Adverse pregnancy outcomes as a risk factor for new-onset metabolic dysfunction-associated steatotic liver disease in postpartum women: A nationwide study

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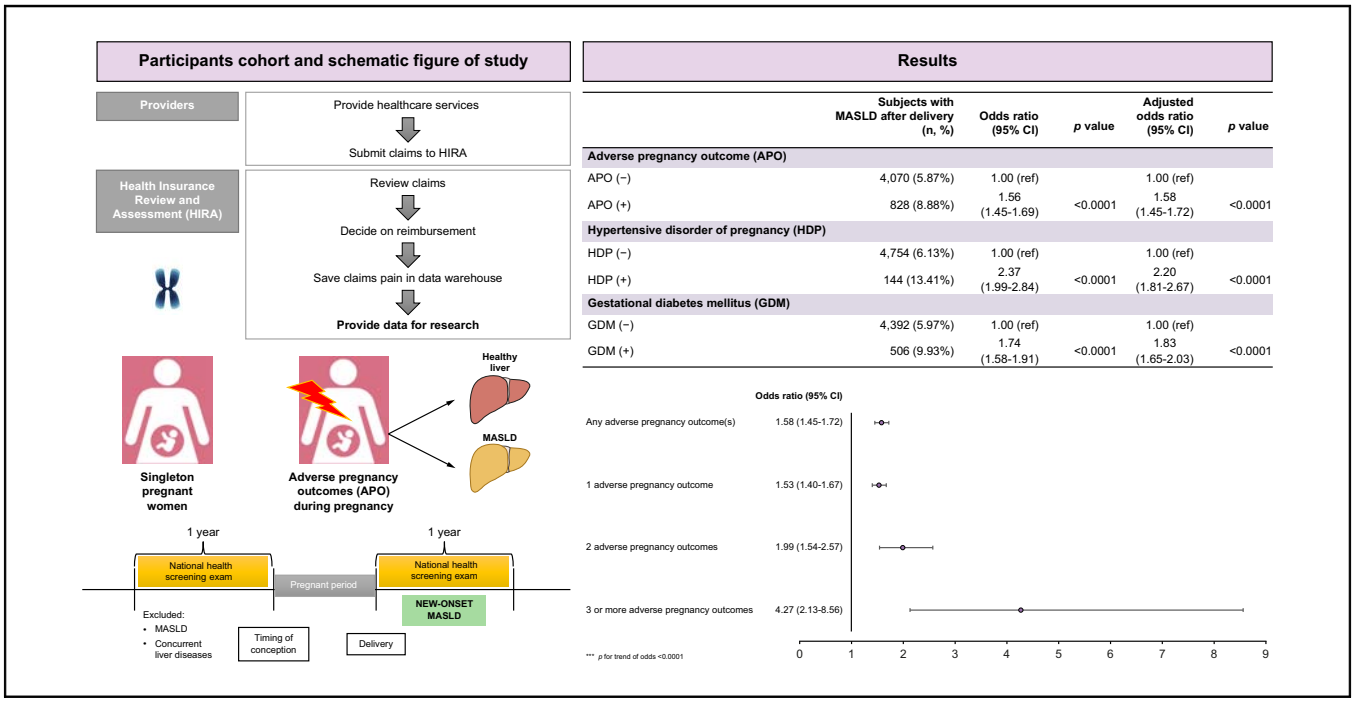
Graphical abstract



Highlights

- Women with a history of APOs had a 58% higher risk of new-onset MASLD after delivery than those without.
- In particular, women with a history of HDP or GDM were at an increased risk of developing new-onset MASLD after delivery.
- A prominent tendency toward the increased risk of new-onset MASLD after delivery was observed as the number of pregnancy complications increased.

Impact and implications

This nationwide cohort study confirms that postpartum women with a history of adverse pregnancy outcomes (APOs) are at an increased risk of developing metabolic dysfunction-associated steatotic liver disease (MASLD). These findings may bring us one step closer to understanding the exact mechanisms underlying such an important association between prior APOs and cardiovascular disease (CVD) risk among postpartum women. This bidirectional association between APOs and MASLD highlights the importance of considering pregnancy history in assessing CVD risk in women. It suggests a need for closer monitoring and lifestyle interventions for women with a history of APOs to reduce the risk of MASLD and subsequent CVD complications.

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Research article

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Adverse pregnancy outcomes as a risk factor for new-onset metabolic dysfunction-associated steatotic liver disease in postpartum women: A nationwide study

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Background & Aims: Adverse pregnancy outcomes (APOs) can worsen cardiometabolic risk factors in women, raising their likelihood of developing cardiometabolic diseases at a young age after their initial pregnancy. Nevertheless, there are limited data on the risk of newly developing metabolic dysfunction-associated steatotic liver disease (MASLD) in women who have had APOs. This study aimed to evaluate the risk of new-onset MASLD after experiencing APOs.
Methods: Singleton pregnant women who underwent national health screenings 1 year before pregnancy and 1 year after delivery were included in this study. APOs were defined as the presence of at least one of the followings: hypertensive disorders of pregnancy (HDP), gestational diabetes mellitus (GDM), preterm birth, low birth weight, and placental abruption. The primary outcome was new-onset MASLD based on the presence of APOs.
Results: Among 80,037 study participants, 9,320 (11.6%) experienced APOs during pregnancy. Women who experienced APOs had an increased risk of developing new-onset MASLD after delivery even after adjustments for various covariates (adjusted odds ratio [OR] 1.58, 95% CI 1.45–1.72). In particular, women who experienced either HDP or GDM showed a significantly increased risk of developing new-onset MASLD (adjusted OR 2.20, 95% CI 1.81–2.67, for HDP and adjusted OR 1.83, 95% CI 1.65–2.03, for GDM). Moreover, there was a tendency toward an increased risk of new-onset MASLD according to the number of APOs (p <0.001 for trend of odds).
Conclusions: APOs were associated with the risk of new-onset MASLD after delivery. Specifically, only HDP or GDM were identified as risk factors for new-onset MASLD.
Impact and implications: This nationwide cohort study confirms that postpartum women with a history of adverse pregnancy outcomes (APOs) are at an increased risk of developing metabolic dysfunction-associated steatotic liver disease (MASLD). These findings may bring us one step closer to understanding the exact mechanisms underlying such an important association between prior APOs and cardiovascular disease (CVD) risk among postpartum women. This bidirectional association between APOs and MASLD highlights the importance of considering pregnancy history in assessing CVD risk in women. It suggests a need for closer monitoring and lifestyle interventions for women with a history of APOs to reduce the risk of MASLD and subsequent CVD complications.

Introduction

Physiological changes that occur during pregnancy are designed to support and sustain pregnancy and affect nearly every organ system.[1,2] However, some of these changes can negatively impact vulnerable women and lead to adverse pregnancy outcomes (APOs). These include gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy (HDP), intrauterine growth restriction, small-for-gestational age (SGA) delivery, placental

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abruption, and preterm delivery. APOs are more likely to occur in women with pre-existing cardiometabolic risk factors and a genetic or environmental predisposition to these complications.[3,4]

APOs may also exacerbate the trajectory of cardiovascular and metabolic risk factors in pregnant women, further increasing their risk of developing cardiovascular disease (CVD)[5] or other chronic diseases.[6] As the response to pregnancy-related stress serves as an indicator of future CVD risk, the 2011 update of the American Heart Association guidelines for CVD prevention in women recommends including a history of APOs, such as GDM, pre-eclampsia, preterm birth (PTB), or birth of an SGA infant, in the assessment of CVD risk.[7]

Women who experience specific pregnancy complications have an increased risk of developing CVD at a relatively young age after their first pregnancy.[8] In addition, accumulating evidence supports the notion that non-alcoholic fatty liver disease (NAFLD) serves as a predictor of CVD in non-pregnant adults.[9–12] Although the exact biological mechanisms underlying this relationship have not been completely elucidated, insulin resistance, chronic inflammation, dysregulated lipid metabolism, and endothelial dysfunction likely play integral roles in the relationship between NAFLD and CVD.[13] To date, a substantial number of studies have shed light on the adverse outcomes in pregnant women with NAFLD, highlighting a pathogenic role of NAFLD as a risk factor for APOs, including GDM, fetal overgrowth, and HDP.[14–19] On the contrary, there are scarce data on the risk of new-onset metabolic dysfunction-associated steatotic liver disease (MASLD) in postpartum women who experience APOs during pregnancy. Exploring this topic may provide new insights into the pathogenic mechanisms by which APOs increase the susceptibility of women to subsequent metabolic diseases, including MASLD. Therefore, we investigated the risk of developing new-onset MASLD in postpartum women who experience APOs using a Korean nationwide cohort of pregnant women.

Patients and methods

Data source

This retrospective study was based on a comprehensive nationwide analysis conducted in South Korea using data from the Health Insurance Review and Assessment (HIRA) of the National Health Insurance Service (NHIS) database. The NHIS is the sole healthcare insurer in the country, providing coverage to over 97% of the population. In Korea, individuals under insurance coverage are encouraged to undergo biannual national health screening examinations (NHSE) free of charge.[20] Furthermore, infants and children born in Korea undergo a free National Health Screening Program for Infants and Children (NSHP-IC) aimed at detecting abnormal growth or developmental delays at an early stage. This study was approved by the Institutional Review Board of Korean University Guro Hospital (Approval No. 2020GR0105). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study population

Singleton pregnant women who delivered between 2012 and 2020 and met the following criteria were included in this study: (1) those who underwent NHSE and became pregnant within 1 year, (2) those whose newborns underwent NSHP-IC after delivery, and (3) those who underwent NHSE within 1 year after delivery. Women who were diagnosed with MASLD before pregnancy or who had other concomitant liver diseases as underlying morbidities were excluded from this study.

Adverse pregnancy outcomes

APOs were defined as at least one of several maternal or fetal complications, including HDP, GDM, PTB, neonatal low birth weight (LBW), or placental abruption.[21] HDP, GDM, and placental abruption were identified using International Classification of Diseases, 10th Revision (ICD-10) codes. PTB was defined as delivery occurring before the completion of 37 weeks of gestation. Similarly, LBW was defined as birth weight <2.5 kg.

Outcome measures

Demographic information and reimbursement claims, including ICD-10 diagnoses before and during pregnancy, were made accessible by the NHIS following de-identification. The primary outcome was new-onset MASLD after delivery. MASLD is defined as the presence of hepatic steatosis along with at least one cardiometabolic risk factor. The cardiometabolic risk factors are as follows: (1) BMI ≥23 kg/m^2 or waist circumference (WC) ≥80 cm, (2) fasting serum glucose ≥100 mg/dl or type 2 diabetes or treatment for type 2 diabetes, (3) blood pressure ≥130/85 mmHg or antihypertensive drug treatment, and (4) triglycerides (TG) ≥150 mg/dl or lipid-lowering treatment, and (5) HDL cholesterol ≤50 mg/dl or lipid-lowering treatment.[22,23] The fatty liver index (FLI) has been recognized as a substitute for imaging modalities in defining hepatic steatosis.[24] Hepatic steatosis was defined as an FLI ≥30.[25] Several studies have been conducted in the Asian population,[25,26] specifically targeting Asian females, and these studies have shown that an FLI cut-off of ≥30 demonstrates the best performance in detecting steatosis.[27]

The FLI was calculated based on various factors, including anthropometric measurements such as BMI and WC, as well as laboratory parameters such as TG and gamma-glutamyl transferase (GGT) levels, which were obtained from NHSE data.[28] Individuals with concurrent liver diseases, such as viral hepatitis (hepatitis B or C infection), alcohol-related liver disease, drug-induced liver disease, primary biliary cirrhosis and biliary cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis, Wilson disease, or haemochromatosis, were excluded from the analysis (for relevant ICD-10 codes, B15–B19, K70, K71, K74.3–K74.5, K75.4, K83.01, E83.0, and E83.1, respectively).

Statistical analysis

Continuous variables are described using either the mean with SDs when they follow a normal distribution or the median with IQRs when they do not adhere to a normal distribution. Variables were compared using the Student *t* test. Categorical variables are presented as counts with percentages and were compared using the Chi-square test. The adjusted odds ratios (ORs) and 95% CIs for the risk of new-onset MASLD in women with APOs compared with those without APOs were calculated using multivariable logistic regression analysis. Statistical analyses were performed using SAS for Windows (version 9.4; SAS Inc., Cary, NC, USA). The level of statistical significance was set at p <0.05.

Results

Baseline and pregnancy characteristics

During the study period, 209,116 women underwent NHSE within 1 year of pregnancy or 1 year after delivery. Finally, 78,658 women with singleton pregnancies and without concomitant liver disease

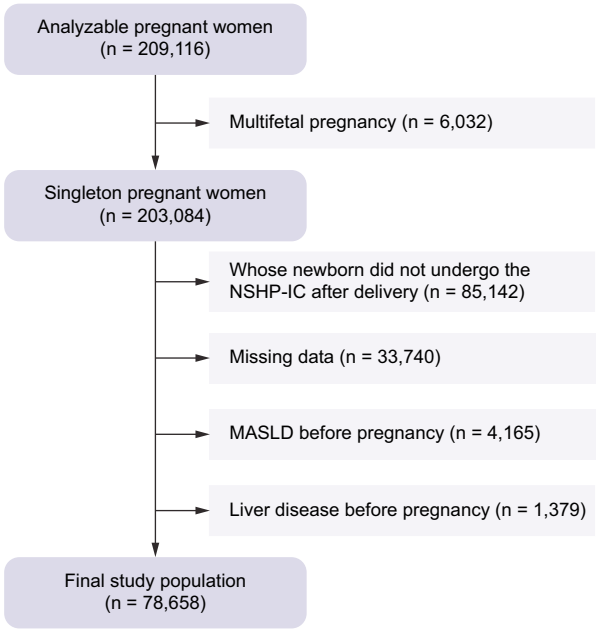

Fig. 1. Flowchart for inclusion of study population. MASLD, metabolic dysfunction-associated steatotic liver disease; NSHP-IC, National Health Screening Program for Infants and Children.

were included in this study (Fig. 1). Of the 78,658 women included in the current study, 9,320 (11.8%) had a history of APOs, and a total of 4,898 women (6.2%) developed new-onset MASLD after delivery. Table 1 shows the baseline characteristics including clinical and biochemical features and pregnancy outcomes of the study population before and during pregnancy. Women with a history of APOs had a higher BMI, WC, and systolic and diastolic blood pressures before pregnancy.

In laboratory evaluations conducted during the NHSE within a year preceding pregnancy, women who had a prior history of APOs showed higher levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), cholesterol, TG, GGT, and fasting glucose but lower HDL cholesterol levels than those who had no prior history of APOs.

During pregnancy, women with a history of APOs were older at delivery, more likely to be nulliparous, and more likely to have overt diabetes mellitus (DM), chronic hypertension, or a family history of DM. Women with a history of APOs were more likely to have undergone a cesarean section during pregnancy and had a higher likelihood of giving birth to babies with a lower birth weight.

Metabolic and biochemical features

Metabolic and biochemical features after pregnancy are shown in Table 2. As expected, women with a history of APOs had higher BMI, WC, and systolic and diastolic blood pressures after

Table 1. Baseline clinical, biochemical features, and pregnancy outcomes of study population.

	APO (-) (n = 69,338)	APO (+) (n = 9,320)	*p* value
Baseline characteristics before pregnancy			
Ever smoking	602 (0.87)	95 (1.02)	0.1439
Alcohol consumption			
None*	47,396 (68.36)	6,391 (68.57)	0.6958
Mild†	19,917 (28.72)	2,671 (28.66)	
Moderate to severe‡	2,025 (2.92)	258 (2.77)	
Charlson Comorbidity Index			<0.0001
0	47,670 (68.75)	6,240 (66.95)	
1	16,947 (24.44)	2,313 (24.82)	
≥2	4721 (6.81)	767 (8.23)	
BMI before pregnancy (kg/m^2)	20.97 ± 2.50	21.37 ± 2.77	<0.0001
WC before pregnancy (cm)	70.16 ± 6.73	71.06 ± 7.24	<0.0001
Systolic blood pressure (mmHg)	109.30 ± 10.46	111 ± 11.41	<0.0001
Diastolic blood pressure (mmHg)	68.70 ± 7.88	69.92 ± 8.59	<0.0001
Biochemical features before pregnancy			
AST (IU/L)	18.78±10.25	19.23±9.16	<0.0001
ALT (IU/L)	14.4 ± 14.0	15.5 ± 12.5	<0.0001
Cholesterol (mg/dl)	177.7 ± 30.4	181 ± 30.9	<0.0001
HDL-cholesterol (mg/dl)	63.46 ± 17.67	62.75 ± 14.92	<0.0001
Triglycerides (mg/dl)	75.70 ± 39.36	81.71 ± 45.41	<0.0001
GGT (IU/L)	15.45 ± 10.46	16.96 ± 14.31	<0.0001
Fasting glucose (mg/dl)	88 ± 9.59	90.14 ± 13.17	<0.0001
Baseline characteristics at pregnancy			
Age at delivery (years)	32.64 ± 3.86	33.58 ± 4.09	<0.0001
Nulliparity	42,514 (61.31)	5,842 (62.68)	0.0108
Family history of type 2 diabetes mellitus	8,153 (11.76)	1,507 (16.17)	<0.0001
Overt diabetes mellitus before pregnancy	546 (0.79)	179 (1.92)	<0.0001
Chronic hypertension before pregnancy	330 (0.48)	130 (1.39)	<0.0001
Pregnancy outcomes			
Cesarean section	25,589 (36.90)	4,318 (46.33)	<0.0001
Birth weight (kg)	3.28 ± 0.79	2.81 ± 0.99	<0.0001

Data are presented as n (%) or mean ± SD. Differences between APO and non-APO groups were examined using the *t* test (for continuous variables) and the Chi-square test (for categorical variables). The level of statistical significance was set at p <0.05.
ALT, alanine aminotransferase; APO, adverse pregnancy outcome; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; WC, waist circumference.
* Never drink alcohol.
† ≤20 g/day for women.
‡ >20 g/day for women.

Table 2. Metabolic and biochemical features after pregnancy.

	APO (-) (n = 69,338)	APO (+) (n = 9,320)	*p* value
Metabolic features after pregnancy			
BMI after pregnancy (kg/m^2)	22.02 ± 2.92	22.32 ± 3.18	<0.0001
WC after pregnancy (cm)	74.11 ± 16.01	74.85 ± 20.77	0.0011
Systolic blood pressure (mmHg)	109.5 ± 10.6	111.3 ± 11.6	<0.0001
Diastolic blood pressure (mmHg)	68.55 ± 7.97	69.89 ± 8.72	<0.0001
Biochemical features after pregnancy			
AST (IU/L)	19.18 ± 16.69	19.71 ± 8.76	<0.0001
ALT (IU/L)	16.84 ± 14.98	18.18 ± 15.20	<0.0001
Cholesterol (mg/dl)	184.60 ± 33.88	188.10 ± 34.16	<0.0001
HDL-cholesterol (mg/dl)	61.03 ± 16.01	60.21 ± 13.71	<0.0001
Triglycerides (mg/dl)	87.88 ± 52.67	96.46 ± 61.41	<0.0001
GGT (IU/L)	15.59 ± 15.30	17.21 ± 17.39	<0.0001
Fasting glucose (mg/dl)	88.88 ± 9.75	91.14 ± 13.48	<0.0001

Data are presented as mean ± SD. Differences between APO and non-APO groups were examined using the *t* test (for continuous variables). The level of statistical significance was set at p <0.05.
ALT, alanine aminotransferase; APO, adverse pregnancy outcome; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; WC, waist circumference.

pregnancy. In addition, women with a history of APOs showed higher levels of AST, ALT, cholesterol, TG, GGT, and fasting glucose than those who had no prior history of APOs in laboratory evaluations conducted during the NHSE after pregnancy.

Characteristics according to the presence of MASLD

We also compared the baseline characteristics and biochemical features before pregnancy according to the presence or absence of MASLD (Table S1). Women in the MASLD group had higher frequencies of smoking and alcohol consumption before pregnancy. In addition, women in the MASLD group had higher BMI, WC, and blood pressure. Laboratory tests revealed elevated liver enzyme levels and higher levels of cholesterol, TG, and fasting glucose in the MASLD group. Women who developed MASLD after delivery were older at delivery and more likely to have overt DM, chronic hypertension, and a family history of DM. Women who developed MASLD after delivery were more likely to have undergone cesarean section during pregnancy and had a higher likelihood of giving birth to babies with a higher birth weight. Metabolic and biochemical features after pregnancy according to the development of new-onset MASLD are shown in Table S2.

Changes in parameters before and after pregnancy

The results of the analysis of changes in various parameters before and after pregnancy are presented in Table 3. In women with a history of APOs, a greater increase in AST, ALT, TG, and GGT levels and a more significant decrease in HDL cholesterol level were observed. Changes in various parameters before and after pregnancy according to the presence or absence of MASLD are shown in Table S3. In the MASLD group, more significant changes were observed in metabolic and biochemical features. Specifically, women with MASLD, a greater increase in BMI, WC, blood pressure, AST, ALT, TG, and GGT levels and a more significant decrease in HDL cholesterol level were observed.

Risk of new-onset MASLD according to APOs

Table 4 shows the ORs of various APOs for the development of new-onset MASLD after delivery. Women with a prior history of APOs were at an increased risk of developing new-onset MASLD after delivery even after adjustments for various risk factors (adjusted OR 1.58, 95% CI 1.45–1.72, p <0.0001). Specifically, those with a prior history of HDP or GDM during pregnancy had

Table 3. Changes in metabolic and biochemical features before and after pregnancy.

	APO (-) (n = 69,338)	APO (+) (n = 9,320)	*p* value
Changes in metabolic features			
BMI (%)	5.07 ± 7.56	4.54 ± 7.67	<0.0001
WC (%)	5.98 ± 22.08	5.70 ± 29.87	0.3779
Systolic blood pressure (%)	0.68 ± 10.67	0.85 ± 10.85	0.151
Diastolic blood pressure (%)	0.63 ± 13.26	0.80 ± 13.36	0.2287
Changes in biochemical features			
AST (%)	7.03 ± 87.94	8.43 ± 48.48	0.021
ALT (%)	29.12 ± 98.35	31.79 ± 99.35	0.014
Cholesterol (%)	4.98 ± 16.93	5.01 ± 16.47	0.8504
HDL-cholesterol (%)	-1.64 ± 27.2	-2.10 ± 20.52	0.0499
Triglycerides (%)	28.16 ± 71.62	30.80 ± 75.46	0.0014
GGT (%)	5.50 ± 62.07	7.48 ± 68.48	0.0082
Fasting glucose (%)	1.84 ± 13.54	2.05 ± 14.61	0.1914

Changes = (Measurements after pregnancy - Measurements before pregnancy)/ Measurements before pregnancy × 100. Data are presented as mean ± SD. Differences between APO and non-APO groups were examined using the *t* test (for continuous variables). The level of statistical significance was set at p <0.05.
ALT, alanine aminotransferase; APO, adverse pregnancy outcome; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; WC, waist circumference.

an increased risk of developing MASLD after delivery (adjusted OR 2.20, 95% CI 1.81–2.67, p <0.0001 for HDP and adjusted OR 1.83, 95% CI 1.65–2.03, p <0.0001 for GDM). In contrast, women with a history of PTB, LBW, or placental abruption had no increased risk of MASLD. Moreover, there was a tendency toward an increased risk of developing MASLD, along with an increasing number of complications (Fig. 2). The results of the sensitivity analysis, using FLI ≥60 as the criterion, are presented in Table S4. In the analysis using FLI ≥60 as the threshold for hepatic steatosis, it was also observed that even after adjusting for covariates, women with a history of APO were at an increased risk of new-onset MASLD (adjusted OR 2.05, 95% CI 1.79–2.33, p <0.0001).

Subgroup analyses

Subgroup analyses based on age, parity, BMI before pregnancy, WC before pregnancy, smoking status, alcohol consumption, hypertension before pregnancy, DM before pregnancy, TG before pregnancy, HDL before pregnancy, and family history of DM before pregnancy were conducted to identify the independent relationship between APOs during pregnancy and new-onset MASLD after delivery. APOs significantly increased the risk of new-onset MASLD after delivery regardless of pre-pregnancy

Table 4. Association between adverse pregnancy outcomes and the risk of MASLD.

	Participants with MASLD after delivery, n (%)	Odds ratio >(95% CI)	*p* value	Model 1 adjusted odds ratio* (95% CI)	*p* value	Model 2 adjusted odds ratio† (95% CI)	*p* value	Model 3 adjusted odds ratio‡ (95% CI)	*p* value	Model 4 adjusted odds ratio§ (95% CI)	*p* value
APO											
(-)	4,070 (5.87)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
(+)	828 (8.88)	1.56 (1.45–1.69)	<0.0001	1.33 (1.22–1.44)	<0.0001	1.32 (1.21–1.43)	<0.0001	1.59 (1.46–1.72)	<0.0001	1.58 (1.45–1.72)	<0.0001
Hypertensive disorder of pregnancy											
(-)	4,754 (6.13)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
(+)	144 (13.41)	2.37 (1.99–2.84)	<0.0001	1.94 (1.59–2.36)	<0.0001	1.90 (1.55–2.31)	<0.0001	2.19 (1.80–2.66)	<0.0001	2.20 (1.81–2.67)	<0.0001
Gestational diabetes mellitus											
(-)	4,392 (5.97)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
(+)	506 (9.93)	1.74 (1.58–1.91)	<0.0001	1.35 (1.21–1.50)	<0.0001	1.34 (1.21–1.50)	<0.0001	1.84 (1.66–2.04)	<0.0001	1.83 (1.65–2.03)	<0.0001
Preterm birth											
(-)	4,879 (6.22)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
(+)	19 (9.74)	1.63 (1.01–2.62)	0.0439	1.57 (0.94–2.63)	0.0872	1.55 (0.92–2.60)	0.1005	1.53 (0.92–2.56)	0.1012	1.55 (0.93–2.58)	0.0909
Low birth weight											
(-)	4,653 (6.19)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
(+)	245 (7.06)	1.15 (1.01–1.32)	0.0374	1.15 (1.00–1.33)	0.0493	1.15 (0.99–1.32)	0.0644	1.11 (0.96–1.28)	0.1581	1.11 (0.96–1.28)	0.1529
Placenta abruptio											
(-)	4,878 (6.23)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
(+)	20 (6.47)	1.04 (0.66–1.64)	0.8554	0.97 (0.60–1.60)	0.9359	0.97 (0.59–1.58)	0.8926	1.12 (0.69–1.82)	0.6397	1.12 (0.69–1.81)	0.6461

The adjusted odds ratios and 95% CIs for the risk of new-onset MASLD in women with APOs compared with those without APOs were calculated using multivariable logistic regression analysis. The level of statistical significance was set at $p < 0.05$.

APO, adverse pregnancy outcome; MASLD, metabolic dysfunction-associated steatotic liver disease.

* Adjusted for maternal age, parity, waist circumference before pregnancy, and Charlson Comorbidity Index.

† Adjusted for maternal age, parity, waist circumference before pregnancy, diabetes before pregnancy, hypertensive disorder before pregnancy, and Charlson Comorbidity Index.

‡ Adjusted for maternal age, parity, changes in waist circumference before and after pregnancy, changes in diastolic blood pressure before and after pregnancy, changes in triglycerides before and after pregnancy, changes in HDL cholesterol before and after pregnancy, and Charlson Comorbidity Index.

§ Adjusted for maternal age, parity, changes in waist circumference before and after pregnancy, changes in diastolic blood pressure before and after pregnancy, changes in triglycerides before and after pregnancy, changes in HDL cholesterol before and after pregnancy, changes in fasting plasma glucose, and Charlson Comorbidity Index.

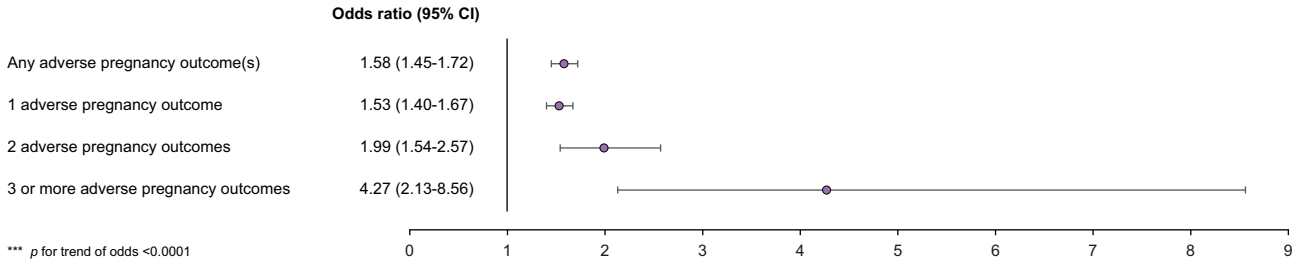

Fig. 2. Association between adverse pregnancy outcomes and the risk of postpartum new-onset MASLD according to the number of adverse pregnancy outcomes. The forest plot shows the odds ratios derived from multivariable logistic regression analysis adjusted for maternal age, parity, changes in waist circumference before and after pregnancy, changes in diastolic blood pressure before and after pregnancy, changes in triglycerides before and after pregnancy, changes in HDL cholesterol before and after pregnancy, changes in FPG, and Charlson Comorbidity Index. FPG, fasting plasma glucose; MASLD, metabolic dysfunction-associated steatotic liver disease; OR, odds ratio.

BMI, DM, hypertriglyceridemia, and alcohol consumption. However, individuals with hypertriglyceridemia before pregnancy were more apparently affected by APOs in regard to the risk of new-onset MASLD after delivery (Table 5).

Discussion

In this nationwide cohort study that included 78,658 postpartum women, we demonstrated that 9,320 women (11.8%) had a history of APOs, and 4,898 women (6.2%) developed new-onset

Table 5. Subgroup analyses on the risk of new-onset MASLD according to adverse pregnancy outcomes.

	Adjusted odds ratio			
	APO (-)	APO (+)	*p* value	*p* for interaction
Age at pregnancy				0.2538
<35 years	1.00 (reference)	1.26 (1.12–1.42)	0.0001	
≥35 years	1.00 (reference)	1.15 (0.99–1.34)	0.0558	
Nulliparity				0.5543
No	1.00 (reference)	1.15 (0.99–1.34)	0.0606	
Yes	1.00 (reference)	1.25 (1.11–1.41)	0.0002	
BMI before pregnancy				0.1798
<23 kg/m^2	1.00 (reference)	1.32 (1.13–1.54)	0.0005	
≥23 kg/m^2	1.00 (reference)	1.21 (1.09–1.35)	0.0004	
WC before pregnancy				0.0841
<80 cm	1.00 (reference)	1.26 (1.13–1.41)	<0.0001	
≥80 cm	1.00 (reference)	1.12 (0.96–1.31)	0.1659	
Ever smoking				0.779
No	1.00 (reference)	1.56 (1.44–1.69)	<0.0001	
Yes	1.00 (reference)	1.63 (0.89–3.01)	0.1156	
Alcohol consumption				0.6716
None*	1.00 (reference)	1.21(1.08–1.35)	0.001	
Mild†	1.00 (reference)	1.24 (1.05–1.46)	0.0116	
Moderate to severe‡	1.00 (reference)	–	–	
HTN before pregnancy				0.4092
No	1.00 (reference)	1.22 (1.11–1.34)	<0.0001	
Yes	1.00 (reference)	0.99 (0.49–2.00)	0.9888	
DM before pregnancy				0.1605
No	1.00 (reference)	1.20 (1.10–1.32)	0.0001	
Yes	1.00 (reference)	1.90 (1.00–3.59)	0.0495	
TG before pregnancy				0.0014
<200 mg/dl	1.00 (reference)	1.17 (1.06–1.29)	0.0012	
≥200 mg/dl	1.00 (reference)	2.28 (1.49–3.47)	0.0001	
HDL before pregnancy				0.5580
<40 mg/dl	1.00 (reference)	1.17 (0.76–1.79)	0.4856	
≥40 mg/dl	1.00 (reference)	1.21 (1.10–1.34)	<0.0001	
Family history of DM				0.7558
No	1.00 (reference)	1.22 (1.10–1.35)	0.0001	
Yes	1.00 (reference)	1.20 (0.96–1.51)	0.1072	

The adjusted odds ratios and 95% CIs were calculated using multivariable logistic regression analysis. The level of statistical significance was set at p <0.05. Adjusted for age, nulliparity, BMI before pregnancy, WC before pregnancy, ever smoking, alcohol consumption, HTN before pregnancy, DM before pregnancy, total cholesterol before pregnancy, and family history of DM before pregnancy.
APO, adverse pregnancy outcome; DM, diabetes mellitus; HTN, hypertension; MASLD, metabolic dysfunction-associated steatotic liver disease; TG, triglycerides; WC, waist circumference.
* Never drink alcohol.
† ≤20 g/day for women.
‡ >20 g/day for women.

MASLD after delivery. Women with a history of APOs had a 58% higher risk of new-onset MASLD after delivery than those without. In particular, women with a history of HDP or GDM were at an increased risk of developing new-onset MASLD after delivery. By contrast, the risk of new-onset MASLD did not significantly increase in women with other APOs such as PTB, LBW, and placental abruption. In addition, the risk of new-onset MASLD after delivery tended to increase as the number of pregnancy complications increased.

APOs are associated with an increased risk of CVD in postpartum women.[8,21] Several studies have shown that obstetric conditions, such as pre-eclampsia, GDM, PTB, and LBW, are associated with a higher likelihood of developing CVD in the future.[3,5,8,29–33] These APOs may serve as an early surrogate marker for future CVD risk and provide opportunities for targeted interventions and preventive measures. Healthcare providers should be aware of these associations between APOs and CVD, and carefully evaluate them when predicting the risk of CVD in postpartum women.

Based on these findings, numerous studies have been conducted to understand the mechanisms underlying the increased risk of CVD in postpartum women with a history of APOs. However, to date, no study has specifically examined the risk of new-onset MASLD in women with a prior history of APOs. In the current study, we demonstrated an increased risk of new-onset MASLD in postpartum women who experienced APOs during pregnancy. Indeed, MASLD is not only a liver-related condition but also a multisystemic disease with implications beyond the liver. Individuals with NAFLD are at a higher risk of developing cardiometabolic diseases, such as type 2 DM, metabolic syndrome, CVD, and chronic kidney disease, and various hepatic and extrahepatic cancers.[9,34–38] However, the underlying mechanisms that link MASLD to these cardiometabolic diseases and various cancers remain unclear. During pregnancy, the body undergoes significant metabolic changes to support fetal growth and development. These changes include insulin resistance, adipose tissue deposition, and altered lipid metabolism. In cases where APOs occur, such as GDM, insulin resistance becomes more pronounced, leading to elevated blood glucose level and increased lipolysis, which results in higher circulating free fatty acid level. These metabolic changes contribute to the accumulation of fat in the liver, leading to MASLD. In addition, insulin resistance impairs the ability of the liver to regulate glucose and lipid metabolism, further exacerbating MASLD. Moreover, APOs, such as HDP, may also lead to chronic low-grade inflammation and oxidative stress, which contribute to the development and progression of NAFLD.[39–41] In addition, shared risk factors between NAFLD and cardiometabolic diseases, such as obesity, sedentary lifestyle, unhealthy diet, and genetic predisposition, may further contribute to the increased risk of cardiometabolic diseases in individuals with NAFLD.[42,43]

In a previous study, we confirmed an increased risk of various APOs, such as GDM, HDP, and macrosomia, in women with NAFLD in early pregnancy.[14–16] Furthermore, through this current study, we also observed an increased incidence of new-onset MASLD after childbirth in women who experienced APOs during pregnancy. Given that both MASLD and APOs are common risk factors for future CVD, we can anticipate a bidirectional relationship between MASLD and APOs. In addition, it is evident that the shared mechanisms mentioned earlier are interacting between the two risk factors.

In the current study, subgroup analyses showed that only hypertriglyceridemia before pregnancy had a significant interaction with APOs in predicting the risk of new-onset MASLD after delivery. This suggests that pre-pregnancy hypertriglyceridemia and post-pregnancy APOs might additively increase the risk of new-onset MASLD after delivery. Therefore, lifestyle modifications to reduce serum TG levels before conception, such as dietary interventions and physical activity, may effectively prevent the risk of incident MASLD in postpartum women.

In the current study, women who developed new-onset MASLD after delivery had higher BMI and WC; higher levels of AST, ALT, cholesterol, LDL cholesterol, TG, GGT, and glucose; and a lower HDL cholesterol level. These are also known as well-established risk factors for CVD. Considering their shared risk factors and mechanisms, individuals with MASLD may also have an increased risk of developing CVD. In this context, APOs that increase the risk of CVD can also serve as a risk factor for MASLD, which has never been investigated before. Through this large-scale nationwide cohort study, we confirmed an increased risk of developing MASLD in postpartum women experiencing APOs. These findings may bring us one step closer to understanding the exact mechanisms underlying such an important association between prior APOs and CVD risk among postpartum women. The metabolic and hormonal changes that occur during pregnancy and subsequent physiological adaptations may influence liver homeostasis, lipid metabolism, insulin sensitivity, and systemic inflammation, predisposing women to MASLD and further increasing their risk of CVD.

To the best of our knowledge, this was the first study to confirm an increased risk of developing MASLD after delivery in pregnant women experiencing APOs. Moreover, this was a large-scale nationwide representative study conducted on individuals without pre-existing liver diseases, suggesting that the risk of developing new-onset MASLD increased with the number of pregnancy complications. The current study had several limitations. First, the lack of ethnic diversity within the cohort may preclude the generalizability of our findings to other ethnic populations. Further research is required to validate these findings in other ethnic populations. Second, owing to the utilization of NHSE data, we operationally defined hepatic steatosis as an FLI value of 30 or higher. It remains uncertain how these findings would be affected if alternative diagnoses of hepatic steatosis, such as histologic or radiologic examinations, were adopted. Finally, to alleviate the stigma associated with 'fatty liver disease' and emphasize cardiometabolic risk factors, a consensus statement recently introduced the new terminology 'metabolic dysfunction-associated steatotic liver disease' (MASLD).[22] The revised diagnostic criteria for MASLD should undergo extensive validation to assess their ability to predict clinical outcomes.

In conclusion, a prior history of APOs may be a risk factor for the development of new-onset MASLD after delivery, suggesting a bidirectional relationship between maternal MASLD and APOs. Moreover, of the various APOs, only those related to the mother but not to the fetus were identified as a risk factor for new-onset MASLD after delivery. The association between APOs and new-onset MASLD as an early reflection of CVD risk highlights the importance of incorporating the pregnancy history into a potential risk prediction model when evaluating women's cardiovascular health in future. Moreover, the comprehensive evaluation of the prior history of APOs along with the extent of APOs prompts us to

monitor women at risk of CVD more closely and manage them appropriately by implementing lifestyle modifications. Therefore, our findings emphasize the need for appropriate monitoring, follow-up, and preventive measures in women who have experienced APOs to mitigate the risk of new-onset MASLD and subsequent cardiovascular complications.

Abbreviations

ALT, alanine aminotransferase; APO, adverse pregnancy outcome; AST, aspartate aminotransferase; CVD, cardiovascular disease; DM, diabetes mellitus; FLI, fatty liver index; GDM, gestational diabetes mellitus; GGT, gamma-glutamyl transferase; HDP, hypertensive disorders of pregnancy; HIRA, Health Insurance Review and Assessment; ICD-10, International Classification of Diseases, 10th Revision; LBW, low birth weight; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; NHIS, National Health Insurance Service; NHSE, national health screening examinations; NSHP-IC, National Health Screening Program for Infants and Children; OR, odds ratio; PTB, preterm birth; SGA, small-for-gestational age; TG, triglycerides; WC, waist circumference.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Designed the research: YMJ, SML, JSP, GJC, WK. Conducted the research: YMJ, SML, WW, MJO, JSP, GJC, WK. Analyzed the data: YMJ, SML, WW. Wrote the manuscript: YMJ, SML, JSP, GJC, WK. Revised the manuscript: YMJ, SML, WW, MJO, JSP, GJC, WK. Had access to all the data and had primary responsibility for the final content: GJC, WK.

Data availability statement

The data analyzed in this study are not available for public use. However, researchers can apply for the National Health Insurance data-sharing service upon their IRB approval. After a review by the Korea National Health Insurance Sharing Service Institutional Data Access/Ethics Committee, researchers must pay a data access fee before accessing the data, similar to the authors of this article. Data are available from the National Health Insurance Service (NHIS), which owns the data. Requests for data can be sent to the data owners, NHIS (http://www.nhiss.nhis.or.kr/).

Supplementary data

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