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Pregnancies With Cirrhosis Are Rising and Associated With Adverse Maternal and Perinatal Outcomes

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Abstract

Objectives: Cirrhosis incidence in pregnancies from outside the United States (U.S.) is rising, though contemporary data including maternal and perinatal outcomes within the U.S. are lacking.

Methods: Using discharge data from the racially diverse U.S. National Inpatient Sample, temporal trends of cirrhosis in pregnancies were compared to non-cirrhotic chronic liver disease (CLD) or no CLD. Outcomes included preterm birth, postpartum hemorrhage, hypertensive complications (pre-eclampsia, eclampsia, and/or hemolysis, elevated liver enzymes, and low platelets syndrome), and maternal or fetal death. Logistic regression was adjusted for age, race, multiple gestation, insurance status, and pre-pregnancy metabolic co-morbidities.

Results: Among 18,573,000 deliveries from 2012–2016, 895 had cirrhosis, 119,875 had non-cirrhotic CLD, and 18,452,230 had no CLD. Pregnancies with cirrhosis increased from 2.5/100,000 in 2007 to 6.5/100,000 in 2016 (p=0.01). On adjusted analysis, cirrhosis was associated with hypertensive complications (vs no CLD, OR 4.9, 95% CI 3.3–7.4; vs non-cirrhotic CLD, OR 4.4, 95% CI 3.0–6.7), postpartum hemorrhage (vs no CLD, OR 2.8, 95% CI 1.6–4.8;

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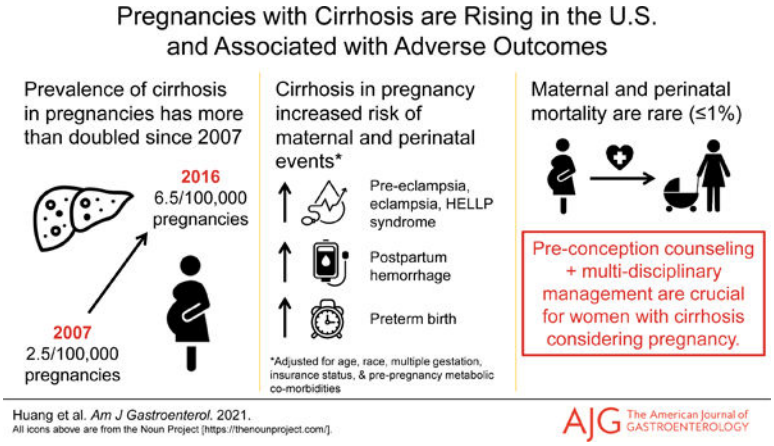
vs non-cirrhotic CLD, OR 2.0, 95% CI 1.2–3.5), and preterm birth (vs no CLD, OR 3.1, 95% CI 1.9–4.9; vs non-cirrhotic CLD, OR 2.0, 95% CI 1.3–3.3, p≤0.01). Cirrhosis was statistically associated with maternal mortality though rarely occurred (≤1%).

Conclusions: In this racially diverse, U.S. population-based study, cirrhosis in pregnancy more than doubled over the last decade. Cirrhosis conferred increased risk of several adverse events, though maternal and perinatal mortality was uncommon. These data underscore the need for reproductive counseling and multidisciplinary pregnancy management in young women with cirrhosis.

Graphical Abstract



Keywords

Chronic liver disease; reproductive health; portal hypertension; family planning; childbirth

Introduction

Pregnancy in women with cirrhosis was previously assumed to be uncommon, as cirrhosis leads to alterations along the hypothalamic-pituitary-ovarian axis, which can result in amenorrhea and impaired fertility (1–4). However, the incidence of pregnancy and childbirth in women with cirrhosis is now rising, which likely relates to improved treatments for chronic liver disease and thus improvement in liver function, as well as the sheer rise in the number of young women now affected by nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) (5–8). NAFLD incidence has experienced the greatest rise in young adults, such that NAFLD is now the most common cause of cirrhosis in pregnancy (9,10). Maternal mortality in cirrhosis has historically been reported in up to 20% of women (3), though recent studies outside of the United States (U.S.) demonstrate much lower maternal mortality rates of <2% (5,11,12). Studies from more racially homogenous cohorts in Canada and Sweden have reported an association between cirrhosis and other adverse maternal and perinatal outcomes (5,6), although contemporary population-based data from the U.S. are lacking (12).

In the current study, we leveraged discharge records from the racially diverse U.S. National Inpatient Sample (NIS) database to evaluate maternal and perinatal outcomes in pregnancies with cirrhosis, as compared to pregnancies with non-cirrhotic chronic liver disease (CLD) or pregnancies without CLD. We also aimed to further characterize temporal trends in pregnancies with cirrhosis over the preceding decade. Understanding maternal and perinatal risks of cirrhosis is paramount to guiding liver-related and obstetric care within our growing population of young women with advanced liver disease. These data can help guide preconception counseling such that women can be made aware of potential maternal and perinatal risks with pregnancy and work with their providers prior to conception to lower these risks.

Methods

Study Population

Using the U.S. 2007–2016 NIS database, we retrospectively evaluated hospital discharge records identifying pregnancies in women 18 years or older with a diagnosis or procedure indicating a delivery event including live and stillbirths after 20 weeks of gestation. Only codes for a final pregnancy event were included to avoid double counting records for the same pregnancy. Extra-uterine pregnancies, non-natural terminations, miscarriages, spontaneous and missed abortions were excluded.

Pregnancies from each delivery discharge were classified as having cirrhosis, non-cirrhotic CLD, or no CLD using corresponding International Classification of Diseases (ICD) 9 and 10 codes (Table, Supplemental Digital Content 1). Cirrhosis was classified as decompensated if the following were coded: variceal hemorrhage, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, spontaneous bacterial peritonitis, or ascites. As ascites can result from non-liver related etiologies, ascites was considered a decompensation event only if a code for portal hypertension and/or a code for CLD was also present. Non-cirrhotic CLD included ALD, chronic viral hepatitis, NAFLD, autoimmune conditions, and disorders of copper or iron metabolism. Acute liver injury, acute liver failure, and prior liver transplant were excluded. Cirrhosis and CLD etiologies were determined by associated ICD codes; ALD also included pregnancies with otherwise unknown etiology paired with a code for non-liver related alcohol use or disorder (Table, Supplemental Digital Content 1). Mixed etiologies were defined by the presence of two or more etiologies of cirrhosis or CLD on discharge codes.

Data Source

The NIS is the largest all-payer U.S. inpatient care database, designed to provide nationally representative, weighted estimates of hospital discharges using a sample of approximately 8 million inpatient admissions annually (13). In 2016, data was collected from 46 states, plus the District of Columbia, representing over 97% of the U.S. population. Data elements include primary and secondary diagnoses and procedures, discharge status, and demographic and clinical variables. The NIS was redesigned to improve national estimates in 2012. It now approximates a 20% stratified sample of all discharges from U.S. community hospitals, while previous years used a sample of hospitals from which all discharges were retained.

The NIS is sampled from the State Inpatient Databases, which contributes to the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (HCUP).

Study outcomes:

Maternal pregnancy outcomes included hypertensive complications (defined as a pre-eclampsia, eclampsia, or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome), postpartum hemorrhage, or death during the delivery admission. HELLP was included in the hypertensive complications category as it reflects a more severe variant of pre-eclampsia (14). Additional maternal pregnancy outcomes included postpartum hemorrhage, gestational diabetes (GDM), gestational hypertension, and caesarean section.

Perinatal outcomes included preterm birth (<37 weeks), fetal growth restriction (FGR), large for gestational age (LGA), and fetal death (intrauterine fetal demise). Apart from maternal death, identified using the variable “DIED”, each outcome used the ICD Ninth and Tenth Revision, Clinical Modification (Table, Supplemental Digital Content 1). Outcomes were not mutually exclusive.

Covariates of interest:

Covariates included demographics (age, race, rural-based hospital defined as population <50,000), insurance status, multiple gestation, and metabolic comorbidities including obesity, diabetes, dyslipidemia, systemic non-gestational hypertension. Demographic data were collected directly from the NIS database while other variables were based on discharge diagnosis and procedural codes (Table, Supplemental Digital Content 1). Codes were chosen based on review of pregnancy-related HCUP publications (15,16), HCUP comorbidity software, and ICD manuals (13).

Statistical analysis:

Cirrhosis prevalence and 95% confidence intervals (CI) were estimated per 100,000 pregnancies by calendar year from 2007–2016, and temporal trend in cirrhosis prevalence in pregnancy was tested by linear regression. NIS trend weight files (17) were used to allow for a continuous study of national trends spanning the 2012 database redesign (18).

Using the most recent 5 years of data (2012–2016), the association of cirrhosis with maternal and perinatal outcomes was assessed by logistic regression adjusting for baseline pregnancy factors with plausible associations with cirrhosis or outcomes of interest. These included age, race, insurance status, multiple gestation, pre-pregnancy diabetes, obesity, dyslipidemia and hypertension. The analysis was restricted to 2012–2016 due to the redesign in the NIS database, with change in hospital sampling in 2012.

Adjusted odds ratios (AORs) and CIs were computed for each study outcome using logistic regression, accounting for the complex survey design via Taylor series linearization for variance estimation. Descriptive statistics were evaluated via t-test for age and via Rao-Scott (sample-design adjusted) chi-square goodness-of-fit tests for categorical variables. All statistical tests were two-sided at significance level of 0.05, including significance levels for interaction terms. Computations were completed in SAS version 9.4 (SAS Institute; Cary,

North Carolina). The analyzed NIS dataset was purchased by the University of California, San Francisco and a signed Data Use Agreement form was completed to obtain permission for analysis. The exact number of outcomes for those ≤10 could not be reported per HCUP requirements to minimize risk of patient identification.

Results

Prevalence of cirrhosis in pregnancy

During the study period of 2007–2016, there were 37,773,398 eligible pregnancies: 1,591 with cirrhosis, 203,580 with non-cirrhotic CLD, and 37,568,227 with no CLD. The rate of pregnancies with cirrhosis more than doubled during this time, from 2.5/100,000 pregnancies in 2007 to 6.5/100,000 pregnancies in 2016 (p=0.01) (Figure 1).

In the most recent five years of data (2012–2016), there were 18,573,000 eligible pregnancies for evaluating the association of cirrhosis with maternal and perinatal outcomes. Of these, 895 had cirrhosis, 119,875 had non-cirrhotic CLD, and 18,452,230 had no CLD. The baseline characteristics of this study population are summarized in Table 1. The mean age of women in the cirrhosis, non-cirrhotic CLD, and no CLD groups were 32, 30, and 29 years, respectively (p<0.001). Notable racial differences included higher proportion of whites in the cirrhosis group, higher proportion of Asian/Pacific Islanders in the non-cirrhotic CLD group, and higher proportion of blacks and Hispanics in the no CLD group (p<0.001). There was a higher proportion of patients with private insurance in the no CLD group compared to the cirrhosis and non-cirrhotic CLD groups (p<0.001). A slightly higher proportion of pregnancies with cirrhosis had multiple gestation versus non-cirrhotic CLD and no CLD (3.4% vs 1.9% and 1.8%, respectively, p<0.001). Comorbid diabetes and hypertension were more common in pregnancies with cirrhosis, compared to non-cirrhotic CLD and no CLD (p<0.001). Obesity and dyslipidemia were also more common in pregnancies with cirrhosis, compared to the no CLD group (p=0.04 and 0.003, respectively) but similar to the non-cirrhotic CLD group (p values ≥0.09).

Among pregnancies with known etiologies of cirrhosis, the most common etiologies were viral hepatitis (39.4%), mixed (26.9%), autoimmune (18.3%), and ALD (7.7%) (Table 2). The etiology was unknown in 375 of the total 895 pregnancies with cirrhosis. As the number of pregnancies with unknown cirrhosis etiologies may relate to undiagnosed NAFLD, we performed a post hoc analysis to determine the proportion of pregnancies with obesity or diabetes in the NAFLD, unknown, and composite group with all other etiologies (excluding mixed etiologies). Obesity or diabetes was noted in 15 of 25 (60.0%) pregnancies with NAFLD, 65 of 375 (17.3%) pregnancies with unknown etiology, and 45 of 355 (12.7%) pregnancies with all other etiologies, other than mixed. This analysis supports the likelihood that the unknown etiology group may be enriched with pregnancies affected by NAFLD. Notable differences in etiologies between cirrhosis and non-cirrhotic CLD groups included more autoimmune liver disease (18.3% vs 1.3%), mixed etiologies (26.9% vs 1.0%), and ALD (7.7% vs 0.1%, all p values <0.001) in the cirrhosis group. There was less chronic viral hepatitis (39.4% vs 91.3%, p<0.001) in the cirrhosis group.

Maternal pregnancy outcomes

The prevalence of maternal outcomes by group are summarized in Table 3. Compared to non-cirrhotic CLD or no CLD, pregnancies with cirrhosis had significantly more hypertensive complications, caesarean section, and postpartum hemorrhage. Hypertensive complications occurred in 16.2% of pregnancies with cirrhosis versus 4.3% and 3.9% in non-cirrhotic CLD and no CLD groups, respectively ($p<0.001$). Caesarean section occurred in 55.9% of cirrhotic pregnancies versus 36.9% and 32.9% in non-cirrhotic CLD and no CLD, respectively ($p<0.001$). GDM was more common in pregnancies with cirrhosis compared to non-cirrhotic CLD (12.8% vs 8.7%, $p=0.05$) and no CLD (12.8% vs 7.0%, $p=0.002$). Maternal mortality was also more common in pregnancies with cirrhosis compared to non-cirrhotic CLD (0.02%) and no CLD (0.01%), with p values <0.001, although the exact number of cirrhosis deaths cannot be reported per HCUP restrictions given 10 or fewer events.

After adjusting for age, race, multiple gestation, insurance status, and pre-existing diabetes, hypertension, dyslipidemia, and obesity, cirrhosis remained associated with notable adverse maternal outcomes (Table 4). This included a more than four-fold higher odds of hypertensive complications when compared to both non-cirrhotic CLD (AOR 4.4, 95% CI 3.0–6.7, $p<0.001$) and no CLD (AOR 4.9, 95% CI 3.3–7.4, $p<0.001$). Cirrhosis was associated with postpartum hemorrhage compared to non-cirrhotic CLD (AOR 2.0, 95% CI 1.2–3.5, $p<0.01$) and no CLD (AOR 2.8, 95% CI 1.6–4.8, $p<0.001$), as well as increased adjusted odds of caesarean section compared to non-cirrhotic CLD (AOR 1.8, 95% CI 1.3–2.5, $p<0.001$) and no CLD (AOR 2.1, 95% CI 1.5–2.9, $p<0.001$). The adjusted odds of GDM were also higher in pregnancies with cirrhosis compared to no CLD (AOR 1.6, 95% CI 1.0–2.6, $p=0.04$), and non-cirrhotic CLD (AOR 1.6, 95% CI 0.98–2.5, $p=0.06$), although the latter did not reach statistical significance. There was a statistically significant association of cirrhosis with maternal mortality (vs non-cirrhotic CLD, AOR 37.0, 95% CI 3.6–380.9, $p=0.002$; vs no CLD, AOR 108.8, 95% CI 13.6–867.8, $p<0.001$). Mortality confidence intervals were wide as estimates reflected 10 or less deaths in the cirrhosis group.

Perinatal outcomes

The prevalence of perinatal outcomes by group are summarized in Table 3. Preterm birth was more common in cirrhosis than non-cirrhotic CLD (16.2% vs 6.9%) and no CLD (16.2% vs 4.6%, $p<0.001$). Fetal death was also more common in cirrhosis versus non-cirrhotic CLD (2.8% vs 0.9%, $p=0.01$) and no CLD (2.8% vs 0.7%, $p<0.001$). There was no difference in prevalence of FGR and LGA between groups.

On adjusted analysis, cirrhosis was associated with preterm birth compared to non-cirrhotic CLD (AOR 2.0, 95% CI 1.3–3.3, $p=0.003$) and no CLD (AOR 3.1, 95% CI 1.9–4.9, $p<0.001$) (Table 4). The odds of FGR, LGA, and fetal death were similar between groups.

Decompensated cirrhosis

Pregnancies with cirrhosis were stratified into compensated (n=735) and decompensated cirrhosis (n=160) based on their associated ICD-9 and 10 codes. Postpartum hemorrhage was more common in pregnancies with decompensated versus compensated cirrhosis

(25.0% vs 7.5%, p<0.01). There were no significant differences in prevalence of GDM, gestational hypertension, hypertensive complications, caesarean section, or maternal death between groups. Preterm birth and fetal death were also similar by decompensated status. No pregnancies with decompensated cirrhosis had FGR or LGA. The modest number of pregnancies with decompensated cirrhosis and limited outcome events precluded adjusted analysis by decompensation status.

Discussion

In this racially diverse, U.S. population-based study, we found that pregnancies with cirrhosis have more than doubled over the preceding decade. Cirrhosis in pregnancy was associated with notable adverse maternal and perinatal risks, including hypertensive complications, postpartum hemorrhage, and preterm birth. Although cirrhosis had a statistical association with maternal mortality, these events were reassuringly rare, and perinatal mortality was not increased. Although these data mirror the rise in prevalence of cirrhosis in pregnant women seen in Canada (5) and Europe (6), we identified distinct risks within the U.S. population of pregnant women with cirrhosis that underscore the need for close collaboration between obstetric and liver providers to optimize underlying liver disease prior to conception and throughout pregnancy.

The incidence of cirrhosis and CLD has increased globally (19). In North America, the rising incidence of cirrhosis is highest in younger adults, particularly women (20), likely driven by the growing incidence of NAFLD (9,21) and ALD (8,20,22). In particular, NAFLD rates during pregnancy have tripled since 2007 in the U.S. (7). This changing epidemiology of CLD and cirrhosis supports the importance of enhancing reproductive health care in women with cirrhosis. Indeed, the mounting clinical relevance of cirrhosis in pregnancy has come to the forefront with the recent Reproductive Health in Liver Disease Guidance on behalf of the Association for the Study of Liver Diseases (AASLD) which provides management recommendations for the growing population of women with pregnancies in the setting of cirrhosis (23).

Due to hormonal and metabolic changes with advanced liver disease, including alterations along the hypothalamic-pituitary-ovarian axis, anovulation and amenorrhea are common in cirrhosis (24,25). However, recent data highlight that rates of childbirth are no lower in women with compensated cirrhosis as compared to the general population (5). For this reason, family planning and pregnancy intentions should be routinely evaluated in adolescents and young women with cirrhosis, particularly as pregnancies in these women are often unplanned (11,23). There are a variety of safe and highly effective contraceptive options in CLD and cirrhosis, including hormonal contraception (though estrogen-containing agents should be avoided in decompensated cirrhosis) as well as long-acting reversible contraceptives, such as intrauterine devices (23).

A notable finding from the current study was the four-fold higher risk of hypertensive complications (pre-eclampsia, eclampsia, or HELLP syndrome) in pregnancies affected by cirrhosis. This increased risk was present even when compared to pregnancies affected by CLD without cirrhosis, supporting that cirrhosis itself is an independent risk factor

for hypertensive complications. The underlying mechanism for this association is not clear, though endothelial dysfunction has been implicated in the pathophysiology of these hypertensive complications (23,24,26), similar to that seen in portal hypertension (27). Microthrombi in the setting of cirrhosis may also potentially contribute to this association (28). NAFLD has been shown to increase hypertensive complications of pregnancy (7), thus, underlying NAFLD may have contributed to our observations. It is likely that some women with unknown causes of cirrhosis in our current study had undiagnosed NAFLD, with our post hoc analysis demonstrating that 17% of pregnancies with unknown etiology had obesity or diabetes, compared to 13% of pregnancies with all other etiologies.

In the current study, cirrhosis also increased the risk of postpartum hemorrhage and preterm birth. The two- to three-fold increased risk for postpartum hemorrhage may be due to underlying thrombocytopenia, as well as high rates of caesarean section (29). In the Canadian study, pregnancies with compensated cirrhosis were significantly associated with preterm birth compared to the general population, although the association with postpartum hemorrhage did not reach statistical significance (5). Differences likely relate to overall fewer postpartum hemorrhage events in 7% of pregnant women in their cohort, which included only compensated cirrhosis in contrast to 11% of our U.S. cohort, which also included decompensated disease (5). Caesarean delivery was also less common in the Canadian cohort at 32% compared to 56% in our U.S. cohort (5). The AASLD guidance specifies that mode of delivery should be guided by obstetric indications only, as the presence of cirrhosis alone is not an indication for caesarean section (23). Appropriate multidisciplinary management of pregnant patients with cirrhosis, with input from high-risk obstetrics and hepatology, is crucial to minimize unnecessary abdominal surgery in this patient population.

Importantly, maternal and perinatal death in women with cirrhosis was rare. Though point estimates were increased for maternal mortality, these must be interpreted with caution given wide confidence intervals. Likewise, in the recent study from the Canadian cohort, the maternal death rate was only 0.03% (5), and no maternal deaths were reported in the Swedish study (6). Moreover, the observed number of deaths in the current study are lower than that of a prior NIS study reflecting outcomes in the U.S. between 1993–2005 (12). While cirrhosis is indeed a higher risk condition in pregnancy, with improved cirrhosis care, maternal mortality has markedly decreased from historic rates of up to 20% (3).

The clinical management of cirrhosis in women seeking pregnancy should include counseling regarding the risks of pregnancy in both maternal and perinatal health. Though not the focus of our current study, other publications have evaluated risk factors for decompensation during pregnancy which include MELD score of >10 or existing hepatic decompensation at the time of pregnancy (5,11). As noted above, women with cirrhosis wishing to avoid pregnancy should be encouraged to use safe and effective contraception. In the context of pregnancy, variceal bleeding carries a distinct risk due to physiologic changes of pregnancy such as increased circulating blood volume, increased cardiac output, and hormonally induced systemic vasodilation (30). These changes lead to an increase in variceal growth and risk of variceal bleeding. Thus, upper endoscopy should be performed within one year prior to conception, and if not recently performed, then completed during

the second trimester of pregnancy (23). Women with small varices should consider initiation of a nonselective beta-blocker (propranolol favored), and those with larger varices should be started on a nonselective beta-blocker or undergo band ligation as advised by the recent AASLD Reproductive Health in Liver Disease Guidance (23).

The current study has some notable strengths and limitations. This was a large, nationally representative dataset, though the use of administrative data could result in misclassification from incomplete or inaccurate reporting from discharge diagnoses and ICD codes. Reliance on a single hospital ICD code for cirrhosis, though specific, has been shown to have a sensitivity of only 57–77% (31). Likewise, ICD-10 codes for NAFLD or non-alcoholic steatohepatitis may underestimate prevalence by 43–45% (32). As we have shown NAFLD to be the most common cause of cirrhosis in pregnancy (10), our current findings undoubtedly reflect an underestimation of true disease. The NIS also lacks more granular cirrhosis data, such as laboratory parameters, medication use, or prior variceal screening. As the NIS changed its sampling scheme after 2012, we were careful to analyze our data to account for this issue. As a U.S. cohort, our results may not be generalizable to other parts of the world, although the consistency with studies from Canada and Europe (5,6) lend confidence to our findings. Importantly, in contrast to studies from outside the U.S., the current study also reflects a racially and ethnically diverse population.

In summary, we identified a doubling of cirrhosis prevalence in pregnancies over the past 10 years, underscoring the growing importance of clinical management of cirrhosis in pregnancy in contemporary clinical practice. Cirrhosis was associated with notable adverse maternal and perinatal outcomes, particularly hypertensive complications, preterm birth, and postpartum hemorrhage. These findings support the need for reproductive planning in reproductive-age women with cirrhosis, including safe and effective contraception in women wishing to avoid pregnancy, as well as optimization of cirrhosis-related complications prior to conception. Women with cirrhosis who pursue pregnancy are faced with unique challenges and risks, warranting multidisciplinary management from high-risk obstetrics, hepatologists, and neonatologists to optimize maternal and perinatal health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

What Is Known:

- Data from outside the United States (U.S.) indicate rising rates of cirrhosis in pregnancy.
- The association of cirrhosis with obstetric outcomes are heterogeneous across studies, with no contemporary data available in the U.S.

What Is New Here:

- The prevalence of cirrhosis in pregnancies has more than doubled in the U.S. since 2007.
- Like other studies, cirrhosis was associated with preterm birth.
- In contrast to non-U.S. data, cirrhosis was also independently associated with hypertensive complications, including pre-eclampsia, eclampsia, or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, as well as postpartum hemorrhage.
- Maternal and perinatal mortality was rare.

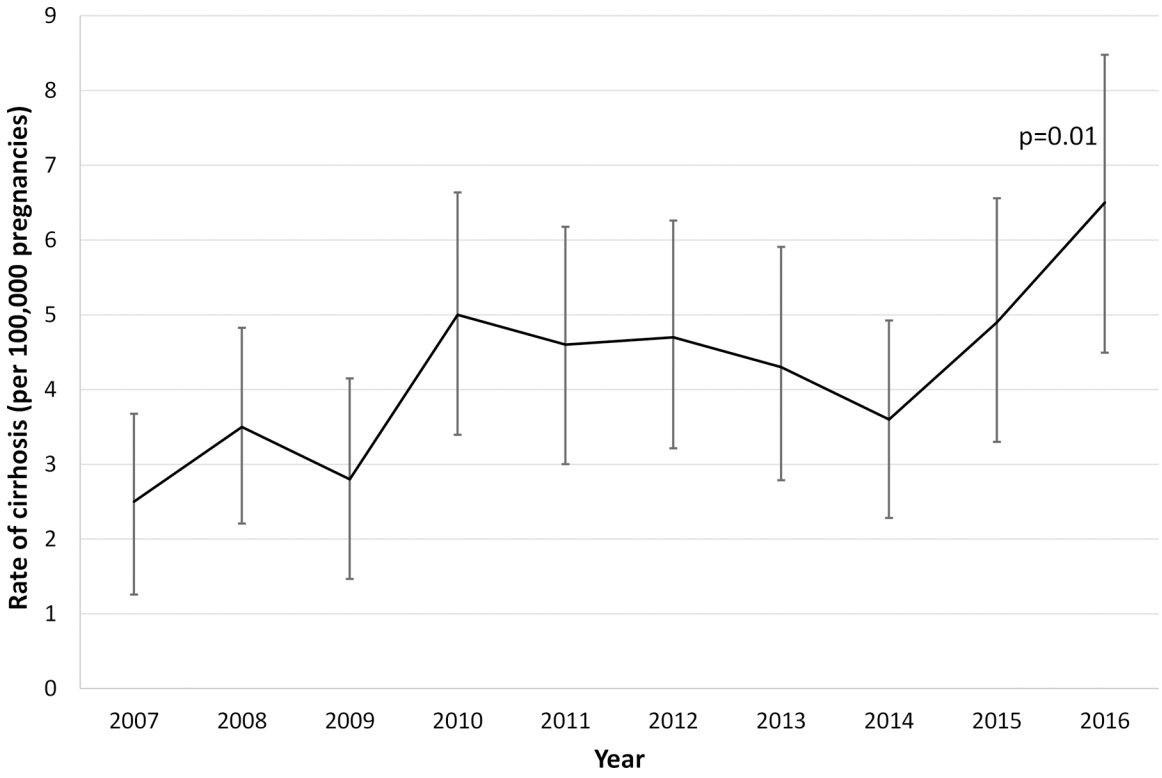

Figure 1:
Ten-year trend in rate of cirrhosis among pregnancies in the United States

Table 1.

Baseline cohort characteristics by cirrhosis and chronic liver disease (CLD) status in pregnancy

Characteristic	Cirrhosis n=895	Non-cirrhotic CLD n=119,875	No CLD n=18,452,230	Cirrhosis vs non-cirrhotic CLD p-value	Cirrhosis vs no CLD p-value
Age, mean (SE), years	31.8 (0.08)	29.5 (0.009)	28.5 (0.005)	<0.001	<0.001
Race/ethnicity, n (%)[a]					
White	520 (61.5)	63,475 (56.7)	9,265,472 (53.6)	<0.001	<0.001
Black	85 (10.1)	12,665 (11.3)	2,504,555 (14.5)		
Hispanic	125 (14.8)	9,545 (8.5)	3,561,424 (20.6)		
Asian/Pacific Islanders	50 (5.9)	20,395 (18.2)	998,950 (5.8)		
Other	65 (7.7)	5,915 (5.3)	951,775 (5.5)		
Rural-based hospital (vs urban), n (%)[a]	115 (12.8)	19,460 (16.3)	2,558,582 (13.9)	0.22	0.69
Multiple gestation, n (%)	30 (3.4)	2,275 (1.9)	327,945 (1.8)	<0.001	<0.001
Diabetes, n (%)	85 (9.5)	2,150 (1.8)	202,295 (1.1)	<0.001	<0.001
Obesity, n (%)	100 (11.2)	9,410 (7.8)	1,336,265 (7.2)	0.09	0.04
Dyslipidemia, n (%)	*	670 (0.6)	33,325 (0.2)	0.32	0.003
Hypertension, n (%)	155 (17.3)	5,290 (4.4)	565,540 (3.1)	<0.001	<0.001
Insurance status, n (%)					
Private	330 (36.9)	33,110 (27.6)	9,431,032 (51.1)	<0.001	<0.001
Medicare	80 (8.9)	2,290 (1.9)	132,600 (0.7)		
Medicaid	440 (49.2)	77,650 (64.8)	7,837,023 (42.5)		
Other/Unknown	45 (5.0)	6,825 (5.7)	1,051,575 (5.7)		

T-test and chi-squared tests were used to compare continuous and categorical measures, respectively, with $p<0.05$ considered statistically significant.

[a] Missing in n=50 cirrhosis cases (5.6%); 7,880 (6.6%) non-cirrhotic CLD; 1,117,055 (6.3%) no CLD.

* Indicates ≤ 10 outcomes, thus exact estimates cannot be reported per Healthcare Cost and Utilization Project restrictions.

CLD, chronic liver disease; SE, standard error.

Table 2.

Etiology of liver disease by cirrhosis and chronic liver disease (CLD) status in pregnancy

Etiology, n (%)[a]	Cirrhosis n=895	Non-cirrhotic CLD n=119,875	p-value
Chronic viral hepatitis	205 (39.4)	108,510 (91.3)	<0.001
Alcoholic liver disease	40 (7.7)	70 (0.1)	<0.001
Nonalcoholic fatty liver disease	25 (4.8)	5605 (4.7)	0.97
Autoimmune[b]	95 (18.3)	1495 (1.3)	<0.001
Disorders of copper or iron metabolism	15 (2.9)	1390 (1.2)	0.10
Other	0	620 (0.5)	N/A
Mixed	140 (26.9)	1160 (1.0)	<0.001
Unknown[c]	375	1025	N/A

[a]Proportions reflect pregnancies with known etiology, excluding unknown etiology category.

[b]Includes autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis.

[c]Etiology is considered unknown if International Classification of Diseases codes indicated cirrhosis with no mention of alcohol or any other causes listed here. This number includes n=100 where cirrhosis designation was assigned due to presence of a decompensation event.

CLD, chronic liver disease.

Table 3.

Prevalence of maternal and perinatal outcomes by cirrhosis and chronic liver disease (CLD) status in pregnancy

	Prevalence, n (%)			p-values (vs cirrhosis)	
	Cirrhosis n=895	**Non-cirrhotic CLD n=119,875**	**No CLD n=18,452,230**	**Non-cirrhotic CLD**	**No CLD**
Maternal Outcomes, n (%)					
Gestational diabetes	115 (12.8)	10,440 (8.7)	1,289,525 (7.0)	0.05	0.002
Gestational hypertension	45 (5.0)	4,195 (3.5)	717,770 (3.9)	0.27	0.43
Hypertensive complications[a]	145 (16.2)	5,120 (4.3)	712,970 (3.9)	<0.001	<0.001
Caesarean section	500 (55.9)	44,185 (36.9)	6,075,828 (32.9)	<0.001	<0.001
Postpartum hemorrhage	95 (10.6)	5,515 (4.6)	589,600 (3.2)	<0.001	<0.001
Maternal death	*	25 (0.02)	925 (0.01)	<0.001	<0.001
Perinatal Outcomes, n (%)					
Preterm birth (<37 weeks)	145 (16.2)	8,290 (6.9)	846,605 (4.6)	<0.001	<0.001
Fetal growth restriction	35 (3.9)	4,145 (3.5)	372,880 (2.0)	0.74	0.07
Large for gestational age	15 (1.7)	2,185 (1.8)	489,760 (2.7)	0.88	0.42
Fetal death	25 (2.8)	1,105 (0.9)	127,725 (0.7)	0.01	<0.001

[a]Includes pre-eclampsia, eclampsia, and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome

*Indicates ≤10 outcomes, thus exact estimates cannot be reported per Healthcare Cost and Utilization Project restrictions.

CLD, chronic liver disease; HELLP, hemolysis, elevated liver enzymes, and low platelets.

Table 4.

Association of cirrhosis with adverse maternal and fetal outcomes

	Cirrhosis vs non-cirrhotic CLD		Cirrhosis vs no CLD	
	AOR[a] (95% CI)	p-value	AOR[a] (95% CI)	p-value
Maternal Outcomes				
Gestational diabetes	1.6 (0.98–2.5)	0.06	1.6 (1.0–2.6)	0.04
Hypertensive complications[b]	4.4 (3.0–6.7)	<0.001	4.9 (3.3–7.4)	<0.001
Caesarean section	1.8 (1.3–2.5)	<0.001	2.1 (1.5–2.9)	<0.001
Postpartum hemorrhage	2.0 (1.2–3.5)	0.01	2.8 (1.6–4.8)	<0.001
Maternal death	37.0 (3.6–380.9)	0.002	108.8 (13.6–867.8)	<0.001
Perinatal Outcomes				
Preterm birth (<37 weeks)	2.0 (1.3–3.3)	0.003	3.1 (1.9–4.9)	<0.001
Fetal growth restriction	0.5 (0.2–1.6)	0.25	0.8 (0.3–2.6)	0.74
Large for gestational age	0.8 (0.2–2.5)	0.67	0.5 (0.2–1.7)	0.29
Fetal death	1.5 (0.5–5.0)	0.49	2.1 (0.6–6.7)	0.23

[a]Adjusted for age, race, multiple gestation, insurance status, and pre-existing diabetes, hypertension, dyslipidemia, obesity; n=17,262,645 for all models except maternal death (n=17,259,720) and caesarean section (n=17,187,190 due to missing data on delivery).

[b]Includes pre-eclampsia, eclampsia, and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome

AOR, adjusted odds ratio; CLD, chronic liver disease; CI, confidence interval; HELLP, hemolysis, elevated liver enzymes, and low platelets.