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Pregnancy outcome in patients with non-alcoholic fatty liver disease: a prospective cohort study

Razieh Mohammad Jafari[1,2], Elham Karimi Moghaddam[2], Azar Ahmadzadeh[2], Samaneh Bahrami[2], Pezhman Alavinejad[3], Samira Manouchehri Zanjani[2]

[1]Fertility, Infertility and Perinatology Center, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2]Department of Obstetrics and Gynecology, School of Medicine, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[3]Department of Internal Medicine, School of Medicine, Alimentary Tract Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

ABSTRACT

Aim: The purpose of this investigation was to examine the potential association between non-alcoholic fatty liver disease (NAFLD) and adverse maternal and perinatal outcomes during pregnancy.

Background: Gaining insights into the effect of NAFLD on pregnancy outcomes is essential to ensure the health and well-being of mothers and infants.

Methods: This prospective cohort study was conducted at Imam Khomeini and Razi hospitals of Ahvaz City in 2022. Totally, 180 pregnant women in the NAFLD group to 180 in the control group. In this study, a researcher-made checklist was used to collect the background information, medical history, and lab data during their initial visit using. Follow-up continued until one week after delivery, with pregnancy outcomes assessed. Statistical analysis used student's t-test and the Chi-Square test for group comparisons.

Results: Significant differences were observed between the NAFLD, and control groups in terms of age (P=0.003), BMI (P=0.016), ALT and AST measures (P<0.001), and hypertensive complications (P=0.044). The NAFLD group had higher rates of gestational diabetes (P<0.001) and gestational hypertension (P=0.003). However, no significant differences were found in gestational age at delivery, early postpartum hemorrhage rates, birth weight, and neonatal Apgar scores (P>0.05).

Conclusion: The pregnant women with NAFLD may be at risk for various complications during pregnancy, including a higher prevalence of gestational diabetes, elevated liver enzymes, and higher blood pressure compared to healthy pregnant women. However, the research failed to identify any statistically significant disparities between infants born to mothers with NAFLD and those delivered to healthy mothers in relation to birth weight, Apgar scores, or neonatal mortality.

Keywords: Non-alcoholic fatty liver disease, Pregnancy outcomes, Gestational diabetes mellitus

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Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) refers to the accumulation of fat in the liver when there is no other apparent cause for secondary hepatic fat accumulation. NAFLD can progress towards cirrhosis, and may be a significant cause of cryptogenic cirrhosis (1). It is a globally observed condition, and the most common liver disorder in western industrialized countries (2). There have been reports indicating a significant rise in the incidence of metabolic syndrome and obesity in numerous Asian countries, as well as Western countries, as a result of changes in diet and lifestyle (3). These modifications subsequently contribute to an increased prevalence of NAFLD (4). NAFLD stands as the predominant cause of chronic liver disease on a global scale, exhibiting

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Reprint or Correspondence: **Samira Manouchehri Zanjani**, *Department of Obstetrics and Gynecology, School of Medicine, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*
E-mail: samira.manouchehri1@gmail.com
ORCID ID: 0009-0001-4202-4356

varying regional prevalence rates spanning from 13.5% to 31.8% (5).

NAFLD is a complex disorder influenced by environmental and genetic factors. Previous studies showed a strong genetic component, accounting for approximately 50% of the variance in liver fat content and fibrosis (6). Most individuals with NAFLD are asymptomatic, although some with Non-Alcoholic Steatohepatitis (NASH) may experience fatigue, weakness, and vague discomfort in the right upper abdomen (7).

Recent data from the United States showed a significant surge in NAFLD incidence, particularly among adults under 40 years old (8). Among women of reproductive age, especially among the ages of 20 and 40 years, the prevalence of NAFLD has been reported to be about 10% (9).

NAFLD is considered a hepatic manifestation of the metabolic syndrome which is closely associated with obesity, and diabetes (DM) (10). The obesity epidemic has significantly affected reproductive-age women, with over one-third of women aged 20 to 39 being obese (11). Pregnancy itself is relatively insulin-resistant, and maternal obesity increases the risk of gestational diabetes (12). Preeclampsia, gestational diabetes, and cesarean section births are among the unfavorable pregnancy outcomes associated with maternal obesity (13). The risk of developing NAFLD is higher in women with a history of gestational diabetes (14). Physiological and pathological fluctuations in estrogen, and rapid weight changes during pregnancy may play a significant role in the development of NAFLD in both the mother and the newborn.

We aimed to investigate the potential association between NAFLD during pregnancy and adverse maternal and perinatal outcomes. To provide appropriate guidance and optimize the healthcare strategies for women with this condition, it is essential to evaluate the impact of NAFLD on pregnancy outcomes for ensuring the health and well-being of both mothers and infants.

Methods

The present prospective cohort study was conducted on pregnant women attending Gynecology and Obstetrics wards of Imam Khomeini and Razi hospitals affiliated to Ahvaz University of Medical Sciences, Ahvaz, Iran during 2022.

Smoking, drinking alcohol, having had multiple pregnancies, having chronic hepatitis, having HIV, taking drugs linked to fatty liver (like tamoxifen), and having a history of diseases like Wilson's disease, uncontrolled thyroid disorders, lacking LCAT, cholesterol storage disease, Wolman disease, and having previously experienced chronic liver disease were all considered exclusion criteria. To study the pregnancy outcomes in patients with NAFLD referred to Ahvaz University of Medical Sciences hospitals, sample sizes were determined based on Mousa et al., study (15). By considering an effect size of 1.0, a 95% confidence level, and 85% power of the test, the minimum required sample size was estimated at 180 individuals for both the NAFLD and control groups.

After obtaining the ethical approval code of Ahvaz University of Medical Sciences (Ethics code: IR.AJUMS.HGOLESTAN.REC.1401.023), pregnant women referring to the hospitals affiliated with Ahvaz University of Medical Sciences were underwent an assessment for the existence of NAFLD via abdominal ultrasound scans. The assessment followed established criteria, which encompassed identifying specific indicators, such as a distinct bright hepatic echo pattern relative to the right kidney, the presence of a homogeneous or coarse echo pattern, heightened attenuation of ultrasound beam, and the absence of intrahepatic architectural details. Following the detection of NAFLD in each pregnant woman by convenience sampling, a pregnant woman without liver steatosis was chosen from the same hospital and matched in gestational week. The sample selection process continued until the sample size was completed (180 samples in each group).

In the first visit after obtaining the informed consent of the participants, their background characteristics, medical history, and laboratory data on each woman in both groups were entered into a researcher-made checklist. This information included maternal age, BMI, location (urban/rural), history of diabetes and hypertension, and serum ALT and AST measurements. BMI was calculated by dividing a person's weight in kilograms by the square of his/her height in meters. Diabetes mellitus cases were the patients with fasting plasma glucose ≥126 mg/dL and/or 2-h plasma glucose

Table 1. Comparison of baseline continuous variables between the two groups

Variable	NAFLD group	Control group	P.Value
Age (year)	29.17±7.26	27.06±5.86	0.003
BMI (kg/m^2)	25.57±8.78	24.29±7.33	0.016
ALT (U/L)	34.97±32.04	20.34±10.11	<0.001
AST (U/L)	34.65±30.81	19.98±6.62	<0.001

≥200 mg/dL after a 75 gr oral glucose intake. Patients who presented with hypertension were defined as those who maintained a systolic blood pressure of 140 mmHg or higher on two consecutive occasions, or a diastolic blood pressure of 90 mmHg or higher. The pregnant women were followed up until one week after delivery. The pregnancy outcomes were gestational age at delivery (<37 week/≥ 37 weeks), gestational diabetes and gestational hypertension, delivery method (cesarean/ vaginal), early postpartum hemorrhage during 24 hours after delivery, birth weight (1000-1500 gr, 1500-2500 gr, 2500-4000 gr and >4000 gr), acute fatty liver of pregnancy, and early neonatal death.

Continuous variables were described using mean ± standard deviation (SD), and categorical variables were described using frequency and percentage. Kolmogorov-Smirnov test was used to assess the normality of the distribution of quantitative variables. Student's t-test was employed to compare quantitative variables between two studied groups, and the Chi-Square test was used to evaluate the qualitative data. SPSS software (version 22, SPSS Inc., Chicago, IL, USA) was used for all analyses. P-values less than 0.05 were considered statistically significant.

Results

In this study, 180 pregnant women with NAFLD were compared with 180 healthy pregnant women as control group. There was a significant difference between two groups in terms of age (29.17±7.26 vs. 27.06±5.86, P=0.003) and BMI (25.57±8.78 vs. 24.29±7.33, P=0.016) between NAFLD and control groups. Based on the results, the ALT and AST measures were significantly higher in the NAFLD group (P<0.001) (Table 1). In NAFLD group, 110 patients (61.11%) had Grade 1 fatty liver, 55 patients (30.56%) had Grade 2, and 15 patients (8.33%) had Grade 3.

In two separate groups, the majority of participants were urban dwellers, comprising 83.89% in the NAFLD group and 80% in the control group (P=0.34). Two groups were homogenous in terms of gestational age at delivery (P=0.25). It is noteworthy that the prevalence of diabetes was higher in the NAFLD group (5.56% vs. 1.67%, P=0.086). The incidence of hypertensive problems was 7.22% in pregnant women with NAFLD, compared to 2.22% in the control group (P=0.044). In NAFLD group, hypertensive complications comprised 9 cases of preeclampsia and 4 cases of HELLP syndrome. In contrast, the control group experienced 2 cases of preeclampsia, 1 case of HELLP syndrome, and 1 case of eclampsia. The incidence of gestational diabetes (29.44% vs. 12.78%, P<0.001) and gestational hypertension (16.11% vs. 6.11%, P=0.003) was significantly higher in the NAFLD group (Table 2).

Table 2. Comparison of baseline demographic and clinical variables between the two groups

Variable		NAFLD group	Control group	P.Value
Location	Rural	29 (16.11)	36 (20)	0.34
	Urban	151 (83.89)	144 (80)	
Gestational age at delivery	< 37 weeks	32 (17.78)	24 (13.33)	0.25
	≥ 37 weeks	148 (82.22)	156 (86.67)	
Pre-existing diabetes	No	170 (94.44)	177 (98.33)	0.086
	Yes	10 (5.56)	3 (1.67)	
Choronic hypertension	No	176 (97.78)	178 (93.89)	0.69
	Yes	4 (2.22)	2 (1.11)	
Hypertensive complications	No	167 (92.78)	176 (87.78)	0.044
	Yes	13 (7.22)	4 (2.22)	
Gestational diabetes	No	127 (70.56)	157 (87.22)	<0.001
	Yes	53 (29.44)	23 (12.78)	
Gestational hypertension	No	151 (83.89)	169 (93.89)	0.003
	Yes	29 (16.11)	11 (6.11)	

Table 3. Comparison of pregnancy outcome between two groups

Variable		NAFLD group	Control group	P.Value
Delivery method	Cesarean	89 (49.44)	74 (41.11)	0.11
	Vaginal	91 (50.56)	106 (58.89)	
Early postpartum hemorhhage	No	170 (94.44)	174 (96.67)	0.31
	Yes	10 (5.56)	6 (3.33)	
Birth weight	>4000 gr	9 (5)	8 (4.44)	0.80
	2500-4000 gr	133 (73.89)	141 (78.33)	
	1500-2500 gr	34 (18.89)	28 (15.56)	
	1000-1500 gr	4 (2.22)	3 (1.67)	
Apgar score	<7	7 (3.89)	5 (2.78)	0.56
	≥7	173 (96.11)	175 (97.22)	

Acute fatty liver of pregnancy did not occur in any of the cases in either of the two groups.

The pregnancy outcomes for pregnant women in both the NAFLD and control groups are detailed in Table 3. Both groups had a predominant method of birth, which was vaginal delivery. The rate of vaginal delivery was 50.56% in the NAFLD group and 58.89% in the control group (P=0.11). However, there were no significant differences between two groups in terms of early postpartum hemorrhage rates, birth weight, and neonatal Apgar scores (P>0.05). No case of early neonatal death was observed in any of the two groups.

Table 4 shows the pregnancy outcomes in the two studied groups based on complications during pregnancy. The results indicated a higher association between GDM and cesarean section in the both groups. Moreover, there was a more pronounced correlation between prenatal hypertension and hypertensive problems and delivery before 37 weeks of gestation in both groups.

Discussion

The study was conducted to investigate the consequences of pregnancy in the patients with NAFLD who referred to the hospitals of Ahvaz University of Medical Sciences, Ahvaz, Iran. In comparison to the non-NAFLD group, NAFLD patients had a greater incidence of hypertensive complications, gestational diabetes, and gestational hypertension. Moreover, the mean age and BMI in the NAFLD group was significantly higher than that of the controls.

The findings of this study indicated a higher rate of gestational diabetes in women with NAFLD. The results of previous studies are consistent with the findings of this study (16, 17). However, the findings of Sattari et al., study did not report a statistically significant association between NAFLD in the third trimester of pregnancy and gestational diabetes (18). The relationship between NAFLD and gestational diabetes appears to be reciprocal and bidirectional. Moreover, gestational diabetes may potentially predict the development of NAFLD in the future (18). This variation in the reported results may be associated with the differences in the criteria used for diagnosing diabetes. The criteria of

Table 4. Pregnancy outcome in two investigated group based on complications during pregnancy

Outcome	NAFLD group					Control group				
	With complication				Without complication	With complication				Without complication
	CHTN + HC	GHTN + HC	PED	GDM		CHTN + HC	GHTN + HC	PED	GDM	
C/S	2 (2.25%)	19 (21.35%)	6 (6.74%)	31 (34.83%)	31 (34.3%)	1 (1.35%)	6 (8.11%)	2 (2.7%)	14 (18.9%)	51 (68.92%)
GA< 37 week at delivery	2 (6.25%)	13 (40.63%)	2 (6.25%)	5 (15.63%)	10 (31.25%)	1 (4.17%)	5 (20.85)	1 (4.17%)	3 (12.5%)	14 (58.38)
APGAR<7	1 (14.29%)	3 (42.86%)	1 (14.29%)	-	2 (28.57%)	1 (20%)	2 (40%)	-	-	2 (40%)

American Diabetes Association (ADA) was used for diagnosing gestational diabetes (19).

Although no association was observed between the two groups in terms of type 2 diabetes. Moreover, the results of a study in pregnant women showed that grade II fatty liver is associated with a remarkable 12.5-fold increased risk of developing diabetes (16). Some current evidence demonstrated an increased risk of type 2 diabetes in association with NAFLD (20). On the basis of comparable mechanisms involving elevated insulin resistance, NAFLD may promote the development of diseases such as type 2 diabetes (17). Fat deposition in the liver results from the accumulation of fatty acids and a decrease in lipolysis, which is caused by increased insulin resistance (21). The results of this study showed that the pregnant women with NAFLD exhibited a higher BMI. Present evidence suggested that a high BMI is considered a known risk factor for NAFLD (16). Results of a cross-sectional study in Sri Lanka showed that individuals with NAFLD had higher BMI, which is consistent with our findings (19). The observed higher BMI in the NAFLD group in our study is likely explained by the well-established association of this condition with escalating levels of obesity.

The prevalence of grade II and III fatty liver disease population was estimated to be 30.56% and 8.33%, respectively. In another cohort study, the prevalence of grade II fatty liver was estimated to be 14% (16). The prevalence of NAFLD and its grades varies in different populations (16, 19). The highest prevalence of NAFLD was reported among Asian populations (21). There is some evidence suggesting that Asian populations might possess distinct environmental and genetic sensitivities in comparison to western nations, which could result in reduced insulin resistance (19). However, the precise mechanism underlying this relationship is still unknown. Elevations in ALT and AST are considered liver markers for NAFLD (21). Compared to the healthy group, patients in the NAFLD group had elevated levels of liver enzymes (AST and ALT) in the current investigation. The results of a recent study showed that women with NAFLD have higher plasma levels of ALT and AST (22). The results of Mousa et al., study showed that NAFLD in mothers is only associated with an increase in AST, not ALT (15). However, the findings of another study did not show statistically significant differences in AST and ALT levels between two groups with and without NAFLD (18).

In contrast to the findings of Foghsgaard et al.'s study (22) and in support of the present study's conclusion that expectant women with NAFLD have elevated blood pressure in comparison to the healthy group, the present study found the opposite to be true. Moreover, Sarkar et al., reported more than three-fold higher risk of hypertensive complications in pregnancies affected by NAFLD, which is consistent with our findings (23).

No cases of neonatal mortality were reported in either of the two groups, and two groups were homogenous in terms of birth weight and Apgar score. In Herath et al., study, no case of neonatal mortality was observed, which is consistent with our findings (19). In contrast to our results, some previous studies considered NAFLD as a risk factor for preterm births (16). Furthermore, the results of a meta-analysis have indicated that NAFLD is associated with potential adverse fetal outcomes (20). The differences may be due to changes in the populations being researched and the existence of different additional exposures in each study. Increased awareness of maternal and perinatal risks associated with NAFLD should stimulate further prospective mechanistic studies.

The findings of this study emphasize the identification and early diagnosis of NAFLD in pregnant women. It is recommended to include the NAFLD screening as part of routine prenatal screenings, in terms of adverse outcomes associated with developing fatty liver in mothers. Early identification of pregnant women with NAFLD can help prevent possible adverse conditions. The study had several limitations that should be considered when interpreting its results. An identified constraint was the disparity in the average age of participants in the two examined groups, which has the potential to complicate the comparison. Besides, the study had a relatively short follow-up duration, which was limited to the period of pregnancy and childbirth. This limited follow-up duration may not cover the long-term outcomes related to NAFLD. Regarding the observational nature of current study, future studies should be designed to address the relationship between NAFLD, insulin resistance, dyslipidemia, and BMI more comprehensively. Longitudinal studies with

extended follow-up periods that track participants over a longer timeframe can provide a more comprehensive understanding of the long-term consequences of NAFLD and its associated factors.

Conclusion

The pregnant women with NAFLD may be at risk for various complications during pregnancy, including a higher prevalence of gestational diabetes, elevated liver enzymes, and higher blood pressure compared to healthy pregnant women. Nevertheless, the research did not discover any noteworthy disparities in birth weight, Apgar scores, or newborn death rates between children delivered to women with NAFLD and infants born to moms without any health issues. It is noteworthy that while this study provides valuable insights, research in the field of NAFLD and pregnancy is ongoing, and additional studies may be needed to confirm and expand upon these findings.

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Conflict of interests

The authors report no conflicts of interest in this work.

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