

Acute Hepatitis A Infection in Pregnancy Is Associated With High Rates of Gestational Complications and Preterm Labor

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Background & Aims: Hepatitis A virus (HAV) infection is the most common cause of acute hepatitis but is rarely reported during pregnancy. Our aim was to evaluate the impact of acute HAV infection on pregnancy outcome. **Methods:** Consecutive admissions of 79,458 pregnant females during a 25-year period were retrospectively reviewed. **Results:** Thirteen cases of second and third trimester HAV infection were found and evaluated. Nine of the 13 patients (69%) developed gestational complications, including premature contractions ($n = 4$), placental separation ($n = 2$), premature rupture of membranes ($n = 2$), and vaginal bleeding ($n = 1$). In 8 of these patients, complications led to preterm labor, at a median of 34 gestational weeks (range, 31–37 weeks). Delivery was vaginal in 12 of the 13 cases; fetal distress was noted in a single case, and meconium in amniotic fluid in 2 cases. Median birth weight was 1778 grams and 3040 grams in preterm and term deliveries, respectively ($P < .05$). Child outcome was favorable in all cases. In 4 cases, neonatal serum HAV RNA levels were measured and found negative. The presence of fever and hypoalbuminemia were associated with delivery at an earlier gestational week. There was a positive relation between gestational week at diagnosis of HAV infection and birth week ($r = 0.68$, $P = .02$), suggesting a causality relationship. All mothers featured full recovery from HAV infection. **Conclusions:** Acute HAV infection during pregnancy is associated with high risk of maternal complications and preterm labor. HAV serology and maternal vaccination during prepregnancy evaluation should be considered in areas of the world in which susceptible adult populations exist.

Hepatitis A virus (HAV) infection is the most common cause of acute viral hepatitis, affecting 1.4 million people annually and accounting for 20%–40% of cases of adult viral hepatitis in the Western world.¹ The National Notifiable Disease Surveillance System has reported approximately 30,000 annual cases of hepatitis A in the United States. However, because most cases are not reported, the true number was estimated to be 180,000 patients acquiring asymptomatic infection and

90,000 patients suffering symptomatic disease, including 100 fatalities. A Centers for Disease and Prevention (CDC) surveillance study estimated that 15 cases of HAV infection were detected per 100,000 individuals.² With improved socioeconomic conditions, adults are more frequently seronegative for HAV and therefore susceptible to infection. In a study of adult employees in a pediatric medical center in Israel, only a 48.3% rate of HAV seropositivity was noted.³

Marked increase of liver enzymes (clinical acute hepatitis) during pregnancy may be caused by pregnancy-related liver disorders such as pre-eclampsia; hemolysis, elevated liver enzymes, low platelets (HELLP syndrome); and acute fatty liver of pregnancy or alternatively by intercurrent liver disease. Of the nonpregnancy-related causes of acute hepatitis, viral hepatitis is the most common cause. However, in contrast to HAV infection being the most common cause of acute viral hepatitis in the general population, it has been infrequently reported among pregnant females.^{4–13}

In a study from Ireland, 13,181 consecutive deliveries were retrospectively reviewed.⁴ HAV infection was responsible for only 2% of hepatitis cases during pregnancy (1 patient). In a series from India of 127 consecutive pregnant patients with acute or fulminant hepatitis, no case of HAV infection was identified.⁵ Another prospective 3-year study of pregnant women with acute hepatitis from India identified no case of HAV infection among the 76-patient study population.⁶ In other retrospective patient series, the incidence of HAV infection during pregnancy was also extremely low.^{7–12} Among 313 patients affected by the urban HAV epidemic reported in Tennessee during 1994–1995, 4 individuals were pregnant. Two of the 4 females were in their third trimester of pregnancy, and both experienced premature delivery

Abbreviations used in this paper: HAV, hepatitis A virus; HELLP, hemolysis, elevated liver enzymes, low platelets; HEV, hepatitis E virus.

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with subsequent full recovery of mother and child.¹³ None of these series reported maternal-fetal transmission of HAV. Two subsequent case reports, however, suggested that maternal-fetal transmission of HAV infection does rarely occur. In both cases, HAV infection was associated with fetal ascites and meconium peritonitis, necessitating postnatal surgical intervention.^{14,15}

From these reports, it was inferred that, in HAV hepatitis during pregnancy, the prognosis of both mother and child is excellent because no cases of mortality were reported. However, the paucity of reports regarding HAV infection in pregnancy precludes accurate evaluation of its clinical course and of maternal and neonatal complications. In the present study, we reviewed the records of 79,458 consecutive pregnant females admitted to a university hospital during a 25-year period. Among 34 females identified with acute hepatitis, 13 suffered HAV infection. The clinical and laboratory characteristics of this unique patient group, as well as outcome and complications of HAV hepatitis, are presented.

Materials and Methods

Patients

We reviewed the computerized diagnoses of all pregnant patients who were admitted to Hadassah-Hebrew University Medical Center, Mount Scopus Campus, Jerusalem, Israel, between the years 1980 and 2005. The participating hospital serves as primary, secondary, and tertiary medical care facility. Included were patients who presented with HAV-induced acute hepatitis during pregnancy, diagnosed by positive anti-HAV immunoglobulin (Ig)M serology and absence of other etiologies for acute liver injury. The study met the requirements of the institution's review board for the protection of human subjects.

Clinical Information

Information was retrospectively gathered using the patients' medical charts and computerized files, including patient clinical records and reports from follow-up outpatient clinic visits. Data included age, background medical and obstetric conditions, and gestational and delivery information, including maternal and fetal complications and outcome. Data regarding HAV infection included gestational date of diagnosis, clinical manifestations, and outcome.

Laboratory Information

Blood count, aminotransferase activity, bilirubin, creatinine, urea, albumin, and prothrombin time were recorded using standard automated procedures (automated chemistry analyzer Kodak-Vitros 950, Rochester, NY, and the coagulation time analyzers Acl 200 and Acl 1000). Acute HAV-induced hepatitis was defined as a combination of acute ele-

vation of hepatic aminotransferase levels to more than 2 times the upper limit of normal values, positive IgM, and negative IgG anti-HAV antibodies (Abbott Diagnostics, Abbott Park, IL), and absence of other cause of acute hepatitis. Neonatal HAV RNA levels were measured using in-house nested polymerase chain reaction (PCR) test. The same laboratory, using the same kits, made all laboratory tests.

Data Analysis

Data concerning numeric variables are presented as median and range (minimum-maximum) unless stated otherwise. Pearson correlation was used to assess the relationship between gestational age at diagnosis of HAV and at the time of delivery. Associations between dichotomic clinical and laboratory parameters and gestational age at delivery were explored using analysis of covariance (with gestational age at HAV diagnosis as covariate). Two-sided *P* values of less than .05 were considered significant. Analyses were made with StatistiXL version 1.5 (2005), Kalamunda, Western Australia.

Results

Baseline Characteristics of the Study Population

At the Hadassah-Hebrew University Medical Center, Mount Scopus Campus, 79,458 deliveries were carried out during 1980–2005. Thirty-four cases of acute hepatitis were recognized among hospitalized pregnant individuals. Among these, 13 cases of acute hepatitis caused by HAV infection were identified by a combination of acute elevation of serum aminotransferase activity, positive IgM anti-HAV serology, and absence of other causes of acute hepatitis. The 21 cases of non-HAV acute hepatitis were caused by benign cholestasis of pregnancy (7 cases); acute cholecystitis (3 cases); acute fatty liver of pregnancy (2 cases); hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome (2 cases); sepsis of unknown origin (1 case); acute Brucellosis (1 case); acute Epstein Barr virus infection (1 case); and undefined hepatitis (4 cases). All patients with HAV hepatitis were previously healthy and consumed no prescribed, over-the-counter, or natural medications other than folic acid additives. Median age was 25 years (range, 22–34 years), and median parity was 4 (range, 2–7). The median gestational week at the time of HAV diagnosis was 31 (range, 20–40 weeks). Eleven of the 13 HAV infections (85%) occurred between 1991 and 1999, none during documented HAV epidemics. Admission of all 13 patients was directly related to symptoms attributable to HAV hepatitis.

Clinical and Laboratory Manifestations

Clinical and laboratory results of the study population are listed in Table 1. Prior exposure to household

Table 1. Demographic, Clinical, and Laboratory Characteristics of the Study Population

Characteristic	Patients with complications (n = 9)	Patients without complications (n = 4)	All patients (n = 13)
Age, y ^a	25 (22–32)	28 (24–34)	25 (22–34)
Parity ^a	3 (2–5)	5 (5–7)	4 (2–7)
Household exposure to HAV, No. (%)	4 (44)	0 (0)	4 (31)
Gestational age at HAV diagnosis, wk ^a	31 (20–37)	37 (24–40)	31 (20–40)
Clinical manifestations, No. (%)			
Fatigue	6 (67)	2 (50)	8 (62)
Jaundice	5 (56)	3 (75)	8 (62)
Pruritus	4 (44)	1 (25)	5 (39)
Fever	4 (44)	0 (0)	4 (31)
Abdominal pain	3 (33)	0 (0)	3 (23)
Laboratory parameters ^a			
ALT, U/L	341 (103–2240)	432 (329–2470)	341 (103–2470)
AST, U/L	466 (106–2615)	647 (203–6857)	466 (106–6857)
LDH, U/L	983 (338–5098)	843 (755–931)	928 (338–5098)
AP, U/L	222 (113–365)	274 (221–433)	233 (113–433)
γ GTP, U/L	63 (10–214)	74 (63–90)	68 (10–214)
Total bilirubin, μ mol/L	65 (32–336)	73 (72–91)	72 (32–336)
Albumin, g/L	30 (24–34)	31 (26–32)	30 (24–34)
Prothrombin time, INR	1.1 (0.8–1.5)	1.1 (1.1–1.6)	1.1 (0.8–1.6)
Hemoglobin, g/L	11.4 (7.8–13.8)	11.9 (10.9–12.4)	11.9 (7.8–13.8)
WBC, 10^3 cells/ μ L	8.8 (3.4–11.8)	12.7 (8.3–14.4)	9.2 (3.4–14.4)
Platelets, 10^6 cells/ μ L	205 (125–347)	246 (210–347)	219 (125–347)
Gestational age at labor, wk ^a	34 (31–37)	39 (38–40)	34 (31–40)

INR, international normalized ratio; WBC, white blood cell count.

^aValues are reported as median (range)

members with acute HAV hepatitis, a known risk factor for the acquisition of the disease,¹⁶ was identified in 4 subjects (31%). Disease manifestations were as follows: fatigue in 8 subjects (62%), jaundice in 8 (62%), pruritus in 5 (39%), fever in 4 (31%), and abdominal pain in 3 (23%). Serum liver enzymes were notable for moderately to markedly elevated activity of alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase, along with mildly elevated alkaline phosphatase and γ -glutamyl transpeptidase activities. Bilirubin levels were elevated in all patients, whereas serum albumin was moderately reduced. Hemoglobin levels were generally reduced, whereas white blood cell and platelet counts varied. Prothrombin time was normal to minimally prolonged. Abdominal ultrasonography and Doppler studies were performed in 7 cases, and all were normal. All cases of hepatitis demonstrated complete resolution of the disease, with no cases of fulminant hepatic failure or cholestatic hepatitis noted. One patient featured relapsing HAV hepatitis, first appearing at the fourth gestational month and subsequently reappearing during the seventh gestational month and ultimately fully resolving. Median gestational week at labor was 34 (range, 31–40 weeks). One patient had prolonged jaundice and elevated aminotransferase activity after delivery, which ultimately resolved.

Gestational Course and Perinatal Complications of Acute HAV Infection

Nine of 13 patients (69%) with HAV infection during pregnancy developed gestational complications, including premature contractions (4 subjects), placental separation (2 subjects), premature rupture of membranes (2 subjects), and uterine bleeding (1 subject). Eight of these 9 patients with complications ultimately experienced preterm labor, at a median of 34 weeks of gestation (range, 31–37 weeks). Delivery was vaginal in all but 1 of the cases (cesarean section because of placental separation). Fetal distress was noted in a single case and meconium in amniotic fluid (by itself a sign of fetal distress) in 2 additional cases. Birth weight was 1788 (range, 1518–2840) grams and 3040 (range, 2830–3490) grams in preterm and term neonates, respectively ($P < .05$). Placentas appeared normal in all cases. Child outcome was favorable in all cases. In 4 cases in which serum neonatal HAV RNA levels were measured, no evidence of mother-child transmission of infection was noted.

Clinical and Laboratory Characteristics Associated With Preterm Delivery

Prenatal clinical and laboratory parameters were analyzed for association with preterm delivery. A strong

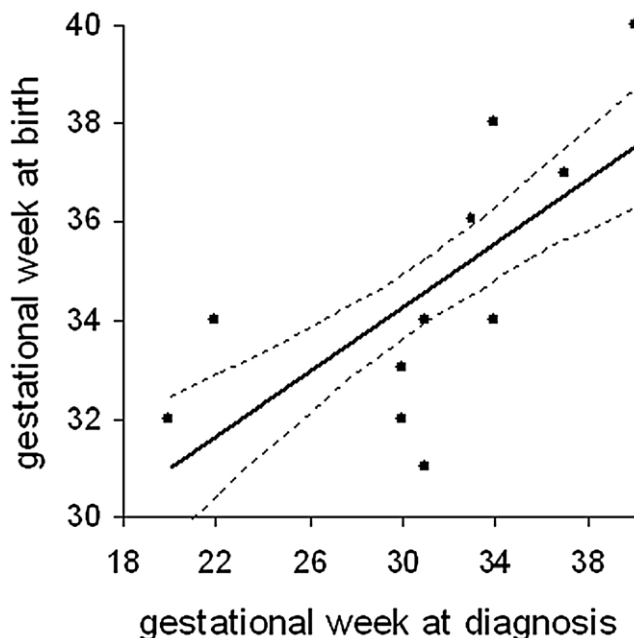


Figure 1. A scatter plot disclosing significant positive correlation between gestational age at diagnosis of acute hepatitis A and gestational age at labor, $r = 0.68$, $P = .02$. The dotted lines represent 95% confidence intervals.

association was found between gestational week at diagnosis of HAV and gestational week at labor. As apparent in Figure 1, these 2 occurrences were positively correlated ($r = 0.68$, $P = .02$).

Of the various clinical manifestations reported (jaundice, pruritus, abdominal pain, and others) only fever was found to predict preterm labor. The presence of fever, as a categorical variable, was associated with an earlier birth week 32.8 ± 1.5 (mean \pm SD) vs 34.8 ± 2.6 weeks in the absence of fever ($P < .05$ by ANOVA, which included gestational week at diagnosis as covariate). Of the measured laboratory parameters (liver enzymes, prothrombin time, blood count, and others), an association with preterm labor was found for serum albumin. Birth week was 32.3 ± 1.5 (mean \pm SD) weeks in women with albumin levels below 30 g/L vs 34.7 ± 2.3 weeks in subjects with serum concentrations ≥ 30 g/L ($P < .05$ by ANOVA, which included gestational week at diagnosis as covariate). None of the other recorded demographic or clinical parameters differentiated the 4 patients who did not develop gestational complications from the 9 who did develop gestational complications.

Discussion

This retrospective study, focusing on the clinical characteristics of acute HAV hepatitis during pregnancy, reveals that HAV infection during second and third trimester of pregnancy is associated with a high rate of

gestational complications and preterm labor. Furthermore, in our study, a causal relationship between HAV infection and preterm labor is suggested by the temporal association between the 2 events. Considering the relatively mild nature of maternal disease noticed in our subjects, the 69% rate of gestational complications and preterm labor is appreciably higher than the rate of preterm labor observed in association with other acute infections.

In comparison, pyelonephritis, a well-known cause of preterm labor and the leading infectious cause of hospitalization during the third trimester of pregnancy, is associated with premature birth in only 5%–10% of affected women.¹⁷ An explanation for the difference in gestational complications between HAV and other infections may be related to the frequency of uterine contractions. A recent study among pregnant women with pyelonephritis reported a positive correlation between uterine contraction frequency and premature birth, independent of fever.¹⁸ A possible effect of viral hepatitis A infection on the rate of uterine contractions, indirectly implied by our data, may be associated with higher rates of premature birth.

Our data imply that clinical features associated with HAV infection in pregnancy may predict preterm delivery. Thus, despite the small sample size, significant associations were observed between preterm labor and the presence of both fever and hypoalbuminemia. Whether these associations reflect nonspecific effects of intercurrent illness upon pregnancy, or rather are particular consequences of viral hepatitis, is not known. Notably, despite prematurity, the neonatal outcome of babies born to HAV-infected mothers was benign, and mother-to-child transmission of HAV was not identified.

Prior characterization of HAV infection in pregnancy comes from only a handful of reported cases.⁴ Among 313 patients affected by the urban hepatitis A epidemic, 4 individuals were pregnant, 2 of whom experienced premature delivery with subsequent full recovery of mother and child.¹³ In all other patient series of hepatitis during pregnancy, mainly originating in southeastern Asia, no cases of acute hepatitis A infection were identified, whereas most cases of acute viral hepatitis during pregnancy were attributed to hepatitis E virus (HEV) infection.^{5–12} The paucity of reported HAV cases in pregnant females may be attributed to the true infrequency of HAV infection during pregnancy, under diagnosis of the disorder in pregnant patients, and to the fact that many of the studies concerning acute viral hepatitis in pregnancy were conducted in hyperendemic areas, in which the incidence of symptomatic HAV infection in adults is extremely low. In contrary to these

studies, ours was conducted in Israel, a country that lies within the outskirts of the HAV hyperendemic area. The intermediate endemicity of HAV infection in Israel's population has manifested in multiple annual cases of HAV infection in adults.¹⁹ In the last 5 years, a universal childhood HAV immunization program has resulted in a steady decline in new cases of childhood HAV infection and is expected to affect similarly the rate of adult HAV infection in years to come.²⁰

The epidemiology and mode of transmission of acute HEV infection is similar to acute HAV infection.²¹ A unique, unexplained feature of HEV infection is an unusually high rate of transmission to pregnant individuals and high rates of gestational and medical complications, including progression to fulminant hepatic failure.^{6,22} However, studies reporting high rates of HEV infection during pregnancy originate from Asia, Africa, and Central America.^{5,6,23-25} In these areas, exposure to HAV predominantly occurs during early childhood, making HAV infection in adults extremely rare. This geographic and epidemiologic difference, and not a true difference between the nature of HAV and HEV infections in pregnancy, may explain the extremely low or nonexistent rates of HAV infections during pregnancy noted in these studies in comparison with HEV infection.

The presented series suggests that, like many of the other clinical and epidemic similarities between HAV and HEV infections, these 2 hepatotropic viruses may also share the tendency for high rates of gestational complications and preterm labor. The pathophysiologic basis for this phenomenon is unknown. It may involve direct viral inoculation of placental tissues, or alternatively a remote effect such as accumulation of bile acids, that have been recently suggested to be associated with high fetal complication rates in benign cholestasis of pregnancy.²⁶ In contrast to studies from HEV endemic areas, none of the pregnant individuals with acute HAV hepatitis in our study progressed to develop fulminant hepatic failure. This difference may reflect a milder clinical course of HAV infection during pregnancy or may stem from the small scale of our series. In addition, no viral transmission into the newborn was noted in our study, in contrast to rare reports of HAV and HEV transmission to the newborn during third trimester infection.^{14,15,27}

All cases of HAV infection in our study occurred during the second and third trimester of pregnancy. We do not know whether the clustering of HAV hepatitis in the third trimester represents a true phenomenon, a selection bias because of milder subclinical disease at earlier stages of pregnancy, or to the fact that early HAV-induced miscarriage was erroneously presumed to

be spontaneous. Interestingly, none of the patients with gestational HAV infection were nulliparous. This observation may stem from a greater tendency of multiparous patients to acquire the disease from their children. Indeed, 4 of the 13 pregnant HAV patients (31%) had documented household exposure to a person with acute HAV infection.

The American College of Obstetricians and Gynecologists (ACOG) recommends that a standard infectious panel be obtained on every pregnant woman at the first prenatal visit. This includes urinary infection screen; serology for rubella, syphilis, human immunodeficiency virus, and hepatitis B surface antigen; and screening for chlamydia infection. At-risk women should also be screened for gonorrhea and toxoplasmosis.²⁸ Like most of these infections, the risk of HAV infection in pregnancy revealed in this study can possibly be eliminated by universal early antepartum screening for the disease. Vaccination of indicated cases with one of the inactivated hepatitis A vaccines that are available for preexposure prophylaxis is considered safe for use in pregnancy.²⁹ In our opinion, the addition of HAV serology to maternal screening at the first prenatal visit deserves further evaluation.

Our study has several limitations. First, it is retrospective and as such is subjected to selection bias. Second, the study only includes hospitalized pregnant patients with acute hepatitis and does not include pregnant individuals with HAV infection that may have not been diagnosed or were treated in an outpatient setting. Thus, this study cannot assess the true incidence of HAV infection in pregnancy. Rather, it is designed to evaluate the clinical course of hospitalized pregnant patients with HAV infection. Taking this limitation into account, our personal experience clearly demonstrates that the vast majority of pregnant individuals who develop acute hepatic damage during the second and third trimester of pregnancy are referred for hospitalization for maternal and fetal monitoring and for ruling out of pregnancy-associated hepatitis (secondary to disorders such as HELLP syndrome and acute fatty liver of pregnancy). Thus, we believe that our patient group includes the majority of pregnant individuals who developed symptomatic hepatitis in our community during the study period. Until larger, prospective studies validate our findings, the study conclusions should be interpreted cautiously. Nevertheless, our study points to an extremely high rate of gestational complications and preterm labor and suggests clinical clues for a direct cause and effect relationship between infection and preterm labor.

In conclusion, this study demonstrates that acute HAV hepatitis during the third trimester of pregnancy is

associated with a high 69% risk of gestational complications and preterm labor. A direct correlation between the gestational age at diagnosis of HAV infection and the week of delivery suggests that HAV was responsible for the early labor. Fever and hypoalbuminemia are suggested as markers for a more aggressive course of disease, leading to pregnancy complications. We believe that the hepatologist and obstetrician communities should promote a prospective evaluation to assess the implications of the addition of HAV serology and vaccination to the battery of prepregnancy screening examinations in countries with intermediate endemicity of the disease. This may prevent this potentially harmful, yet totally avoidable disease.

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