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The risk of pregnancy-associated hypertension in women with nonalcoholic fatty liver disease

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Abstract

Background & Aims: Nonalcoholic fatty liver disease (NAFLD) is an independent predictor of cardiovascular disease (CVD) in non-pregnant adults. Although the biological mechanisms underlying this association are not completely understood, metabolic factors, inflammation, and endothelial dysfunction are likely all involved. The association between NAFLD and pregnancy-associated hypertension (HTN) has not been systematically examined. The aim of this study is to assess the risk of pregnancy-associated HTN in pregnant women with NAFLD.

Methods: This is secondary analysis of a prospective study of healthy pregnant women. Liver ultrasonography was performed at 10-14 weeks of gestation and maternal blood was taken for the measurement of selenoprotein P (SeP), a hepatokine independently associated with both NAFLD and CVD. Pregnancy-associated HTN was defined as the development of gestational HTN, preeclampsia, or eclampsia.

Results: Among 877 pregnant women, the risk of developing pregnancy-associated HTN was significantly increased in women with NAFLD compared to those without NAFLD. Grade 2-3 steatosis was a significant predictor of pregnancy-associated HTN, even after adjustment for metabolic risk factors. Circulating levels of SeP were significantly higher in women with versus those without NAFLD (P = .001) and was significantly higher also in women who subsequently developed pregnancy-associated HTN compared with those who did not (P < .005).

Conclusions: Sonographic evidence of NAFLD at 10-14 weeks is an independent predictor of pregnancy-associated HTN. Circulating levels of SeP at that same gestational

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; ELISA, enzyme-linked immunosorbent assay; FLI, fatty liver index; GGT, gamma-glutamyl transferase; hsCRP, high sensitive C-reactive protein; HSI, hepatic steatosis index; HTN, hypertension; NAFLD, nonalcoholic fatty liver disease; ROC, Receiver operating characteristics; SeP, selenoprotein P; TG, triglycerides; WC, waist circumference.

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age are significantly increased in pregnant women with NAFLD who subsequently develop pregnancy-associated HTN.

KEYWORDS
nonalcoholic fatty liver disease, pregnancy-associated hypertension, selenoprotein P

1 | INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is sonographic or histologic diagnosis, the underlying cause of which ranges from steatosis to cirrhosis. It is often referred to as the hepatic manifestation of metabolic syndrome,[1,2] and its prevalence is increasing worldwide due to the increasing incidence of obesity resulting from unfavorable changes in dietary and life style behaviors.[3,4] Considerable data exists to show that NAFLD is a predictor of cardiovascular disease (CVD) in non-pregnant adults.[5,6] Although the underlying biological mechanisms are not fully understood, insulin resistance, inflammation, dysregulated lipid metabolism, and endothelial dysfunction are likely all involved.[6,7]

Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality. Strategies to prevent preeclampsia have been largely unsuccessful.[8] Although the pathophysiology of preeclampsia is not well understood, women who have preexisting conditions associated with endothelial cell activation or inflammation are more likely to develop this disorder.[9,10] It is biologically plausible, therefore, that pregnant women with NAFLD are at increased risk of preeclampsia; however, the risk of pregnancy-associated hypertension (HTN) in women with NAFLD has not been systematically examined. If patients with NAFLD are indeed at high risk of developing preeclampsia, early identification of such patients may help in the development of future preventive strategies.

Selenoprotein P (SeP), a glycoprotein produced mainly in the liver, is associated with insulin signaling and glucose metabolism.[11] Increased plasma SeP levels are related with NAFLD, inflammation, and atherosclerosis.[12] Recently, It has been reported that SeP has deleterious effects on tubule formation and migration in endothelial cells by inhibiting vascular endothelial growth factor.[13] These findings suggest that SeP works some actions on vascular endothelial cells and may be related with hypertensive disorders.

In this study, we examined the risk of pregnancy-associated HTN in pregnant women diagnosed with NAFLD at 10-14 weeks of gestation. We also investigated the association between circulating levels of the hepatokine, SeP, and the development of pregnancy-associated HTN.

Lay Summary

- NAFLD is as an independent predictor of pregnancy-associated HTN.
- Circulating levels of selenoprotein P are significantly increased in pregnant women with NAFLD who subsequently develop pregnancy-associated HTN.

2 | MATERIALS AND METHODS

2.1 | Study design

This is secondary analysis of a large prospective cohort study designed to examine the risk of gestational diabetes mellitus (GDM) in women with NAFLD ("Fatty Liver in Pregnancy" registry

[NCT02276144]). We enrolled singleton pregnant women who visited our institution (Seoul Metropolitan Government, Seoul National University Boramae Medical Center and Incheon Seoul Women's Hospital) for prenatal care during the first trimester (prior to 14 weeks of gestation).[14] The enrolled pregnant women underwent liver ultrasound routinely at the time of routine fetal ultrasound according to a prespecified clinical protocol, and were followed till delivery. From this cohort, we selected consecutive women who met the following criteria: (a) were enrolled between October 2014 and October 2017; (b) were followed throughout pregnancy and delivery; and (c) for whom data was available on pregnancy outcomes, including the occurrence of pregnancy-associated HTN.

We collected the following general clinical characteristics were collected: maternal age, parity, pre-pregnancy body mass index (BMI), and pre-pregnancy waist circumference (WC), which were obtained using self-reported numbers. WC during 10-14 weeks of gestation was measured and recorded by a well-trained examiner according to a consistent protocol. WC was measured at the end of normal expiration, measuring at the mid-point between the highest point of the iliac crest and the last floating rib to the nearest 0.1 cm.[15] Those with preexisting chronic HTN and/or chronic liver disease other than NAFLD and/or heavy drinkers according to alcohol consumption before and during pregnancy using the validated cut-annoyed-guilty-eye questionnaire[16] were excluded from this analysis. Chronic HTN was defined as hypertension present before pregnancy or before 20 weeks of gestation.[17] Chronic liver disease other than NAFLD was defined as the presence of hepatitis B or C virus infection, autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, hemochromatosis, and Wilson disease.

The presence or absence of NAFLD was determined at 10-14 weeks of gestation by means of liver ultrasound, using both the fatty liver index (FLI) and hepatic steatosis index (HSI) as previously described.[14] The risk of pregnancy-associated HTN was evaluated according to the presence and severity of NAFLD. The study was approved by the Institutional Review Board of Seoul Metropolitan Government, Seoul National University Boramae Medical Center, and the Public Institutional Review Board designated by the Ministry of Health and Welfare of Korea. Informed consent was obtained from all subjects who were included in this study.

2.2 | Definition and severity of NAFLD based on liver ultrasonography

In all cases, liver ultrasonography was performed for the diagnosis of NAFLD at the time of routine fetal ultrasonography at 10-14 weeks of gestation. The presence of bright hepatic echoes was assessed and semi-quantified (grades 0-3) by ultrasonography according to the standardized rating system.[18,19] B-mode images of the liver and right kidney were included for subsequent review. Two experienced radiologists (SY Kim and GM Kim), who were blinded to the patient's clinical information, independently reviewed and scored the stored images. Whenever there was a difference in the interpretation of the results, the final diagnosis was determined by consensus after a discussion between the two radiologists.

2.3 | Diagnosis of pregnancy-associated HTN

Pregnancy-associated HTN was defined as the development of gestational HTN, preeclampsia, or eclampsia after 20 weeks of gestation. Hypertension was diagnosed when blood pressure (BP) measurements exceeded 140 mmHg systolic or 90 mmHg diastolic in a sustained fashion. The diagnosis of gestational HTN was made in women whose BP reached 140/90 mmHg or greater for the first time after mid-pregnancy, but in whom proteinuria or other features of end-organ damage was not identified. Preeclampsia was diagnosed when HTN and other features of end-organ damage (proteinuria, thrombocytopenia, renal insufficiency, liver involvement, cerebral symptoms, and pulmonary edema) were identified together. Preeclampsia complicated by convulsion was diagnosed as eclampsia.[20]

2.4 | Measurement of selenoprotein P concentrations and other laboratory values

Blood samples for the measurement of selenoprotein P (SeP) were collected at 10-14 weeks of gestation at the same time as the liver ultrasonography was performed. Samples were centrifuged and stored at −70°C until analysis. Stored samples were analyzed for SeP (μg/mL) using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Cloud-Clone Corp.). The levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, HDL-cholesterol, LDL-cholesterol, gamma-glutamyl transferase (GGT), triglycerides (TG), and fasting glucose were measured with a Roche/Hitachi Modular DP Chemistry Analyzer (Roche diagnostics International).

2.5 | Statistical analysis

Proportions were compared using the chi-squared test or Fisher's exact test, as appropriate. Comparison of continuous variables between groups was performed using the Mann-Whitney *U* test. Receiver operating characteristics (ROC) curve analysis was generated to investigate the utility of SeP to predict the development of pregnancy-associated HTN, and the optimal cut-off value was determined using the highest Youden's index. The association between NAFLD and pregnancy-associated HTN was assessed by modified Firth's penalized likelihood logistic regression to adjust for clinical and laboratory confounding factors.[21] A *P*-value of <.05 was considered statistically significant. SPSS version 23.0 software (IBM Inc) and R version 3.6.1 (http://www.r-project.org) were used for statistical analysis.

TABLE 1 Baseline clinical, anthropometric, biochemical, and metabolic features, and pregnancy outcomes of the study population

Characteristics	Pregnancy-associated HTN (–) (n = 857)	Pregnancy-associated HTN (+) (n = 20)	*P*-value
Baseline characteristics before pregnancy			
Maternal age (years)	32 (30-35)	33 (30-35)	.557
Nulliparity	454 (53.0%)	3 (65.0%)	.287
BMI before pregnancy (kg/m^2)	21.5 (19.6-23.6)	25.7 (23.8-28.4)	<.001
WC before pregnancy (cm)	71.0 (69.0-74.0)	76.0 (70.8-79.0)	<.01
Baseline characteristics at the time of liver ultrasonography			
Gestational age (weeks)	12.4 (12.0-12.9)	12.4 (11.9-12.6)	.161
Systolic blood pressure (mmHg)	111 (104-119)	127 (120-129)	<.001
Diastolic blood pressure (mmHg)	67 (62-73)	80 (72-83)	<.001
Biochemical and metabolic features at the time of liver ultrasonography			
AST (IU/L)	16 (14-19)	19 (15-31)	<.05
ALT (IU/L)	11 (8-15)	17 (10-21)	<.05
Total cholesterol (mg/dL)	170 (155-189)	188 (161-214)	.066
HDL-cholesterol (mg/dL)	67.3 (57.9-76.4)	67.7 (65.8-71.1)	.971
LDL-cholesterol (mg/dL)	81.8 (67.8-96.1)	89.2 (73.4-113.2)	.192
Triglycerides (mg/dL)	104 (82-134)	140 (97-165)	<.05
GGT (IU/L)	12 (10-16)	18 (14-22)	<.01
Fasting glucose (mg/dL)	78 (72-84)	82 (77-90)	<.05
Pregnancy outcome			
Gestational age at delivery (weeks)	39.1 (38.2-40.0)	37.2 (36.4-38.6)	<.001
Birthweight at delivery (kg)	3.22 (2.98-3.48)	2.96 (2.43-3.35)	<.01
GDM	43/822 (5.2%)	3/19 (15.8%)	.080

Note: Data are presented as proportion (%) or median (IQR).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GDM, gestational diabetes mellitus; GDM, gestational diabetes mellitus; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; WC, waist circumference.

3 | RESULTS

3.1 | Subject population

A total of 948 pregnant women were enrolled and underwent liver ultrasonography at 10-14 weeks of gestation between October 2014 and October 2017. Among them, 71 subjects (11 with viral hepatitis, 9 with chronic HTN, 5 who experienced spontaneous abortion before 14 weeks, 4 who withdrew consent, and 42 who were lost to follow-up) were excluded from the final analysis. The remaining 877 study subjects were included as the final study population.

3.2 | Clinical characteristics according to pregnancy-associated HTN status

Among the study population, 2.2% (20/877) developed pregnancy-associated HTN (14 with gestational hypertension, 6 with preeclampsia). Table 1 shows the baseline characteristics and obstetric outcomes of the study population by HTN status. Women who developed pregnancy-associated HTN had a higher BMI, greater WC before pregnancy, and higher systolic and diastolic BP at 10-14 weeks than women who did not develop pregnancy-associated HTN. In addition, the study population that was diagnosed with pregnancy-associated HTN had higher baseline circulating levels of AST, ALT, GGT, TG, and fasting glucose. In terms of delivery outcomes, women with pregnancy-associated HTN delivered earlier (37.2 weeks vs. 39.1 weeks, $P < .001$) and had babies with lower birth weight (2.96 kg vs. 3.22 kg, $P < .01$).

3.3 | Radiologic features and non-invasive steatosis indices according to HTN status

The overall prevalence of NAFLD in the study population was 15.6% (137/877) based on liver ultrasonography at 10-14 weeks of gestation. Of these, 11.6% had grade 1 steatosis and 4.0% had grade 2-3 steatosis. Subjects who subsequently developed pregnancy-associated HTN had a higher rate of fatty liver based on liver ultrasonography, and had higher FLI and HSI at the time of liver ultrasonography (Table 2). Women with fatty liver at 10-14 weeks

TABLE 2 Radiologic findings and noninvasive steatosis indices at 10-14 weeks of gestation

Characteristics	Pregnancy-associated HTN (–) (n = 857)	Pregnancy-associated HTN (+) (n = 20)	*P*-value
Liver ultrasonography			
Grade 0 steatosis	728 (84.9%)	12 (60.0%)	<.001
Grade 1 steatosis	99 (11.6%)	3 (15.0%)	
Grade 2 steatosis	23 (2.7%)	3 (15.0%)	
Grade 3 steatosis	7 (0.8%)	2 (10.0%)	
Presence of fatty liver by ultrasonography	129 (15.1%)	8 (40.0%)	<.01
FLI at the time of liver ultrasonography	11.25 (6.08-21.39) (n = 767)	36.85 (21.47-67.56) (n = 17)	<.001
Risk subgroups based on the FLI			
Low-risk of steatosis (FLI ≤ 20)	558/767 (72.8%)	4/17 (23.5%)	<.001
Intermediate-risk of steatosis (20 < FLI < 60)	170/767 (22.2%)	8/17 (47.1%)	
High-risk of steatosis (FLI ≥ 60)	39/767 (5.1%)	5/17 (29.4%)	
HSI at the time of liver ultrasonography	29.4 (27.1-33.1) (n = 769)	35.7 (32.1-38.1) (n = 18)	<.001
Risk subgroups based on the HSI			
Low-risk of steatosis (HSI < 30)	432/769 (56.2%)	3/18 (16.7%)	<.001
Intermediate-risk of steatosis (30 ≤ HSI ≤ 36)	243/769 (31.6%)	6/18 (33.3%)	
High-risk of steatosis (HSI > 36)	94/769 (12.2%)	9/18 (50.0%)	
Circulating biomarkers at the time of liver ultrasonography			
Selenoprotein P (μg/mL)	5.82 (2.74-15.00)	16.76 (11.45-21.85)	<.001
Selenoprotein P >7.64 μg/mL	260/633 (41.1%)	15/17 (88.2%)	<.001

Note: Data are presented as proportion (%) or median (IQR).

Abbreviations: FLI, fatty liver index; HSI, hepatic steatosis index; HTN, hypertension.

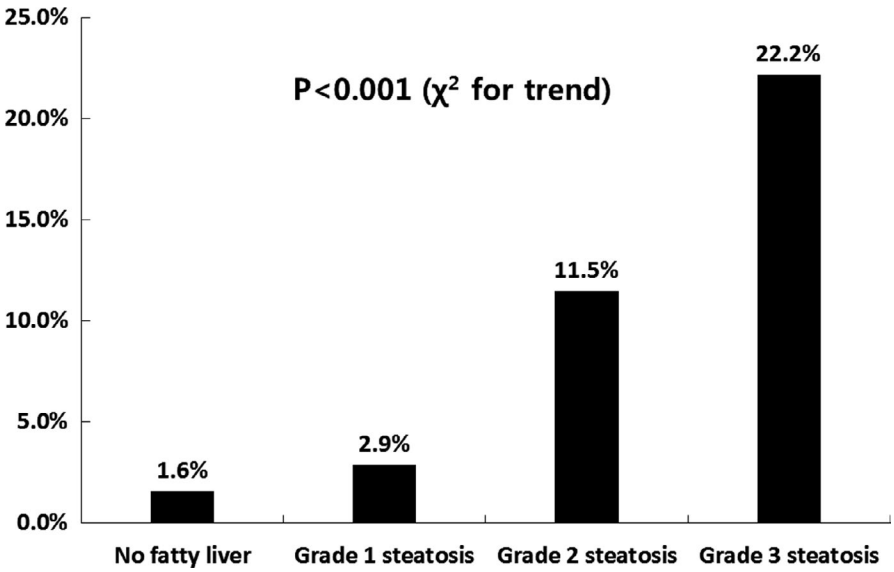

FIGURE 1 Prevalence of pregnancy-associated HTN according to the radiologic severity of NAFLD. HTN, hypertension; NAFLD, nonalcoholic fatty liver disease

were significantly more likely to develop pregnancy-associated HTN, and this risk increased with the severity of NAFLD based on liver ultrasonography: the incidence of pregnancy-associated HTN was 1.6% in women with grade 0 steatosis, 2.9% in those with grade 1 steatosis, 11.5% in those with grade 2 steatosis, and 22.2% in those with grade 3 steatosis ($P < .001$, chi-squared for trend; Figure 1).

3.4 | Relationship between maternal serum SeP, NAFLD, and pregnancy-associated HTN

Circulating SeP concentrations were significantly higher in patients with NAFLD than in those without NAFLD ($P < .01$) (Table S1). In addition, maternal serum SeP concentrations at 10-14 weeks were significantly higher in subjects who subsequently developed

pregnancy-associated HTN than in those who did not (Table 2, Figure 2). The optimal cut-off value for SeP was 7.64 μg/mL (88.2% sensitivity, 58.9% specificity) with 88.2% of women who developed pregnancy-associated HTN having SeP levels above this cut-off.

We also evaluated whether circulating SeP concentrations at 10-14 weeks were associated with the risk of developing pregnancy-associated HTN independent of NAFLD. Even among women without NAFLD, high SeP concentrations were associated with the subsequent development of pregnancy-associated HTN ($P < .01$, Figure 3). Among women with NAFLD, those with high SeP concentrations had a higher risk of developing pregnancy-associated HTN than those with low SeP concentrations (13.6% vs. 0%, $P < .01$).

3.5 | Relationship between NAFLD and pregnancy-associated HTN

Table 3 presents the odds ratios (ORs) of predictors of pregnancy-associated HTN. We adjusted for waist circumference, blood pressure, fasting glucose, and SeP which are known predictors of pregnancy-associated hypertension.[22,23] In the WC- and systolic BP-adjusted (Model 1) or WC- and diastolic BP-adjusted (Model 2) analysis, NAFLD was associated with the subsequent development of pregnancy-associated HTN (Model 1; OR, 3.78; 95% confidence interval [CI], 1.03-11.94; $P < .05$ and Model 2; OR, 4.70; 95% CI, 1.27-14.78; $P < .05$). This association persisted even after additional adjustment for fasting glucose and SeP (Model 4; OR, 4.77; 95% CI, 1.26-15.83; $P < .05$).

The severity of steatosis in the study subjects was assessed using both the FLI and HSI. These indices were also evaluated in multivariable logistic regression analysis to determine their effects on the development of pregnancy-associated HTN. In the WC- and systolic BP-adjusted (Model 1) or WC- and diastolic BP-adjusted (Model 2) analysis, we confirmed a positive correlation between FLI and pregnancy-associated HTN (Model 1; OR, 1.04; 95% CI, 1.01-1.07; $P < .01$ and Model 2; OR, 1.04; 95% CI, 1.01-1.07; $P < .01$). This correlation remained significant after additional adjustment for fasting glucose and SeP (Model 4; OR, 1.03; 95% CI, 1.01-1.05; $P < .01$). The HSI had a similar correlation, which also remained significant after multivariable adjustment (Models 1-4; Table 3).

4 | DISCUSSION

The major findings of this study are: (a) NAFLD defined either by ultrasonography or non-invasive steatosis indices at 10-14 weeks of gestation was an independent predictor of the subsequent development of pregnancy-associated HTN; (b) this significant association persisted after adjustment for WC, BP, and fasting glucose; (c) circulating SeP levels were significantly increased in patients with NAFLD and independently associated with the development of pregnancy-associated HTN; and (d) patients with NAFLD and increased SeP levels had the highest risk of developing pregnancy-associated HTN.

The risk of pregnancy-associated HTN in women with NAFLD has not been well characterized. A 2016 Swedish study suggested that NAFLD is associated with an increased risk of developing preeclampsia, with an adjusted OR of 1.95 (95% CI, 1.03-3.70).[24] However, since they used a national database to identify pregnant women with NAFLD, the overall incidence of NAFLD in their cohort was very low (110 women among 1 960 416 women or 0.006%). In the current study, we used routine liver ultrasonography in women at 10-14 weeks and standardized metrics to define NAFLD in a Korean population. In our cohort, the prevalence of NAFLD was 15.6% (137/877). We further demonstrated that NAFLD determined either by ultrasonography or noninvasive steatosis indices was significantly associated with the development of

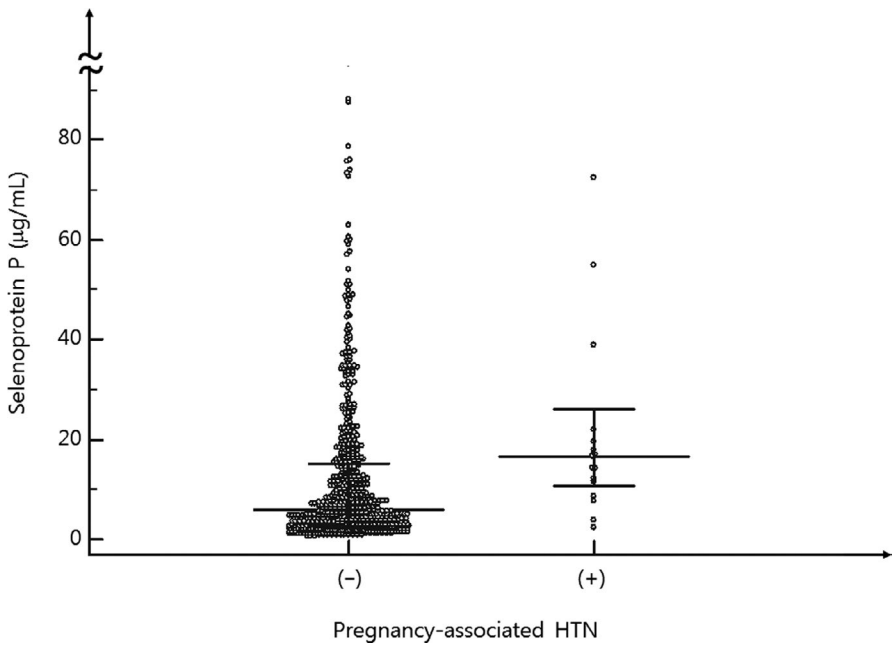

FIGURE 2 Concentration of selenoprotein P in women with pregnancy-associated HTN and in normotensive women. HTN, hypertension. Horizontal bold lines indicate median and interquartile ranges

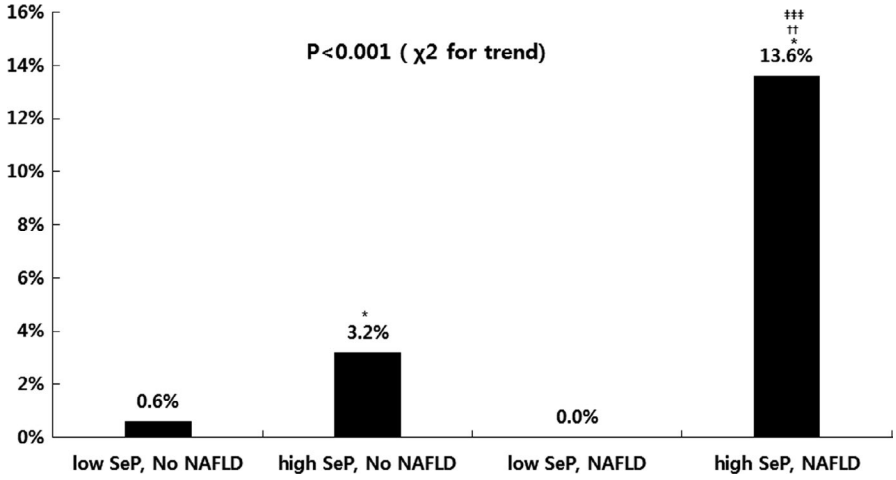

FIGURE 3 Prevalence of pregnancy-associated HTN according to maternal blood selenoprotein P level and NAFLD status. HTN, hypertension; NAFLD, nonalcoholic fatty liver disease. *P < .05 vs. low SeP without NAFLD. †† P < .01 vs. high SeP without NAFLD. ‡‡‡ P < .01 vs. low SeP with NAFLD

pregnancy-associated HTN, which was consistent with the previous Swedish study.

The study population who were diagnosed with pregnancy-associated HTN had higher baseline circulating levels of AST, ALT, GGT, TG, and fasting glucose than those without. However, there were no significant differences in other lipid profiles including total cholesterol, HDL-cholesterol, and LDL-cholesterol levels. Liver enzymes have been linked to a variety of systemic diseases, such as metabolic disease and cardiovascular disease, as well as chronic liver disease (eg, NAFLD). According to the Cho et al,[25] the abnormal pre-pregnancy ALT level was associated with the development of preeclampsia. In our study, we found that elevated levels of AST, ALT, GGT, and TG at first trimester of pregnancy were associated with the development of pregnancy-associated hypertension.

In addition, we showed that patients with both NAFLD and increased plasma SeP levels had the highest risk of developing pregnancy-associated HTN, estimated at around 13%. Such women may benefit from the implementation of strategies to prevent preeclampsia. Recent clinical guidelines suggest that administration of low-dose aspirin starting in the late first trimester may prevent the development of preeclampsia in pregnant women at high-risk. Risk factors include prior preeclampsia, multifetal gestation, chronic HTN, pregestational diabetes, renal disease, and autoimmune disease.[26] The reported risk of developing preeclampsia is approximately 13% in women with twins,[27] 5%-65% in women with prior preeclampsia,[28-30] and 8.8% in those with rheumatologic disease.[31] Our current data suggest that pregnant women with NAFLD would also benefit from low-dose aspirin prophylaxis. Based on our study results, further randomized controlled studies are warranted to confirm whether pregnancy–associated HTN would be prevented by low-dose aspirin prophylaxis in patients with NAFLD in early pregnancy.

Our study has several strengths. First, we prospectively enrolled all study subjects and collected fasting blood samples and clinical information in the first trimester.[14,32,33] Second, we evaluated the presence of NAFLD not only by liver ultrasonography but also by biochemical indices (both FLI and HSI). Use of ultrasound alone may have limited the confidence of our observations, because of its low sensitivity in detecting mild steatosis.[34] The fact that the risk of pregnancy-associated HTN was increased in patients with NAFLD as defined both by non-invasive steatosis indices (both FLI and HSI) as well as by liver ultrasonography confirms the robust nature of this observation. Third, the relationship between both NAFLD and increased SeP levels and the risk of pregnancy-associated HTN was identified in the first trimester, providing time for closer observation and the implementation of preventative strategies.

The biological mechanisms underlying the association between NAFLD and pregnancy-associated HTN remain unclear. Recent studies have reported a strong and independent association between NAFLD and CVD, and have begun to define the molecular mechanisms involved. Non-pregnant patients with NAFLD have impaired flow-mediated vasodilation[35] and increased carotid-artery intimal medial thickness.[36,37] The accelerated atherosclerosis seen in patients with NAFLD may be related to the expansion of visceral fat, since the liver is the major source of lipid-forming molecules.[6] Moreover, preeclampsia is characterized by accelerated lipid deposition in the walls of the maternal spiral arteries supplying the placenta. These lesions are known to resemble the early stage of atherosclerosis, and acute atherosclerosis may be related to impaired vascular remodeling.[38] Preeclampsia is associated with a failure of spiral artery remodeling at 8-18 weeks of gestation leading to systemic endothelial dysfunction and excessive inflammation.[39,40] Endothelial dysfunction and an excessive inflammatory response are common mechanisms involved in the development of CVD and are also important risk factors for NAFLD.[35,41] Such common mechanisms may explain why it is that pregnant women with NAFLD are more likely to develop pregnancy-associated HTN. In the current study, we unfortunately did not measure inflammation markers (hs-CRP), pro-inflammatory cytokines, such as IL-1, TNF-α, and other hepatokines. Further prospective studies are warranted to confirm the relationship among these markers and NAFLD and pregnancy-associated HTN.

Other publications have reported that approximately 50% of patients with chronic HTN have NAFLD.[42,43] Once again, the molecular mechanisms underlying the relationship between NAFLD and HTN are not well elucidated, but several explanations have been

TABLE 3 Univariable and multivariable analyses producing odds ratios of predictors of pregnancy-associated hypertension

		P-value	Corrected *P*-value*
Characteristics	Fatty liver		
Unadjusted	8.53 (2.64-23.65)	<.001	<.01
Model 1	3.78 (1.03-11.94)	<.05	<.05
Model 2	4.70 (1.27-14.78)	<.05	<.05
Model 3	4.30 (1.10-14.12)	<.05	<.05
Model 4	4.77 (1.26-15.83)	<.05	<.05
Characteristics	Selenoprotein P, log-transformed		
Unadjusted	1.95 (1.30-2.96)	<.01	<.01
Model 1	1.87 (1.24-2.86)	<.01	<.01
Model 2	1.91 (1.26-2.95)	<.01	<.01
Model 3	1.85 (1.23-2.84)	<.01	<.01
Characteristics	Selenoprotein P >7.64 μg/mL		
Unadjusted	9.37 (2.80-49.57)	<.001	<.001
Model 1	9.53 (2.72-52.22)	<.001	<.001
Model 2	9.63 (2.72-53.84)	<.001	<.001
Model 3	10.50 (2.91-60.22)	<.001	<.001
Characteristics	Fatty liver index		
Unadjusted	1.04 (1.02-1.05)	<.001	<.001
Model 1	1.04 (1.01-1.07)	<.01	<.01
Model 2	1.04 (1.01-1.07)	<.01	<.01
Model 3	1.04 (1.01-1.07)	<.01	<.01
Model 4	1.03 (1.01-1.05)	<.01	<.05
Characteristics	Hepatic steatosis index		
Unadjusted	1.17 (1.08-1.26)	<.001	<.001
Model 1	1.10 (1.01-1.21)	<.05	<.05
Model 2	1.11 (1.02-1.21)	<.05	<.05
Model 3	1.11 (1.02-1.21)	<.05	<.05
Model 4	1.10 (1.01-1.21)	<.05	<.05

Note: Model 1: adjusted for waist circumference and systolic blood pressure at liver ultrasound.

Model 2: adjusted for waist circumference and diastolic blood pressure at liver ultrasound.

Model 3: adjusted for waist circumference, diastolic blood pressure at liver ultrasound, and fasting glucose.

Model 4: adjusted for waist circumference, diastolic blood pressure at liver ultrasound, fasting glucose, and selenoprotein P.

*Corrected *P*-value: Benjamini and Hochberg procedure was applied.

proposed. The increased activity of the renin angiotensin system resulting from changes in renal function due to excessive adipose tissue may account for the increased prevalence of HTN in patients with NAFLD.[44] And increased thickening of the left ventricular wall in patients with NAFLD may also lead to the development of HTN.[45]

In the current study, maternal serum SeP concentrations at 10-14 weeks of gestation were positively correlated with the subsequent development of pregnancy-associated HTN, and this relationship persisted after adjustment for BP. SeP is a hepatokine that is produced and secreted by the liver. Little is known about what happens to SeP levels and the relations between various hormones and SeP during pregnancy. However, elevated SeP levels have been associated with abnormal glucose metabolism, insulin resistance, inflammation, and atherosclerosis.[12] One group of investigators suggested that elevated SeP is associated with arterial stiffness and, as such, could serve as a useful surrogate marker for the assessment of CVD risk.[46] SeP also appears to correlate with circulating levels of high sensitive C-reactive protein, a non-specific inflammatory biomarker related to CVD risk.[46,47] Given the relationship between SeP and other predictors of CVD, these data support our observation that SeP in association with NAFLD increases the risk of pregnancy-associated HTN.

The prevalence of pregnancy-associated HTN (gestational hypertension, preeclampsia, or eclampsia) in the current study was

2.2%. This is lower than that reported in other studies, in which the incidence of preeclampsia alone is estimated at 2%-7%.[8] However, Korean women are known to have a lower incidence of preeclampsia than women in Europe and the US. Cho et al reported that the incidence of preeclampsia in a Korean population was only 2.0%.[25] One possible explanation is that Asian women usually have lower BMI than non-Asian women.[48] Taken together, it is perhaps not surprising that the prevalence of pregnancy-associated HTN in our study was lower than those in the previous studies.[49,50] This result may be attributed to different ethnicity[51,52] and lifestyle, including diet, physical activity, and caloric intake. Also, the relatively lower BMI in the current study population might reduce the risk of preeclampsia.[53] Further studies for other ethnic populations are needed to confirm our results of the current study. Another limitation of this study is that we did not identify the family history of pregnancy-associated hypertension which is known as a predictor of pregnancy-associated hypertension.

The gold standard for the diagnosis of NAFLD is histological examination. In this study, instead of liver biopsy, we used noninvasive methods including liver ultrasound and biochemical steatosis indices (FLI and HSI). However, the limitation of liver ultrasound is interobserver variance which may affect the results. To overcome this limitation, when there was a difference in the interpretation of the results, the final diagnosis was determined by consensus after a discussion between the two radiologists. In addition, given the special circumstance of pregnancy, it is clearly more appropriate to use noninvasive diagnostic methods, because liver biopsy can occasionally result in serious morbidity and, in rare cases, even mortality.[54]

In summary, sonographic or biochemical evidence of NAFLD at 10-14 weeks of gestation is an independent predictor of the subsequent development of pregnancy-associated HTN. Circulating levels of SeP at the same gestational age are significantly increased in pregnant women with NAFLD who subsequently develop pregnancy-associated HTN, suggesting the role of SeP as a promising biomarker to predict pregnancy-associated HTN in the early period of gestation.

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CONFLICTS OF INTEREST

None to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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