Research update

Liver Diseases Unique to Pregnancy

Kondratchikienė J, Kupčinskas L
Medicina (Kaunas). 2008;44(5):337-345

Introduction

During pregnancy, the liver’s synthetic and metabolic functions are affected by the increased serum estrogen and progesterone levels. Pregnancy is associated with many normal physiologic changes, which can mimic chronic liver disease. An increase in serum aminotransferase, bilirubin, or serum bile acid concentrations during pregnancy is always pathologic and should prompt further evaluation.

There are liver disorders unique to pregnancy, diseases occurring coincidentally, and preexisting chronic liver diseases. The pregnancy-related liver disorders have characteristic clinical features and timing of onset, whereas diseases unassociated with pregnancy may occur at any time (Table 1). While specific diseases are typically confined to a particular trimester, exceptions exist.

Correct diagnosis is critical because prompt therapy markedly improves the outcome of pregnancy. The diagnostic algorithm should include the following questions:
1. Are there any symptoms of underlying chronic liver disease?
2. Are there any features of biliary disease?
3. Is there any evidence of acute viral hepatitis?
4. Is there any history of drug, herbal medication, and alcohol consumption and travel?

5. Does clinical presentation fit one of the liver diseases unique to pregnancy?

Analyzing the pattern of serum liver tests abnormalities is also helpful in making the diagnosis.

<table>
<thead>
<tr>
<th>Liver disease coincidental with pregnancy</th>
<th>Specific disease</th>
<th>Trimester of pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute viral hepatitis</td>
<td>1</td>
<td>1–2</td>
</tr>
<tr>
<td>Bili/Chol syndrome</td>
<td>1</td>
<td>1, 2, 3, postpartum</td>
</tr>
<tr>
<td>Gallibacter</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Drug-related hepatitis</td>
<td>1</td>
<td>1–3</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic viral hepatitis</td>
<td>1</td>
<td>1–3</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>1</td>
<td>1–3</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>1</td>
<td>1–3</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>1</td>
<td>1–3</td>
</tr>
</tbody>
</table>

Table 1. Causes and Trimester of Liver Disease in Pregnancy

Algorithm of Abnormal Liver Tests

Hepatocellular liver test pattern

- Hepatitis serology
- Autoimmune antibodies
- Drug, alcohol, and viral history

Cholastatic liver test pattern

- Ultrasound
- Alcoholic and viral history

If the result of all tests are negative, suspect liver disease unique to pregnancy

Hyperemesis Gravidarum

Hyperemesis gravidarum (HG) is characterized by intractable nausea and vomiting usually resolving by week 16 to 18 of gestation. Mild nausea with or without vomiting occurs in 50% to 90% of all pregnancies. The prevalence of HG varies from as low as 3 cases per 1000 pregnancies to as high as 1 per 100.

Etiology

HG is generally a diagnosis of exclusion. Other conditions unrelated to pregnancy that can cause persistent nausea and vomiting include gastrointestinal disorders (gastrectomies, hepatitis, pancreatitis, cholecystitis), genitourinary tract disorders, metabolic (eg, diabetes, porphyria) and neurologic diseases (eg, migraine, rumet, vestibular lesions), drug toxicity, and psychological problems.

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disorder unique to pregnancy. In many areas of the world, ICP is a rare disease occurring at a rate of 1 in 1000 to 10000 pregnancies.

Etiology and pathogenesis

The pathogenesis of ICP can be related to abnormalities in the metabolism and disposition of sex hormones and/or bile acids determined by a genetic predisposition and environmental factors.

Clinical features

ICP is characterized by pruritus starting in the second or third trimester of pregnancy and disappearing after delivery. It is often generalized but predominates on the palms and the soles of the feet, and is worst at night. Physical examination may show excoriations due to scratching. Jaundice occurs in 10% to 20% of cases, typically within 4 weeks of the onset of itching.

Serum total bile acid concentrations increase in ICP and may be the first or only laboratory abnormality. The concentration of serum cholic acid increases more than concentration of chenodocholic acid, resulting in a marked elevation of the cholic/chenodocholic acid ratio compared to pregnant women without ICP. Serum aminotransferase levels are elevated and may reach values greater than 1000 U/L, making distinction from viral hepatitis important.

Differential diagnosis

The cardinal feature of ICP (pruritus) helps to distinguish it from other types of pregnancy-related liver disease that can share similar laboratory features (such as early HELLP syndrome or preeclampsia). The main differential diagnoses of pruritus of ICP without icterus are skin diseases, allergic reactions, and abdominal striae.

Preeclampsia

Hypertensive disorders complicate 12% to 22% of pregnancies. Preeclampsia occurs in approximately 3% to 14% of all pregnancies worldwide. Preeclampsia refers to the new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman. The etiology of this condition is unknown, but it seems that uteroplacental ischemia plays a major role.

All of the clinical features of preeclampsia can be explained as maternal responses to generalized endothelial dysfunction. Disturbed endothelial control of vascular tone causes hypertension, increased vascular permeability results in edema and proteinuria, and abnormal endothelial expression of procoagulants leads to coagulopathy.
Introduction
During pregnancy, the human body undergoes several changes in the process of its adaptation to the growing fetus. Although these changes are physiological, there is potential for morbidity and mortality to both mother and fetus. Liver is the site of many important metabolic and synthetic functions of the body. In normal pregnancy, the liver is not palpable. Owing to hemoilidation, biochemical tests may reveal mild increase in liver function tests. Abnormal liver tests occur in 3% to 5% of pregnancies, with many potential causes, including coincidental liver disease (most commonly viral hepatitis or gallstone) and underlying chronic liver disease.

Liver dysfunction can appear at any point of pregnancy, which causes great anxiety to the patient, her family, and sometimes her medical attendants. A number of these diseases have been identified which are responsible for morbidity and mortality. Some of the liver disorders include viral hepatitis, AFLP (acute fatty liver of pregnancy), autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, gallstone disease, and drug-induced hepatitis.

Management
Liver disease makes a normal pregnancy a high-risk pregnancy. Extreme vigilance is needed to detect early signs and symptoms of liver dysfunction and distinguish these from the anticipated benign hepatic changes of pregnancy. Prompt management can save the life of the mother and the baby. Management of liver disease in pregnancy requires a concerted effort from the primary care physician, liver specialist, and obstetrician.

This study evaluated the efficacy and safety of Liv.52 in the management of liver disorders in pregnancy. The study was conducted way back in 1974 to 1975 in 84 cases of liver disorder in pregnancy to evaluate the efficacy and safety of Liv.52 in the treatment of jaundice in pregnancy. This study is believed to be the first of its kind during that period as it involved management of pregnant women with jaundice.

In this study population of 84 patients, there were 9 pregnant women who were down with severe viral hepatitis. A total of 21 of 84 patients had undergone liver biopsy, after their written informed consent. Histopathological examinations of these patients with viral hepatitis had indicated extensive perportal round cell infiltration, fibrosis, and scarring. All these patients recovered completely after 6 weeks of treatment except one patient (19 years, second trimester of pregnancy).

Liv.52 did not produce any adverse effects in any of the patients who underwent Liv.52 drug therapy. Drug therapy with Liv.52 brought down the earlier reported mortality of 26.7% to 1.1% in patients with jaundice during pregnancy. However, a larger trial will be needed to confirm these findings. Liv.52 is a well-studied herbal formulation in various diseases, and thereby could be very useful in the management of liver diseases in pregnancy.

Conclusion
Liver holds a very important position in the metabolic system of the body. Its active participation in metabolism of carbohydrates, proteins, and fats including detoxification of xenobiotics substances gives it a unique position in controlling the metabolic pathways of the body. In spite of tremendous strides in modern medicines, very few drugs are known to protect the liver from damage. Liv.52 holds a great promise in this regard and is known as the safest and effective medication.

Background
In vitro studies indicate that HD-03/ES has surface antigen suppression and hepatoprotective properties. Acute and sub-acute toxicity studies have shown that HD-03/ES is devoid of significant toxicity following acute and repeated administration in rats. This study was undertaken to evaluate the safety and efficacy of the formulation HD-03/ES capsules in the management of patients with chronic hepatitis B infection.

Materials and Methods
Double-blind, randomized, placebo-controlled clinical study was carried out in 50 patients with chronic hepatitis B. The patients were divided into two groups: drug and placebo. The first group received HD-03/ES capsules at a dosage of 2 tablets twice a day for 24 weeks and the second group received placebo. The patients were subjected to biochemical investigations to assess the levels of HBsAg, HBeAg, and HBV DNA at baseline and 24 weeks after therapy. Liver function tests, including assessment of serum protein and total bilirubin levels, and ALT and aspartate aminotransferase (AST) activities were performed every month during the treatment period. The primary endpoint of the study was HBsAg clearance and secondary end points included decrease in HBV DNA levels and ALT normalization.

Results
There was a significant improvement in chief clinical signs and symptoms such as abdominal pain, poor appetite, and jaundice in patients treated with HD-03/ES. Biochemical investigations showed that 41.75% patients who received HD-03/ES therapy had undetectable HBeAg levels when compared to only 5% patients who received placebo (P < 0.001). HBeAg loss occurred more frequently during treatment with HD-03/ES, and 5 of the 9 patients who were positive for HBeAg initially were HBeAg negative at the end of the therapy. HBV DNA levels became undetectable in 6 patients treated with HD-03/ES therapy as compared to just 1 patient in the placebo group (< 0.05). It was also noted that alanine aminotransferase levels were normalized and the normalization was more significant in those who cleared their HBeAg (Tables 1–3). Adverse effects were mild and never warranted withdrawal of the drug.

Conclusion
These findings indicate that HD-03/ES is safe and effective in the outpatient management of chronic hepatitis B.

**Table 1. Effect of HD-03/ES and Placebo Therapy on Weight and Jaundice**

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>HD-03/ES</th>
<th>Placebo</th>
<th>HD-03/ES</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9</td>
<td>16</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>16</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

**Table 2. Effect of HD-03/ES and Placebo Therapy on Liver Function Tests**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>HD-03/ES</th>
<th>Placebo</th>
<th>HD-03/ES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AST (U/L)</strong></td>
<td>82.8±38</td>
<td>16.7±28</td>
<td>13.1</td>
<td>87.5±21</td>
</tr>
<tr>
<td><strong>ALT (U/L)</strong></td>
<td>56.6±21</td>
<td>12.2±24</td>
<td>10.1±8</td>
<td>56.4±23</td>
</tr>
<tr>
<td><strong>Total bilirubin</strong></td>
<td>1.3±0.3</td>
<td>0.9±0.2</td>
<td>0.9±0.2</td>
<td>1.3±0.3</td>
</tr>
<tr>
<td><strong>Albumin (g/L)</strong></td>
<td>3.5±0.1</td>
<td>3.5±0.1</td>
<td>3.5±0.1</td>
<td>3.5±0.1</td>
</tr>
<tr>
<td><strong>Platelet count</strong></td>
<td>140±50</td>
<td>140±50</td>
<td>140±50</td>
<td>140±50</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td>4.2±1.3</td>
<td>4.2±1.3</td>
<td>4.2±1.3</td>
<td>4.2±1.3</td>
</tr>
</tbody>
</table>

**Table 3. Biochemical and Serological Response of HD-03/ES Group as Compared to Placebo Group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>HD-03/ES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg</strong></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>HBsAg</strong></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>ALT Normalization (%)</strong></td>
<td>10.7±2.4</td>
<td>10.7±2.4</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td>4.2±1.3</td>
<td>4.2±1.3</td>
</tr>
</tbody>
</table>

**Note:** *P* < 0.05 is considered significant.
Influencing Factors of Mother–Infant Vertical Transmission of Hepatitis B Virus
Zhang WL, et al.

The aim of this study was to investigate factors influencing mother–infant vertical transmission of hepatitis B virus (HBV). A total of 635 pregnant women with chronic hepatitis B or chronic asymptomatic HBV carriers were enrolled. The rate of HBV infection was compared between the infants born from the pregnant women of different HBV-DNA load, different ways of delivery, and different liver functions at birth and 3 months after birth. The newborn infants were routinely injected with hepatitis B immunoglobulin (200 IU) and hepatitis B vaccine (10 μg) within 12 hours of birth. The newborns presenting HBV infection within 24 hours were excluded. The rate of HBV infection in infants with maternal HBV-DNA load >105 copies/mL was higher than in those with maternal HBV-DNA load ≤105 copies/mL at birth (44.9% vs 4.1%; P<0.01) and 3 months after birth (4.7% vs 0%; P<0.01). The rate of HBV infection in infants was lowest at birth in both groups. The rate of HBV infection in infants born by natural labor was higher than in those born by caesarean section at birth (P<0.05). However, by 3 months after birth, the rate of HBV infection between the two groups was similar. It might thus be effective to decrease the rate of HBV infection in infants by decreasing maternal HBV-DNA load. With the administration of hepatitis B immunoglobulin and hepatitis B vaccine, the delivery way and the liver function of pregnant women may not be factors influencing mother–infant HBV vertical transmission.

Liver Disorders in Pregnancy

How frequently do you see cases of jaundice during pregnancy? What are the common causes of jaundice during pregnancy?

In tropical countries like India, liver diseases during pregnancy are associated with high risk of morbidity and mortality. According to a 2001 report, jaundice is responsible for 5% to 20% of maternal deaths in the developing countries of Asia. Morbidity is more likely in the presence of a preexisting liver disease such as autoimmune hepatitis or when a new onset liver disease occurs during pregnancy as in viral hepatitis.

Viral hepatitis is the most common cause of jaundice during pregnancy. The incidence of hepatitis in pregnancy varies widely across the world, with around 0.1% in developed countries and 3% to 20% in higher in developing countries. Certain causes of jaundice that are unique to pregnancy include cholestasis of pregnancy, preeclampsia, acute fatty liver of pregnancy.

Why are pregnant women prone to liver disorders?

During pregnancy, the synthetic and metabolic functions of liver are affected by increased serum estrogen and progesterone levels. Although these changes are physiological, there is potential for morbidity and mortality to both mother and fetus. Probably, there is a decline in immunity.

Abnormal liver tests are observed in 3% to 5% of pregnant women with many potential causes, coincidental liver disease (most commonly viral hepatitis or gallstones) and underlying chronic liver disease.

How do you manage liver disorders during pregnancy?

Liver disorders could make normal pregnancy a high-risk pregnancy. Thereby extreme vigilance is needed to detect early signs and symptoms of liver dysfunction to distinguish these from the anticipated benign hepatic changes of pregnancy. An increase in serum aminotransferase, bilirubin, or serum bile acid concentrations during pregnancy is always pathologic and requires evaluation since the underlying liver disease could be severe and result in an increased risk to the mother and fetus. Drug therapy is often required, and clinicians need to be familiar with which drugs are safe and which can be dangerous during pregnancy. Early diagnosis of liver disorders and prompt delivery with supportive therapy help in improving maternal and perinatal outcome.

Maternal Hepatitis B and Hepatitis C Carrier Status and Perinatal Outcomes
Connel LE, et al.

The aim of this study was to examine the association between maternal hepatitis B and C mono- and co-infections with singleton pregnancy outcomes in the state of Florida. The researchers analyzed all Florida births from 1998 to 2007 using birth certificate records linked to hospital discharge data. The main outcomes of interest were selected pregnancy outcomes including preterm birth, low birth weight (LBW), small for gestational age (SGA), fetal distress, neonatal jaundice, and congenital anomaly.

The study sample consisted of 1,670,369 records. Human immunodeficiency virus co-infection and all forms of substance abuse were more frequent in mothers with hepatitis B and C infection. After using multivariable modeling to adjust for important socio-demographical variables and obstetric complications, women with hepatitis C infection were more likely to have infants born preterm (OR, 1.40; 95% CI, 1.15–1.72), with LBW (OR, 1.39; 95% CI, 1.11–1.74), and congenital anomaly (OR, 1.55; 95% CI, 1.14–2.11). In addition, women with hepatitis B infection were less likely to have infants born SGA (OR, 0.79; 95% CI, 0.66–0.95). These findings provide further understanding of the association between maternal hepatitis B or C carrier status and perinatal outcomes. Infants born to women with hepatitis C infection appear to be at risk for poor birth outcomes, including preterm birth, LBW, and congenital anomaly.

What is your opinion about use of Liv.52 in the management of liver disorders during pregnancy?

Liv.52, a polyherbal formulation from The Himalaya Drug Company, is a well-known hepatoprotective drug, useful in the treatment of various liver dysfunctions/disorders including viral hepatitis, alcoholic liver disease, anorexia, and drug-induced hepatitis. Several studies have proven its safety and efficacy in the management of jaundice during pregnancy. I regularly see good results, as it definitely improves appetite and gives sense of well being. It is a very useful drug in jaundice during pregnancy. Several studies have proven its safety and efficacy in the management of jaundice during pregnancy. I regularly see good results, as it definitely improves appetite and gives sense of well being. It is a very useful drug in jaundice during pregnancy.

Characteristics of Ascites in Patients with Pregnancy-specific Liver Diseases
Devarthavi H, et al.

The characteristic of ascites in patients with pregnancy-specific liver disease (PSLD), which comprise acute fatty liver of pregnancy, hemolysis, increased levels of liver enzymes, low platelet syndrome, and preeclampsia-associated liver dysfunction are unknown.

The researchers evaluated the cellular and biochemical characteristics, and model for end-stage liver disease (MELD) scores, in patients with PSLD. A total of 46 consecutive patients with PSLD were investigated for the presence of ascites. The study assessed cellular and biochemical characteristics of the ascites fluid from these patients.

Ascites was observed in 35 of 46 patients with PSLD (76%). In 25 patients tested (71.4%), the ascites fluid had low levels of albumin (<0.2 g/dL) and protein (<1 g/dL) and high serum-ascites albumin gradients (SAAG), indicating portal hypertension. Spontaneous bacterial peritonitis (SBP) was observed in 48% of patients tested and was not associated with mortality. Patients with ascites had significantly low serum levels of protein and albumin (P<0.001).

MELD scores did not differ between patients with or without ascites (32 vs 27; P=1). Ascites occurs in 76% of women with PSLD, is transient, and has characteristics of portal hypertension based on a high SAAG. Almost half of patients with PSLD develop SBP which does not affect survival.
HELLP Syndrome

HELLP syndrome occurs in approximately 1 per 1000 pregnancies. The majority of cases are diagnosed between 28 and 36 weeks of gestation. The disease presents prior to delivery in 70%, postpartum in 30% of cases, usually within 48 hours, but occasionally as long as 7 days after delivery.

Clinical features

The clinical presentation of HELLP syndrome varies. Although some patients have no symptoms, most complain of abdominal pain and tenderness. The pain is located in the midepigastrium, right upper quadrant, or below the sternum. Many patients also have nausea, vomiting, and malaise. Hypertension and proteinuria are present in approximately 85% of cases, pulmonary edema in 6%, ascites in 8%, and acute renal failure, usually occurring in the setting of DIC (disseminated intravascular coagulation), in 20%.

Differential diagnosis

The differential diagnosis includes AFLP, or, because of similar symptoms or laboratory findings, gastroenteritis; hepatitis; appendicitis; gallbladder disease; idiopathic thrombocytopenic purpura; hemolytic-uremic syndrome; or thrombotic thrombocytopenic purpura.

Acute Fatty Liver of Pregnancy

The prevalence of acute fatty liver of pregnancy (AFLP) is estimated to be 1 per 16,000 cases to 1 per 7000. AFLP occurs in the second half of pregnancy, usually close to term. However, some patients may present and be diagnosed after delivery.

Etiology

Recently, an association between AFLP and one of the inherited defects in mitochondrial beta-oxidation of fatty acids—long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency—was suggested. This enzyme is one of the four enzymes, which break down long-chain fatty acids in the liver.

Clinical features

AFLP may present with malaise, fatigue, anorexia, nausea, vomiting, headache, abdominal pain, and jaundice. Within 1 to 2 weeks of onset of symptoms, the disease may rapidly worsen. Patients then develop acute liver failure, including hepatic encephalopathy, ascites, edema, and renal insufficiency.

Differential diagnosis

The differential diagnosis of AFLP includes AFLP, or, because of similar symptoms or laboratory findings, gastroenteritis; hepatitis; appendicitis; gallbladder disease; idiopathic thrombocytopenic purpura; hemolytic-uremic syndrome; or thrombotic thrombocytopenic purpura.

Liver}

In jaundice & anorexia during pregnancy...

Liv.52 DS® (SYRUP, TABLET)
Unparalleled in liver care

Exhibits hepatoprotective properties during pregnancy

- Decreases ALT, AST, and normalizes ALP
- Provides prompt relief of symptoms: Pruritus, anorexia, and nausea
- Relieves yellow discoloration of conjunctiva and enlargement of the liver
- Improves patient compliance and general feeling of well-being

Liv.52 DS – Unparalleled in liver care

Jaundice & anorexia during pregnancy

Dosage
1 (teaspoonful/tablet) b.i.d. for 8 weeks.

Laugh lines

As a senior citizen was driving down the freeway, his cell phone rang.

Answering, he heard his wife’s voice urgently warning him, “Herman, I just heard on the news that there’s a car going the wrong way on Route 280. Please be careful!”

“It’s not just one car,” said Herman. “It’s hundreds of them!”

... ... ... ...

A lawyer, an engineer, and a mathematician were called in to write a test. The engineer went in first and was asked, “What is 2+2?” The engineer thought awhile and finally answered, “4.” Then the mathematician was called in and was asked the same question. With little thought he replied, “4.” Then the lawyer was called in, and was asked the same question. The lawyer answered even quicker than the mathematician, “What do you want it to be?”

... ... ... ...

A woman walked into the kitchen to find her husband stalking around with a fly swatter.

“What are you doing?” She asked.

“Hunting flies,” he replied.

“Oh! Killed any?” She asked.

“Yes, 3 males, 2 females”, he replied.

Intrigued, she asked, “How can you tell?”

He responded, “3 were on a beer can, 2 were on the phone.”

... ... ... ...

News flash

Acute Viral Hepatitis During Pregnancy

The course of most viral hepatitis infections (hepatitis A, B, C, and D) is unaffected by pregnancy; however, a more severe course of viral hepatitis in pregnancy has been observed in patients with hepatitis E. Notwithstanding, opinions differ over the maternal and fetal outcome of pregnancy associated with viral hepatitis.

While some studies report that acute viral hepatitis carries a high risk for both mother and fetus, other studies conclude that nonfulminant viral hepatitis does not influence the course of pregnancy or fetal well-being.

Rate of transmission of the virus during pregnancy depends on the virus. For instance, intrauterine transmission of hepatitis A virus is very rare, but perinatal transmission could occur. Conversely, 60% of pregnant women who acquire acute hepatitis B virus (HBV) infection at or near delivery will transmit the HBV virus to their offspring.

Mother to child transmission of hepatitis E virus infection was established between 33.3% and 50%.

Breast feeding is not contraindicated in women infected with the hepatitis A, E, or C. However, for acute hepatitis B, with appropriate immunoprophylaxis, breast-feeding poses no additional risk for the transmission of HBV.

Finally, whether live or inactivated vaccines are used, vaccination of pregnant women should be considered on the basis of risks and benefits associated with them.