Non-alcoholic fatty liver disease in pregnancy is associated with adverse maternal and perinatal outcomes

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Background & Aims: The prevalence of non-alcoholic fatty liver disease (NAFLD) is rising in young adults, with potential implications for reproductive-aged women. Whether NAFLD during pregnancy confers more serious risks for maternal or perinatal health is unclear.

Methods: Using weighted discharge data from the US national inpatient sample, we evaluated temporal trends of NAFLD in pregnancies after 20 weeks gestation, and compared outcomes to pregnancies with other chronic liver diseases (CLDs) or no CLD. Study 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. NAFLD prevalence was estimated by calendar year and temporal trends tested by linear regression. Outcomes were analyzed by logistic regression adjusted for age, race, multiple gestation, and pre-pregnancy diabetes, obesity, dyslipidemia and hypertension.

Results: Among 18,574,225 pregnancies, 5,640 had NAFLD and 115,210 had other, non-NAFLD CLD. Pregnancies with NAFLD nearly tripled from 10.5/100,000 pregnancies in 2007 to 28.9/100,000 in 2015 ($p < 0.001$). Compared to the other groups, patients with NAFLD during pregnancy more frequently experienced

gestational diabetes (7–8% vs. 23%), hypertensive complications (4% vs. 16%), postpartum hemorrhage (3–5% vs. 6%), and preterm birth (5–7% vs. 9%), all p values <-0.01. On adjusted analysis, compared to no CLD, NAFLD was associated with hypertensive complications, preterm birth, postpartum hemorrhage and possibly maternal (but not fetal) death.

Conclusion: The prevalence of NAFLD in pregnancy has nearly tripled in the last decade and is independently associated with hypertensive complications, postpartum hemorrhage and preterm birth. NAFLD should be considered a high-risk obstetric condition, with clinical implications for pre-conception counseling and pregnancy care.

Keywords: Non-alcoholic steatohepatitis; Reproductive health; Complications; Chronic liver disease

Lay summary: The prevalence of non-alcoholic fatty liver disease (NAFLD) in pregnancy has almost tripled over the past 10 years. Having NAFLD during pregnancy increases risks for both the mother and the baby, including hypertensive complications of pregnancy, bleeding after delivery, and preterm birth. Thus, preconception counseling is warranted with consideration of highrisk obstetric management among women with NAFLD in pregnancy.

Keywords: Non-alcoholic steatohepatitis; Reproductive health; Complications; Chronic liver disease.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease (CLD) in the US, and includes simple steatosis as well as manifestations of hepatocellular injury and fibrosis, known as non-alcoholic steatohepatitis (NASH).[1] Emerging U.S. data highlight the largest rise in NAFLD incidence among adults under the age of 40.[2] NASH is also the most rapidly growing indication for liver transplantation in young adults, and the single most common indication for transplant in women.[3,4] The public health implications of NAFLD/NASH in young adults, including reproductive-aged women, is therefore vast.

NAFLD is considered the hepatic manifestation of the metabolic syndrome, and is tightly linked with obesity and diabetes mellitus (DM).[5] The obesity epidemic has affected reproductive aged women, with obesity present in

over one-third of US women aged 20–39 years-old.[6] Pregnancy itself is a relatively insulin-resistant state and concurrent maternal obesity further increases the risk of gestational diabetes.[7] The adverse risks of obesity and gestational diabetes on perinatal outcomes are well established, although whether NAFLD is independently associated with more serious pregnancy-related complications is unknown.

In the current study, we leverage discharge records from the National Inpatient Sample (NIS) database to evaluate temporal trends in NAFLD prevalence during pregnancy and to determine whether NAFLD in pregnancy is associated with adverse maternal and perinatal outcomes. Understanding the role of NAFLD in pregnancy outcomes has implications for preconception counseling in women with NAFLD, and in optimizing the management of pregnant women with NAFLD to enhance immediate and long-term maternal and perinatal health.

Patients and methods

Study population

Using the United States 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. Extra-uterine pregnancies were excluded. To avoid double counting records for the same pregnancy, only codes for a final pregnancy event were included. Non-natural terminations, miscarriages, spontaneous and missed abortions were excluded. Pregnancies from each delivery discharge were classified as having NAFLD, non-NAFLD CLD, or no CLD using corresponding ICD 9 & 10 codes (see Table S1 for comprehensive list). Other CLDs included alcohol-related liver disease, chronic viral hepatitis, autoimmune or disorders of copper or iron metabolism, and any unspecified cirrhosis. Acute liver diseases including diagnoses such as acute viral hepatitis or acute liver failure were excluded, as well as

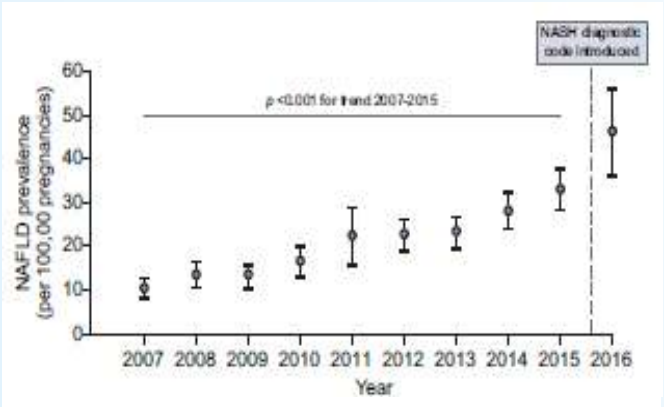

Fig. 1. Temporal trends in NAFLD prevalence in pregnancy (2007–2016). *p* value <0.001 (test of trend). NAFLD, non-alcoholic fatty liver disease.

Table 1. Cohort characteristics by liver disease status.

Characteristic	NAFLD n = 5,640	Other CLD n = 115,210	No CLD n = 18,453,375	NAFLD vs. other CLD p value	NAFLD vs. no CLD p value
Age, mean (SE), years	30.5 (0.17)	29.5 (0.05)	28.5 (0.02)	<0.001	<0.001
Race/ethnicity, n (%)*				<0.001	<0.001
White	2,255 (42.1)	61,490 (57.2)	9,266,372 (53.6)		
Black	395 (7.4)	12,475 (11.6)	2,504,590 (14.5)		
Hispanic	2,045 (38.2)	7,750 (7.2)	3,561,489 (20.6)		
Asian/Pacific Islander	385 (7.2)	20,125 (18.7)	998,985 (5.8)		
Other	270 (5.0)	5,730 (5.3)	951,815 (5.5)		
Urban or rural-based hospital, n (%)**				<0.001	<0.001
Rural	500 (8.9)	19,140 (16.6)	2,558,737 (13.9)		
Urban	5,130 (91.1)	95,840 (83.4)	15,843,742 (86.1)		
Multiple gestation, n (%)	165 (2.9)	2,120 (1.8)	327,995 (1.8)	<0.001	<0.001
Diabetes, n (%)	635 (11.3)	1,610 (1.4)	202,345 (1.1)	<0.001	<0.001
Obesity, n (%)	2,235 (39.6)	7,315 (6.3)	1,336,310 (7.2)	<0.001	<0.001
Dyslipidemia, n (%)	415 (7.4)	240 (0.2)	33,340 (0.2)	<0.001	<0.001
Hypertension, n (%)	875 (15.5)	4,630 (4.0)	565,680 (3.1)	<0.001	<0.001
Cirrhosis, n (%)	5 (0.09)	830 (0.7)	–	0.01	–

CLD, chronic liver disease; NAFLD, non-alcoholic fatty liver disease.

*Missing in n = 290 NAFLD (5.1%), 7,640 other CLD (6.7%), and n = 1,170,125 other CLD (6.3%).

**Missing in n = 10 NAFLD (0.2), 230 other CLD (0.2%), and n = 50,895 other CLD (0.3%). Chi-squared and t tests were used to compare dichotomized and continuous measures, respectively, with p <0.05 considered statistically significant.

pregnancies with discharge codes for dual diagnoses of NAFLD plus another CLD, or NAFLD plus an alcohol use disorder (Table S1).

Data source

The NIS is the largest all-payer US inpatient care database, sampling approximately 8 million hospital stays annually.[8] Data elements include primary and secondary diagnoses and procedures, discharge status, demographic and clinical variables. The NIS is designed to yield nationally representative, weighted estimates of hospital discharges. In 2012, the NIS was redesigned to improve national estimates; it now approximates a 20% stratified sample of all discharges from US community hospitals while years prior to 2012 sampled hospitals from which all discharges were retained.

Table 2. Prevalence of maternal and perinatal outcomes by liver disease status in pregnancy.

	Prevalence, n (%)			*p* values (vs. NAFLD)	
Characteristic	NAFLD n = 5,640	Other CLD n = 115,210	No CLD n = 18,453,375	Other CLD p value	No CLD p value
Maternal outcomes, n (%)					
Gestational DM	1,290 (22.9)	9,225 (8.0)	1,289,640 (7.0)	<0.001	<0.001
Gestational HTN	335 (5.9)	3,920 (3.4)	717,800 (3.9)	<0.001	<0.001
Hypertensive complications (pre-eclampsia, eclampsia, and/or HELLP syndrome)	905 (16.0)	4,380 (3.8)	713,045 (3.9)	<0.001	<0.001
Cesarean section	2,905 (51.5)	41,935 (36.4)	6,076,293 (32.9)	<0.001	<0.001
Postpartum hemorrhage	355 (6.3)	5,235 (4.5)	589,670 (3.2)	0.007	<0.001
Maternal death	5 (0.1)	35 (0.03)	920 (0.005)	0.29	<0.001
Perinatal outcomes, n (%)					
Preterm birth (<37 weeks)	500 (8.9)	7,825 (6.8)	846,805 (4.6)	0.008	<0.001
Fetal growth restriction	75 (1.3)	4,115 (3.6)	372,910 (2.0)	<0.001	0.10
Large for gestational age	300 (5.3)	1,925 (1.7)	489,770 (2.7)	<0.001	<0.001
Fetal death	45 (0.8)	1,085 (0.9)	127,730 (0.7)	0.62	0.67

CLD, chronic liver disease; DM, diabetes mellitus; HELLP, hemolysis, elevated liver enzymes and low platelets; HTN, hypertension. Chi-squared tests were used to compare proportions, with p <0.05 considered statistically significant.

The NIS is sampled from the state inpatient databases, which includes all inpatient data and contributes to the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (HCUP). In 2016, data came from46 states, plus the District of Columbia, representing more than 97% of the US population.

Study outcomes

Maternal pregnancy outcomes included hypertensive complications (defined as 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.[9] Perinatal outcomes included preterm birth (<37 weeks), fetal growth restriction (FGR), large for gestational age (LGA),

Table 3. NAFLD and adverse maternal and perinatal outcomes: adjusted analyses.

	NAFLD vs. other CLD		NAFLD vs. no CLD	
	AOR*, 95% CI	*p* value	AOR*, 95% CI	*p* value
Maternal outcomes				
Hypertensive complications (pre-eclampsia, eclampsia, and/or HELLP syndrome)	3.09 (2.54–3.76)	<0.001	3.13 (2.61–3.75)	<0.001
Postpartum hemorrhage	1.19 (0.91–1.55)	0.20	1.67 (1.28–2.16)	<0.001
Maternal deatht	3.80 (0.37–39)	0.26	17.82 (2.13–149)	0.008
Perinatal outcomes				
Preterm birth (<37 weeks)	1.03 (0.81–1.31)	0.84	1.60 (1.27–2.02)	<0.001
Fetal growth restriction	0.42 (0.25–0.71)	0.001	0.73 (0.44–1.21)	0.22
Large for gestational age	1.84 (1.36–2.48)	<0.001	1.14 (0.86–1.5)	0.36
Fetal death	0.69 (0.35–1.35)	0.28	0.96 (0.5–1.86)	0.90

AOR, adjusted odds ratio; CLD, chronic liver disease; HELLP, hemolysis, elevated liver enzymes and low platelets; NAFLD, non-alcoholic fatty liver disease. Values in bold denote significance. *AORs and CIs were computed for each study outcome using logistic regression and adjusted for age, race, multiple gestation, pre-existing diabetes, hypertension, dyslipidemia, and obesity, with p <0.05 considered statistically significant; N = 17,263,795 for all models except maternal death (17,260,870 for maternal death model) of available 18,574,225. †Reflects 5 deaths in NAFLD group, 35 deaths in other CLD group and 920 deaths in no CLD group.

and fetal death (stillbirth or intrauterine fetal demise). With the exception of maternal death, identified using the variable "DIED", each outcome used ICD-9-CM and ICD-10-CM beginning in October 2015 (Table S1). Outcomes were not mutually exclusive. ICD-9-CM codes primarily came from Chapter 11 of the ICD manual on Complications of Pregnancy, Childbirth, and the Puerperium (codes 630–679), as well as from non-pregnancy-related chapters. ICD-10-CM codes primarily came from Chapter 15 Pregnancy, childbirth and the puerperium (codes O00-O9A) and Chapter 16 Certain conditions originating in the perinatal period (codes P00-P96).

Covariates of interest

Covariates included demographics (age, race/ethnicity, ruralbased hospital defined as population <50,0000), multiple gestation, and pre-existing comorbidities including obesity, diabetes, dyslipidemia, hypertension (HTN), and cirrhosis.

Additional pregnancy characteristics included gestational diabetes (GDM), gestational hypertension, and cesarean section. Demographic data were collected directly from the NIS database; remaining variables were based on discharge diagnosis and procedural codes (see Table S1 for complete list of ICD-9 and ICD-10 codes). Codes were chosen based on review of pregnancy-related HCUP publications,[10,11] HCUP comorbidity software, and ICD manuals.[8]

Statistical analysis

NAFLD prevalence and 95% CIs were estimated per 100,000 pregnancies by calendar year, and the temporal trend in NAFLD prevalence in pregnancy was tested by linear regression. We used the supplemental NIS trend weight files[12] to allow for a continuous study of national trends spanning the 2012 database redesign.[13] The trend analysis was limited to 2007 through the third quarter of 2015 because of changes in NAFLD coding with the release of ICD[10]. Specifically, a code for non-alcoholic steatohepatitis (NASH) was introduced, potentially inflating NAFLD rates after the coding update.

Using the 5 most recent years of data (2012 to 2016), the association of NAFLD with maternal and perinatal outcomes was assessed by logistic regression, adjusting for baseline pregnancy factors with plausible associations with NAFLD or outcomes of interest. These included age, race, multiple gestation, prepregnancy diabetes, obesity, dyslipidemia and hypertension. The analysis was restricted to 2012–2016 due to changes in hospital sampling in 2012. Though GDM does not reflect a baseline pregnancy characteristic, it is associated with NAFLD[14] as well as adverse obstetric outcomes,[15] thus efforts were specifically taken to ensure observed findings were not driven by GDM, including additional adjustment for GDM, as well as testing for interactions between GDM and liver disease categories. Additional sensitivity analyses were also performed to evaluate the consistency of findings. These included: I) restricting analyses to pregnancies without pre-existing diabetes, ii) restricting analyses of hypertensive complications to pregnancies without pre-existing hypertension, iii) restricting analyses to the ICD-9 time period to ensure that findings were not driven by the introduction of NASH coding with ICD-10, and iv) excluding pregnancies with hypertensive complications (which includes HELLP), from the analyses of postpartum hemorrhage to explore

whether observed differences could relate to low platelet counts with HELLP syndrome. Finally, we acknowledged that NAFLD is likely underdiagnosed, and women with metabolic risk factors may have had undiagnosed NAFLD, and misclassified as no CLD. Thus, we additionally performed sensitivity analyses after excluding pregnancies with obesity, diabetes, or dyslipidemia from the no CLD group, and compared those study outcomes to pregnancies with NAFLD.

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 2-sided at a 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 permission obtained for analysis after completion of a signed Data Use Agreement form.

Results

Rising prevalence of NAFLD in pregnancy

During study years 2007–2016, there were 37,775,491 eligible pregnancies; 8,523 with NAFLD, 196,701 with other CLD, and 37,570,267 with no CLD. The prevalence of NAFLD in pregnancy increased over time, with rates nearly tripling from 10.5/100,000 pregnancies in 2007, to 28.9/100,000 pregnancies in 2015 ($p < 0.001$) (Fig. 1).

In the 5 most recent years of data (2012–2016), there were 18,574,225 eligible pregnancies for evaluating the association of NAFLD with maternal and perinatal outcomes; 5,640 with NAFLD (0.1% with cirrhosis), 115,210 with other CLD (0.7% with cirrhosis), and 18,453,375 with no CLD. The mean age of women in the NAFLD, other CLD, and no CLD groups were [31], [30], and [29] years, respectively (Table 1). Notable racial/ethnic differences included a higher proportion of Hispanics with NAFLD and higher proportion of Asian-Pacific Islanders with other CLD. Pre-existing metabolic comorbidities were more common in pregnancies with NAFLD including diabetes, obesity, dyslipidemia, and hypertension (all p values <0.001) (Table 1). Most notably, obesity was present in nearly 40% of pregnancies

with NAFLD (vs. 6–7% in other groups), pre-pregnancy hypertension was thrice as common with NAFLD (15.5% vs. <5% in other groups), and dyslipidemia present in 7.4% of the NAFLD group compared to <0.5% of the other pregnancy groups. A slightly higher proportion of pregnancies with NAFLD had multiple gestation (3% vs. 1.8%, p values <0.001).

Maternal complications in pregnancies with NAFLD vs. non-NAFLD CLD and no CLD

Gestational DM, gestational hypertension, hypertensive complications (pre-eclampsia, eclampsia, and/or HELLP), cesarean section, and postpartum hemorrhage were significantly more common in pregnancies with NAFLD, compared to pregnancies with other CLD or no CLD (p values <0.001) (Table 2). GDM was present in 23% of NAFLD pregnancies vs. 7–8% in the other 2 groups. Hypertensive complications occurred in 16% of NAFLD pregnancies vs. 4% for the other groups; 52% of NAFLD pregnancies resulted in cesarean section, compared to 33% and 36% in the other CLD and no CLD groups, respectively (p values <0.001). Maternal mortality was also more common in the NAFLD group than the no CLD group (0.1% vs. 0.005%, p <0.001).

After adjusting for age, race, multiple gestation and all pre-existing metabolic disease codes (Table 3), NAFLD was associated with higher odds of hypertensive complications and postpartum hemorrhage compared to no CLD (adjusted odds ratio [AOR] 3.1; 95% CI 2.6–3.8; p <0.001 and AOR 1.7; 95% CI 1.3–2.1; p <0.001, respectively). NAFLD also conferred higher odds of maternal mortality (AOR 17.9; 95% CI 2.1–149; p = 0.01), although this estimate reflects only 5 deaths in the NAFLD group. Compared to pregnancies with other CLD, NAFLD was also associated with 3-fold higher odds of hypertensive complications (AOR 3.1; 95% CI 2.5–3.8; p <0.001). The odds of postpartum hemorrhage and maternal death were similar between NAFLD and other CLD groups (Table 3). Perinatal complications in pregnancies with NAFLD vs. non-NAFLD CLD and no CLD

Preterm birth was more common with NAFLD compared to other CLD and no CLD groups (9% vs. 7% and 5%, respectively), as was LGA (5% vs. <3% in other groups), p values <0.001 (Table 2). Conversely, FGR was less common in pregnancies with NAFLD at 1.3% vs. 3.6% in the other CLD group (p <0.001), and 2.0% in the no CLD group (p = 0.10)

(Table 2). On multivariate analysis, adjusting for age, race, multiple gestation and all pre-existing metabolic diseases, NAFLD was associated with higher odds of preterm birth compared to CLD (AOR 1.6; 95% CI 1.3–2.0; p <0.001) (Table 3). Compared to other CLD in pregnancy, NAFLD was associated with a lower odds of FGR (AOR 0.4; 95% CI 0.2–0.7; p <0.001), and conversely a higher odds of having LGA infants (AOR 1.8; 95% CI 1.4–2.5; p <0.001). No differences in fetal growth or size were observed on adjusted analyses comparing pregnancies with NAFLD vs. no CLD (Table 3).

Sensitivity analyses

All statistically significant estimates remained stable with inclusion of GDM to our fully adjusted model (Table S2). No significant interactions between NAFLD and GDM were identified for the observed comparisons between NAFLD and no CLD groups (all interaction p values >0.1). When NAFLD was compared to other CLD, a statistically significant interaction was observed for hypertensive complications, with lower odds of hypertensive complications identified in pregnancies with NAFLD and GDM (AOR 1.97; 95% CI 1.3–3.0; p = 0.001) compared to pregnancies with NAFLD without GDM (AOR 3.29; 95% CI 2.6–4.1; p <0.001), p = 0.03 for the comparison. Observed estimates remained stable after exclusion of pre-existing diabetes (Table S3). We also evaluated the association of NAFLD with hypertensive complications after excluding pre-existing hypertension, and estimates remained stable, including adjusted models for NAFLD compared to other CLD (AOR 3.36; 95% CI 2.74–4.13; p <0.001) and compared to no CLD (AOR 3.37, 95% CI 2.78-4.08, p <0.001). Estimates also remained stable for study outcomes restricted to the ICD-9 time period, with the exception of LGA, for which NAFLD also became significantly associated when compared to the no CLD group (Table S4). In a sensitivity analysis of postpartum hemorrhage excluding hypertensive complications (pre-eclampsia, eclampsia, and/or HELLP) the association of NAFLD was slightly attenuated (AOR 1.4; 95% CI 1.0–1.8) but remained significant compared to pregnancies with no CLD. Moreover, when we excluded women with risk factors for NAFLD from the no CLD group, the observed estimates for NAFLD-associated risks further increased, indicating that our primary models reflect conservative estimates (Table S5).

Discussion

In this large nationally representative US database, we identified a more than tripling of NAFLD prevalence in pregnancies over the past 10 years. Pregnant women with NAFLD had significantly higher odds of serious maternal and perinatal complications, highlighting the importance of this emerging "high-risk pregnancy" group. All metabolic comorbidities, as well as cesarean deliveries, were more common in pregnancies affected by NAFLD. Moreover, after adjusting for metabolic risk factors, NAFLD remained associated with hypertensive complications, postpartum hemorrhage and preterm birth. NAFLD increased the odds of maternal mortality, though maternal death was overall quite rare, thus findings must be interpreted with caution. Overall these data do support the need for increased awareness of the risks of NAFLD in pregnant women and their need for linkage with high-risk obstetric care.

Recent US data show a 5-fold rise in NAFLD incidence over the past 20 years, with the largest rise in adults under the age of 40 years.[2] Our data highlight the impact of this national epidemic on reproductive-aged women in particular, with NAFLD rates in pregnancy tripling since 2007. These findings align with trends in obesity and diabetes in young adults,[16] including a rise in gestational diabetes in US women, thought to relate to the growing number of pregnancies in overweight and obese women.[17] Taken together these data support the need for more routine consideration of NAFLD in pregnancy, particularly in women with existing metabolic comorbidities.

The most striking finding from this study was the more than 3-fold higher risk of hypertensive complications, including preeclampsia, eclampsia, or HELLP in pregnancies affected by NAFLD. Moreover, this increased risk was apparent when compared to pregnancies affected by other CLDs, supporting its more specific association with NAFLD vs. liver disease in general. While obesity and pre-existing HTN are established risk factors for pre-eclampsia,[18] the current study highlights the independent association of NAFLD with the spectrum of hypertensive complications, which persisted despite adjustment for baseline metabolic comorbidities. This finding has direct implications for pregnancy counseling in women with NAFLD, and supports the need for future studies to evaluate

the potential role of prophylactic measures in pregnant women with NAFLD, such as aspirin use to help mitigate this risk.

The mechanisms by which NAFLD may promote adverse maternal and perinatal events are not well defined, although observed estimates remained stable despite extensive efforts to account for potential confounding factors, including sensitivity and stratified analyses evaluating the contribution of preexisting metabolic disease and gestational diabetes. Insulin resistance in the setting of NAFLD is associated with hepatic production of inflammatory mediators such as tumor necrosis factor-alpha and interleukin-1b.[19] Insulin resistance outside of pregnancy interacts with the renin-angiotensin-aldosterone system, contributing to systemic hypertension.[20] Activation of the renin-angiotensin-aldosterone system in women with NAFLD may contribute to their increased risk of hypertensive complications in pregnancy. It is less clear why NAFLD was so strongly associated with postpartum hemorrhage. Under reporting of advanced liver disease is possible, though perhaps less likely in a young cohort of women who were able to conceive. In a sensitivity analysis excluding pre-eclampsia, eclampsia, and HELLP, estimates for postpartum hemorrhage were attenuated though remained significant, indicating that bleeding risk was not entirely explained by these conditions. An enhanced awareness of maternal and perinatal risks in women with NAFLD should promote prospective mechanistic studies to understand these pathways.

A smaller study from Sweden, capturing 110 pregnant women with NAFLD, also identified an increased risk of pre-eclampsia and preterm birth.[21] In that study, NAFLD was associated with low birth weight infants which contrasts with the association of NAFLD with LGA infants observed by us and others.[22] Differences may be due to variability in study populations as well as comorbid exposures; the Swedish study did not capture alcohol history, thus alcoholic steatosis could have been misclassified as NAFLD. A smaller cross-sectional study from Sri Lanka also identified NAFLD as a risk factor for having either pre-eclampsia or gestational hypertension,[23] although due to the modest sample size, more serious outcomes (HELLP, eclampsia, postpartum hemorrhage, or maternal and fetal mortality) were not evaluated.

The current study did focus on serious adverse maternal and perinatal

outcomes rather than the more established association of NAFLD with gestational diabetes. Pregnancy is an insulin resistant state, which is a normal physiologic adaptation to ensure adequate carbohydrate supply to the growing fetus.[24] Concurrent NAFLD in pregnancy appears to compound this insulin-resistant state, leading to increased risk of GDM. A prospective Korean study found that the presence and severity of steatosis on ultrasound was associated with the development of GDM.[25] In a similar study from Canada, hepatic steatosis in early pregnancy was associated with a composite outcome of impaired fasting glucose, impaired glucose tolerance, or GDM at 24–28 weeks of gestation.[26] In our study cohort, GDM was nearly 3 times as common in pregnancies with NAFLD, though additional adjustment for GDM did not explain their higher risk for maternal and perinatal complications.

In addition to more immediate peripartum risks, NAFLD in pregnant mothers may adversely affect the long-term health of their children. Parental history of NAFLD is associated with risk of NAFLD in children[27] although whether having NAFLD during pregnancy influences this risk is unknown. Other forms of metabolic disease during pregnancy do appear to contribute to childhood NAFLD, including baseline and trajectory of weight gain in pregnancy.[28] Higher maternal BMI is also predictive of greater hepatic lipid and fat content in infants, as measured by magnetic resonance imaging in early neonatal life.[29–31] Stillborn babies of mothers with GDM also have increased prevalence of histologically-confirmed steatosis.[32] At the time of pediatric NAFLD diagnosis, between 25–50% of children have been shown to have NASH, up to 25% of whom have advanced fibrosis.[33] Thus, the rising rates of NAFLD in pregnancy may have much farther reaching implications for liver disease in youth.

The current study has some notable limitations and important strengths. The NIS is a large, nationally representative dataset, although our study was dependent upon discharge diagnoses to ensure that we only captured study outcomes from individual pregnancies. Although we do not know the timing of NAFLD diagnosis, this chronic liver condition is expected to have been present throughout pregnancy. We were careful to analyze our data with attention to the nuances of NIS discharge records as well as changes in sampling schemes over time.[34] The rising prevalence

of NAFLD in pregnancy likely reflects both the growing awareness of NAFLD, in addition to its rising incidence. Excluding ICD10 data, which introduced a dedicated NASH code, did not affect our results. Our findings also mirror other studies that show increased NAFLD incidence across study settings, including in women of child-bearing age.[2,35] The prevalence of NAFLD in our study was also low, and thus likely underestimates disease, although we remained adequately powered to detect clinically relevant risks in pregnancies with NAFLD compared to non-NAFLD groups. It is also likely that some pregnancies in the no CLD group included undiagnosed NAFLD, particularly those with metabolic risk factors. However, this misclassification would bias results towards the null, which we confirmed to be the case in sensitivity analyses excluding pregnancies with metabolic conditions from the no CLD group. The NIS does lack patient identifiers, thus the same participant may have been captured during multiple pregnancies. However, prevalence estimates reflect person-year within a calendar period, which is less likely to result in double counting. Furthermore, each pregnancy provides unique information on individual perinatal outcomes. Pre-pregnancy metabolic comorbidities and GDM were treated as potential confounders in our analysis, and while we performed extensive sensitivity analyses demonstrating stability of results, residual confounding cannot be excluded. It is also possible that pregnancies with adverse outcomes were more likely to have testing for liver disease (i.e. confounding by indication), leading to increased NAFLD detection. However, for our 3 main study outcomes (preterm birth, postpartum hemorrhage, and hypertensive complications), confounding by indication was not felt to be likely for the following reasons. A prior study also identified an association of NAFLD with preterm birth when NAFLD was assessed earlier in pregnancy, and thus prior to the occurrence of preterm birth.[21] The standard of care evaluation and management of postpartum hemorrhage does not include liver enzymes or abdominal imaging, and when imaging is indicated would typically entail only pelvic ultrasonography.[36,37] Finally, the observed risk of hypertensive complications in NAFLD pregnancies was also noted when compared to pregnancies with other CLDs, for which prior liver tests and/or imaging would also have been performed.

In summary, we identified a near tripling of NAFLD prevalence in

pregnancies over the past 10 years. While pregnancies with NAFLD were more likely to have co-existing metabolic disease, NAFLD was associated with adverse maternal and perinatal outcomes independent of metabolic comorbidities. These data support a critical need to recognize the public health implications of NAFLD in reproductive-aged women, and ensure that women with NAFLD receive adequate pre-conception counseling, including efforts to optimize metabolic health. Moreover, pregnant women with NAFLD may warrant management by high-risk obstetrics, with the goal of improving outcomes in this growing population of mothers and infants.

Abbreviations

AOR, adjusted odds ratio; BMI, body mass index; CLD, chronic liver disease; DM, diabetes mellitus; FGR, fetal growth restriction; GDM, gestational diabetes mellitus; HCUP, healthcare cost and utilization project; HELLP, hemolysis, elevated liver enzymes and low platelets; LGA, large for gestational age; NAFLD, nonalcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NIS, national inpatient sample.

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Conflicts of Interest

MS is the site principal investigator for a NAFLD clinical trial funded by Zydus pharmaceuticals. NT is on the advisory board at Intercept Pharmaceuticals and receives grant support Gilead Sciences. No other authors have relevant conflicts of interest. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

M.S. developed study concept, study design, primary manuscript draft. J.G. and J.D. analyzed data and provided content review and manuscript edits. R.I and MC provided content review and manuscript edits with specific guidance on obstetric content, E.G., J.R, and N.T. provided content review and manuscript edits.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.03.049.

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