CASE REPORT

Acute painless hepatitis in pregnancy—a cause for concern?

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A 26 year old woman, who was 19 weeks’ pregnant, was referred by her general practitioner with acute onset hepatitis and painless jaundice. She described a four week history of lethargy and palpitations on exertion. She also reported febrile episodes over the past three days, with no other clinical features on systems inquiry.

Her medical history included pre-eclampsia in her first pregnancy, which resulted in induction at 40+1 weeks and a caesarean section. She was taking aspirin at presentation but no other drugs. She had a history of allergy to penicillin and latex, which both caused a rash. She was married with a 2 year old son and worked as a pharmacy dispenser. She reported no recent travel outside the UK, no unusual hobbies, no risk factors for acquiring blood borne viruses, and no contacts with similar symptoms.

Baseline bloods tests showed alanine aminotransferase 1779 U/L (reference range 0-41; 1 U/L=0.02 pkat/L), total bilirubin 65 µmol/L (0-21), albumin 33 g/L (35-50), and prothrombin time of 11.4 s (9.7-11.5). Her full blood count was normal. During admission her transaminases rose and her prothrombin time increased.

Questions

1. What are the viral causes of hepatitis in pregnancy and which are of greatest concern?
2. What are the tests for an acute viral hepatitis?
3. How might this patient have acquired this condition?
4. What infection control measures should be taken?
5. How would you manage this patient?

Answers

1. What are the viral causes of hepatitis in pregnancy and which are of greatest concern?

Short answer

Viral causes include hepatitis A, B, C, D, and E, as well as cytomegalovirus and Epstein-Barr virus. These infections can occur during any trimester. Cytomegalovirus is associated with congenital infection and hepatitis E virus is associated with fulminant hepatitis in pregnancy. In rare cases herpes simplex and varicella zoster viruses can cause hepatitis and are associated with congenital and perinatal infection.

Long answer

Common causes of acute viral hepatitis include hepatitis A, B, C, D, or E virus; Epstein-Barr virus; and cytomegalovirus. The viruses of greatest concern are those that are associated with congenital infection, those that can cause fulminant hepatitis in pregnancy, and blood borne viruses that can be transmitted to the fetus.

Cytomegalovirus is associated with congenital infection. In the United Kingdom, primary infection with cytomegalovirus affects 1-4% of pregnant women who are cytomegalovirus negative (and therefore susceptible), with an overall 40% risk of transmission to the fetus (from 30% in the first trimester to 72% in the third). In the UK, 0.3-1% of babies are infected with cytomegalovirus at birth, and the effects of infection range from no apparent symptoms to cytomegalic inclusion disease. Because treatment may be needed to reduce long term complications, including hearing loss and neurodevelopmental delay, infected neonates must be identified early—a diagnosis can be made by a positive cytomegalovirus polymerase chain reaction (PCR).
in urine or saliva during the first 3 weeks of life. It is difficult to diagnose primary cytomegalovirus in pregnancy, because 80% of pregnant women are asymptomatic and therefore go unnoticed. Currently, there is no screening programme in the UK. 

In rare cases herpes simplex virus and varicella zoster virus can cause hepatitis and are associated with congenital and perinatal infection. In the UK, the risk of primary herpetic simplex virus infection during pregnancy is 3.7%, and there is a 57% risk of neonatal infection if it occurs four to six weeks of delivery (85% peripartum, 10% postnatal, and 5% in utero). The skin, eyes, mucous membranes, and central nervous system can be affected or disease can be disseminated, and intravenous treatment with aciclovir is needed. 2 Severe chickenpox in pregnancy can also be associated with hepatitis, and there is a 1-2% risk of congenital varicella syndrome if gestation is less than 20 weeks. The syndrome is characterised by limb hypoplasia, microcephaly, cataracts, skin scarring, and intrauterine growth retardation.

Although the clinical course of acute viral hepatitis, including hepatitis A, B, C, and D virus, is often unaffected by pregnancy, a more severe course has been described with acute hepatitis E virus (HEV). 3 HEV is the most common cause of acute viral hepatitis in developing countries and is associated with fulminant hepatitis and increased mortality in pregnancy. 4 The increased mortality in pregnancy was first described in the early 1980s. 5 Since then reports have varied, with mortality rates ranging from 0% to 73%. 6 Outcomes are worse in pregnant women with HEV than in those with other causes of acute hepatitis, and various hypotheses have been proposed. 7 Both host and viral factors have been implicated. Significantly higher HEV viral loads have been reported in pregnant patients than in non-pregnant patients. 8 Genotypes 1 and 4 are thought to have a greater association with adverse outcomes, but this has not been proved. Host factors relate to the alteration in immunological status and steroid concentrations during pregnancy. CD4 positive T cell counts are generally lower in HEV positive pregnant women and the ratio of CD4 to CD8 T cells in those with fulminant hepatitis was significantly lower when compared with HEV negative patients or controls. 9 Raised steroid concentrations may enhance viral replication. An acute transaminitis (or hepatic flare) can be seen in pregnant women with pre-existing hepatitis B virus (HBV) or those with an acute infection. The clinical course of acute HBV is not thought to be altered by pregnancy, but there may be an increased risk of developing chronic infection. 10 Furthermore, acute HBV in pregnancy may be associated with low birth weight and prematurity. 11 12 The main clinical concern related to acute HBV infection during pregnancy is the increased rate of vertical transmission. The likelihood of vertical transmission ranges from 10% in early pregnancy to 60% close to the time of delivery. 11 13 14 If a baby acquires HBV at this stage there is a 90% chance of chronicity and thus an increased risk of liver cirrhosis and hepatocellular carcinoma. 10 11 The mainstay of prevention of mother to child transmission is the use of neonatal vaccination, with the addition of HBV immunoglobulin in defined circumstances. Nucleos(t)ides have been given successfully to pregnant women with high levels of HBV DNA (>10^6 IU/mL) and in isolated cases of acute HBV to prevent mother to child transmission. 16 17 In addition to acute viral hepatitis, other causes of deranged liver function tests should be considered. Of note, acute fatty liver of pregnancy can easily be confused with acute viral hepatitis. The table lists the differential diagnosis that should be considered with acute derangement of liver function tests in pregnancy.

2. What are the tests for acute viral hepatitis?

Short answer

A combination of serological and PCR tests is recommended. Serology for hepatitis A, B, and E virus; cytomegalovirus; and Epstein-Barr virus should be requested as well as PCR for hepatitis C virus. The patient tested positive for hepatitis E virus IgM, and this was confirmed by PCR.

Long answer

A combination of serological and PCR tests is recommended for the detection of these viruses in acute hepatitis. Serological screening for acute hepatitis A and E virus, cytomegalovirus, and Epstein-Barr virus looks for specific IgM antibodies. Acute HBV is confirmed by screening with a surface antigen test, and if this is positive all serology markers are tested (HBV e antigen, e antibody, core IgM, total core antibody, and PCR). The detection of HBV core IgM confirms acute infection. Hepatitis D virus is tested only in patients with confirmed HBV, and serology and PCR for hepatitis D virus are recommended. PCR for hepatitis C virus is used in the acute setting, because viraemia precedes the development of hepatitis C virus antibodies, which can take up to three months to develop. The diagnosis of HEV relies mainly on serology. IgM may be detectable as early as the fourth day after the development of jaundice in acute infection, making this the diagnostic test of choice. HEV IgM can persist for up to five months, and is therefore an important serological marker. 11 70% of patients with serological evidence of acute HEV infection are also HEV PCR positive. It is standard practice in our laboratory to test for HEV in all patients with alanine aminotransferase greater than 500 U/L. If there is any difficulty in the serological interpretation or in people who are immunocompromised, confirmatory testing and HEV PCR (performed by Public Health England Colindale) are recommended. Given the increasing rates of HEV in the UK, virology laboratories are re-evaluating their algorithms for routine HEV testing. 17 18 A lack of clinical suspicion and the perception that HEV is still associated only with travel probably result in cases being missed.

3. How might this patient have acquired this condition?

Short answer

There are four main routes of transmission: faeco-oral (contaminated water), zoonotic (food borne), blood transfusion, and vertical. The incidence of autochthonous (locally acquired) cases without a history of foreign travel is increasing in the UK.

Long answer

HEV occurs both sporadically and as an epidemic. The infection has traditionally been associated with travel to endemic regions in the developing world. More recently, it has been recognised that autochthonous (locally acquired) cases associated with genotype 3 occur in the UK and are rising. In 2012, more than 70% of acute HEV infections confirmed at reference laboratories in England and Wales were thought to have been acquired locally. 21 Transmission varies with geographical region and there are four main routes: faeco-oral (contaminated water), zoonotic (food borne), blood transfusion, and vertical.
The faeco-oral route is the main method of transmission worldwide and is associated with genotypes 1 and 2. Epidemic outbreaks occur through faecal contamination of drinking water in the developing world and may lead to infection in travellers. Large outbreaks have been reported in China, India, Somalia, and Uganda.22

By contrast, sporadic cases of genotypes 3 and 4 HEV are increasingly being diagnosed in developed countries.23 These cases are thought to be zoonotic and have been linked to the consumption of food products such as undercooked pork, wild boar, deer, and mussels.23-25 Although no direct evidence exists for pork products being the major source of sporadic transmission of HEV in the UK, the supporting evidence is compelling. Evidence includes the high seroprevalence of anti-HEV IgG (>80%) in British pigs, the high sequence homology between pig and human strains of the virus, and the detection of HEV RNA at several stages in the UK pork food chain.27 29 30

Blood products are known to be a potential source of HEV, but the extent of the risk has yet to be defined. Cases of HEV infection associated with blood transfusion have been reported outside of the UK.31 33 Although no cases have been documented within the UK, the theoretical risk remains because HEV RNA was detectable in 0.7% of pooled UK plasma donation samples tested in 2007.34

The fourth main route of transmission is from mother to child. Vertical transmission occurs in utero and various studies have shown transmission rates of 23-50%.35 36

4. What infection control measures should be taken?

Short answer

The patient should be isolated and barrier nursed as an inpatient during the infectious period.

Long answer

This patient was positive for HEV genotype 1, which is transmitted through the faeco-oral route. Therefore infection control precautions within a hospital setting should include hand washing, nursing in a side room, the use of gloves and gowns by all people in contact with the patient, and attention to personal hygiene.

The duration of infectiveness is unknown, but the virus has been isolated from patients up to two weeks after the resolution of jaundice.37 38 Hand hygiene and infection control measures should therefore be taken for this period. Control measures may be needed for longer in immunocompromised patients, who may shed virus particles for a prolonged period of time. Chronic infection in this cohort is defined as persisting HEV RNA in serum or stools for six months or more. All contacts should be offered screening and advice regarding infection control.

In an outpatient setting the public health risk is thought to be low because hepatitis E does not readily transmit from person to person. Nonetheless, Public Health England currently recommends excluding patients from work or school during the first two weeks of illness but no longer than one week after the onset of jaundice.39

Overall, the main prevention strategies include infection control and vaccination. Infection control is complex because of the multitude of transmission routes but encompasses enhanced provision of clean water in developing countries, adequate sanitation, advice regarding thorough cooking and safe handling of uncooked meat, and safe disposal of pig faeces.

5. How would you manage this patient?

Short answer

Treatment of acute HEV is mainly supportive. Regular clinical and laboratory evaluation is recommended to assess for acute liver failure and early discussion with the local transplant unit may be indicated.

Long answer

Ribavirin has recently been reported to be highly effective in the treatment of solid organ transplants chronically infected with HEV.43 A recent case of acute HEV was treated successfully with ribavirin, and a prospective study has looked at outcomes in both acute and chronic infection. Results were promising, but further data on dosing are needed.44 45 Preclinical data showed a risk of teratogenicity, but human studies have not confirmed this. Nevertheless, its use in pregnancy is recommended by the UK teratology service for life threatening infections only.46

Liver transplantation should be considered in this setting, and a case of transplantation in pregnancy with favourable outcomes for both the mother and baby has been reported.47 Currently, human immunoglobulin has not been shown to prevent HEV infection, even when the immunoglobulin comes from countries where HEV is endemic.48

Vertical transmission through cord blood is recognised to cause miscarriage, stillbirth, and acute hepatitis in newborn babies. A study of 19 newborn babies born to mothers infected with hepatitis E found that 15 had evidence of HEV infection at birth.49 Seven babies died in the first week after birth and all the surviving ones had self limited disease, while none had prolonged viraemia.49
Patient outcome

This patient had confirmed acute hepatitis as a result of HEV infection (IgM and PCR positive). Serial blood tests showed rising transaminases (peak alanine aminotransferase) and prolongation of the prothrombin time (peak prothrombin time), but clinical parameters for the assessment of encephalopathy were negative.

The virus was confirmed as genotype 1 although the patient had not travelled abroad in the three months before her illness. She also had no other identifiable risk factors, including direct contact with a positive source, food worker, or someone who had recently travelled abroad. As far as we are aware this is the first reported case of autochthonous HEV genotype 1 infection in a pregnant woman in the UK.

She was referred to the local transplant unit and transferred for monitoring and supportive measures. Fortunately she did not need a transplant and made a spontaneous clinical recovery. Before referral, treatment with ribavirin was considered, but because of the clinical context, the absence of further clinical deterioration, concerns about teratogenicity, and the lack of efficacious data, the decision was made not to treat.

A baby girl was born at term plus eight days, delivered by vaginal delivery with ventouse assist. The patient required labelato after delivery for pre-eclampsia, but the baby needed no specific treatment. The baby developed complications due to caecele atresia, which has not been described as being associated with HEV infection, and she was confirmed to be HEV PCR negative. Mother and baby are currently and have no long term sequelae from acute HEV in pregnancy.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following interests: none.

Provenance and peer review: Not commissioned; externally peer reviewed.

Patient consent obtained.

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### Table

**Causes of deranged liver function tests in pregnancy*†**

<table>
<thead>
<tr>
<th>Causes</th>
<th>Trimester 1</th>
<th>Trimester 2</th>
<th>Trimester 3</th>
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<tbody>
<tr>
<td>Viruses</td>
<td></td>
<td></td>
<td>- Hepatitis A, B, C, and E virus; EBV and CMV; rarely HSV and VZV</td>
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<tr>
<td>Pregnancy specific causes</td>
<td></td>
<td></td>
<td>- Pre-eclampsia or eclampsia; HELLP syndrome</td>
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<tr>
<td>Hyperemesis gravidarum</td>
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<td>Intrahepatic cholestasis of pregnancy</td>
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<td>Acute fatty liver of pregnancy</td>
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<tr>
<td>Miscellaneous</td>
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<td>- Autoimmune hepatitis, drugs, Budd-Chiari syndrome, hepatic infarction</td>
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</table>

*Pregnancy specific causes typically occur at the particular gestational ages shown, although there are exceptions. In particular, HELLP can occur postpartum.

†CMV=cytomegalovirus; EBV=Epstein-Barr virus; HELLP=haemolysis, elevated liver enzymes, and low platelets; HSV=herpes simplex virus; VZV=varicella zoster virus.