptomatic [8]. Chronic infections are often discovered during screening or other workups in women with raised transaminases. In acute HCV infection, patients may present with malaise, fatigue, anorexia, nausea and epigastric pain [8]. The diagnosis of HCV is based on positive anti HCV, and the presence of HCV RNA indicates active infection [39]. HCV has been

associated with a poor obstetric outcome, with a higher incidence of gestational diabetes, gestational hypertension, preterm delivery rate (600 000 IU/ mL), HIV HCV co-infection (increased fourfold), prolonged rupture of membranes, invasive fetal monitoring with fetal blood sampling and scalp electrodes [46][47]. The high risk of perinatal transmission found in injection drug use mothers seems to be dependent on maternal peripheral blood mononuclear cell infection by hepatitis C virus and therefore represents one of the most important risk factors for hepatitis C virus perinatal transmission [48]. There is as yet no vaccine for HCV and drug treatment is still controversial. Before the era of direct-acting antivirals (DAA), pegylated interferon-alpha (PEG-IFN-α) and ribavirin form the mainstay of treatment [49]. Ribavirin is considered teratogenic and is associated with malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract [41,50] while, interferon is associated with intrauterine growth restriction [47,51]. Thus, treatment using these drugs is no longer recommended either in pregnancy or as a prophylactic in new-borns [50]. Newer drugs such as the protease inhibitor simeprevir, and sofosbuvir (HCV polymerase inhibitor) are interferon-free regimens that have been recently introduced. These medications have been approved by the FDA, but not been studied enough for use during pregnancy [52]. If found safe, they will be a useful addition in suppressing viral load in pregnancy and thus reducing the risk of MCTC. Reinfection could also occur after treatment if the underlying risk factor persists [53]. Unfortunately, caesarean section (CS) does not reduce the risk of MTCT [47,51,54] hence HCV is not an indication for CS. Breast feeding does not increase MTCT and is, therefore, not contra indicated [47,54].

Conclusion. The global prevalence of viral hepatitis is high and is rising. It can profoundly affect pregnant women causing significant mater nal and perinatal morbidity and mortality. Hepatitis A and E, which are transmitted mainly through the faecal-oral route mostly present as acute hepatitis during pregnancy, and are responsible for most local epidemic outbreaks. Hepatitis A remains self limiting during pregnancy while HEV has a higher prevalence and morbidity as well as high maternal mortality rate (20 %) during pregnancy. Hepatitis B is the most prevalent form of viral hepatitis and is routinely screened for in pregnancy. The presence of HBeAg is associated with high viral loads and infectivity, and antiviral therapy may be required for pregnant women who are HbeAg positive, and the neonates should receive active and passive immunisations. Hepatitis C and D are usually found as chronic infections in the pregnant and non-pregnant population. Screening for hepatitis C during pregnancy and its subsequent management is still unsettled, but the introduction of direct-acting antiviral (DAA) drugs will change the picture if their safety is established in pregnancy. HDV is an incomplete virus linked to HBV and cannot establish an infection on its own. Controlling HBV is paramount to controlling HDV. HGV is quite prevalent and looked upon as hepatotropic. It seems to be quite prevalent in some blood donor populations and co-infection with HCV. It has a high MTCT but causes little or no illness in infected infants, and antenatal screening is not justified.

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