

Hepatitis A virus infection during pregnancy in Korea: Hepatitis A infection on pregnant women

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Objective

Although there is a large body of data on acute hepatitis A virus (HAV) worldwide, data regarding the occurrence of HAV during pregnancy is limited. It is commonly acknowledged that HAV is not associated with severe outcomes or complications during pregnancy. In contrast, there are several reported cases of vertical HAV transmission. Moreover, it has been recently reported that HAV infection during pregnancy is associated with gestational complications. In Korea, the incidence of HAV infection has increased from 317 cases in 2002 to 13,117 cases in 2009. However, HAV infection during pregnancy is rarely reported in Korea.

Methods

This study was conducted as a retrospective cohort series of pregnant women presenting to Korea University Medical Center between January 2000 and October 2009 in whom a diagnosis of HAV infection was made.

Results

During study period, there were 12 cases of HAV in pregnant women, including two cases with preterm contraction, two cases with cholestatic hepatitis, and one case with fetal ascites and intra-abdominal calcification.

Conclusion

HAV infection during pregnancy is associated with high prevalence of maternal and fetal complications. Because the incidence of HAV infection in women of reproductive age is increasing, a further focus on preventing HAV infection during pregnancy is warranted.

Keywords: Hepatitis A; Pregnancy; Pregnancy complications

Introduction

Hepatitis A virus (HAV) is an enterovirus of the family *Picornaviridae* that is transmitted primarily via the fecal-oral route. Most infections in children younger than six years of age are mild or asymptomatic. However, infections in older children and adults are usually symptomatic, with a small number (less than 1%) of patients experiencing a fulminant course of illness that may result in death or emergent liver transplantation in those with advanced or comorbid conditions [1].

HAV incidence rates have decreased dramatically in the

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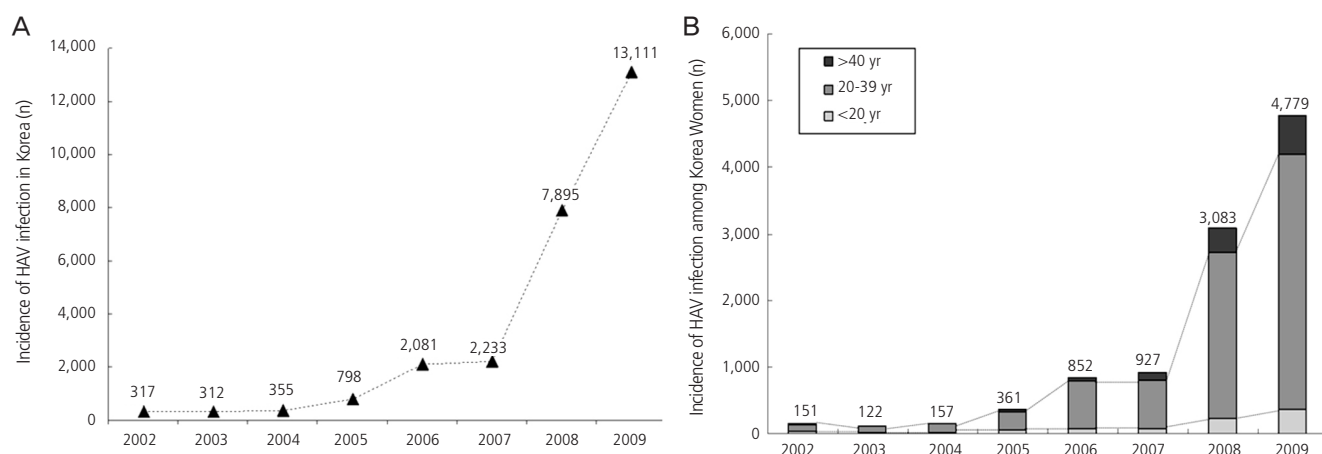


Fig. 1. (A) Incidence of hepatitis A virus (HAV) infection from January 2002 to October 2009 in Korea and (B) Korean women by age.

United States due to improved hygiene, sanitation, socioeconomic conditions, and vaccination programs [2]. Poor sanitation and contaminated water supplies may lead to infection in early childhood, resulting in mild illness. Therefore, as sanitation and living standards improve and fewer young children are infected, more adults are seronegative for HAV and are therefore susceptible to infection [3,4].

Despite the large body of data on HAV worldwide, little information is available regarding HAV infection during pregnancy. HAV infection is not associated with severe outcomes or complications during pregnancy [5] and maternal-infant HAV transmission is thought to be uncommon [6]. On the other hand, Elinav et al. [3] reported that HAV infection during pregnancy is associated with gestational complications, including preterm contraction. There are also numerous reported cases of vertical HAV transmission [7-14], with two cases reporting that HAV infection was associated with meconium peritonitis and perforation of the distal ileum in the infant, requiring postnatal surgery [7,8].

Currently, Korea has a low endemicity for HAV. However, recent reports from the Korea Centers for Disease Control and Prevention show that there has been a sharp increase in incidence of HAV infection from 317 cases in 2002 to 13,111 cases in 2009 (<http://www.cdc.go.kr/kcdchome/jsp/home/main/Main.jsp>) (Fig. 1). This may be partially explained by a dramatic drop in seroprevalence rates among children and adolescents under 20 years of age (from over 63.8% in 1979 to 4.6% in 1996) [15]. A potential concern arising from this incidence pattern in Korea is that approximately 80% of women with HAV infection are between the ages of 20 and 39 (Fig. 2), indicating that the incidence of HAV infec-

tion during pregnancy in Korea will increase. However, to our knowledge, there are no studies investigating the relationship between HAV infection and pregnancy in Korea.

The aim of this study is to review cases of HAV infection during pregnancy and to evaluate any associated clinical characteristics and maternal and fetal complications.

Materials and methods

This study was conducted as a retrospective cohort series of pregnant women presenting to Korea University Medical Center between January 2000 and October 2009 in whom a diagnosis of HAV infection was made. Cases were identified by reviewing the computerized diagnoses of all pregnant women who were patients at the hospital during that period of time. Comprehensive clinical and laboratory information were extracted from medical and obstetric records of all identified cases.

HAV infection was defined as positive immunoglobulin M and negative immunoglobulin G anti-HAV antibodies with acute elevation of hepatic aminotransferase levels in the absence of other etiologies for acute liver injury (including preeclampsia, hemolysis, elevated liver enzymes, low platelets [HELLP] syndrome, and acute fatty liver of pregnancy or intercurrent liver disease).

Results

Sixteen thousand nine hundred forty four deliveries were car-

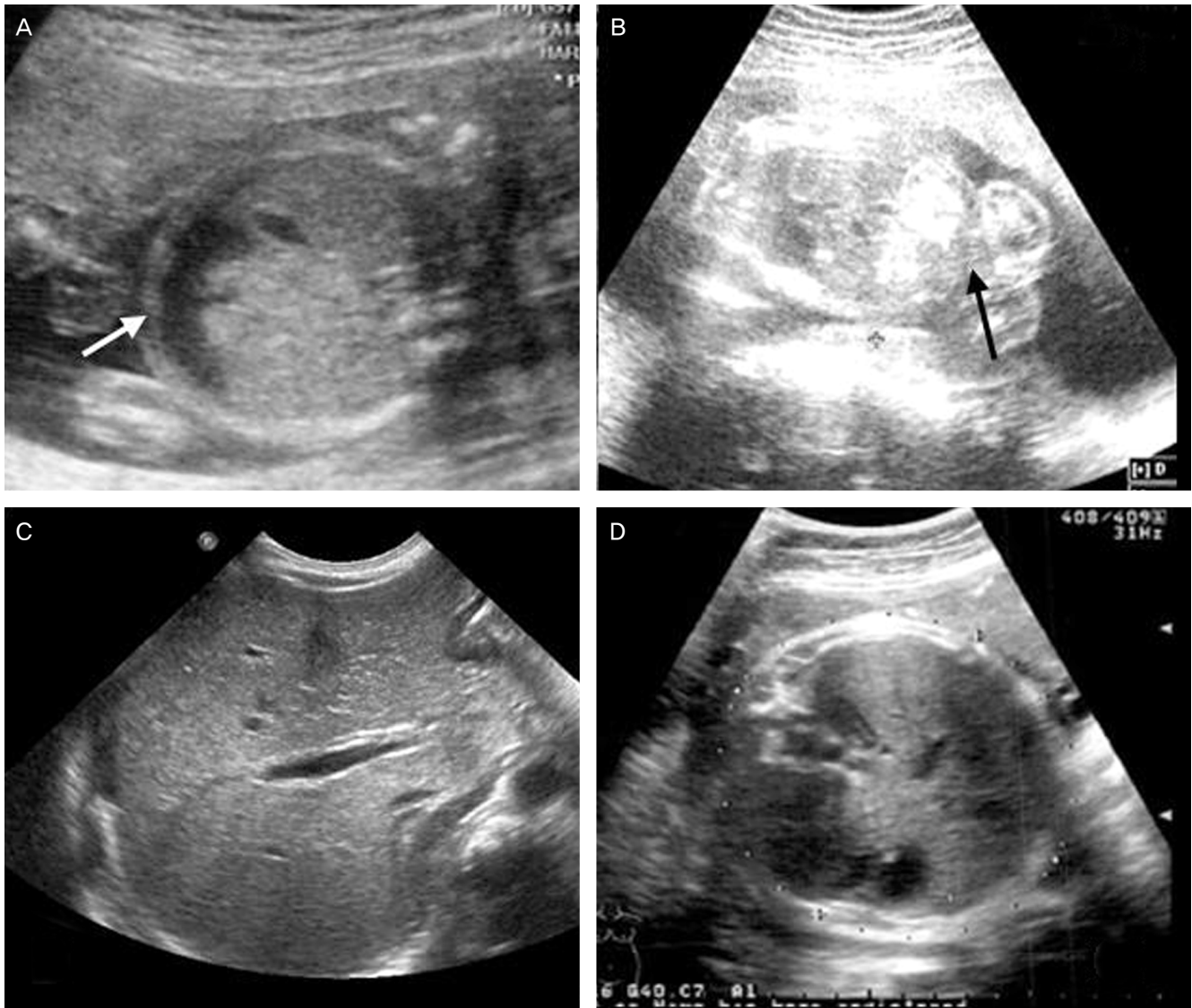


Fig. 2. Prenatal (A-C) and neonatal (D) sonography were performed in case 9. (A) Ascites was found at 20 weeks gestation (white arrow), and (B) an intra-abdominal calcification was seen at 22.1 weeks gestation (black arrow). (C) However, prenatal sonography at 38.1 weeks gestation showed (D) spontaneous resolution of the ascites and intra-abdominal calcification, which was confirmed by postnatal sonography at 3 days of life.

ried out between January 2000 and October 2009 at Korea University Medical Center. Among these 12 cases of maternal HAV infection were identified. The obstetric characteristics of study sample are noted in Table 1. The mean age of the 12 HAV cases was 29.0 years (range, 25–36 years), range of parity was 0-1, and mean gestational age at diagnosis was 18.3 (range, 5.5–35.1 weeks). Five cases (41.7%) occurred in 2009.

Among the 12 patients, there were two cases of cholestatic hepatitis (cases 7 and 8), two cases of involving preterm

contraction and subsequent preterm labor (cases 8 and 11), and one case of the fetus presenting with ascites and intra-abdominal calcification (case 9). In one case, the pregnant patient underwent elective termination after the diagnosis of HAV infection in early pregnancy (case 3). Vertical transmission was confirmed in case 8.

Table 2 shows the clinical and laboratory characteristics of the study sample. All cases developed prodromal symptoms, including malaise, anorexia, and nausea. Laboratory findings were consistent with hepatitis.

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Table 1. Obstetric characteristics of the study sample

Case	Age (yr)	Years at diagnosis	Parity (n)	GA at diagnosis (wk)	GA at labor (wk)	Delivery mode	Maternal complications	Fetal complications	Neonatal birthweights (g)	Neonatal complications
1	28	2004	0	35.1	39.3	V/D	No	No	2,620	No
2	29	2004	0	28.4	38.3	V/D	No	No	3,330	No
3	34	2004	1	5.5	–	–	–	–	–	–
4	25	2005	1	15.4	38.5	C/S	No	No	3,070	No
5	25	2006	0	5.6	40.1	V/D	No	No	3,420	No
6	27	2006	0	8.0	39.1	C/S	No	No	3,910	No
7	31	2008	0	13.0	38.4	V/D	Cholestatic hepatitis	No	2,380	No
8	36	2009	1	30.5	34.4	C/S	Preterm contraction, cholestatic hepatitis	No	2,200	No
9	29	2009	0	19.5	40.2	V/D	Polyhydramnis	Ascites, intraabdominal calcification	3,420	No
10	29	2009	1	17.4	40.2	V/D	No	No	3,420	No
11	27	2009	0	33.2	33.4	V/D	Preterm contraction, PROM	No	2,208	No
12	28	2009	0	8.0	–	–	No	No	–	–

GA, gestational age; V/D, vaginal delivery; C/S, Cesarean section; PROM, premature rupture of membrane.

Table 2. Clinical and laboratory characteristics of the study sample at admission

Case	Prodromal symptoms	Jaundice	Fever	AST (IU/L)	ALT (IU/L)	Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)	Albumin (g/dL)	Prothrombin time, INR	Hemoglobin (g/dL)
1	Yes	Yes	No	2,920	2,020	2.9	2.58	3.1	0.87	11.4
2	Yes	Yes	No	286	287	6.9	6.1	2.8	0.91	10.2
3	Yes	No	No	635	630	1.4	0.7	4.0	1.05	11.7
4	Yes	Yes	No	188	>400	5.6	3.9	3.4	1.07	6.7
5	Yes	No	No	1,852	2,417	2.2	1.7	3.6	1.08	13.7
6	Yes	No	No	149	541	1.68	1.18	3.8	0.94	13.3
7	Yes	Yes	No	3,009	1,089	22.71	13.7	3.4	0.93	11.6
8	Yes	Yes	Yes	1,814	1,474	9.3	6.9	2.5	1.11	10.4
9	Yes	Yes	No	1,909	1,691	2.16	1.61	3.8	1.20	12.1
10	Yes	Yes	No	619	216	4.83	2.98	3.1	0.88	11.2
11	Yes	Yes	Yes	62	296	2.96	Not measured	3.3	0.90	11.2
12	Yes	No	No	1,376	1,784	4.6	2.97	4.2	1.09	14.3

Prodromal symptoms, malaise, anorexia, and nausea; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio.

1. Case 7

A 31-year-old gravida 1 para 0 presented to our hospital with fever, fatigue, malaise, pruritus, and jaundice at 15.2 weeks gestation and was diagnosed with HAV infection. Because of protracted jaundice, pruritus, and an increase in serum bilirubin level, the patient was treated with prednisone 20 mg/day. The patient subsequently experienced symptomatic relief and a rapid drop in serum bilirubin level. Prednisone was tapered. No clinical or laboratory deterioration was observed after discontinuation of therapy. She was followed up, her pregnancy continued unremarkably, and she vaginally delivered a male baby at 38.4 weeks gestation.

2. Case 11

A 29-year-old gravida 1 para 0 was admitted at 33.2 weeks gestation with preterm contractions and premature rupture of membranes. Laboratory tests revealed abnormal liver function tests, and a diagnosis of HAV infection was eventually made. At 33.4 weeks gestation, she vaginally delivered a 2208 g male infant with Apgar scores of 8 and 10 at 1 and 5 minutes, respectively. The neonate was negative for HAV.

3. Case 9

A 29-year-old gravida 1 para 0 was referred to our hospital at 19.5 weeks gestation for suspected maternal HAV infection. After the diagnosis of maternal HAV infection, sonographic examination of the fetus was performed, which revealed ascites at 20.2 weeks of gestation (Fig. 2A), and polyhydramnios and intra-abdominal calcified lesions at 22.1 weeks of gestation (Fig. 2B), indicating meconium peritonitis. However, serial sonography showed spontaneous resolution of the intra-abdominal calcified lesions, ascites, and polyhydramnios (Fig. 2C). At 40.2 weeks of gestation, the patient delivered a 3,420 g male baby vaginally with Apgar scores of 9 and 10 at 1 and 5 minutes, respectively. Three days after birth, sonography of the patient's abdomen showed no abnormalities (Fig. 2D). The baby fed uneventfully and no problems have been reported at 6 months of age.

Discussion

In our sample, there were two cases of preterm contraction with subsequent preterm delivery, as in previously-reported cases [3,16]. In some previous cases of preterm labor, the

exact cause was never identified [10,11]. While the exact mechanism by which HAV causes preterm contraction is not clear, there are several possible explanations. First, viral hepatitis presents with a markedly proinflammatory milieu [17]. In particular, serum levels of interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha are significantly increased in patients with acute HAV infection [18]. These cytokines are also known to be associated with preterm contraction [19-22]. Therefore, preterm contraction may be precipitated by cytokine release as a result of systemic inflammatory response due to HAV infection. This is similar to the pathophysiologic mechanisms by which pyelonephritis causes preterm contraction [3].

It has also been reported that fulminant hepatitis is associated with an increased risk of preterm labor [23]. Acute HAV infection results in metabolic abnormalities throughout the body, causing insufficient energy generation and blood and oxygen supply through the placenta. Accordingly, preterm labor is likely to develop [23]. This may be another possible explanation for the association between HAV infection and preterm contractions. Therefore, preterm contraction and preterm labor may develop due to both the direct release of inflammatory cytokines and changes in utero-placental circulation that occur as a consequence of HAV infection.

In this study, we presented the case of a fetus with ascites and intra-abdominal calcifications at around 20 weeks gestation. Interestingly, we discovered two case reports with a nearly identical time course and presentation [7,8], but these cases necessitated post-natal surgery. These infections occurred at 13 and 20 weeks gestation. Other cases of vertical transmission following HAV onset in the mother at later than 33 weeks of gestations have reported favorable neonatal outcomes [9-14] with the exception of mild neonatal jaundice [9,11,12,14]. The inconsistencies in the reported effects of maternal HAV infection on fetus may be due to varying susceptibility of the fetus to maternal infection according to gestational age. Infection early in gestation (as fetal organs are developing) can cause more severe damage or stillbirth. It has been known that the risk of congenital varicella syndrome is highest between 13 and 20 weeks gestation, with an overall incidence of 0.55% in the first trimester, 1.4% in the second trimester, and 0% in the third trimester [24]. These results suggest that the fetus may have critical periods of high susceptibility for HAV infection and that the spectrum of clinical disease that occurs may be correlated with the gestational age of the fetus.

In this study, all of the patients presented with prodromal symptoms that included malaise, anorexia, and nausea. All of these are similar to pregnancy-related symptoms, which makes it difficult to correctly diagnose and treat HAV in the early stages prior to the onset of jaundice. Considering that fertile women have lower seroprevalence rates in Korea [15] and that the HAV vaccine is safe for use in pregnancy [25], addition of HAV serology to maternal screening at the first prenatal visit and vaccination of seronegative pregnant women may eliminate the risk of HAV infection during pregnancy [3].

As only 12 cases of symptomatic women were identified during the study period, we did not perform statistical analysis for maternal or fetal complications in this study. HAV may be low relatively low in incidence compared to other infections; however, asymptomatic pregnant women and pregnant women with mild disease (with symptoms similar to those expected in normal pregnancy) may not be diagnosed. Therefore, the true incidence may be underestimated. Further studies are needed to evaluate the epidemiology of HAV infection during pregnancy and its clinical consequence in maternal and fetal aspects.

In conclusion, we present 12 cases of HAV infection during pregnancy, including cases with maternal and fetal complications. Because the incidence of HAV infection in women of reproductive age is increasing, a further focus on preventing HAV infection during pregnancy is warranted.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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