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Overview of infection causing hepatitis other than non-A to E hepatitis virus during pregnancy

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A B S T R A C T

Abnormal liver function tests during pregnancy are common. While hepatic injury during pregnancy mostly has minimal adverse influence on maternal and fetal outcomes, severe maternal and fetal morbidities, and even death, sometimes occur. Here, we review the epidemiology, clinical features, diagnosis, and management of hepatitis during pregnancy caused by the less common pathogens, including Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes simplex viruses (HSVs), dengue fever, malaria, leptospirosis, Q fever, typhoid fever, and other occasional infections, as well as the implications on breastfeeding of the infants. Hepatitis during pregnancy with fever and systemic clinical presentations, which are not attributable to the common infectious agents, should raise the suspicion of infection with above-mentioned pathogens, and appropriate laboratory tests are required. Early recognition of severe hepatitis or acute liver failure is critical in initiating appropriate and specific therapy, together with systemic supportive care, to reduce maternal and fetal mortality and long-term sequelae.

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Introduction

Abnormal liver function tests during pregnancy, which are indicative of hepatitis, are not uncommon. The incidence in pregnant women in developed countries is estimated to be 3–5% [1], but the figures in developing countries are unavailable. Hepatotropic viruses, including hepatitis A, B, C, D, and E viruses (HAV to HEV), are the most common pathogens. The management of hepatitis A to E is covered in other chapters of this issue. Here we focus on the diagnosis and management of hepatitis caused by the less common but still important infectious pathogens during pregnancy. The differentiation of hepatitis A to E from other causes is based on the laboratory tests for viral markers (Table 1). If hepatitis A to E are excluded in a pregnant woman, or if there are symptoms and signs suggestive of other pathogens, uncommon causes should be considered and further laboratory tests are required to establish or exclude these diagnoses. This review aims to provide the quick up-to-date information on the management of the expectant mothers with hepatitis, and therefore, will not cover various aspects of in utero infection by these pathogens.

The occurrence of typical hepatitis symptoms such as fatigue, anorexia, nausea, and vomiting, with or without right upper abdomen pain and/or jaundice, should remind physicians the possibility of hepatitis. However, a considerable proportion of hepatitis patients are asymptomatic, so that, it is important to perform liver function test in pregnant women whenever there is suspicion. Hepatitis is determined based on the elevation of aspartate aminotransferase (AST), alanine transaminase (ALT), and/or bilirubin. In the following sections, hepatitis due to specific pathogens is discussed.

Epstein–Barr virus

EBV, a member of the γ-subfamily of *Herpesviridae*, is transmitted through contact with nasopharyngeal or oral secretions as it replicates mainly in epithelial cells and B cells in the oropharynx. Primary EBV infection occurs mostly during infancy and early childhood. Like other members of *Herpesviridae*, EBV cannot be completely cleared after the primary infection and it can maintain its replication in B cells throughout the life span of its host, resulting in latent infection. By early adulthood, the seroprevalence of EBV immunoglobulin G (IgG) is >90% [2]. Latent EBV infection is associated with nasopharyngeal carcinoma, non-Hodgkin's lymphoma, and Burkitt's lymphoma.

Clinical features

EBV hepatitis occurs mostly during the primary infection and occasionally during the reactivation of latent infection. Primary EBV infection in adolescents and adults frequently causes infectious

Table 1
Serological markers for diagnosing hepatitis A to E.

Viral marker[a]	Clinical implication
Hepatitis A and E	
IgM+/IgG+	Recent infection
IgM-/IgG+	Past infection or convalescence
IgM+/IgG-	False positive or very early phase. Retest after one week: IgG seroconversion, recent infection; otherwise, false positive
Hepatitis B[b]	
HBsAg+/anti-HBc+	Infection
Hepatitis C	
Anti-HCV+	Infection
Hepatitis D[c]	
HBsAg+/anti-HDV+	Infection

[a] A positive result of the nucleic acid of hepatitis viruses in serum detected by real-time qPCR supports the diagnosis but is not essential, and a negative result cannot exclude diagnosis.

[b] HBsAg: hepatitis B surface antigen. Some HBsAg-positive patients are also positive for hepatitis B e antigen, a marker of active viral replication.

[c] HDV is a defective virus that requires HBsAg in its infection.

mononucleosis, characterized by the classic triad of fever, sore throat (tonsillitis and/or pharyngitis), and lymphadenopathy. Around 50–90% of these patients are complicated with hepatitis. Less frequently, EBV can cause hepatic and bacillary injury in the absence of fever and sore throat. Therefore, young pregnant women with unknown hepatitis or jaundice should be ruled out for EBV infection.

EBV hepatitis mostly manifests as asymptomatic elevation of AST/ALT which is self-limiting; but cholestasis occurs occasionally; and very rarely, fatal acute liver failure (ALF) [3]. The levels of AST and ALT are usually mildly elevated to <5 times of the upper limit of normal (ULN), and normalize within 2–3 weeks. Jaundice can be an initial clinical manifestation, with or without fever and abdominal pain. The presentation of ALF associated with EBV is similar to that caused by other agents, including severe jaundice, coagulopathy, hepato-encephalopathy, reduction in liver size, and other severe systemic symptoms.

Diagnosis

The clinical diagnosis of EBV hepatitis may be presumed based on the association of elevated AST/ALT with the classical triad of fever, sore throat, and lymphadenopathy. Lymphocytosis ($\geq 4 \times 10^9$/L) favors the diagnosis. The etiologic diagnosis depends upon laboratory findings of recent EBV infection (Table 2). Detection of antibodies against EBV viral capsid antigen and nuclear antigen is important to differentiate between acute and past infection [4]. Quantification of EBV DNA using cell-free DNA extracted from plasma, rather than from cell-derived DNA, can substantiate the diagnosis of active infection [5].

Effects on the mother and fetus/newborn infant

Generally, the impact of EBV hepatitis on pregnant women is mild [6], but it is dependent upon the severity of hepatitis. Asymptomatic elevation of AST/ALT or mild hepatitis has minimal impact. Moderate to severe hepatitis may result in spontaneous abortion or preterm labor. Very rarely, EBV-associated fulminant hepatitis or hemophagocytic lymphohistiocytosis is life-threatening [7,8]. Maternal EBV infection does not affect breastfeeding.

Table 2
Serological markers for diagnosing EBV, CMV, and HSV.

Viral marker	Clinical implication
EB virus (EBV)[a]	
VCA IgM+/VCA IgG+/EBNA-1 IgG-	Recent infection
VCA IgM-/VCA IgG+/EBNA-1 IgG+	Past infection
VCA IgM+/VCA IgG-/EBNA-1 IgG-	Recent infection or false positive[b]
VCA IgM+/VCA IgG+/EBNA-1 IgG+	Convalescence or reactivation[b]
VCA IgM-/VCA IgG+/EBNA-1 IgG-	Recent or past infection[b]
VCA IgM-/VCA IgG-/EBNA-1 IgG+	Past infection or false positive[b]
VCA IgM-/VCA IgG-/EBNA-1 IgG-	No infection
Cytomegalovirus (CMV)	
IgM-/IgG+	Latent infection
IgM+/IgG+	Active infection[c]
IgM+/IgG-	False positive or very early phase[b]. Retest after 1 week: IgG seroconversion, primary infection; otherwise, false positive
IgM-/IgG-	No infection
Herpes simplex virus (HSV)	
IgM-/IgG+	Latent infection
IgM+/IgG+	Active infection[c]
IgM+/IgG-	False positive or very early phase[b]. Retest after one week: IgG seroconversion, primary infection; otherwise, false positive
IgM-/IgG-	No infection

[a] VCA, viral capsid antigen; EBNA, EB nuclear antigen.
[b] Retest after one week.
[c] CMV IgG avidity index (AI) measurement is helpful to determine primary or recurrent infection. AI≤30%, primary infection; ≥50%, recurrent infection; 30–50%, indeterminate.

Management

Usually, treatment of EBV hepatitis is supportive. Table 3 shows the general recommendation in managing a pregnant woman with hepatitis, which is also applicable for hepatitis associated with other causes. Subclinical and mildly symptomatic hepatitis reflects the functional impairment of widespread changes in the non-necrotic hepatocytes, whereas severe hepatitis or ALF indicates diffuse alterations and necrosis, or even mass necrosis, of hepatocytes. Importantly, hyperbilirubinemia or jaundice, after excluding hemolytic and obstructive causes, is a marker of hepatic necrosis, and when both AST and ALT are significantly increased, the ratio of AST/ALT greater than one (AST/ALT >1) also indicates severe hepatic injury. Untimely and/or inappropriate management of subclinical and mild symptomatic hepatitis may result in severe or fatal hepatitis, particularly during pregnancy. Pregnant women with severe hepatitis should be managed together with infectious diseases physicians and hepatologists. If severe EBV hepatitis during pregnancy is not alleviated after supportive cares for several days, or EBV is highly suspected to be the cause of ALF, steroids and antiviral therapy (acyclovir) can be used [3].

Cytomegalovirus

Human cytomegalovirus (CMV), a member of the β-subfamily of *Herpesviridae*, is ubiquitous throughout the world. Once infection occurs, CMV persists in myeloid cells in a non-replication state leading to the lifelong latent infection (CMV IgG-positive). The prevalence of CMV IgG in women of childbearing age is 40–70% in developed countries and >90–100% in developing countries [9], with most of the primary infection being acquired in the first year of life [10].

Clinical features

Active CMV infection can be due to primary infection, re-infection, or reactivation of latent infection. In pregnant women, primary CMV infection causes flu-like symptoms or persistent fever in nearly a third of the patients, 35% with elevation of AST/ALT [11]. Occasionally, CMV infection during pregnancy may cause typical acute hepatitis, ALF, or HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome-like diseases [12,13]. Therefore, elevation of AST/ALT or presentation of overt hepatic injury with unknown etiology should include active CMV infection in its differential diagnoses.

Diagnosis

The diagnosis of active CMV infection depends upon the detection of CMV immunoglobulin M (IgM) and IgG Table 2). Positivity for both CMV IgM and IgG indicates active infection. Detection of CMV DNA in urine sediment by quantitative polymerase chain reaction (qPCR) can establish an active infection. The avidity index (AI) of CMV IgG is helpful to distinguish primary from recurrent infection (Table 2). Serial tests for CMV IgM and IgG in pregnant women with negative CMV IgG can help to define primary infection when seroconversion of CMV IgG is observed [13].

Table 3
Management recommendation for pregnant women with abnormal liver function tests.

Symptom and sign	AST/ALT	Bilirubin	Recommendation
No	<5 ULN	Normal	Home rest; follow up every 1–2 weeks
No	5–<10 ULN	Normal	Home rest; follow up every 3–4 days
No	≥10 ULN	Normal	Hospitalization
Mild to moderate	<5 ULN	Normal	Home rest; follow up every 3–4 days
Severe	≥5 ULN	Normal	Hospitalization
No	<5 ULN	<2 ULN	Home rest; follow up every 3–4 days
No/mild to moderate	Whatever	≥2 ULN	Hospitalization
Severe	Whatever	≥2 ULN	Hospitalization as soon as possible
Whatever	Whatever	≥5 ULN	Immediate hospitalization

ULN: upper limit of normal.

Effects on the mother and fetus/newborn infant and treatment

Usually, active CMV infection during pregnancy has minimal maternal sequelae. Treatment of CMV with antiviral agents is not indicated because of the side effects on fetus and the self-limiting nature of CMV infection. In the rare circumstance such as ALF, aggressive supportive care becomes important. Although there was one case report showing the value of antiviral therapy (parenteral ganciclovir) in improving liver function [14], it is currently uncertain whether antiviral agents should be used in pregnant women without other immunosuppression conditions [15]. When pregnant women with active CMV infection are co-infected with HIV, anti-CMV therapy favors maternal outcomes.

Breastfeeding

Breastfeeding is the most common route for postnatal CMV infection, because >95% CMV IgG-positive puerperants can shed virus in their breast milk [16]. However, breastfeeding is encouraged for infants with gestational age ≥32 weeks because the transmission has minimal influence on the infants [17]. For extremely low birth weight (<1500 g) preterm infant, the value of breastfeeding outweighs the risks of adverse events; and it is recommended that all preterm infants be fed with mothers' fresh breast milk [18]. Freezing and thawing of the milk can decrease the infectivity of CMV to some extent. Holder pasteurization can almost completely inactivate CMV infectivity.

Herpes simplex virus

HSV contains two types of viruses, HSV-1 and HSV-2. Generally, HSV-1 causes primary oropharyngeal infection and recurrent labial infection, whereas HSV-2 causes primary and recurrent genital (vulva and penis) infection, characterized by local mucocutaneous lesions. Both HSV-1 and HSV-2 can cause HSV hepatitis that is rare, accounting for <1% of all ALF cases and <2% of all viral causes of ALF [19], but it is frequently fatal if treatment is delayed. Pregnant women, particularly in the third trimester, are one of the most vulnerable groups to have HSV hepatitis because of the suppression of cell-mediated immunity.

Clinical features

The clinical presentation of HSV hepatitis is one of the typical hepatitis presentations. ALF associated with HSV is similar to that caused by other causes except that jaundice is mild or moderate, or even absent. The characteristic mucocutaneous lesions are present in fewer than half patients. Some patients with HSV-associated ALF also have involvement of other systems, such as urinary urgency and frequency, or respiratory symptoms, which are not alleviated after antibiotics treatment. Blood tests can reveal progressive deterioration of liver function, leucopenia, thrombocytopenia, and coagulopathy.

Diagnosis

Any pregnant woman with fever, hepatitis symptoms, and abnormal liver functions with unknown cause should be suspected of HSV hepatitis [20]. Detailed history and careful physical examination to detect herpetic lesions are supportive of the diagnosis. Specific laboratory tests, including detection of HSV IgG and IgM (Table 2), HSV DNA in the circulation by polymerase chain reaction (PCR), HSV antigen on smears, and virus culture should be performed. These tests should be repeated if necessary. Liver biopsy is recommended in highly suspected pregnant women. The diagnosis of HSV hepatitis can be established based on the positive results of the above tests, or liver-specific pathologic presentation [21,22].

HSV hepatitis during pregnancy is easily confused with pregnancy-specific liver diseases such as HELLP syndrome and acute fatty liver of pregnancy (AFLP) [23]. However, fever is absent in the latter two conditions, which will be alleviated after pregnancy termination.

Effects on the mother and fetus/newborn infant

The prognosis of HSV hepatitis during pregnancy depends upon the early recognition and initiation of antiviral therapy. Delayed antiviral treatment is associated with higher mortality or requiring liver transplantation [24]. The maternal mortality varies from 20% in antiviral treated women to 67% in delayed or untreated women [25].

Maternal management

Early recognition of HSV hepatitis and prompt antiviral therapy is critical. Empirical treatment with acyclovir (10 mg/kg, IV, every 8 h) should be started when HSV hepatitis is suspected, rather than starting treatment only after the diagnosis is established, because the laboratory tests require several days to provide the results, during which time the disease can worsen rapidly. A few hours' delay in the initiation of antiviral treatment may result in vastly different outcomes [26]. Even if HSV hepatitis is finally ruled out, acyclovir is a pregnancy category B drug and inexpensive; and acyclovir therapy for several days does not have significantly adverse fetal outcome [25,26].

Genital HSV infection can cause transmission of the virus during labor and vaginal delivery, thus cesarean section is recommended, if a pregnant woman has ongoing genital HSV infection.

Management of infants and breastfeeding

Empirical acyclovir treatment for 2–3 weeks in newborn infants of HSV hepatitis mothers is recommended. Breastfeeding is encouraged if the mother is not critically ill because breastfeeding is unlikely to cause neonatal infection [27]. If the mother has lesions on the breast, direct breastfeeding should be temporally avoided; the infant can be bottle-fed after pasteurization of the expressed milk.

Dengue fever

Dengue fever is an acute infection of capillary endothelial cells and monocyte system with dengue virus (a member of *Flaviviridae*) transmitted by mosquitoes. It is endemic in tropical and subtropical regions, particularly in the Asia-Pacific region, Africa, and the Americas and Caribbean region. Infection occurs mainly in children, causing a wide spectrum of diseases from subclinical infection, self-limiting dengue fever, to severe hemorrhagic fever, or even fatal dengue shock syndrome. The incidence in adults is increasing. Dengue fever during pregnancy is not uncommon during epidemic periods. Pregnant women with dengue fever have increased risk of miscarriage, fetal death, preterm birth, and vertical transmission.

Clinical features and diagnosis

Dengue fever is clinically characterized by acute fever, myalgia, arthralgia, and petechiae. Routine laboratory findings are leukopenia, thrombocytopenia, and lymphocytosis. Abnormal liver function tests occur in more than half the patients, sometimes with enlarged liver, which is similar to HELLP syndrome [28]. Therefore, acute febrile pregnant women with hepatic dysfunction should be considered dengue fever in endemic regions during mosquito seasons.

The diagnosis of dengue fever depends upon the detection of non-structural antigen of dengue virus in the early phase (within 1 week after illness onset), or specific IgM and IgG against dengue virus by enzyme-linked immunosorbent assay (ELISA), and/or the virus RNA by reverse-transcription polymerase chain reaction (RT-PCR).

Maternal management

The management of dengue fever during pregnancy is mainly by supportive and symptomatic treatment, including uterine tocolysis if necessary. If indicated, antipyretic therapy with acetaminophen (paracetamol) is recommended. However, a recent randomized, double-blind, placebo-controlled trial

demonstrated that use of standard dose acetaminophen increases the incidence of hepatic injury [29]. Since acetaminophen is the most common cause of drug-induced ALF in the United States and Europe, it should be judicious in the use of acetaminophen in dengue fever. On the other hand, although nonsteroidal anti-inflammatory drugs are not recommended in dengue fever because of potentially increased bleeding risk in the presence of thrombocytopenia, systemic review shows that ibuprofen, a drug with the lowest bleeding risk, appears to have equivalent or superior antipyretic activity and comparable safety [30]. Additionally, uterine inhibition with tocolytic treatment in pregnant women with preterm labor during severe dengue fever could be beneficial for both mothers and infants [31].

Breastfeeding

Dengue virus can be detected in breast milk [32,33]. Animal studies show that dengue virus can be transmitted by milk [34], and one infant was infected with dengue virus probably by breastfeeding [32]. Thus, direct breastfeeding should be avoided when the mother is in the acute phase; however, infants can receive pasteurized breast milk. As dengue viremia is usually short [35], direct breastfeeding appears to be safe 10 days after illness onset in the mother.

Malaria

Malaria, caused by *Plasmodium*, mainly occurs in tropical and subtropical developing areas due to the presence of mosquitoes. Africa has the highest prevalence of malaria. Rural areas of some countries in South Asia and South America also have relatively high infection rate. In addition, travelers from areas without malaria are at risk of malaria transmission when they go to the endemic areas. Because the immunological changes occur during pregnancy and *Plasmodium falciparum* has tropism for the placenta, pregnant women are one of the groups who are most vulnerable to acquire malaria, and have a higher risk of developing severe malaria [36].

Clinical features

Malaria has typical presentation with myalgia, shaking chills, high fever, and sweating. Hepatic injury is also a clinical feature as 15–22% of acute malaria have abnormal liver function tests [37,38]. Some pregnant women infected with malaria can present with atypical presentations such as only fever with abnormal liver function tests and low platelets [39], or a picture similar to HELLP syndrome [40,41]. Therefore, a febrile pregnant woman with hepatic injury should raise the suspicion of malaria in endemic areas. A detailed history of travelling to endemic areas, or working in international airports, transportation ports or seaports, where exposure to mosquitoes carrying the parasites is possible, favors further tests to rule out the diagnosis [40]. In addition, asymptomatic malarial infection can be maintained in the host for more than 1 year, and then reactivates during pregnancy [39], thus highlighting the importance of taking a detailed and extended travel history when malaria is suspected.

Diagnosis

Microscopy of stained thick and thin blood smears to find *Plasmodium* is the gold standard to define malaria. If negative, blood smears should be repeated several times in the next days. Rapid diagnostic test by detecting histidine-rich protein 2 and 3 antigens in blood and/or urine can also be used. Detection of malaria DNA by real-time qPCR is most sensitive. Additionally, diagnostic therapy can be tried in the cases with highly suspected women without laboratory evidence of malaria infection.

Effects on the mother and fetus/newborn infant

Maternal malaria can cause adverse pregnancy and birth outcomes because malaria parasites can preferentially accumulate in placental intervillous spaces. If treatment is delayed or not provided, maternal death can occur in over 25% of the cases infected with *P. falciparum*. Maternal malaria can

cause intrauterine growth retardation, low birth weight, stillbirth, and fetal death. In endemic regions, maternal malaria accounts for 12–20% of the total stillbirths [42].

Management and breastfeeding

Pregnant women with malaria should receive antimalarial treatment. The choice of antimalarials depends upon the trimester, malaria parasite species, severity, and complications [42]. Artemisinins are most effective. Because of the embryotoxicity and teratogenicity in experimental animal models, World Health Organization (WHO) does not recommend use them in the first trimester in women without complications. However, artemisinins are recommended in the first trimester for severe malaria due to the high maternal mortality. The infants born to mothers with malaria who had received antimalarial therapy can receive breastfeeding. Exclusive breastfeeding is protective against infant malaria [43].

Leptospirosis

Leptospirosis, caused by pathogenic *Leptospira* species, is a zoonosis and is endemic in subtropical and tropical countries. Human leptospirosis mostly occurs in individuals by close contact with domestic livestock and their products, particularly after natural flood calamities. The incidence varies substantially, ranging from 0.1 to 1/100,000 persons in non-endemic areas to 10–100/100,000 persons in tropical endemic areas [44]. Leptospirosis in pregnancy is rare, but can result in devastating effects on the woman and fetus.

Clinical features and effect on mothers and fetus

The clinical features of leptospirosis vary widely, ranging from subclinical infection to severe conditions that are characterized by hepatic or renal failure or pulmonary hemorrhage with high mortality. Fever and toxemia invariably exist in overt leptospirosis. Weil's syndrome, a severe form of leptospirosis characterized by progressive course of jaundice, hemorrhage, hepatic, and renal failure, and high mortality [44], can mimic HELLP syndrome or AFLP [45,46]. Therefore, a pregnant woman with fever, toxemia, and hepatic injury should have leptospirosis ruled out in endemic areas.

Diagnosis

Routine laboratory tests for leukocytosis, thrombocytopenia, and proteinuria should be performed on pregnant women with suspected leptospirosis. Microscopic hemagglutination test for *Leptospira* titers or ELISA for leptospiral IgM is pathogen-specific, and positive results usually confirm the diagnosis. Detection of the nucleic acid of *Leptospira* by real-time PCR is more sensitive [47].

Management

Delayed use of antibiotics may lead to severe maternal and fetal morbidity and mortality. Therefore, early recognition and administration of antibiotics as well as systemic supportive care are critical. Penicillin is the first choice because it is safe and can pass through the placental barrier. But if allergic to penicillin, ceftriaxone is the alternative as it can also efficiently pass into the fetus. Streptomycin, doxycycline, chloramphenicol, and erythromycin are effective in non-pregnant patients, but these may be harmful to the fetus or cannot efficiently pass through the placenta barrier, and therefore should be avoided during pregnancy. Physicians should be alerted to the possibility of Jarisch–Herxheimer reaction during treatment with antibiotics [48].

Breastfeeding

Leptospira species exists in milk of puerpera with leptospirosis because it can go everywhere in the host. However, antibiotic treatment is highly effective to clear the *Leptospira* in the host. A mother who has been treated with antibiotics for 5–7 days can safely breastfeed her baby.

Q fever

Query (Q) fever is a zoonosis caused by *Coxiella burnetii* (*C. burnetii*), which replicates only inside cells. *C. burnetii* is mainly transmitted by inhalation of contaminated aerosol. The common source of human infection is farm animals, such as cattle, goats, and sheep, which shed the organisms in urine, feces, milk, and, particularly in amniotic fluid and the placenta. Consumption of unpasteurized animal milk can also cause transmission. In addition, pets, particularly cats, have been considered as an important potential infection source of Q fever in urban areas. *C. burnetii* can exist in natural environments for several weeks and can be spread by wind. Therefore, Q fever can occur in individuals without animal contact history.

The incidence of human Q fever is unknown in most countries because of poor surveillance. Q fever in pregnancy is uncommon, with an estimated incidence of 0.2–0.5% in some areas of France [49], but it can cause severe obstetric complications, such as spontaneous abortion, intrauterine growth retardation, fetal death, preterm birth, and others [50,51].

Clinical features

Most (~60%) cases of *C. burnetii* infections are asymptomatic. The clinical features of symptomatic Q fever are nonspecific, such as self-limited fever, flu-like illness, with a varied proportion of hepatitis, pneumonia, or involvement of other systems. Hepatitis may occur in 18–85% hospitalized patients [52,53]. In addition, in the pregnant women, asymptomatic infection appears to be more frequent that in non-pregnant women [54]. The hepatitis is usually mild to moderate (AST/ALT elevation <5 UNL). Q fever should be suspected in pregnant women with unknown abnormal liver function tests, particularly in endemic areas and/or in those with animal contact histories.

Diagnosis

Diagnosis of Q fever relies on laboratory tests. The immunofluorescence assay (IFA) for detecting IgM and IgG antibodies against phase II (acute infection) and phase I (chronic infection) antigens of *C. burnetii* is the reference method. The ELISA for specific IgM and IgG can be also used, but the positive results usually require further IFA validation. If necessary, the ELISA or IFA should be repeated. Detection of *C. burnetii* DNA by PCR in patients' samples, even in paraffin-embedded tissues and frozen samples, can be used to diagnose Q fever.

Management and breastfeeding

Doxycycline is the first line treatment for Q fever, but it is contraindicated during pregnancy. Cotrimoxazole (trimethoprim and sulfamethoxazole) is usually used to treat Q fever in pregnancy and the duration requires at least 5 weeks or even for the whole duration of pregnancy [55–57]. Recently, roxithromycin was reported to be effective to treat Q fever during pregnancy [58].

To date, there is no report on the issue of whether breastfeeding can transmit Q fever in human. However, in theory, breastfeeding may transmit Q fever because the milk from animals with Q fever has viable *C. burnetii* [59]. Thus, breastfeeding should be avoided if the mother with Q fever is not treated.

Typhoid fever

Typhoid fever, caused by *Salmonella enterica* (*S. enterica*) *serotype Typhi*, is endemic in developing countries, with estimation by the WHO of annually 11–22 million cases and 128,000–161,000 deaths worldwide [60].

Clinical features

Generally, typhoid fever has typical clinical features such sustained fever, bradycardia relative to fever, "rose spots," and neutropenia. However, the clinical presentation of typhoid fever during pregnancy may be atypical, often presenting with remittent or irregular fever, mild to moderate elevation of ALT and AST, splenomegaly, and/or hepatomegaly. A pregnant woman with fever over 1 week and abnormal liver function tests should be suspected of typhoid fever, particularly in an endemic area or having travel history to an endemic area.

Diagnosis

Bacterial blood culture is the gold test to confirm typhoid fever. Additionally, a positive result for DNA of *S. enterica serotype Typhi* in blood, urine, or feces by PCR, in combination of clinical presentations, can also indicate the diagnosis. Widal agglutination test is suboptimal in its sensitivity and specificity; however, this test is inexpensive and is still useful to define typhoid fever in resource-limited regions. A positive Widal test has H antigen agglutinin titers $\geq$160 and O antigen agglutinin titers $\geq$80. A febrile patient with positive Widal test, particularly high O agglutinin titers, is likely to have typhoid fever.

Management and breastfeeding

Because more than half of untreated typhoid fever during pregnancy can cause fetal infection, antibiotics that can efficiently pass through the placental barrier should be used during pregnancy. Quinolones have adverse effects on fetus, thus they are contraindicated during pregnancy and lactation. Ceftriaxone, a third generation cephalosporin, is effective in most typhoid fever during pregnancy. If the pathogen is drug-resistant, choice of antibiotics is dependent upon the results of antimicrobial susceptibility testing. No transmission of typhoid fever has been reported to be associated with breastfeeding after the patient is treated.

Other occasional infections giving rise to hepatic inflammation

Varicella–zoster virus

Varicella–zoster virus (VZV), a member of the α-subfamily of *Herpesviridae*, usually causes self-limiting infection in children as chickenpox. VZV cannot be completely cleared by its host. Reactivation of VZV is not uncommon during pregnancy, presenting with herpes zoster, a localized vesicular eruption. Occasionally, abnormal liver function tests may occur with the reactivation of VZV, with mild to moderate elevation of AST/ALT. ALF associated with primary infection or reactivation of VZV has been reported in immunocompromised patients [61,62]. A presumptive clinical diagnosis can be made based on the typical localized vesicular eruption and abnormal liver function tests. The etiologic diagnosis requires detection of VZV DNA in liver biopsy by PCR or VZV antigen by immunohistochemistry or IFA. Asymptomatic or mildly symptomatic elevation of liver enzymes has minimal influence on the fetus and does not need hospitalization, but requires regular follow-up. Intravenous acyclovir is recommended only in severe disseminated VZV infection.

Yellow fever

Yellow fever, caused by the yellow fever virus, is a mosquito-borne flavivirus disease. Almost all yellow fever occurs in tropical South America and Saharan Africa. The disease is characterized by fever, chills, headache, myalgia, hemorrhage, coagulopathy, neutropenia, and elevated AST and ALT with hyperbilirubinemia. About 10–15% of the patients can progress to severe yellow fever, with the mortality as high as 20–50% [63]. Yellow fever may occasionally occur during pregnancy.

A pregnant woman with fever and hyperbilirubinemia, living in or recent travelling to tropical South America or Saharan Africa, should be suspected of yellow fever. The detection of yellow fever virus RNA in the circulation by RT-PCR can confirm the disease. Detection of yellow fever virus-specific IgM and neutralizing antibodies is more commonly used in the diagnosis; the specific IgM alone is not enough to define a case because of the cross-reactive with other flaviviruses [64]. Because of similar clinical presentations, yellow fever is easily confused with malaria, leptospirosis, viral hepatitis, other hemorrhagic fever, and infection with other flaviviruses like dengue fever. Differential diagnosis should include these diseases.

Co-infections

Childbearing age women have very high prevalence of latent infection of EBV, CMV HSV, and VZV. Reactivation of two or more viruses is possible, particularly in pregnant women infected with HIV. Thus, in defining the cause of unknown abnormal liver function tests during pregnancy, these etiologic agents should be considered in the differentiation diagnosis.

Malaria, Q fever, leptospirosis, dengue, yellow fever, and typhoid fever are endemic in tropical or subtropical regions. Therefore, pregnant women with abnormal liver function tests can potentially be associated with dual or multiple pathogen infections. In the Brazilian Amazon, 2.8% of the hospitalized patients were co-infected with dengue and malaria, causing more severe clinical presentations [65]. Co-infection of influenza A virus and dengue virus during pregnancy caused fatal complications [66], suggesting that accepting a single diagnosis, especially in countries endemic to multiple tropical diseases, may delay the recognition and treatment of other pathogens in pregnant patients.

Summary

Hepatic injury or hepatitis during pregnancy caused by non-A to E hepatitis viruses is less common but still important because of its potential severity, and similarity to HELLP syndrome or AFLP, and the high mortality in some cases. Unknown hepatic injury during pregnancy, symptomatic or otherwise, should be closely monitored. Symptomatic hepatitis with fever and systemic clinical presentations should raise the suspicion of the aforementioned uncommon pathogens, and further laboratory tests are necessary to determine the etiology. Early recognition of severe hepatitis or ALF is critical in reversing the course by early initiation of specific therapy and systemic supportive care.

Declaration of Competing Interest

The author has no conflicts of interest to report.

Practice points

- A pregnant woman with elevated AST/ALT and/or hyperbilirubinemia requires laboratory tests to clarify the cause.
- In addition to hepatitis A to E viruses, less common pathogens, including EBV, CMV, HSV, VZV, dengue fever, Q fever, yellow fever, malaria, leptospirosis and typhoid fever, can also cause hepatitis during pregnancy.
- A pregnant woman with fever, systemic toxemia, and hepatic injury should be suspected of infection with above less common pathogens.
- Early recognition of severe hepatitis and ALF is critical in the immediate commencement of specific and supportive treatments to improve maternal and fetal outcomes.
- Mothers infected with above less common pathogens usually can breastfeed their infants after appropriate treatment.

Research agenda

- More research is required to differentiate HELLP syndrome or AFLP like disease associated with less common pathogens from pregnancy-specific liver diseases.
- Early markers indicative of severe hepatitis and ALF associated with HSV should be explored.
- The choice of antipyretic drugs in treating febrile pregnant women with dengue fever and hepatic injury warrants further studies.

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References

*[1] Tran TT, Ahn J, Reau NS, ACG Clinical Guideline. Liver disease and pregnancy. Am J Gastroenterol 2016;111(2):176–94.
[2] Cohen JI. Epstein-Barr virus infection. N Engl J Med 2000;343(7):481–92.
*[3] Crum NF. Epstein Barr virus hepatitis: case series and review. South Med J 2006;99(5):544–7.
[4] De Paschale M, Clerici P. Serological diagnosis of Epstein-Barr virus infection: problems and solutions. World J Virol 2012;1(1):31–43.
[5] Kanakry JA, Hegde AM, Durand CM, Massie AB, Greer AE, Ambinder RF, et al. The clinical significance of EBV DNA in the plasma and peripheral blood mononuclear cells of patients with or without EBV diseases. Blood 2016;127(16):2007–17.
[6] Avgil M, Ornoy A. Herpes simplex virus and Epstein-Barr virus infections in pregnancy: consequences of neonatal or intrauterine infection. Reprod Toxicol 2006;21(4):436–45.
[7] Ontanilla Clavijo G, Praena Segovia J, Gallego Á Giráldez, Cordero Matía ME, Sousa Martín JM. Severe acute hepatitis and cold agglutinin-related hemolytic anemia secondary to prime infection with Epstein-Barr virus. Rev Esp Enferm Dig 2017;109(5):388–90.
[8] Sarkissian S, Khan Y, Farrell D, Constable D, Brem E. Hemophagocytic lymphohistiocytosis in the setting of HELLP Syndrome. Clin Case Rep 2018;6(12):2466–70.
*[9] Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol 2010;20(4):202–13.
[10] Chen J, Hu L, Wu M, Zhong T, Zhou YH, Hu Y. Kinetics of IgG antibody to cytomegalovirus (CMV) after birth and seroprevalence of anti-CMV IgG in Chinese children. Virol J 2012;9:304.
*[11] Nigro G, Anceschi MM, Cosmi EV, Congenital Cytomegalic Disease Collaborating Group. Clinical manifestations and abnormal laboratory findings in pregnant women with primary cytomegalovirus infection. BJOG 2003;110(6):572–7.
[12] Chan Y, Kean-Chong M, Gonzalez D, Apuzzio J. Cytomegalovirus hepatitis during pregnancy. Infect Dis Obstet Gynecol 1995;3(4):164–5.
[13] Ohkuchi A, Minakami H, Suzuki I, Ayustawati Izumi A, Sato I. Liver dysfunction in late pregnancy: cytomegalovirus-induced hepatitis or the HELLP syndrome? J Obstet Gynaecol Res 2001;27(6):319–23.
[14] Miguelez M, Gonzalez A, Perez F. Severe cytomegalovirus hepatitis in a pregnant woman treated with ganciclovir. Scand J Infect Dis 1998;30(3):304–5.
[15] Rogan SC, Beigi RH. Treatment of viral infections during pregnancy. Clin Perinatol 2019;46(2):235–56.
[16] Hamprecht K, Maschmann J, Vochem M, Dietz K, Speer CP, Jahn G. Epidemiology of transmission of cytomegalovirus from mother to preterm infant by breastfeeding. Lancet 2001;357(9255):513–8.
[17] Zhu X, Chen L, Liu L, Xu C, Xu B, Xu B, et al. Effect of different feeding patterns and delivery modes on cytomegalovirus infection in infants and their outcomes. Chin J Prev Med 2017;20(8):571–6 [in Chinese].
*[18] Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics 2012;129(3):e827–41.
[19] Brennan PN, Donnelly MC, Simpson KJ. Systematic review: non A-E, seronegative or indeterminate hepatitis; what is this deadly disease? Aliment Pharmacol Ther 2018;47(8):1079–91.
[20] Masadeh M, Shen H, Lee Y, Gunderson A, Brown K, Bellizzi A, et al. A fatal case of herpes simplex virus hepatitis in a pregnant patient. Intractable Rare Dis Res 2017;6(2):124–7.
[21] Nienaber JH, McNamara DR, Banerjee R, Pritt BS, Karre T, Sohail MR. Fulminant gestational hepatitis due to primary herpes simplex type 2 infection: use of serum HSV polymerase chain reaction for noninvasive diagnosis. Diagn Microbiol Infect Dis 2012;72(2):181–4.
[22] Halliday J, Lokan J, Angus PW, Gow P. A case of fulminant hepatic failure in pregnancy. Hepatology 2010;51(1):341–2.
[23] White WM, Tran D, Garovic VD, Brost B. Acute interstitial nephritis proteinuria and herpes simplex virus hepatitis in pregnancy mimic HELLP syndrome (Hemolysis, Elevated Liver Enzymes, Low Platelets). AJP Rep 2011;1(2):115–8.
[24] Norvell JP, Blei AT, Jovanovic BD, Levitsky J. Herpes simplex virus hepatitis: an analysis of the published literature and institutional cases. Liver Transplant 2007;13(10):1428–34.
[25] Kang AH, Graves CR. Herpes simplex hepatitis in pregnancy: a case report and review of the literature. Obstet Gynecol Surv 1999;54(7):463–8.

*[26] Navaneethan U, Lancaster E, Venkatesh PG, Wang J, Neff GW. Herpes simplex virus hepatitis - it's high time we consider empiric treatment. J Gastrointestin Liver Dis 2011;20(1):93–6.
[27] No authors listed. ACOG practice bulletin. Management of herpes in pregnancy. Number 8 October 1999. Clinical management guidelines for obstetrician-gynecologists. Int J Gynaecol Obstet 2000;68(2):165–73.
[28] Chhabra A, Malhotra N. Anesthetic management of a pregnant patient with dengue hemorrhagic fever for emergency cesarean section. Int J Obstet Anesth 2006;15(4):306–10.
*[29] Vasikasin V, Rojdumrongrattana T, Chuerboonchai W, Siriwiwattana T, Thongtaeparak W, Niyasom S, et al. Effect of standard dose paracetamol versus placebo as antipyretic therapy on liver injury in adult dengue infection: a multicentre randomised controlled trial. Lancet Glob Health 2019;7(5):e664–70.
[30] Kellstein D, Fernandes L. Symptomatic treatment of dengue: should the NSAID contraindication be reconsidered? Postgrad Med 2019;131(2):109–16.
[31] Escobar MF, Mora BL, Cedano JA, Loaiza S, Rosso F. Comprehensive treatment in severe dengue during preterm and term labor: could tocolysis be useful? J Matern Fetal Neonatal Med 2019. :[Epub ahead of print].
[32] Barthel A, Gourinat AC, Cazorla C, Joubert C, Dupont-Rouzeyrol M, Descloux E. Breast milk as a possible route of vertical transmission of dengue virus? Clin Infect Dis 2013;57(3):415–7.
[33] Arragain L, Dupont-Rouzeyrol M, O'Connor O, Sigur N, Grangeon JP, Huguon E, et al. Vertical transmission of dengue virus in the peripartum period and viral kinetics in newborns and breast milk: new data. J Pediatric Infect Dis Soc 2017;6(4):324–31.
[34] Mann TZ, Haddad LB, Williams TR, Hills SL, Read JS, Dee DL, et al. Breast milk transmission of flaviviruses in the context of Zika virus: a systematic review. Paediatr Perinat Epidemiol 2018;32(4):358–68.
[35] Tang KF, Ooi EE. Diagnosis of dengue: an update. Expert Rev Anti Infect Ther 2012;10(8):895–907.
[36] Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. N Engl J Med 2014;370(23):2211–8.
[37] Woodford J, Shanks GD, Griffin P, Chalon S, McCarthy JS. The dynamics of liver function test abnormalities after malaria infection: a retrospective observational study. Am J Trop Med Hyg 2018;98(4):1113–9.
[38] Kaeley N, Ahmad S, Shirazi N, Bhatia R, Bhat NK, Srivastava S, et al. Malarial hepatopathy: a 6-year retrospective observational study from Uttarakhand, North India. Trans R Soc Trop Med Hyg 2017;111(5):220–5.
[39] Milne K, Dallard T, Douglas JG. Fever of unknown origin in pregnancy: the need for a full history. BMJ Case Rep 2012;2012:bcr2012006307.
[40] Tournoy J, Dapper I, Spitz B, Meersseman W, Van Wijngaerden E, Lagrou K, et al. Haemolysis, elevated liver enzymes, and thrombocytopenia in a 34-year-old pregnant woman. Lancet 2006;368(9529):90.
[41] Ducarme G, Thuillier C, Wernet A, Bellier C, Luton D. Malaria in pregnant woman masquerading as HELLP syndrome. Am J Perinatol 2010;27(2):171–2.
*[42] Bauserman M, Conroy AL, North K, Patterson J, Bose C, Meshnick S. An overview of malaria in pregnancy. Semin Perinatol 2019;43(5):282–90.
[43] Brazeau NF, Tabala M, Kiketa L, Kayembe D, Chalachala JL, Kawende B, et al. Exclusive breastfeeding and clinical malaria risk in 6-month-old infants: a cross-sectional study from Kinshasa, Democratic Republic of the Congo. Am J Trop Med Hyg 2016;95(4):827–30.
*[44] Puliyath G, Singh S. Leptospirosis in pregnancy. Eur J Clin Microbiol Infect Dis 2012;31(10):2491–6.
[45] Baytur YB, Lacin S, Koyuncu FM, Cabuk M, Cabuk M, Ceylan C, et al. Weil's syndrome in pregnancy. Eur J Obstet Gynecol Reprod Biol 2005;119(1):132–3.
[46] Gaspari R, Annetta MG, Cavaliere F, Pallavicini F, Grillo R, Conti G, et al. Unusual presentation of leptospirosis in the late stage of pregnancy. Minerva Anestesiol 2007;73(7–8):429–32.
[47] Alia SN, Joseph N, Philip N, Azhari NN, Garba B, Masri SN, et al. Diagnostic accuracy of rapid diagnostic tests for the early detection of leptospirosis. J Infect Public Health 2019;12(2):263–9.
[48] Butler T. The Jarisch-Herxheimer reaction after antibiotic treatment of spirochetal infections: a review of recent cases and our understanding of pathogenesis. Am J Trop Med Hyg 2017;96(1):46–52.
[49] Mboussou Y, Jaubert J, Larrieu S, Atiana L, Naze F, Folio C, et al. Pregnancy outcomes of Q fever: prospective follow-up study on Reunion island. BMC Infect Dis 2019;19(1):1001.
[50] Million M, Roblot F, Carles D, D'Amato F, Protopopescu C, Carrieri MP, et al. Reevaluation of the risk of fetal death and malformation after Q Fever. Clin Infect Dis 2014;59(2):256–60.
[51] Ghanem-Zoubi N, Paul M. Q fever during pregnancy: a narrative review. Clin Microbiol Infect 2019 [Epub ahead of print].
[52] Rodríguez-Alonso B, Almeida H, Alonso-Sardón M, López-Bernus A, Pardo-Lledias J, Velasco-Tirado V, et al. Epidemiological scenario of Q fever hospitalized patients in the Spanish Health System: what's new. Int J Infect Dis 2019;90:226–33.
[53] Chang K, Lee NY, Chen YH, Lee HC, Lu PL, Chang CM, et al. Acute Q fever in southern Taiwan: atypical manifestations of hyperbilirubinemia and prolonged fever. Diagn Microbiol Infect Dis 2008;60(2):211–6.
[54] Tissot-Dupont H, Vaillant V, Rey S, Raoult D. Role of sex, age, previous valve lesion, and pregnancy in the clinical expression and outcome of Q fever after a large outbreak. Clin Infect Dis 2007;44(2):232–7.
*[55] Raoult D, Fenollar F, Stein A. Q fever during pregnancy: diagnosis, treatment, and follow-up. Arch Intern Med 2002;162(6):701–4.
[56] Carcopino X, Raoult D, Bretelle F, Boubli L, Stein A. Managing Q fever during pregnancy: the benefits of long-term cotrimoxazole therapy. Clin Infect Dis 2007;45(5):548–55.
[57] Carcopino X, Raoult D, Bretelle F, Boubli L, Stein A. Q Fever during pregnancy: a cause of poor fetal and maternal outcome. Ann N Y Acad Sci 2009;1166:79–89.
[58] Coste Mazeau P, Hantz S, Eyraud JL, Donadel L, Lacorre A, Rogez S, et al. Q fever and pregnancy: experience from the limoges regional university hospital. Arch Gynecol Obstet 2016;294(2):233–8.
[59] Barandika JF, Alvarez-Alonso R, Jado I, Hurtado A, García-Pérez AL. Viable Coxiella burnetii in hard cheeses made with unpasteurized milk. Int J Food Microbiol 2019;303:42–5.
[60] World Health Organization (WHO). Typhoid. Geneva: WHO [Accessed: December 16, 2019]. Available from: https://www.who.int/immunization/diseases/typhoid/en/.

[61] Zandvakili I, Lloyd JW, Giridhar KV. Hepatitis, pancreatitis and rash in a patient with chronic lymphocytic leukemia. Gastroenterology 2019;157(4):e8–9.
[62] Matsuda Y, Nonaka K, Seki A, Kakizaki M, Takakuma S, Hamamatsu A, et al. Disseminated varicella zoster virus infection and acute hepatitis: autopsy-proven cases from a single institute. Pathol Int 2019;69(6):378–80.
[63] Song ATW, Carneiro D'Albuquerque LA. Acute liver failure secondary to yellow fever: a challenging scenario. Clin Liver Dis 2019;13(2):58–61.
[64] Wilder-Smith A. Yellow fever in travelers. Curr Infect Dis Rep 2019;21(11):42.
[65] Magalhães BM, Siqueira AM, Alexandre MA, Souza MS, Gimaque JB, Bastos MS, et al. Vivax malaria and dengue fever co-infection: a cross-sectional study in the Brazilian Amazon. PLoS Neglected Trop Dis 2014;8(10):e3239.
[66] Guzmán-Rodríguez M, Acosta-Ñañez HF, Mantilla JC, Bonelo A. Dengue virus and influenza A virus co-infection in pregnancy: a case report. Trav Med Infect Dis 2019;4(2):E84.