

## OBSTETRICS

# Recent trends in hepatic diseases during pregnancy in the United States, 2002–2010

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**OBJECTIVE:** While pregnancy-related severe liver disorders are rare, when they occur morbidity and mortality rates are increased for mothers and infants. The objective of this study was to examine the prevalence and trends of hepatic diseases during pregnancy hospitalizations from 2002 through 2010 in the United States.

**STUDY DESIGN:** Hospital discharge data were obtained from the Nationwide Inpatient Sample, the largest all-payer hospital inpatient care database in the United States that provides nationally representative estimates. Pregnancy hospitalizations with the following diagnoses were identified: hepatitis B, hepatitis C, gallbladder disease/cholelithiasis, liver disorders of pregnancy, chronic/alcohol-related liver disease, biliary tract disease, and HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome. Age, insurance status, hospital location, and hospital region were compared among women with and without hepatic diseases using a  $\chi^2$  test. Trends in rates of pregnancy

hospitalizations and mean charges were analyzed using multi-variable logistic and linear regression, respectively.

**RESULTS:** From 2002 through 2010 there were an estimated 41,479,358 pregnancy hospitalizations in the United States. Gallbladder disease and liver disorders of pregnancy were the most common hepatic diseases (rates = 7.18 and 4.65/1000 pregnancy hospitalizations, respectively). Adjusted rates and mean charges significantly increased for all hepatic diseases during pregnancy over the study period. All hepatic diseases were associated with significantly higher charges compared to all pregnancy hospitalizations. HELLP syndrome was associated with the highest mean charges.

**CONCLUSION:** This large study among a representative sample of the US population provides valuable information that can aid policy planning and management of these hepatic diseases during pregnancy in the United States.

**Key words:** hepatic disease, hepatitis, liver disease, pregnancy

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During pregnancy women may experience physiologic changes in their liver biochemical profile; however, pregnancy-related severe liver diseases are uncommon. When these complications occur, the morbidity and mortality rates are increased for the mother and

fetus.<sup>1-4</sup> Some liver diseases are unique to pregnancy, including acute fatty liver of pregnancy (AFLP), HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, and intrahepatic cholestasis of pregnancy (ICP), all of which primarily occur in the third trimester. As previously documented, AFLP has affected between 1 in 7000 and 1 in 20,000 pregnancies, and the maternal and fetal mortality rate is high.<sup>1,2,5</sup> HELLP syndrome affects 0.5–0.9% of all pregnancies and 10–20% of severe preeclampsia cases<sup>6</sup> and is associated with outcomes such as disseminated intravascular coagulopathy, placental abruption, acute renal failure, pulmonary edema, and cardiopulmonary arrest.<sup>5</sup> Additionally, HELLP syndrome is associated with a fetal mortality of 7–20%.<sup>5</sup> ICP affects approximately 0.5–1% of pregnancies in the United States. Maternal complications from ICP are very rare, but fetal complications including prematurity, respiratory distress syndrome, and death can occur.<sup>1,5</sup>

In addition to liver diseases unique to pregnancy, other hepatic diseases such as viral hepatitis, biliary tract disease, and gallbladder disease create complications for mother and fetus during pregnancy. Approximately 1 million people are chronically infected with hepatitis B virus (HBV) in the United States.<sup>7</sup> In 2005, approximately 24,000 chronically HBV-infected women gave birth in the United States.<sup>8</sup> Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States with approximately 3.9 million people chronically infected.<sup>9,10</sup> Among women of reproductive age in the United States, the prevalence of HCV infection is approximately 1%, with an estimated 40,000 deliveries among HCV-infected women each year.<sup>11</sup>

Historically, the incidence of gallbladder and other biliary tract diseases during pregnancy has ranged from 0.05–0.3%.<sup>12-16</sup> However, current estimates of incidence are lacking.<sup>1</sup> Among

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pregnant women, gallbladder disease is the second most common non-obstetrical indication for surgical intervention, as 5-12% of pregnant women have gall stones and the risk increases with gravidity.<sup>14</sup>

Cirrhosis is rare among pregnant women due in part to the low prevalence of cirrhosis in women of reproductive age (0.0004%). Additionally, most women with advanced cirrhosis have amenorrhea and anovulation.<sup>2,17,18</sup> However, for women with cirrhosis who do become pregnant, the risk of maternal and fetal complications has been reported in up to 50% of cases and maternal mortality has been reported in up to 10% of cases.<sup>2,19,20</sup>

There is little information about the prevalence of and trends in hepatic diseases in pregnancy in the United States. The Healthcare Cost and Utilization Project's (HCUP) Nationwide Inpatient Sample (NIS) database provides a nationally representative sample of US hospitalizations. The objective of this study was to examine the prevalence and trends of select hepatic diseases during pregnancy hospitalizations over 9 years in the United States.

## MATERIALS AND METHODS

We obtained hospital discharge data without identifiers from the HCUP NIS. The NIS, one of a family of research databases and software tools sponsored by the Agency for Healthcare Research and Quality in partnership with state-level data-collection organizations, provides research databases of national and regional inpatient care delivered in the United States.<sup>21</sup>

The NIS is a stratified probability sample of approximately 20% of all US community hospitals as defined by the American Hospital Association (AHA). Hospitals are selected for the NIS on the basis of 5 characteristics: geographic region, ownership, rural/urban location, teaching status, and bed size. The NIS includes all inpatient stays from an average of roughly 1000 hospitals; when weighted, the NIS data on 7 million discharges provide national estimates of inpatient care.<sup>22</sup> It is the largest collection of inpatient care data in the United

States and includes patient demographic data and diagnostic/procedural data, as well as facility information.

We analyzed NIS data for a 9-year period from 2002 through 2010, a period during which several revisions were made to the NIS design. The number of states in the NIS has increased from 35 in 2002 to 45 in 2010. This expanded the number of sampled hospitals from 995 in 2002 to 1051 in 2010. By 2010, these states included >96% of the US population. Beginning in 2004, NIS changed the classification of urban or rural hospital location for the sampling strata to use the newer Core Based Statistical Area codes, rather than the older Metropolitan Statistical Area codes. The Core Based Statistical Area groups are based on 2000 Census data, whereas the Metropolitan Statistical Area groups were based on 1990 Census data. Also, the criteria for classifying the counties differ.<sup>23</sup> Before 2005, the AHA defined community hospitals as nonfederal, short-term (average length of stay <30 days) general and specialty hospitals whose facilities are open to the public. Starting in 2005, the AHA also included long-term acute-care facilities (stays of >25 days) in the definition of community hospitals, therefore such facilities are included in the NIS sampling frame.<sup>22</sup>

Our analysis was restricted to pregnant girls and women 15 years of age and older. We attempted to identify all pregnancy hospitalizations (excluding those for ectopic/molar pregnancy or spontaneous abortion) by searching for those with a primary or secondary *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) discharge code of 640-677, V22-V24, V27-V28, or 792.3. Pregnancy hospitalizations that resulted in a delivery were identified by ICD-9-CM codes 650 and V27, in addition to procedure codes of 720, 721, 722.1, 722.9, 723.1, 723.9, 724, 725.1-725.4, 726, 727.1, 727.9, 728, 729, 732.2, 735.9, 736, 740-742, 744, and 749.9, and diagnosis-related group codes of 370-375.

We examined all data in the following 3-year intervals: 2002 through 2004, 2005 through 2007, and 2008 through

2010. We compared age distribution, insurance status, hospital location, and hospital region for pregnant women with and without the following hepatic diseases: hepatitis B, hepatitis C, gallbladder disease/cholelithiasis, liver disorders of pregnancy, chronic and alcohol-related liver disease, biliary tract disease, and HELLP syndrome, using a  $\chi^2$  test with a significance level of 0.0018 that adjusts for multiple corrections using a Bonferroni correction. Up to 25 diagnoses were examined for each pregnancy hospitalization. We used ICD-9-CM codes to identify pregnancy hospitalizations with these morbidities: (i) for HBV infection, ICD-9-CM codes 070.2, 070.3, 070.42, 070.52; (ii) for HCV infection, ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, 070.7; (iii) for other viral hepatitis including hepatitis A, hepatitis E, and unspecified viral hepatitis, ICD-9-CM codes 070.0, 070.1, 070.43, 070.49, 070.53, 070.59, 070.6, 070.9, 573.1, 573.2; (iv) for gallbladder disease/cholelithiasis, ICD-9-CM codes 574, 575; (v) for liver disorders of pregnancy including AFLP, ICP, icterus gravis pregnancy, necrosis of liver of pregnancy, and hepatorenal syndrome following delivery, ICD-9-CM codes 646.7, 674.8; (vi) for chronic and alcohol-related liver disease including cirrhosis, ICD-9-CM codes 571, 572; (vii) for other biliary tract diseases including cholangitis and obstruction, perforation, and fistula of the bile duct, ICD-9-CM code 576; and (viii) for hepatobiliary malignancies, ICD-9-CM codes 155.0, 155.1, 155.2, 156.0, 156.1, 156.2, 156.8, 156.9. There is no ICD-9-CM code specifically for HELLP syndrome; rather it is typically coded as severe preeclampsia. We defined HELLP syndrome as severe preeclampsia (ICD-9-CM 642.5) with presence of at least one of the following: other disorders of the liver (ICD-9-CM codes 570, 573.0, 573.3, 573.4, 573.8, 573.9), liver disorders of pregnancy (ICD-9-CM codes 646.7, 674.8), or thrombocytopenia (ICD-9-CM codes 287.3, 287.4, 287.5).

Age was categorized as follows: 15-24 years, 25-34 years, and  $\geq 35$  years. Insurance status was dichotomized into private insurance and public/self-pay.

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