



# Liver Disorders of Pregnancy

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## Liver disorders of pregnancy

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### Introduction

Changes of liver anatomy, physiology, biochemistry and liver metabolism are well studied in pregnancy. During the course of pregnancy the liver is pushed superiorly and posteriorly. As a consequence, a palpable liver edge is considered to be an abnormal finding in pregnancy. While the absolute blood flow to the liver remains constant, the proportion of cardiac output supplying the liver falls during pregnancy. As more blood is diverted through the azygos system of veins, upto 60% of healthy pregnant women develop transient esophageal varices, spider nevi, palmar erythema and oedema. These findings are common in pregnancy and should not be confused with liver pathology.

Synthesis of proteins also increases with pregnancy resulting in increased levels of coagulation factors (Factor VII, Factor VIII, Factor X and Fibrinogen). Fibrinogen level is doubled by the last trimester. Therefore, normal levels of fibrinogen should be viewed as an abnormal finding. Abnormal Prothrombin Time is considered as one of the first signs of coagulopathy because ProThrombin has the shortest half-life of the factors of coagulation manufactured by the liver.

Albumin production is not affected in pregnancy but the level falls due to hemodilution. Levels less than 30g/l are commonly encountered. Many binding proteins are increased due to reduced metabolism rather than increased synthesis.

Level of Urea is reduced in pregnancy due to the increased glomerular filtration rate with no changes to the liver metabolism.

Cholesterol concentration rises by 50% with concomitant increase of up to 300% in the levels of triglycerides. This takes a considerable time to return to normal after delivery.

In pregnancy, the liver is responsible for post-prandial glucose release and storage during fasting as per usual physiology. Any disease which leads to liver cell necrosis subsequently leads to hypoglycemia in pregnancy as well. Liver function tests, mainly ALT and AST fall by 25% in pregnancy mainly due to the dilution of blood. Alkaline Phosphatase shows a rise up to 300% by the end of pregnancy. However, this is due to the Heat Labile Placental form of Alkaline Phosphatase. The Alkaline Phosphatase level reaches normal values by about the 14th day in most women. ALT and AST show a rise during the first five days of puerperium. These levels could go over the normal non-pregnant range. This phenomenon can be explained by the fact that these transaminases are not just specific to the liver but are also found in other tissues.

It has been the common clinical experience that being subjected to high levels of bilirubin in utero does not appear to affect the foetus. This is true regarding toxic products released as a result of maternal liver failure

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as well. Unconjugated bilirubin crosses placenta bidirectionally and is the main route of foetal clearance. Relationships between maternal and foetal bilirubin levels are unpredictable. Unconjugated bilirubin is water insoluble when bound to albumin, unable to pass through the kidney or the blood brain barrier. Conversely, unbound and unconjugated bilirubin is lipid soluble and could pass through the blood brain barrier. When bilirubin is conjugated, it is water soluble but remains inside the liver cell unless the cell is damaged. Protein bound conjugated bilirubin is the cause of jaundice and hyperbilirubinemia in liver cell disease. The secretion of conjugated bilirubin into the bile canaliculus is active and energy dependent.

## Liver Disease in Pregnancy are of two types

1. Pregnancy Specific Liver Disorders
2. Liver Diseases Incidental to Pregnancy

The guidance here will focus mainly on liver disease specific to pregnancy and incidental liver diseases of higher clinical prevalence.

### 1. Liver Disease Specific to Pregnancy are

- Hyperemesis Gravidarum
- Obstetric Cholestasis
- Acute Fatty Liver of Pregnancy
- HELLP Syndrome

### 2. Liver Disease Incidental to Pregnancy are

- Hepatitis A Infection
- Hepatitis B Infection
- Hepatitis C Infection
- Biliary Disease

## Pregnancy Specific Liver Disease

### Hyperemesis Gravidarum (HG)

Hyperemesis Gravidarum is defined as intractable nausea and vomiting requiring hospitalization, in order to save the life of the pregnant woman. It occurs in about 0.3 to 2% of pregnancies. Intractable vomiting results in weight loss, electrolyte imbalance, ketonuria, reduced urine output and dehydration<sup>1</sup>. About 10% of pregnant ladies experience persistence of symptoms

throughout the pregnancy to finally resolve after the delivery of the baby. HG is seen more often in multiple pregnancies, molar pregnancies, pregnancies with preexisting diabetes, thyroid disease and women with psychiatric conditions. Diagnosis is usually clinical and the derangement of liver biochemistry is seen in up to 50% of the subjects. The aminotransferase increase could range from mild to 10% of the upper limit of normal<sup>2</sup>. Jaundice is rare. The diagnosis of HG is a diagnosis of exclusion of other pre-existing liver and other disorders. It is common practice to use Pregnancy Unique-Quantification of Emesis (PUQE) Score to establish and monitor the severity of the disease. Please see Annexure 1.

Management of HG is supportive. This includes correction of dehydration, electrolyte imbalance, and Thiamine supplementation (to prevent Wernicke's encephalopathy). Specific abnormalities of thyroid function need to be treated with thyroxine or anti-thyroid drugs.

A centrally acting antiemetic could be used for the control of nausea and vomiting. Commonly used antiemetic medications are Domperidone, Metoclopramide and Ondansetron. It is our experience that a person who may not respond to one category of antiemetic medication could respond well to another group of antiemetics. The role of corticosteroids on HG is not confirmed but may come useful in refractory cases<sup>3</sup>. Successful treatment resolves all abnormal chemistry of liver function tests.

### Obstetric Cholestasis (OC/ICP – Intrahepatic Cholestasis of Pregnancy)

Intrahepatic Cholestasis of Pregnancy is diagnosed when pruritus develops in pregnancy with abnormal liver function tests and increased bile acids. This condition resolves after delivery. Pruritus of ICP classically affects palms and soles of the body. The exclusion of other types of dysfunction is essential. While making the diagnosis of ICP, pregnancy specific ranges of LFTs should be used as the yardstick. However in a case of clinically suspected obstetric cholestasis, if there is an absence of abnormal liver functions, this should be followed up with the repetition of LFTs every one to two weeks. Post natal resolution of symptoms is essential for the diagnosis<sup>4</sup>.

In women of Chilean, Scandinavian, Indian/Asian or Pakistani Asian descent, this condition occurs in about 1.2 to 1.5% of pregnancies. Highest incidence is reported in Chile (14%) with Araucanian population showing the highest incidence. Some of these cases have been described to be due to dietary Selenium deficiency<sup>5,6</sup>. This condition recurs in 45-95% of women in subsequent pregnancies<sup>7</sup>. This suggests genetic predisposition with incomplete penetrance. The aetiology of ICP is not well described but it is likely that the factors are genetic, hormonal and exogenous.

The involvement of a genetic component is supported by the clustering of ICP in families, with increased incidence in specific ethnicities and higher incidence in multiple pregnancies. Biochemical research points to evidence identified for the genetic component as a defect in ATP-Binding Cassette B (ABCB) 4 and (ABCB) 11, with mutations of these transporters conferring increased susceptibility to ICP<sup>8,9,10</sup>. Furthermore, some studies have shown decreased expression of bile acid transporters in the placenta<sup>11</sup>. In addition, hormonal components are highlighted by the fact that the severity of the disease peaks at the 3<sup>rd</sup> trimester. Vulnerability of individuals to the disease seems to vary according to the level of exposure to exogenous hormones and the particular time in the menstrual cycle. Both estrogens and progesterone metabolites can increase the likelihood of cholestasis<sup>12,13</sup>.

Known risk factors for the disease include preexisting hepatobiliary disease, personal or family history of ICP, and advanced maternal age<sup>39</sup>. In addition, women with twin pregnancies are 5 times more likely to develop ICP than women with a singleton pregnancy<sup>40</sup>.

ICP has little consequences on the long-term health of the mother. The symptoms are mainly limited to pruritus. Some may have mild jaundice, malabsorption and clinically apparent gallstone disease.

The common perception is that there is increased morbidity and mortality for the foetus in a case of an ICP pregnancy. This is more apparent when the serum bile acid level is 40  $\mu\text{mol/l}$  or higher. Foetal problems are mostly due to preterm delivery ((iatrogenic in part) and sudden foetal loss. Passage of meconium is considered to be increased in ICP pregnancies. However, this is more common in preterm pregnancies with ICP than term pregnancies with the same condition. Yet, all studies do not support this finding. Meconium passage is more common with severe

cholestasis compared to mild cases. The current RCOG Green Top Guideline on ICP describes linear increase in the passage of meconium with the bile acid concentration.

Although Postpartum Haemorrhage is described as a condition which has a higher incidence in ICP, it has not been substantiated with the current practice data (RCOG Green Top Guideline; #43). Pruritus is a commonly found symptom in pregnancy seen in up to 23% of pregnancies. However, only a small percentage fits into the diagnosis of ICP. In ICP, the pruritus is worse at night. It involves palms and soles in addition to other parts of the body. Other causes for pruritus, pregnancy specific and otherwise, need to be excluded. Increase in LFTs over the normal pregnancy range should be the main indicator of the presence of the disease. But consideration should be given to the fact that the upper limit of transaminases is 20% lower than the normal non-pregnant range. With regard to bile acid levels, pregnancy specific ranges are given by most laboratories. However, this should be confirmed and not taken for granted. It is also important to note that the bile acid levels are raised significantly after food intake. Therefore, fasting values may help the diagnosis to be more accurate. It is notable that most studies have measured bile acid levels in a random manner.

The development of pruritus may precede the derangements in LFTs and bile salts by a few weeks. Isolated elevation of bile salts is an uncommon entity. When the initial diagnosis is made, checking the coagulation profile is recommended at least once. It is recommended to screen for infective Hepatitis A, B and C, other viruses (SMV), chronic autoimmune conditions and Primary Biliary Cirrhosis by doing necessary investigations such as Anti-Smooth Muscle and Anti-Mitochondrial Antibodies. Both pregnancy specific diseases, HELLP syndrome and Acute Fatty Liver of Pregnancy, although affect the liver, are unlikely to be confused with ICP (RCOG Green-top Guideline; #43).

Once diagnosed with ICP, it is recommended to monitor LFTs and bile acids weekly until delivery. Recommendation for a postnatal check on LFTs should be deferred for at least 10 days from delivery (RCOG Green-top Guideline; #43).

It is of paramount importance that the postnatal resolution of LFTs is used as the mandatory factor in the confirmation of correct diagnosis of ICP.

## Intrahepatic Cholestasis of Pregnancy: Management

Management of ICP is achieved at symptomatic control. For the control of symptoms, there have been reported use of Antihistamines, Benzodiazepines, Dexamethasone, s-adenosyl-l-methionine and ursodeoxycholic acid (UDCA). UDCA shows most valuable data for the relief of symptoms and questionable prevention of adverse foetal outcomes<sup>14,15,16</sup>. UDCA has been shown to reduce the severity of the pruritus, bile acid levels, ALT and bilirubin. Recent meta-analysis has given the green light for UDCA's use in improving the above-mentioned symptoms and foetal outcomes<sup>17</sup>. UDCA 10-15mg/kg is the preferred treatment for ICP coupled with appropriate timing of delivery. The inclination towards early delivery rises with bile acid levels over 40 µmol/l. There is no certain cut off to bile acid levels and foetal outcome although agreement exists in that over 40 µmol/l, adverse effects are increasingly expected (RCOG Green-top Guideline; #43). According to the latest Green Top Guideline, there is sufficient data to inform the patient about the best intervention practices to prevent foetal death. Therefore, SLCOG advocates appropriate timing of delivery, taking all clinical factors of the relevant woman with gestation of the foetus into consideration.

SLCOG recommends avoiding unnecessary interventions in the absence of robust indications for delivery. However consideration of delivery should be made in the presence of symptoms when the gestational age reaches 35 weeks. Moreover, with clearer understanding of the pathology of the disease, SLCOG supports the goal to aim for greater maturity and hence increased chance of vaginal delivery. In ICP pregnancies SLCOG recommends continuous foetal monitoring when facilities are available.

The past consensus has been that ICP is a contraindication for OCP use. However, some sources suggest that the newer low-dose pills can be safely used as long as liver function test results are followed and patients are aware of possible recurrence risks<sup>41</sup>.

### Acute Fatty Liver of Pregnancy (AFLP)

Acute Fatty Liver of Pregnancy is a pregnancy specific syndrome causing microvesicular fatty infiltration of the liver with varying degrees of liver dysfunction. It

is known to affect about one in 7000 - 20000 pregnancies.

Risk factors include multiple pregnancies and low body mass index. Median presentation time is at the 36th week of Period Of Gestation (POG). It could be complicated by encephalopathy thrombocytopenia, varying degrees of coagulopathy and renal involvement. AFLP remains a serious disease with high mortality from 16.5-26.7%<sup>35,36</sup> due to severe complications such as DIC, renal function impairment, hepatic encephalopathy, hypoglycemia, Multi Organ Failure, etc.<sup>37</sup>. In the past, maternal and perinatal mortality were reported to be as high as 75% and 85%, respectively<sup>38</sup>.

AFLP never develops after delivery. Fifty percent of the patients with acute AFLP have coexisting pre-eclampsia. It could be difficult to distinguish AFLP from HELLP syndrome in a few cases. Some overlap of symptoms are seen with Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura. Early recognition, delivery and aftercare are essential for good prognosis of both mother and the baby. Postpartum clinical course depends on the action interval between the occurrence of symptoms and the delivery of the baby<sup>18</sup>. Most reviews attended by the SLCOG noticed a delay in the diagnosis of this condition.

Pathophysiology is mostly unknown. However, defects in foetal mitochondrial fatty acid oxidation due to defects in two key enzymes have been identified as a cause: (Long Chain-3-Hydroxyl-coenzyme A Dehydrogenase; LCHAD). The exact mechanism of action is not known. However, accumulation of fatty acid metabolites produced by the foetus and placenta is identified as a toxic product which can lead to disease in a predisposed mother.

Although this is a known fact, mitochondrial defect is found in only 20% of the babies born to mothers with AFLP. The babies with the mutation need close perinatal management. Risk factors: primigravidas (first pregnancy), pre-eclampsia, male fetus and multiple gestation<sup>42,43</sup>. However, there is no causal relationship identified between these potential risk factors and AFLP as yet<sup>44</sup>.

Although the gold standard in diagnosis is liver biopsy, it is rarely done or advocated. Use of Swansea Criteria is used commonly. Please see Table 1.

**Table 1.**

**Swansea criteria for diagnosis of acute fatty liver of pregnancy**

**Six or more criteria required in the absence of another cause**

- Vomiting
- Abdominal pain
- Polydipsia/polyuria
- Encephalopathy
- Elevated bilirubin >14 µmol/l
- Hypoglycemia <4 mmol/l
- Elevated urea >340 µmol/l
- Leukocytosis >11×10<sup>6</sup> cells/l
- Ascites or bright liver on ultrasound scan
- Elevated transaminases (AST or ALT) >42 IU/l
- Elevated ammonia >47 µmol/l
- Renal impairment; creatinine >150 µmol/l
- Coagulopathy; prothrombin time >14 s or APPT>34 s
- Microvesicular steatosis on liver biopsy

ALT, Alanine Transaminase; APPT, Activated Partial Thromboplastin Time; AST, Aspartate Transaminase.

Swansea Criteria could predict AFLP with an 85% of Positive Predictive Value and 100% Negative Predictive Value for Microvesicular Steatosis as assessed by biopsy in research trials<sup>19</sup>.

In Acute Fatty Liver of Pregnancy, the liver biochemistry is disturbed to a more severe extent than other pregnancy specific liver disorders. As a result, coagulopathy, encephalopathy and hypoglycemia may be pronounced. Accompanied polydipsia is a pathognomonic symptom of AFLP once Diabetes Mellitus is ruled out<sup>20</sup>.

### **AFLP: Management**

This is an obstetric emergency needing optimization of the patient with early delivery.

### **The delay in delivery in hours could lead to poor outcomes**

Multidisciplinary support with bedside participation of specialists for discussion in Transfusion Medicine, Anaesthetist, Intensivist, Liver Specialist, General Physician and the Neonatologist is very important. Consideration of providing management with ICU is encouraged by SLCOG.

The delivery should be carried out by the specialist consultant with the best experience. The improvement of liver functions is seen by about the fifth day after the delivery of the baby. The maternal mortality rate has decreased from 90% to less than 10% over the past 30 years due to advances in early detection, early delivery and intensive care support<sup>21,22</sup>. Recurrent risk in subsequent pregnancy is 25%<sup>23</sup>.

The use of postpartum contraception with hormones has been discouraged but the pathophysiological basis for such is poor.

### **HELLP Syndrome**

HELLP syndrome is a clinical entity consisting of hemolysis, elevated liver enzymes, and low platelets. It is an entity within the clinical syndrome of Pregnancy Induced Hypertension of Pregnancy (PIH of Pregnancy comprises of Preeclampsia, Eclampsia and HELLP Syndrome). The risk of Preeclampsia of pregnancy is present in 0.6-1.2% of pregnancies of which about 20% of severe cases go on to develop HELLP syndrome. Higher risk for development of HELLP Syndrome is found in patients with

1. History of Diabetes
2. Chronic Hypertension
3. Multiparity
4. Old Age<sup>24,25</sup>

Clinicians should keep in mind the significant overlap of signs and symptoms and biochemistry with Hemolytic Uremic Syndrome, Acute Fatty Liver of Pregnancy and Thrombotic Thrombocytopenic Purpura. The criteria used for diagnosis of HELLP syndrome in the presence of PIH are

- Platelets < 100000 /mm<sup>3</sup>
- LDH > 600 U/l
- Liver transaminase level > 70 U/l

Although there are several classifications by symptoms to assess the severity, such as The Mississippi Classification of HELLP Syndrome, practical use is not that effective (26, 27). In HELLP Syndrome, Preeclampsia is associated with significant liver derangements, Thrombocytopenia and Hemolysis. Development of HELLP Syndrome carries a higher risk for poor outcomes for both the mother and the foetus. Apart from the given references for investigation, a high degree of suspicion is needed for the confirmation of the diagnosis of HELLP Syndrome, to pursue the necessary tests. Most patients complain of non-specific fatigue and malaise. Fifty percent of patients report epigastric or right upper quadrant pain. Degree of jaundice is mild. Microangiopathic Hemolytic Anaemia could be noted on the peripheral blood smear examination. This hemolysis is thought to be caused by endothelial injury to the vasculature, fibrin deposition in blood vessels and platelet activation (28). Histological features of HELLP is that of periportal or focal parenchymal hepatic necrosis with hyaline deposition of fibrin material in liver sinusoids. However, biopsies are rarely done to confirm the diagnosis. The effect on the liver sinusoids probably causes right upper quadrant abdominal pain.

In comparison to severe PIH per se, women with HELLP Syndrome have a higher incidence of Disseminated Intravascular Coagulation (DIC), Acute Renal Failure, Pulmonary Oedema, Intracerebral Haemorrhage (ICH), Subcapsular Liver Hematomas, wound hematomas, and death. They are known to require more blood transfusions in management. These complications significantly decrease with higher gestational age as concomitant foetal risk also diminishes with advanced gestation.

### HELLP Syndrome: Management

Once suspected, the patient needs to be hospitalised. When confirmed, the ideal place of management should be a high dependency patient care unit or Intensive Care Unit, whenever it is possible. The recommendations are for the use of MgSO<sub>4</sub> for prophylaxis against seizures. Use of antihypertensives are recommended to lower blood pressure to safe levels. Foetus should be assessed for its growth and well being.

The definite management is by the delivery of the foetus. It results in the resolution of the symptoms mostly within five days although some complications could still occur in the postpartum.

In the case of a pregnancy which has advanced more than 34 weeks +6 days, there should be prompt delivery. In the case of foetuses with likelihood of lung prematurity, use of corticosteroids and supportive management for 48 hours till delivery is practiced aiming for lung maturity, if the obstetrician is happy about the stability of the patient's systems<sup>29</sup>.

Recently case reports have come up for the use of Eculizumab, a targeted inhibitor of complement C5 resulting in the added opportunity of conservative management of the pregnancy for an increased 17 days, without adverse events<sup>30</sup>.

However, both foetal and maternal complications are higher without prompt delivery. In the case of the rare complication of Hepatic Subcapsular Hematoma Formation, surgical exploration, embolization of hepatic artery, and liver transplantation have been described to have some success<sup>31, 32</sup>.

### Incidental Diseases of Liver in Pregnancy

Any incidental disease affecting the liver could occur during pregnancy as well. But this guideline focuses on the most common and important incidental liver diseases of pregnancy. As such we would focus mainly on viral infections of the liver and Biliary Disease incidental to pregnancy.

#### Viral Infections of the Liver

- Hepatitis A – HAV
- Hepatitis B – HBV
- Hepatitis C – HCV

#### Hepatitis A

Hepatitis A is a virus belonging to the Picornaviridae family. It was first identified in 1973. It is a relatively stable virus in the environment, resistant to heat and inactivation of dessication for up to one month<sup>33</sup>. Autoclaving, one minute at a temperature of 185F or disinfecting with dilute Hypochlorite solution will inactivate the virus. The virus is shed through faeces of an infected person. Faeco-oral route is the normal method of infection. Prenatal transmission is rare as the virus is present only transiently in the serum.

Vaccine for HAV was introduced in 1995. Clinical infection is less severe than other viral hepatitis

infections. Serious complications are rare and uncommon. A point to note is that not all infections are symptomatic. In natural infection, 80-95% infected adults are symptomatic and 2/3rd of them are icteric. Severity of the illness appears to be related to the patient's age as well as the initial size of viral load. Incubation period is 15 to 50 days with a mean of 28 days. Symptoms are that of general viral infection with icterus becoming apparent within 10 days of the onset of generalised symptoms. This is preceded by palpable hepatomegaly. Liver biochemistry shows higher elevation of ALT than AST, with peak values obtained prior to the appearance of jaundice. Elevated liver functions may remain elevated for over a month in adults. In rare occasions, prolonged elevation of liver function tests lasting more than a year has been reported in about 10% of older patients, with persistence of jaundice and pruritus despite overall improvement of clinical symptoms. Fulminant hepatic failure resulting in death occurs in fewer than 1% of cases.

HAV specific IgM is a reliable test to identify acute infection. The IgM level is present by the time the patient is symptomatic and remains positive for 4 to 6 months. IgG on the other hand will remain positive for years to come.

Disease is self-limiting and non-life-threatening in most pregnant women. Management is supportive. However, infection acquired in the latter part of the second trimester and third trimester could cause preterm labour, placental abruption and premature rupture of membranes<sup>34</sup>.

Vaccination even during pregnancy appears to be safe. Admission of immunoglobulin is recommended for neonates born within 2 weeks of acute maternal illness with 80% to 90% efficacy of protection<sup>33</sup>.

No specific antiviral treatment is currently available but vaccination to prevent and post exposure immunoglobulin for treatment are available for use. In 2007, Advisory Committee on Immunization Practices (ACIP) guidelines were revised to recommend hepatitis A vaccine to be given following exposure based on data indicating that the use of immunoglobulin and vaccine have similar post exposure efficacy of adults up to 40 years. In older people, immunoglobulin is preferred to the vaccination within 2 weeks of exposure.

## Hepatitis B

Hepatitis B belongs to the Hepadnaviridae class of viruses. HBV is a fairly stable virus and remains stable on surfaces up to 7 days. Although transmission among family members are common, it is mainly contracted through sexual contact than through fomites. Only rarely has non-sexual household transmission has been established as a route for HBV infection. The surfaces contaminated could be cleaned with 1: 10 dilution of Sodium Hypochlorite. In areas of Asia 8-10% of the population is chronically infected by HBV. High infection rates are found in the Middle East and the Indian subcontinent with up to 5% of the adult population infected.

The likelihood of a person infected becoming chronic carriers depends on the age when the person was infected. Earlier the age at infection, higher the risk of being a chronic carrier. The risk of chronic HBV infection for a child infected in the newborn period in the absence of prophylactic therapy is 70-90%<sup>33</sup>. The main method of transmission is by inoculation with infected body fluids. It has been shown that in seronegative babies born to mothers with HBV infection, almost 10% acquired HBV infection in the absence of vaccination by end of first year of age.

HBV is a viral disease with a long incubation period of 1-6 months. The presence of extrahepatic symptoms such as joint pains, rash and muscle pain occur in about 20% of patients. Hepatitis B consists of 3 antigens which are structural; Surface, Core and the Envelope antigens. Appearance of the surface antigen usually predates clinical symptoms in about 28 days. On average it remains detectable up to 6 weeks in most patients. In people who do not go on to develop chronic disease (up to 95% non-chronic) HBS titres come down as symptoms settle. The antibody for HBS is a marker for the absence of carrier state. Its titer increases slowly during clinical recovery and continues to rise up to one year, after the disappearance of HBS antigen. In practical terms patients with milder disease which is self-limiting, antibody for HBS is detectable only after antigen disappears from the serum. Therefore, a period or window could exist where the patient's antigen and antibody are both negative. In this window period, detection of Hepatitis B Core antibodies could help in diagnosis (Hepatitis Core antibodies start rising about 3-5 weeks after the HbS antigen rise). Although Hepatitis Core antibodies drop after one to two years, they could be detectable for

years to come. The Hepatitis B Env antigen follows a similar appearance to that of Hepatitis B Surface antigen in self-limited infections. The antibody for the envelope is detectable shortly after the disappearance of HB Env antigen. The chronic carrier state is diagnosed when HBS antigen is detectable for more than 20 weeks after the initial diagnosis. The vaccination granted immunity can be diagnosed from natural infection mediated immunity by the presence of HBS antibody in the absence of HBS antigen and HB Core antibody.

In other words, in the absence of HBS antigen and Hep B antibody, the presence of Hep B surface antibody is indicative of vaccine acquired immunity.

The HBV infection in pregnancy does not differ much from non-pregnant patients. Treatment is supportive other than in cases of severe infection where Lamivudine and Tenofovir may be used to decrease the viral load. This therapy could help to reduce the number of people with chronic infection. The vertical transmission of HBV is a clinically important condition as most infected infants in utero become chronic carriers.

Up to 95% of transmission occurs in the third trimester especially near birth or immediate postpartum period infection of mother compared to 10% at first trimester. The quantified HBV envelope antigen with high viral load (more than 10<sup>6</sup> copies/ml) is indicative of risk of vertical transmission. The development of fulminant hepatitis is no different to that of Hepatitis A infection.

The indicators of serious infection are suggested by presence of encephalopathy, coagulopathy or fluid imbalances. In severe cases the diagnosis from HELLP Syndrome could be a challenging task. No teratogenicity has been found with the HBV virus. There is limited evidence of prematurity and HBV infection. The presence of HBS antigen does not appear as a marker for increased adverse outcomes in pregnancy. Similarly, pregnancy has no effect on the pathogenesis of the disease.

Screening for HBV in pregnancy is needed because the diagnosis of infection or the carrier state helps to initiate therapy to prevent acquisition of disease by the neonate. The ACOG and the CDC recommend routine prenatal screening of mothers with HBS antigen regardless of individual risk. Although SLCOG supports

inclusion of HBV Screening in antenatal care, the decision needs to be taken by the government balancing the cost and benefit. Further CDC recommends women with high risk to be retested in the absence of detection in early pregnancy when they are admitted for labour and delivery. The use of Hepatitis B immunoglobulin, though effective, is now historical. Currently post-exposure treatment consists of a single dose of Hepatitis B immunoglobulin given immediately or up to within 7 days of exposure with 75% efficacy. The HBV vaccination also should be initiated especially when there is an ongoing risk of further exposure. Administering the vaccine and the immunoglobulin simultaneously does not affect the efficacy of the vaccine. In treatment aimed at preventing vertical transmission, one should note that multiple indicators are contributing to the risk of vertical transmission.

They are

- Gestational age
- Placental factors
- HBV viral load
- Genetic susceptibility of the foetus

Immunoglobulin vaccination and Lamivudine have been used to reduce the risk. Lamivudine is licensed for use in pregnancy.

Timing of delivery is not influenced by the HBV infection per se.

The route of delivery has not shown to influence the risk of HBV transmission. CDC recommends lactation even prior to infants receiving vaccine and immunoglobulin of an infected mother. However, it should be kept in mind that the risk of being infected at delivery whatever the mode is high for a seronegative foetus, as most sero-convert by third month after birth in the absence of therapy. Vaccine alone in the perinatal period confers 75-85% of protection against infection of neonate. Combining with HBV Immunoglobulin increases the efficacy up to 95%. The infants after optimal therapy, developing infection subsequently are supposed to have acquired infection in utero, although it was not detectable at the time of delivery. By and large, delivery of the baby and the mode of delivery is decided after closely following the acute infection with other routine pregnancy related factors taken into consideration.

## Hepatitis C

Hepatitis C is the most common bloodborne infection in the United States of America. Intravenous drug abuse has been the most common risk factor for such infection. Even in pregnancy the majority are intravenous drug abusers in the USA. Transfusion associated HCV infections are extremely rare. Significance of sexually transmitted HCV is controversial and it appears to be a rare incident.

The concomitant infection of HIV increases the likelihood of vertical transmission by five times. The incubation period of HCV is 30 to 60 days. It is asymptomatic in 75%. The most common symptoms are that of any viral infection. Fulminant liver disease is uncommon. However, progression to chronic liver disease is upto 85% in acutely infected individuals. Diagnosis is done apart from common biochemistry by negative immunological numbers for HAV and HBV in the presence of anti-HCV positive screening test.

It is worth noting that there are limitations of interpretations of currently available HCV screening assays. Because HCV has at least six genotypes and 50 subtypes, genotype 1 is the most common genotype found in the USA and is less responsive to treatment than type 2 and 3.

Therapy is by using Interferon Alpha or combination of Interferon Alpha and Ribavirin. Treatment is contraindicated during pregnancy which includes Ribavirin. New therapy with boceprevir and sofosbuvir comes with Category 4 recommendations from the

FDA. Vertical transmission plays a small role in HCV. The vertical transmission rate increases with maternal viral load, maternal peripheral blood mononuclear infection by HCV, premature rupture of membranes of more than 6 hours, and any procedure associated with exposure of foetus to maternal blood. Optimal route of delivery in the presence of maternal HCV infection has not been decided. In the absence of any other confounding factors, breast milk has not been found to increase risk of HCV transmission. But data for such is not robust.

## Biliary Disease in Pregnancy

Biliary Disease is not a rare problem in pregnancy as hormonal changes in pregnancy have an effect on smooth muscle and bile transporters. High oestrogen levels increase the risk of gallstone formation. The biliary problems in pregnancy present with right hypochondrial pain and/or fever. In the presence of obstruction and an obstruction site, there could be jaundice. Although ultrasound scan is the commonly used diagnostic tool, the detection of choledocholithiasis is only 50%. Use of MRI is aimed for better diagnosis. Giving Gadolinium for better study is considered safe after the first trimester. Endoscopic procedures are not contraindicated. Treatment is aimed at relieving obstruction, managing pain, antibiotics for infection and supportive measures. Surgical intervention should be contemplated only after discussion among specialty teams of surgery, obstetrics and gynaecology, GI Medicine and Anesthesiology and Neonatology with the patient.

### Annexure 1: Modified Pregnancy Unique – Quantification of Emesis (PUQE) Score

Score/ Question	1	2	3	4	5
1. For how long have you felt nauseated?	Not at all	<1 hour	1-3 hours	3-6 hours	>6 hours
2. How many times do you vomit?	Never	1 to 2	3-4	5-6	>7
3. How many times have you had retching or dry heaves without bringing anything up?	Never	1 to 2	3-4	5-6	>7

Total score 4 to 6: mild nausea and vomiting of pregnancy. Total score 7 to 12: moderate nausea and vomiting of pregnancy. Total score  $\geq$ 13: severe nausea and vomiting of pregnancy.

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