Acute hepatitis C during the third trimester of pregnancy

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SUMMARY

A pregnant woman presented at 32 weeks of amenorrhea with jaundice secondary to acute hepatitis C. Spontaneous delivery took place 3 days later. The infant’s serum tested negative for C viral RNA 6 months after delivery. Treatment with high doses of interferon-alpha for a period of 4 weeks was begun 4 days after delivery. Although a virological response was noted at the end of the treatment, the hepatitis relapsed and progressed toward chronicity. Case reports of acute hepatitis C during pregnancy are very rare, as the methods used for the follow-up of pregnant women render the diagnosis of asymptomatic forms difficult. In one case, the acute hepatitis C was severe. The occurrence of acute hepatitis C during pregnancy seems to increase the risk of premature delivery, but not that of vertical transmission. Given the frequency of side effects, it seems preferable not to begin interferon treatment until after delivery.

RÉSUMÉ

Hépatite aiguë C au cours du 3e trimestre de grossesse

Florent GONZALEZ, Michèle-Ange MEDAM-DJOMO, Damien LUCIDARME, Ali KHALIL, Anne DECOSTER, Denis HOUZE DE L’AULNOIT, Bernard FILOCHE

Une femme enceinte présentait à 32 semaines d’aménorrhée un ictère secondaire à une hépatite aiguë C. La malade accouchait spontanément 3 jours plus tard. La recherche négative de l’ARN viral C dans le sérum du nourrisson 6 mois après l’accouchement excluait une transmission verticale du virus. Un traitement par interféron alpha à forte dose pendant 4 semaines était débuté 4 jours après l’accouchement. Malgré une réponse biochimique et virologique en fin de traitement, l’hépatite rechutait et évoluait vers la chronicité. Les observations d’hépatite aiguë C pendant la grossesse sont très rares car les modalités de suivi des femmes enceintes rendent difficile le diagnostic des formes asymptomatiques. Dans un cas, il s’agissait d’une forme sévère. La survenue d’une hépatite aiguë C en cours de grossesse semble augmenter le risque de prématurité sans majorer le risque de transmission materno-fœtale. La fréquence des effets secondaires sous interféron suggère d’attendre le post-partum avant de débuter un éventuel traitement anti-viral.

Introduction

Intravenous drug use has become the main mode of transmission of hepatitis C virus (HCV). The high prevalence rates of anti-HCV observed among pregnant women, which vary between 0.3 and 3.9% in France, evidences a significant risk of HCV infection in women of reproductive age [1]. However, the diagnosis of acute hepatitis C is very rarely made in pregnant women. To our knowledge, only 6 case reports of acute hepatitis C during pregnancy have been published [2-7]. Besides the fact that pregnancy favors a decrease in risk-inducing practices, the exceptional nature of acute hepatitis C in pregnant women might either be explained by the difficulty of diagnosing asymptomatic forms — taking into account the methods of follow-up of pregnant women — and by the rarity of symptomatic forms. Notably, it is possible that the immunological changes associated with pregnancy influence the development of jaundice, as suggested in patients coinfected with human immunodeficiency virus (HIV) [8]. We present a further case of acute hepatitis C revealed by jaundice, quickly followed by a premature delivery.

Case report

A young woman 22 years old, pregnant at 32 weeks of amenorrhea, was hospitalized in October 1999 for jaundice, and pruritus that had begun 2 weeks before, without pain or fever. The past medical and surgical history was uneventful, except for another pregnancy which had gone to term in 1995. There was no alcohol abuse. No drug intake was stated. The patient had used heroin briefly, about 10 intravenous injections, in 1998. Substitution treatment with buprenorphine HD (Subutex®) had been instituted and then interrupted 3 months before the beginning of the pregnancy. Her husband, a former heroin user, had been followed since 1998 for a chronic HCV genotype 1a infection.

Upon admission, the systolic arterial blood pressure was 110 mm Hg and abdominal exam was normal. Urine tests did not show any proteinuria or infection. Initial blood chemistry tests showed elevated serum transaminase activity, predominantly related to elevated alanine-amino-transferase (ALAT) 900 UI/L (that is, 26 times the upper normal limit (N)), compared to 720 UI/L (that is, 20 N) of aspartate-aminotransferase (ASAT). Total serum bilirubin was 230 µmol/L, 190 µmol/L of which was conjugated bilirubin. Blood count, prothrombin index, blood urea and creatinine were normal. The patient tested negative for anti-nuclear, anti-smooth muscle, anti-LKM1 and anti-mitochondrial antibodies. Blood copper and ceruloplasmin were normal. The serological profile showed immunization by vaccination against hepatitis B virus and long-term immunity against hepatitis A virus, cytomegalovirus, herpes, Epstein-Barr virus and toxoplasmosis. Serum tests for hepatitis E virus and HIV were negative. Finally, the ELISA test for third-generation anti-HCV antibodies proved positive. The presence of HCV-RNA in the serum was detected by polymerase chain reaction. The viral genotype was 1a and the viral load was more than 1 million copies/mL. Tests for anti-HCV antibodies carried out on samples frozen in July and September 1999 were negative. An abdominal ultrasound did not show an abnormality of the biliary tract, liver parenchyma or hepatic veins. There

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was no sign of fetal distress. A diagnosis of acute hepatitis C during the third trimester of pregnancy was made.

Three days after admission, the patient gave birth spontaneously by vaginal delivery without obstetrical maneuvers to a healthy little girl weighing 2.5 kg. The infant was bottle-fed. Six months after delivery, HCV-RNA could not be detected in the infant’s serum, indicating that there had not been any mother-to-infant transmission of HCV.

Four days post-partum, interferon (IFN) alpha-2b treatment was begun at a daily dose of 9 million IU for a period of 28 days, within the framework of a protocol [9]. After 2 weeks of treatment, HCV-RNA could not be detected in the serum and transaminase levels were back to normal. In February 2000, the patient suffered a relapse, with HCV-RNA present in the serum as evidenced by qualitative polymerase chain reaction, while the ALAT level had increased to 3 N.

**Discussion**

The diagnosis of acute hepatitis C during pregnancy could be validated since seroconversion was documented and the main differential diagnoses, such as intrahepatic cholestasis of pregnancy, acute liver steatosis of pregnancy and the hepatic lesions present in the serum as evidenced by qualitative polymerase chain reaction, while the ALAT level had increased to 3 N.

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**Table I**

<table>
<thead>
<tr>
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<td>1b</td>
<td>1b</td>
<td>1b</td>
<td>1a</td>
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<td>25</td>
<td>44</td>
<td>41</td>
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<td>Gestational diabetes (ALAT activity measurement)</td>
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<td>31 WA</td>
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<td>24 WA</td>
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<td>32 WA</td>
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<tr>
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<td>607</td>
<td>1430</td>
<td>1217</td>
<td>364</td>
<td>1312</td>
<td>900</td>
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<tr>
<td><strong>Bilirubin (µmol/L)</strong></td>
<td>97</td>
<td>141</td>
<td>64</td>
<td>69</td>
<td>11.9</td>
<td>230</td>
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<td>10⁴</td>
<td>10⁴</td>
<td>1,6·10⁴ IU/mL</td>
<td>&gt; 10⁶</td>
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<tr>
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<td>10⁶</td>
<td></td>
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<td>10⁶</td>
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<td><strong>Later developments</strong></td>
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<tr>
<td><strong>Mother</strong></td>
<td>Treated with IFN beginning at J40, cured, distance 17 M**</td>
<td>Lost to follow-up</td>
<td>Refused treatment during pregnancy</td>
<td>Treated with IFN during pregnancy, cured, distance 18 M</td>
<td>Non Treated, cured, distance 3 ½ years</td>
<td>Treated with IFN alpha (post partum), relapse, chronicity</td>
<td></td>
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<tr>
<td><strong>Child</strong></td>
<td>Anti HCV (-) at age 4</td>
<td>RNA (-) at birth</td>
<td>RNA (-) at 6 weeks</td>
<td>RNA (-) at birth</td>
<td>Twins RNA (-) at 12 M</td>
<td>RNA (-) at 3 M</td>
<td>RNA (-) at 6 M</td>
</tr>
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</table>

*WA: weeks of amenorrhea, **M: months.
encountered in pre-eclampsia [10], had been ruled out. In the six other published case reports of acute hepatitis C during pregnancy, documented hepatitis C virus seroconversion and negative tests for pregnancy-associated or intercurrent liver disease also confirmed the diagnosis.

While the fact that in 5 out of 7 reported cases the disease was revealed by jaundice suggests a diagnostic bias rather than a pregnancy-specific trait, it should be stressed that the icteric forms included a case of severe acute hepatitis [3]. In that particular case, acute hepatitis C was diagnosed in a pregnant woman at 31 weeks of amenorrhea, in connection with jaundice with no encephalopathy (Table I). Elevated ALT activity (607 IU/L), hyperbilirubinemia (141 μmol/L) and a decrease in in the prothrombin index to 15% were found. The patient gave birth spontaneously by vaginal delivery 3 days later, without any bleeding complications. A course of treatment with IFN alpha begun on the fortieth day, a few days after, the bilirubin and prothrombin index had completely returned to normal, led to a long-lasting virological response. To our knowledge, this is the only reported case of severe acute hepatitis C during the third trimester of pregnancy. However, considering the rarity of severe forms of acute hepatitis C outside pregnancy, specific severity associated with pregnancy cannot be ruled out on the basis of this case report alone, considering the existence of severe forms of acute hepatitis E with a high fatality rate during the third trimester of pregnancy [11].

Bacterial or viral infections contracted during the third trimester of pregnancy are responsible for premature deliveries [12]. Three of the 7 reported cases of acute hepatitis C in pregnant women, ours included, were accompanied by premature delivery occurring soon after the diagnosis was made, between 30 and 32 weeks of amenorrhoea [3, 7]. Premature birth is the main risk for the newborn, together with that of vertical transmission of HCV. In recent studies, the risk of mother-to-infant transmission of virus in chronic hepatitis C, in the absence of coinfection by HIV, has been estimated at 0 and 9.9% [1]. The risk is believed to be increased in the case of high viremia and HIV co-infection [13-15]. Thus, due to the high levels of viremia during delivery in our patient we feared that there was an increased risk of mother-to-infant transmission of the virus in acute hepatitis C [2, 3]. However, this risk has not been confirmed to date, the infants born to mothers with acute hepatitis C during pregnancy tested negative for HCV-RNA at birth in all cases and between 6 weeks and 12 months after delivery in 4 cases [2, 3, 6, 7].

When seroconversion occurs at the end of pregnancy, whatever the mode of clinical presentation or the genotype, it seems preferable not to begin anti-viral treatment until after delivery. In our case, the presence of jaundice at presentation justified this approach. Outside pregnancy spontaneous resolution of acute hepatitis C may occur in over 50% of symptomatic patients, and anti-viral treatment should only be considered for those who are viremic 12 weeks after the onset of the disease [16, 17]. In our patient, the initial course of treatment with high doses of IFN alpha as early as 4 days post-partum for a short period of time, was begun to “strike fast and hard” [18]. The occurrence of a virological relapse after treatment was discontinued and the progress of the disease toward chronicity illustrates the limitations of this option. Although in 2006 the treatment of acute hepatitis C remains controversial [19], failure of treatment may be related to its duration, which may have been inadequate in view of the high initial viremia and insuspicious genotype and despite rapid initial virological response.

The occurrence of acute hepatitis C early in pregnancy raises the theoretical problem of possible anti-viral treatment during pregnancy to prevent chronicity. The use of IFN during pregnancy is contraindicated [20, 21]. In animals, however, no teratogenic effects have been found with IFN alpha — as opposed to ribavirin [22, 23] — even at high doses [20, 21]. In a study carried out on rhesus monkeys, the administration of IFN alpha induced abortion only at doses 90 to 360 times those recommended in humans [24]. Cases of pregnancy under treatment with IFN are very rare [7, 25-29]. IFN alpha therapy was administered to a pregnant woman at 16 weeks of amenorrhoea for anicteric acute hepatitis C at a dose of 3 million IU three times a week for 12 weeks [7]. Treatment was discontinued early due to a depressive syndrome. The patient delivered healthy twins at 30 weeks amenorrhoea, that is, 2 weeks after IFN was discontinued; the babies tested negative for anti-HCV antibodies at 12 months. Treatment was associated with a long-lasting virological response. IFN alpha was also administered just before conception or during the first trimester of pregnancy to 3 women with liver disease, without any mutagenic or teratogenic effects [25-27]. Thus without clear proof of the harmfulness of IFN for the development of pregnancy and considering its functional and systemic side effects, which may be severe, treatment should be delayed until after delivery when there is persistent viremia. This attitude seems especially reasonable since treatment delayed for a few months after the acute phase seems to be more effective than treatment begun at the chronic stage of the disease [30].

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