GUIDELINE FOR THE MANAGEMENT OF HEPATITIS B IN PREGNANCY AND THE EXPOSED INFANT

BRITISH VIRAL HEPATITIS GROUP

MATERNAL AND PAEDIATRIC SUBGROUP 2021

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2. Guideline development

Patient participation, consultation and dissemination

This guideline is aimed at all healthcare professionals involved in antenatal and postnatal care within the UK, including those specialising in the care of women with hepatitis B and their infants. Clinicians from the British Viral Hepatitis Group (BVHG), Obstetricians, associate healthcare professionals, patient representatives and Public Health England have all been involved in guideline development. Guideline consultation has been undertaken through display on the BVHG website.

In many areas covered in this guideline there is a lack of evidence and several recommendations are based on expert opinion (EO). International clinical guidelines e.g. European Associaton for the Study of the Liver (EASL) are referred to where appropriate. The National Screening Committee Infectious Diseases in Pregnancy Screening (IDPS) Standards and Key Performance Indicators (KPI) and Joint Committee on Vaccination and Immunisation (JCVI) and Public Health England (PHE) recommended immunisation schedule for infants (as detailed in the Green Book on Immunisation against Infectious Disease[1]) are also included as recommendations and these are indicated accordingly. These BVHG clinical guidelines should therefore be read in conjunction with the PHE Guidance on the hepatitis B antenatal screening and selective neonatal immunisation pathway.[2]

We recognise that a small number of trans and non-binary people living with HBV will also experience pregnancy. We use the term 'woman' or 'women' in these guidelines for brevity, on the understanding that guidance also applies to trans and non-binary individuals.

3. Summary recommendations

There are no recommendations for sections 1-4.

Section 5: Antenatal screening for hepatitis B

5.01	**Routine screening for hepatitis B (HBV) in pregnancy should be offered, and recommended, to all women at first contact with antenatal services, ideally at booking visit during first trimester**
5.02	**Screening for HBV in pregnancy should involve serological testing for presence of hepatitis B surface antigen (HBsAg). If positive, further serological and molecular testing is required to determine infectivity status**
5.03	**All women with known HBV infection prior to pregnancy should have repeat HBV serology, including e markers, and HBV DNA sent for testing at booking in order to facilitate infectivity status assessment**
5.04	**Women refusing antenatal HBV screening should have testing rediscussed and reoffered at a face-to-face appointment at ≤20 weeks gestation with Infectious Diseases Specialist midwife and/or Screening Coordinator midwife. Testing should be re-offered again in labour if ongoing refusal**

Section 5.1: Reporting and long term follow up – antenatal pathway

5.11	**Antenatal HBV screening results should be reported by the laboratory to maternity services within 8 working days of sample receipt**
5.12	**Women who are known to be HBV positive or have a confirmed screen positive result, should be invited to attend for screening assessment within 10 working days of the positive report being received from the laboratory, or known positive status being reported to the screening coordinator**
5.13	**Household and sexual contacts should be offered screening for HBV by the GP, and vaccinated against HBV if susceptible**

5.14	**All pregnant women with HBV infection should ideally be managed in conjunction with a specialist multi-disciplinary team experienced in management of viral hepatitis during pregnancy**
5.15	**Women newly diagnosed with HBV, and women with known HBV infection and in a high-risk group for HBV infectivity during current pregnancy (see Figure 2) should be offered review by a specialist within 6 weeks of results being reported to maternity services and before 24 weeks gestational age (GA), whichever is sooner, in order to risk assess and decide upon treatment prior to 24 weeks gestation**
5.16	**Women with lower infectivity who are known positive should be offered review by a specialist within 18 weeks. Women with lower infectivity who are a new diagnosis should be offered review by a specialist within 6 weeks regardless of infectivity status**

Section 6.1: Investigation and monitoring of hepatitis B in pregnancy

6.1.11	**All women newly diagnosed with HBV during pregnancy should have confirmatory HBV serology including e markers and anti-HBc IgM undertaken**
6.1.12	**All women with HBV infection should also be offered screening for HIV, HCV and hepatitis delta co-infection during pregnancy**
6.1.13	**HBV DNA should be tested in all women with HBV infection prior to 24 weeks GA to inform HBV infectivity status assessment**
6.1.14	**Quantitative HBsAg testing (if available) prior to 24 weeks GA to inform HBV infectivity status assessment**
6.1.15	**Women with HBV DNA >200,000 IU/ml or quantitative HBsAg >4log10 IU/ml should be offered antiviral treatment to reduce risk of HBV vertical transmission from 24weeks GA**

Section 7: Antiviral therapy during pregnancy

7.01	**Antiviral therapy for HBV during pregnancy should be offered to women considered at high risk of HBV infectivity and those with evidence of liver disease**
7.02	**Tenofovir disoproxil (TD) is currently the preferred choice of antiviral therapy for treatment of hepatitis B during pregnancy**

Section 7.1: Women diagnosed before pregnancy

7.11	**In many women planning to conceive, antiviral treatment of HBV may be deferred, providing there is minimal liver disease**
7.12	**Women on antiviral therapy for HBV prior to pregnancy should continue treatment during and after pregnancy**
7.13	**Women who have conceived on entecavir should be offered the option to switch to TD during pregnancy**

Section 7.3: Antenatal antiviral prophylaxis to prevent HBV Vertical Transmission

7.31	**Women taking antiviral therapy for prevention of HBV vertical transmission should be stopped by 12 weeks post partum**

Section 8.1: Mode of delivery

8.11	**HBV is not an indication for Caesarean section**

Section 8.2: Management of labour

8.21	**Fetal scalp electrodes and fetal blood sampling should be avoided where possible during labour to reduce HBV infectivity status**

Section 8.3: Birthing pools

8.31	**Low-risk women with chronic HBV infection may be considered for delivery in a birthing pool on a case-by-case basis following discussion with the local specialist team**

Section 8.4: Presentation in labour without booking bloods

8.4	**Women presenting in labour with unknown HBV status should be offered urgent HBV testing with results made available within 24 hours.**

Section 9: Breastfeeding and hepatitis B

9.01	**Women monoinfected with HBV can breastfeed providing neonatal immunoprophylaxis is administered within 24 hours of birth**
9.02	**Breastfeeding is discouraged in women with HBV coinfected with HIV**

Section 10.1: Infant post-exposure prophylaxis

10.11	**All infants born to HBV positive mothers should receive hepatitis B vaccine at birth with subsequent doses of monovalent and hexavalent vaccine as per the Green Book[1]**
10.1.11	**Infants at high risk of HBV vertical transmission:** • **maternal HBeAg positive** • **maternal anti-HBe negative** • **maternal HBV DNA ≥1x10^6 IU/ml at any time during pregnancy** • **acute maternal HBV infection during pregnancy** • **or birthweight ≤ 1500g** **should also receive hepatitis B immunoglobulin (HBIG) ideally within 24 hours of birth to reduce HBV infectivity status**

Section 10.2: Infant follow-up

10.21	**All infants born to HBV positive mothers should be tested for evidence of HBV infection by serology for hepatitis B surface antigen (HBsAg) at 12 months of age (chronological), preferably by dried blood spot (DBS) in the community**
10.22	**Each infant born to an HBV positive mother should have a named clinician responsible for ensuring that testing is undertaken and results followed up at 14-15 months**

10.23	**Infants diagnosed with HBV (hepatitis B surface antigen positive) should be referred to paediatric viral hepatitis specialist**

Section 11.2: Postnatal maternal management

11.21	**All women with HBV should receive postnatal hepatitis follow up within 3 months of delivery**

Section 15: Screening flowchart

4. Introduction to hepatitis B

Hepatitis B Virus (HBV) is a blood-borne viral infection affecting the liver cells (hepatocytes). Chronic infection with HBV may cause inflammation of the liver cells (hepatitis), usually characterised by elevated liver enzymes, leading to liver fibrosis, cirrhosis and liver failure. Chronic HBV infection is also associated with hepatocellular carcinoma (HCC), with around 40% of HCC cases in developed countries attributable to viral hepatitis.[3]

Routine screening for HBV in pregnancy has been recommended by the UK National Screening Committee (UK NSC) in order to identify women with HBV infection early in the antenatal period[4]. Safe and effective hepatitis B vaccines exist and the Joint Committee on Vaccination and Immunisation (JCVI) recommends post-exposure immunisation of infants born to women with HBV infection to reduce the risk of transmission to the neonate.

4.1 UK/Worldwide prevalence of hepatitis B in pregnancy

In 2015, the World Health Organisation (WHO) estimated that over 250 million people worldwide were chronically infected with HBV, with the highest prevalence of HBV in Africa and the Western Pacific region[5].

The prevalence of HBV in pregnant women in the UK detected on antenatal screening is low (0.41%)[2], although there is variation nationally rising up to 1% in some inner city areas[6].

4.2 Hepatitis B transmission

Worldwide, the majority of chronic HBV infection is acquired perinatally or in early childhood rather than through sexual contact or other routes of transmission[7].

Established main routes of transmission for HBV include:

- vertical transmission from mother to child
- blood-blood contact (eg sharing of injecting equipment in people who inject drugs (PWID) or 'needlestick' injuries.)
- vaginal/anal intercourse
- human bites from infected source (rare)

Infants who acquire HBV infection vertically are more likely than children and adults to develop persistent, chronic HBV infection (without any symptoms or signs), hence antenatal screening is needed to identify infants at risk of HBV infection and so will benefit from vaccination.

Incubation period of HBV is 40-160 days, with an average of 60-90 days[1]. Risks of transmission vary according to source characteristics and route of transmission, with a 70-90% risk of transmission from a hepatitis B e antigen positive mother and 10-40% in a hepatitis B e antigen negative mother, without prophylaxis[8].

Household contacts of individuals infected with HBV should be considered to be at risk of transmission and should be advised to avoid sharing toothbrushes and razors.

Testing of HBV status should be offered to household and sexual contacts by their GP, with a course of HBV vaccination recommended if not infected and non-immune1.

Contacts found to be HBV infected should be counselled regarding their diagnosis and referred to local services specialised in the management of infectious hepatitis in adults or children services for clinical review and monitoring.

5. Antenatal screening for hepatitis B

5.01	**Routine screening for hepatitis B (HBV) in pregnancy should be offered, and recommended, to all women at first contact with antenatal services, ideally at booking visit during first trimester**
5.02	**Screening for HBV in pregnancy should involve serological testing for presence of hepatitis B surface antigen (HBsAg). If positive, further serological and molecular testing is required to determine infectivity status**
5.03	**All women with known HBV infection prior to pregnancy should have repeat HBV serology, including e markers, and HBV DNA sent for testing at booking in order to facilitate infectivity status assessment**
5.04	**Women refusing antenatal HBV screening should have testing rediscussed and reoffered at a face-to-face appointment at ≤20 weeks gestation with Infectious Diseases Specialist midwife and/or Screening Coordinator midwife. Testing should be re-offered again in labour if ongoing refusal.**

Antenatal screening guidance for laboratories and healthcare providers is regularly updated and available at www.gov.uk/government/collections/infectious-diseases-in-pregnancy-screening-clinical-guidance

Routine screening for HBV in pregnancy has been recommended by the UK NSC and co-ordinated by the Infectious Diseases in Pregnancy Screening programme (IDPS). Screening should be offered, and recommended, to all pregnant women at their first

contact with antenatal services, ideally during the first trimester at the booking visit[2].

Antenatal screening initially should be undertaken using serological testing for hepatitis B surface antigen (HBsAg) to determine whether a patient has evidence of HBV infection. If HBsAg is positive, further testing should be undertaken for other HBV serological markers and HBV viral load (and quantitative HBsAg if available) to determine risk of transmission[11].

Women with known HBV infection prior to pregnancy should have repeat HBV serology, including HBeAg markers, and HBV DNA sent for testing at booking in order to facilitate infectivity status assessment.

If a pregnant woman declines antenatal screening for HBV it is advised that the screening midwife documents this in the patient notes, clearly indicates the decline on the virology request form and alerts the Infectious Diseases Specialist Midwife and/or the Screening Coordinator midwife. Screening should be rediscussed and offered again at 20 weeks gestational age (GA) in a face-to-face meeting by the Infectious Diseases Specialist midwife and/or Screening Coordinator midwife and again in labour should the woman continue to decline[2]. The local multidisciplinary team including paediatric infectious diseases, adult hepatolgy and the obstetrician will be responsible for further review and management in line with local clinical protocols. Consider referral to a regional or national MDT. The woman should also be informed her GP will be notified to inform any future health assessments. The mother should be informed that it is a safeguarding recommendation to consider tesing the newborn at birth for hepatitis B.

5.1 Reporting and long term follow up – antenatal pathway

5.11	**Antenatal HBV screening results should be reported by the laboratory to maternity services within 8 working days of sample receipt**
5.12	**Women who are known to be HBV positive or have a confirmed screen positive result, should be invited to attend for screening assessment within 10 working days of the positive report being received from the laboratory, or known positive status being reported to the screening coordinator**
5.13	**Household and sexual contacts should be offered screening for HBV by the GP, and vaccinated against HBV if susceptible**
5.14	**All pregnant women with HBV infection should be managed in conjunction with a specialist multi-disciplinary team experienced in management of viral hepatitis during pregnancy**
5.15	**Women newly diagnosed with HBV, and women with known HBV infection and in a high-risk group for HBV infectivity during current pregnancy (see Figure 2) should be offered review by a specialist within 6 weeks of results being reported to maternity services and before 24 weeks gestational age (GA), whichever is sooner, in order to risk assess and decide upon treatment prior to 24 weeks gestation or as soon as possible if diagnosed after 24 weeks gestation.**

Antenatal HBV screening results should be reported by the laboratory to maternity services within 8 working days of sample receipt with a laboratory comment interpreting the HBV markers as low or high infectivity[12].

Any woman testing newly positive for HBsAg should be identified and informed of the result at a designated face-to-face appointment with the antenatal screening coordinator, specialist midwife or clinical nurse specialist within 10 days of the result being reported to maternity services.

Household and sexual contacts should be offered screening for HBV by the GP, and vaccinated against HBV if susceptible[1].

All pregnant women with HBV infection should be referred to a specialist (hepatologist/gastroenterologist/virologist/infectious diseases physician or hepatology nurse specialist working within the multidisciplinary team depending upon local practice) and reviewed as per national guidance from Public Health England: Guidance on the hepatitis B antenatal screening and selective neonatal immunisation pathway, Dec 2020[2].

Women newly diagnosed with HBV, and women with known HBV infection and in a high-risk group for HBV vertical transmission during current pregnancy should be offered review by a specialist within 6 weeks of results being reported to maternity services[2] and before 24 weeks GA, whichever is sooner, in order to risk assess and decide upon treatment prior to 24 weeks gestation.

Women identified with chronic HBV infection during pregnancy should have an outpatient appointment within 18 weeks for long-term specialist care .

6. Antenatal monitoring of hepatitis B

6.1 Investigation and monitoring of hepatitis B in pregnancy

Assessment of pregnant women with HBV infection should involve further investigations undertaken in specialist care to determine risk of HBV vertical transmission and severity of liver disease.

6.1.1 Hepatitis B monitoring and risk stratification

6.1.11	**All women newly diagnosed with HBV during pregnancy should have confirmatory HBV serology including HBeAg markers and anti-HBc IgM undertaken**
6.1.12	**All women with HBV infection should also be offered screening for HIV, HCV and hepatitis delta co-infection during pregnancy**
6.1.13	**HBV DNA should be tested in all women with HBV infection prior to 24 weeks GA to inform HBV infectivity status assessment**
6.1.14	**Quantitative HBsAg testing (if available) prior to 24 weeks GA to inform HBV infectivity status assessment**

6.1.15	**Women with HBV DNA >200,000 IU/ml or quantitative HBsAg >4log10 IU/ml should be offered antiviral treatment to reduce risk of HBV vertical transmission from 24weeks GA**

Confirmatory serology should be undertaken to confirm the diagnosis of HBV infection: HBsAg, HBeAg and anti-HBe serological markers should all be tested. Anti-HBc IgM should also be tested in a new diagnosis of HBV infection to determine whether acute HBV has been contracted during pregnancy[11].

Sequencing of HBV in pregnant women, whether they have a new diagnosis or not, is advised to monitor for vaccine escape strains; this is offered free of charge by PHE. An antenatal sampling kit will be provided to the screening team for a surveillance sample to be taken at the screen result follow up appointment (for details, see Guidance for the hepatitis B antenatal screening and selective neonatal immunisation pathway[2]).

Co-infection with other blood-borne viruses may occur and patients diagnosed with HBV should all be offered screening for HIV, HCV and hepatitis delta antibody. If hepatitis delta antibody is positive then hepatitis delta RNA should also be tested. If hepatitis delta RNA is detected clear documentation of hepatitis delta status should be noted although this does not increase vertical transmission.

Once HBV infection is confirmed by serology, risk assessment for HBV vertical transmission should be undertaken. This should include viral load testing for HBV DNA to determine the level of viraemia. Quantitative HBsAg should also be measured if available.

Women in high risk groups for HBV vertical transmission:

- HBeAg positive
- anti-HBe negative
- e markers not known (this should be a rare occurrence)
- HBV DNA >200,000 IU/ml
- quantitative HBsAg >4 log10 IU/ml
- anti-HBc IgM positive

Table 2: High risk groups for HBV vertical transmission

Current European Association for the Study of the Liver (EASL) guidelines[13] recommend antiviral therapy to prevent HBV vertical transmission in women with high HBV DNA (>200,000 IU/ml) or elevated quantitative HBsAg >4 log10 IU/ml, commencing at 24-28 weeks GA.

Treatment of other high risk women during pregnancy to prevent HBV vertical transmission should be considered on an individual case basis by the specialist

team. NICE guidance recommends that women with HBV DNA >10^7 IU/ml should be offered treatment with tenofovir disoproxil to reduce the increased risk of HBV vertical transmission, irrespective of HBeAg status[14].

HBV DNA should be tested before 24 weeks GA, in order to assess HBV vertical transmission risk and aid decision making regarding commencing antiviral treatment and requirement of HBIG for newborn at birth . Quantitative HBsAg can also be tested at the same time, if available. If diagnosed after 24 weeks GA, test HBV DNA as soon as possible.

6.1.2 Assesssment of liver disease

Routine blood tests including full blood count, urea and electrolytes, liver function tests and clotting profile should be undertaken to assess liver function. Alpha fetoprotein is produced by the placenta and should not be used as a screening tool during pregnancy for HCC surveillance.

During 1st trimester, liver ultrasound scanning may be undertaken to assess for chronic liver disease. Transient elastography and scoring systems may be unreliable during pregnancy however arrangements should be made for formal assessment of fibrosis postnatally.

6.2 Complications of hepatitis B in pregnancy

6.2.1 Hepatitis B flares during pregnancy

There are a number of causes of a raised ALT in pregnancy, including obstetric conditions such as HELLP syndrome (haemolysis (H), elevated liver enzymes (EL) and low platelet count (LP)). Elevated ALT in pregnancy may not necessarily be related to HBV, however HBV DNA should be tested to exclude a viral flare.

6.2.2 Management of women with cirrhosis secondary to hepatitis B

Pregnancy in women with cirrhosis is rare and management should be undertaken in conjunction with a specialist hepatology centre.

Women with cirrhosis are at risk of complications from portal hypertension and reduced hepatic synthetic function, including varices, ascites, coagulopathy and encephalopathy. These potential complications should be considered both during pregnancy and in planning for delivery.

In a UK study of 29 women with cirrhosis who had 62 pregnancies, 58% resulted in live birthsand 2/3 of these births were premature deliveries[15]. An Egyptian study of maternal outcomes in pregnant women with cirrhosis has shown increase in rates of hepatic decompensation and mortality compared to non-pregnant women with cirrhosis. Most frequent cause of mortality was variceal bleeding during delivery[16]. Fetal and maternal outcomes are directly related to maternal model for end-stage liver disease (MELD) score at time of conception[17] .

Screening for varices may be undertaken using endoscopy in pregnancy, with optimal timing at 28 weeks. Platelet count may be useful in assessing variceal risk, with 78% sensitivity and 89% specificity for presence of oesophageal varices at endoscopy reported in one study where platelets <110 at conception[18]. Variceal treatment with banding and use of propranolol may both be considered during pregnancy.

Delivery planning should be undertaken with senior anaesthetic, obstetric and hepatology involvement. Caution is advised with Caesarean Section (CS) if abdominal wall varices due to risk of haemorrhage, and ascites may increase risk of poor wound healing and infection post CS. In general, vaginal delivery is not contraindicated due to liver disease, however reduced duration of 2nd stage in women with varices is advised.

6.3 Patient pathway and integration

A multidisciplinary approach should be encouraged when managing pregnant women with viral hepatitis in order to improve health and wellbeing outcomes for the woman and neonate. This should involve empowering women in managing their condition through patient-centred care and ensuring timely delivery of care by the most appropriate clinician. The multidisciplinary plans and a birth plan should be clearly documented in patient notes according to local practice.

Women with uncomplicated HBV infection should be reviewed by the infectious diseases specialist midwife or clinical nurse specialist (CNS) and/or specialist doctor at least twice during the course of their pregnancy. Women receiving antiviral treatment, women experiencing flares or other risk factors may need to be seen more frequently.

Guidance for the hepatitis B antenatal screening and selective neonatal immunisation pathway[2] has been published to provide a guide for providers and commissioners on optimising delivery of these programmes and and enhancing HBV surveillance of pregnant women living with hepatitis B and their babies. This pathway guidance should be followed and read in conjunction with this guidance on the clinical management of the pregnant woman.

6.3.1 First appointment

In women newly diagnosed with HBV infection, the first appointment should occur with the Infectious Diseases Specialist midwife and/or Screening Coordinator midwife within 10 days of HBsAg positive screening result being reported to maternity services. This can be with the specialist midwife if they can see within 10 days.

During this appointment, the team should:

- Discuss and document the natural history of infection with the patient, including recommendation of HBV screening for sexual partners and household contacts
- Perform an initial risk assessment of vertical transmission based upon baseline virology and discuss risk of transmission and role of prophylaxis if high risk (antiviral treatment, vaccination and Hepatitis B Immunoglobulin (HBIG).
- Check that HBV infection status is clearly documented in the maternal notes
- Create a neonatal alert to ensure timely administration of neonatal vaccination on delivery suite within 24 hours of delivery
- Notify patients' GP (as well as CHIS, health visitor) of mother's HBV status and that the infant will need to receive additional doses of hepatitis B vaccine
- Discuss importance of HBV vaccination for the baby and outline vaccination schedule
- Provide patient information leaflets on hepatitis B infection, screening and care in pregnancy and the vaccine which protects babies born to women with hepatitis B.
- Ensure HBIG is ordered, if required, and amend order in case of multiple births or pregnancy loss (see hepatitis B screening and immunisation pathway guidance and HBIG issue request form for ordering HBIG)
- Take additional antenatal blood samples including for HBV DNA testing (if not done already) and PHE antenatal surveillance samples for sequencing (see hepatitis B screening and immunisation pathway guidance)

6.3.2 Second appointment

The second appointment with the specialist team should occur by 24 weeks GA if not with the first appointment or as soon as possible if after 24 weeks GA. At this stage, formal risk assessment of vertical transmission should be undertaken and decision whether antiviral treatment during pregnancy is required should be made.

During this appointment, the specialist should:

- Ensure that the pharmacy, neonatal, and virology teams are aware of the Estimated Due Date (EDD) and the need for vaccine +/- HBIG where indicated.
- Check the availability of HBIG on delivery suite
- Ensure all relevant information is available for delivery team
- Confirm that a process is in place for further follow-up appointments for the mother and the baby, with follow up arranged for the mother with a hepatologist/virologist/infectious diseases specialist according to local practice.

6.4 Special considerations

6.4.1 Antenatal invasive testing

Antenatal invasive testing during the first or second trimester of pregnancy can be undertaken in women with HBV infection. This should happen in a fetal medicine

unit. There are a small number of individual studies assessing the risk of HBV transmission during antenatal invasive testing, and although the risk appears to be low, transmission may occur in women with high viral load and/or positive HBeAg[19]. Benefits of antenatal invasive testing should be balanced against the risk of HBV transmission, however antenatal diagnosis should not be delayed due to concerns regarding HBV transmission risk.

6.4.2 Hepatitis B vaccination in pregnancy

Women who are HBV negative but at ongoing risk of HBV infection during pregnancy for example women who inject drugs or unimmunized women with new sexual partners or with a partner known to have hepatitis B should also be tested for hepatitis B surface antibody levels to determine immunity status. Vaccination should be offered if non-immune or partially immune[1]. Retesting for HBV infection during pregnancy in this patient group should be considered where clinically indicated.

There is no evidence of harm from vaccinating pregnant women[17]. Since the HBV vaccines licensed for use in the UK are recombinant DNA vaccines, the risks to the fetus are likely to be negligible, however vaccination during pregnancy should only be undertaken where there is a definite risk of HBV infection.

There is no value in vaccinating women who are already known to be HBV infected.

7.Use of antiviral therapy for hepatitis B in pregnancy

7.01	**Antiviral therapy for HBV during pregnancy should be offered to women considered at high risk of HBV vertical transmission and those with evidence of liver disease**
7.02	**Tenofovir disoproxil (TD) is currently the preferred choice of antiviral therapy for treatment of hepatitis B during pregnancy**

The majority of women attending antenatal hepatitis clinic will not require antiviral therapy. Antiviral therapy should be considered for women who require treatment of HBV due to liver disease, or in the last trimester where high HBV viral load puts the infant at increased HBV infectivity status. Tenofovir disoproxil (TD) is the recommended treatment for HBV during pregnancy [18] (see section 7.3). Lamivudine and telbivudine have been used in pregnancy in the past, but the lower barrier to resistance as well as FDA classification make these less favourable options.

7.1 Women diagnosed before pregnancy

7.11	**In many women planning to conceive, antiviral treatment of HBV may be deferred, providing there is minimal liver disease**
7.12	**Women on antiviral therapy for HBV prior to pregnancy should continue treatment during and after pregnancy**

7.13	**Women who have conceived on entecavir should be offered the option to switch to TD during pregnancy**

When considering commencing antiviral therapy in women of childbearing age the likelihood of future pregnancy should be taken into account. In many women planning to conceive, antiviral treatment of HBV may be deferred, providing there is minimal liver disease with normal liver function test results[14].

Women who are receiving pegylated interferon alpha for treatment of HBV should be advised regarding use of barrier contraception given FDA category C classification.

Where treatment of HBV is required in a woman of childbearing age, TD is the preferred antiviral agent[15]. This is in view of the more favourable FDA classification (category B) and experience in the first trimester of pregnancy in HIV and/or HBV positive women, where Antiretroviral Pregnancy Register (APR) data have been reassuring in terms of safety[20]. Clinical trials with TD in pregnancy have demonstrated efficacy in reducing HBV vertical transmission [21].

Women who become pregnant whilst on antiviral treatment should be referred urgently to their treating physician for further specialist management. If treatment was required before pregnancy, it should generally be continued during and after pregnancy.

Women who have conceived on entecavir should be offered the option to switch to TD during pregnancy. Effects of entecavir in pregnancy have not been studied in humans, however there is some evidence of carcinogenesis in animal studies at supratherapeutic doses and there is minimal registry safety data available for this agent[22].

Women should be discouraged from stopping antiviral treatment during pregnancy due to concerns regarding drug safety. The risks of a severe hepatitis flare and HBV infectivity status versus the alternative antiviral options and their safety data in pregnancy should be discussed. The maternal HBV DNA should be done in the last trimester to confirm adherence and 36 weeks if concerns about adherence. Where a women insists on stopping antiviral treatment against medical advice during pregnancy close monitoring is essential.

7.2 Women diagnosed for the first time during pregnancy

Women newly diagnosed during pregnancy who require immediate treatment of HBV infection due to liver disease should be offered TD. Treatment will need to be continued in these patients post partum.

7.3 Antenatal antiviral prophylaxis to prevent vertical transmission of hepatitis B

7.31	**Women taking antiviral therapy for prevention of HBV vertical transmission should be stopped by 12 weeks post partum**

Timely neonatal vaccination +/- HBIG are effective in preventing the majority of HBV vertical transmission**.** However, a small proportion of infants born to HBV infected mothers acquire HBV infection despite timely prophylaxis. Estimates vary, but the risk is related to the presence of HBeAg, elevated maternal HBV viral load[23-26] and selection of escape mutants. Maternal HBV viral load greater than 200,000 IU/ml pre-delivery confers up to a 10% risk of transmission despite HBIG and vaccination[27].

Women presenting late should be urgently discussed with a specialist Consultant. The preferred antiviral agent is currently TD (see sections 7.0, 7.1 and 7.2.) Clinical trials are currently in progress to assess impact of TD in 1st and 2nd trimester on HBV transmission[28].

Antiviral therapy should be stopped by 12 weeks post partum if the indication was prevention of HBV vertical transmission. Post treatment monitoring may be indicated due to the risk of hepatitis flares following discontinuation (see section 11.2 Postnatal maternal management).

7.4 Women with previous history of vertical transmission of hepatitis B

These women should be carefully assessed and counselled in the antenatal hepatitis clinic. An antenatal sample from this pregnancy should be sent to the PHE reference laboratory for sequencing for relevant mutations. Antiviral prophylaxis together with vaccination and HBIG for their babies should be discussed on the grounds outlined above.

7.5 Use of antivirals during breastfeeding

HBV can be detected in breast milk, however breastfeeding is not contraindicated in HBV positive mothers in the absence of HIV co-infection so long as the baby is immunised from birth. Women with HBV mono-infection that wish to breastfeed should be counselled regarding the benefits of breastfeeding outweighing the risks of HBV transmission, assuming neonatal vaccination. If a woman choses to breast feed but refuses neonatal vaccination then an individual plan for monitoring for risk of transmission and additional infant testing should be established.

Although breastfeeding while taking TD is not recommended by the manufacturers, peak TD doses in lactating macaques were approximately 2-4% those detected in serum[29]. In human trials, TD concentrations in breast milk of African mothers have also been reported with the median dose ingested via breastfeeding by a 3 kg neonate 0.03% of the TD dose proposed to prevent HIV transmission in neonates[30]. A systematic review concluded that there was no safety-related rationale for discontinuing TD during pregnancy or lactation[31].

Available data suggest that the quantities of TD transmitted in breastmilk are minimal and the benefits of breastfeeding for the neonate should be balanced

against this theoretical risk. To date there is no evidence of teratogenicity from the use of TD in HBV.

8. Obstetric management

8.1 Mode of delivery

8.11	**HBV is not an indication for Caesarean section**

Pregnant women with HBV should be counselled regarding mode of delivery antenatally and encouraged to document their preference in the birth plan. Obstetric factors as well as maternal preference should be taken into account when making this decision. There are few trials comparing vertical transmission rates of HBV from normal vaginal deliveries and elective Caesarean sections which found no difference in transmission rates when infants receive vaccine +/- HBIG. One study found elective caesarian section reduced transmission rates in HBeAg-positive mothers with predelivery levels of HBV DNA $\geq 10^6$ copies/mL Caesarean section should not be recommended solely to avoid HBV vertical transmission[32-33].

8.2 Management of labour

8.21	**Fetal scalp electrodes and fetal blood sampling should be avoided where possible during labour to reduce HBV infectivity status**

A large proportion of HBV vertical transmission occurs during the intrapartum period. Underlying mechanisms may include feto-maternal haemorrhage during contractions, viral transmission after rupture of membranes (ROM) and direct contact of fetus with HBV infected blood and secretions from maternal genital tract during birth passage. Transmission during delivery is most common. Exposure occurs through micro-transfusion or hematologic leaks of mother's blood to the fetus during contractions, or through inoculation of mucosal membranes or breaks in the skin (eg, scalp electrodes). Detection of HBV DNA in cord blood might indicate vertical transmission, but HBV DNA detection could represent maternal-fetal transfusion during labor and delivery or contamination of cord blood samples.

The rate of intrauterine transmission is unknown but considered to be low[32]. The presence of maternal HBeAg is associated with higher HBV DNA levels, and HBeAg is the only structural HBV protein that can pass through the placenta. Some authors speculate HBeAg might establish chronic HBV infection through induction of T-cell tolerance to HBV in utero.

Invasive procedures (fetal blood sampling FBS) and monitoring (fetal scalp electrodes FSE) should be avoided where possible during labour to reduce risk of HBV vertical transmission[3], although there is limited evidence for this and safe delivery of the

baby should be the primary consideration. FSE and FBS are not an indication for HBIG.

8.3 Birthing pools

8.31	**Low-risk women with chronic HBV infection may be considered for delivery in a birthing pool on a case-by-case basis following discussion with the local specialist team**

There are no data to quantify the risk of intrapartum HBV vertical transmission from birthing pools. For low-risk women with chronic HBV infection, delivery in the birthing pool can be considered on a case-by-case basis following discussion in the antenatal period with the virology and neonatal team. Local infection control policies should be followed with regards to cleaning the pool post-delivery.

8.4 Presentation in labour without booking bloods

8.4	**Women presenting in labour with unknown HBV status should be offered urgent HBV testing with results made available within 24 hours.**

Women presenting in labour without booking blood results should be re-offered HBV screening, as well as all other routine booking blood testing including HIV. If consent for testing is obtained, the on call Consultant Virologist/Laboratory responsible locally should be contacted to arrange this urgently and results made available within 24 hours. If available, point of care testing should be considered.

If the mother declines testing, they should be re-offered testing postnatally. In the best interests of the infant, testing for blood-borne viruses (BBV) should ideally be undertaken before the baby goes home, and a first dose of HBV vaccine administered at birth if no maternal HBsAg result is available.

9. Breastfeeding

9.01	**Women monoinfected with HBV can breastfeed providing neonatal prophylaxis is administered within 24 hours of birth**
9.02	**Breastfeeding is discouraged in women with HBV coinfected with HIV**

Women monoinfected with HBV can breastfeed providing neonatal vaccine prophylaxis is administered[32, 35-36]. Guidance on breastfeeding and antiviral therapy for hepatitis B should be discussed with the patient and the specialist team (see section 7.5). Breastfeeding is discouraged if neonatal hepatitis B prophylaxis is refused and in cases of co-infection with HIV (see BHIVA HIV in pregnancy and postpartum guidelines 2020)[37].

10. Neonatal management

10.1 Infant post-exposure prophylaxis

10.11	**All infants born to HBV positive mothers should receive hepatitis B vaccination at birth with subsequent monovalent and hexavalent doses as per the Green Book[1]**
10.1.11	**Infants at high risk of HBV vertical transmission:** • **maternal HBeAg positive** • **maternal anti-HBe negative** • **maternal HBV DNA≥1x10^6 IU/ml at any time during pregnancy** • **acute maternal HBV infection during pregnancy** • **or birthweight ≤ 1500g** **should also receive hepatitis B immunoglobulin (HBIG) ideally within 24 hours of birth to reduce HBV infectivity status**

10.1.1 High risk infants

An infant is classified at high risk of HBV transmission in the following scenarios:

- Maternal HBeAg positive
- Maternal anti-HBe negative
- Maternal HBV DNA ≥1x10^6 IU/ml at any time point during pregnancy
- Evidence of acute maternal HBV infection during pregnancy (Anti-HBc IgM positive)
- Birthweight ≤1500g

These infants need passive immunisation using hepatitis B immunoglobulin (HBIG). HBIG is a blood product, therefore every effort should be made antenatally to obtain full hepatitis B serology, including e markers and HBV DNA to avoid unnecessary administration. HBIG should have been ordered in advance of delivery, based upon blood results during pregnancy, and be available 7 weeks prior to maternal due date. If HBIG is not available at delivery for a baby at high risk of transmission, the Virologist on call should be contacted to arrange urgent supply.

HBIG is indicated for the infant (in addition to vaccine) in situations where the mother is known to be hepatitis B infected but viral load or HBV markers of infectivity for this pregnancy are absent or inconclusive. (See Green Book[1] for details). In these circumstances, an emergency issue of HBIG can be requested.

Active immunisation with HBV vaccine is also required for this group. HBIG and HBV vaccine should each be administered as soon as possible after birth, and certainly within 24 hours of delivery. If delayed, the vaccine should still be given as soon as possible as this is the mainstay of protection; HBIG offers marginal additional benefit.[38-39]

Infants at high risk of vertical transmission should therefore receive:

- 250 IU of HBIG intramuscularly (IM)

AND at a different site

- Engerix B (monovalent HBV vaccine) 0.5ml (10 micrograms) IM OR
- HbVaxPro 0.5 ml (5 microgram) IM

If there is a history of HBV transmission in a previous pregnancy, repeat risk assessment should be undertaken for administration of HBIG. Specialist advice should ideally be sought antenatally in this setting.

Newborn Dried Blood Spot sample and maternal venous sample at birth
A newborn Dried Blood Spot (DBS) test for HBV DNA should be taken on delivery suite from babies born to mothers classified as being at higher infectivity before administration of the vaccine and HBIG. This will generally be done by the delivering midwife. The DBS cards, instructions on collection and pre-paid return envelopes will be provided in the Hep B delivery suite box, which along with the HBIG, will be delivered to maternity units approximately 7 weeks prior to the estimated delivery date.

This surveillance blood sample is different to the newborn blood spot screening sample taken on day 5 after the baby's birth. The mother should be informed that the baby will still need to have the newborn blood spot screen sample on day 5. This surveillance DBS is not subject to the standards or requirements of the newborn blood spot screening programme.

If the woman declines to have maternal serology and / or neonatal DBS taken it should be recorded in her notes and on the completed request forms and returned to PHE Colindale.

For further information on the surveillance e newborn DBS sample and maternal venous sample at delivery, see Guidance for the hepatitis B antenatal screening and selective neonatal immunisation pathway[2].

10.1.2 Low risk infants

Infants of HBV positive mothers not meeting the above criteria should be categorised at low risk of HBV vertical transmission and should receive active immunisation with HBV vaccine as soon as possible after birth, and certainly within 24 hours of delivery. If delayed, the vaccine should still be given as soon as possible. Passive immunisation with HBIG is not required for low risk infants.

Infants at low risk of transmission should therefore receive:

- Engerix B (monovalent HBV vaccine) 0.5 ml (10 microgram) IM OR
- HbVaxPro 0.5 ml (5 microgram) IM

10.1.3 Infants born prematurely

Infants born prematurely to HBV positive mothers should have passive and active immunisation starting at birth if <1500 g.

Public Health England recommends that infants born at or prior to 28 weeks gestation should have respiratory monitoring for 48-72 hours following first dose of HBV vaccine (see Green Book[1]). Should the baby have an apnoea, bradycardia or desaturate then the same monitoring regime should be adhered to in hospital following the second dose[35 phe]. In practice the baby is likely to still be an inpatient at this stage.

Infant vaccination schedule for babies at risk of HBV transmission should subsequently be followed as per chronological age, with next dose of HBV vaccine administered at 4 weeks post delivery[1].

10.1.4 Infants born to hepatitis B negative mother but other household member is hepatitis B infected

Babies born into a household at immediate risk of hepatitis B transmission from non-maternal household contacts should be vaccinated with hepatitis B monovalent vaccine at birth then resume usual childhood vaccination schedule at 8 weeks (see Green Book)[1].

10.2 Infant follow-up

10.21	**All infants born to HBV positive mothers should be tested for evidence of HBV infection by serology for hepatitis B surface antigen (HBsAg) at 12 months of age (chronological), preferably by dried blood spot sample (DBS) in the community**
10.22	**Each infant born to an HBV positive mother should have a named clinician responsible for ensuring that testing is undertaken and results followed up at 14-15 months**
10.23	**Infants diagnosed with HBV (hepatitis B surface antigen positive) should be referred to paediatric viral hepatitis specialist**

Infants at risk of vertical HBV transmission should receive further doses of HBV vaccine according to Public Health England guidance for babies born to HBV infected mothers (see Green Book[1]).

Since the introduction of the HBV containing hexavalent vaccine into the routine childhood immunisation schedule in August 2017, follow up of infants at risk of vertical HBV transmission by their GP should still include the extra HBV monovalent

vaccine doses at 4 weeks and 12 months, but the previously advised HBV booster vaccination at 3 years and 4 months is no longer indicated.

Age	Routine childhood programme	Babies born to hepatitis B infected mothers
Birth	X†	✓Monovalent HepB
4 weeks	X	✓Monovalent HepB
8 weeks	✓DTaP/IPV/Hib/HepB	✓DTaP/IPV/Hib/HepB
12 weeks	✓DTaP/IPV/Hib/HepB	✓DTaP/IPV/Hib/HepB
16 weeks	✓DTaP/IPV/Hib/HepB	✓DTaP/IPV/Hib/HepB
1 year of age	X*	✓Monovalent HepB ✓Test for HBsAg
3 years and 4 months	X*	X*

† Newborn infants born to a hepatitis B negative woman but known to be going home to a household with another hepatitis B infected person may be at immediate risk of hepatitis B infection. In these situations, a monovalent dose of hepatitis B vaccine should be offered before discharge from hospital. They should then continue on the routine childhood schedule commencing at eight weeks.

* Give the recommended vaccines as per the routine schedule

Figure (courtesy of Public Health England): Hepatitis B immunisation schedule for routine childhood and selective neonatal immunisation programmes following introduction of hexavalent hepatitis B containing vaccine and Green Book[1]

Tests should be performed on all infants born to HBV infected mothers to ensure the infant is not infected. PHE offer a free service for dried blood spot (DBS) testing at 12 months, when the booster dose is administered, to check both HBsAg and anti-HBc. Three months after the 6th dose of HBV vaccine (around 15 months of chronological age) infants who have not previously been tested with DBS should have serology for HBsAg assessed. Each infant born to an HBV positive mother should have a named clinician responsible for ensuring testing is undertaken and results followed up. Inform health visitor and local child health information system (CHIS) / child health records department (CHRD) of the child's HBV status.

In children who are hepatitis B surface antigen positive referral should be made to a specialist in paediatric viral hepatitis.

11. Family management

All other household and family members should be tested for HBV infection. Siblings should be referred to a paediatrician specialising in viral hepatitis for testing. Ask the mother about the vaccination status of other members of the household. If there are family members who are unvaccinated or incompletely vaccinated against HBV they will need their serology checked for evidence of HBV infection and non-immune/partially immune members will need vaccination in primary care. All

individuals with ongoing risk of HBV exposure should have booster vaccinations undertaken as per Public Health England (PHE) guidance (see Green Book[1]).

11.1 How to proceed when advice on medical management is declined

Health care professionals providing care for mothers, babies and their families should be offering non-judgemental, culturally-sensitive support at all times. It is rare for situations to arise where discussion and clear information-sharing fails to achieve an agreement with the mother about the appropriate management of the baby.

If for cultural, religious, philosophical or other reasons, the mother or the family are deemed not to be acting in the best interests of their infant, health care professionals have a responsibility under the Children Act 1989 to take action on behalf of the child. For example, if a mother arrives unbooked and refuses rapid tests for blood borne viruses, it is in the best interests of the infant to be tested at birth in order to initiate appropriate management. If the mother or family member with parental responsibility refuses, discuss with a clinician with a specialist knowledge in the field (e.g. paediatric infectious diseases, virologist, hepatologist) and an immediate and urgent referral to the safeguarding team must be made. A member of the safeguarding team may speak to the mother to explain the consequences under British law which makes provision for an urgent Court Order to be sought. When families understand how seriously we take our responsibilities towards the child which could result in them being taken to Court, they may agree to testing and subsequent management. However if they do not, it is important for health care professionals to know that the safeguarding team can seek a magistrate's opinion out-of-hours at any time if the need arises[40].Further advice on managing screening declines and vaccine refusals are in the PHE Guidance on the hepatitis B antenatal screening and selective neonatal immunisation pathway[2].

11.2 Postnatal maternal management

11.21	**All women with HBV should receive postnatal hepatitis follow up within 3 months of delivery**

Women with HBV in pregnancy should be monitored in the postnatal period. Flares may occur, particularly on withdrawal of TD following use in vertical transmission prophylaxis, although are rarely observed. Women should be followed up by 12 weeks unless there are clinical concerns, in which case earlier follow up would be indicated.

12. Areas for future development

There are several areas covered in this guideline which will require specific review in future based upon current research in progress:

- Hepatitis B core-related antigen (HBcrAg) as a non-genotype specific marker for risk stratification[41]
- Prophylactic use of TD in 1st and 2nd trimesters to reduce HBV vertical transmission[16]

Future review of other areas will also be indicated:

- Safety and efficacy of Tenofovir Alafenamide (TAF) in pregnancy
- Indications for HBIG following introduction of antenatal TD prophylaxis to reduce HBV vertical transmission
- Need for HBIG in infants born to mothers who are on long term treatment – HBV DNA VL remains undetectable but they remain HBeAg positive
- Neonatal TD
- Contribution of *in utero* transmission to perinatal transmission

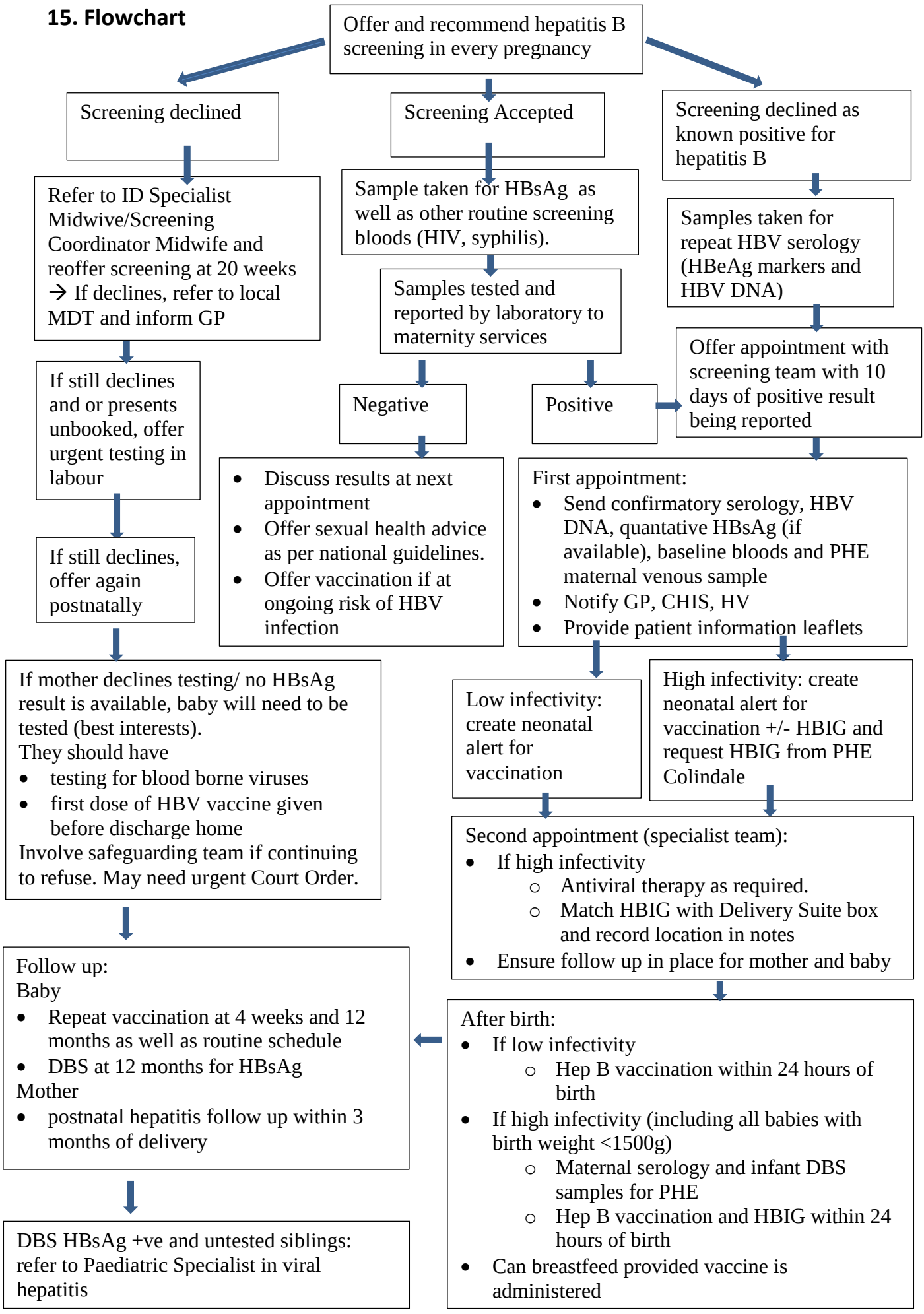
13. Glossary of terms

ALT Alanine Transaminase (liver enzyme)
Anti-HBc: Hepatitis B core antibody
Anti-HBc IgM: Hepatitis B core IgM antibody
Anti-HBe: Hepatitis B envelope antibody
Anti-HBs: Hepatitis B surface antibody
EASL: European Association for the Study of the Liver
EO: Expert Opinion
EDD: Estimated Due Date
FDA: Food and Drug Administration (US)
GA: Gestational Age
HBV: Hepatitis B Virus
HBV DNA: Hepatitis B Virus DNA
HBeAg: Hepatitis B envelope antigen
HBIG: Hepatitis B Immunoglobulin
HBsAg: Hepatitis B surface antigen
HCC: Hepatocellular carcinoma
HCV: Hepatitis C Virus
HIV: Human Immunodeficiency Virus
IDPS: Infectious Diseases in Pregnancy Screening
KPI: Key Performance Indicator
NICE: National Institute for Clinical Excellence
PWID: people who inject drugs
SMI: Standards for Microbiology Investigations
TAF: Tenofovir Alafenamide
TD: Tenofovir disoproxil
UKNSC: UK National Screening Committee
WHO: World Health Organisation

14. Interpretation of HBV serology

Hepatitis B surface antigen	**HBsAg**	Antigen originating from HBV viral envelope (surface). Detection in serum may occur from 40-160 days post infection. Presence of HBsAg indicates that a patient has HBV infection.
Hepatitis B surface antibody	**anti-HBs**	Antibody produced by immune system in response to exposure to HBsAg, including in response to HBV vaccination. Not usually detectable in infected individuals because of immune complexes with HBsAg. Can be used to assess response to HBV vaccination.
Hepatitis B core antibody	**anti-HBc**	Antibody produced by immune system in response to exposure to HBV core antigen. Indicates HBV infection at some time and once produced remains lifelong. In absence of HBsAg suggests past HBV infection and latency of HBV, however in presence of HBsAg indicates chronic HBV infection. Passes across the placenta: maternal anti-HBc detectable in infants up to 15 months of age.
Hepatitis B core IgM antibody	**anti-HBc IgM**	IgM antibody produced by immune system in response to exposure to HBV core antigen. Usually indicates acute HBV infection.
Hepatitis B e antigen	**HBeAg**	Marker of active viral replication. Usually associated with high HBV DNA (viral load)
Hepatitis B e antibody	**anti-HBe**	Antibody produced by immune system in response to exposure to HBeAg. Usually associated with lower HBV DNA (viral load) BUT not always.
Hepatitis B DNA (viral load)	**HBV DNA**	Quantitative level of HBV DNA detected in blood (viral load IU/mL)
Hepatitis B quantitative surface antigen	**Quantitative HBsAg**	Measures titre of HBsAg in blood to guide indication for treatment

15. Flowchart



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