Observational Study

Medicine

OPEN

The presence of hypertension during pregnancy determines the future risk of metabolic syndrome

An observational study

Da-Hye Ju, MD, PhD[a], Hyeyoun Lee, MS[b], Sang Jin Ha MD, PhD[c,*]

Abstract

This study aimed to examine the prevalence and time interval of metabolic syndrome (MS) development among women with hypertensive disorders of pregnancy (HDP) compared to women with a normal delivery. Data (4,723,541 deliveries) from 2002 to 2012 from the National Health Insurance System Database in Korea were used to compare women diagnosed with HDP with those with a normal singleton pregnancy. Using the customized database, we conducted a longitudinal analysis of MS development. MS was observed in 20.3% of the patients in the normal delivery group and 37.1% in the HDP group ($P < .0001$). The time to MS development in the HDP group was significantly shorter than that in the normal delivery group (6.6 ± 3.4 vs 8.2 ± 3.4 years, $P < .0001$). The HDP group had a significantly increased risk [odd ratio (OR) 1.23; 95% confidence interval (CI), 1.12–1.35] of developing MS, and elevated systolic blood pressure strongly contributed to the increased risk of developing MS (OR 1.644; 95% CI, 1.610–1.678). HDP increased the risk of MS development later in life, and MS development exhibited a shorter time period in women with HDP. Women with HDP should undergo intensive assessment for MS components.

Abbreviations: CIs = confidence intervals, CVD = cardiovascular disease, DB = database, FBS = fasting blood sugar, HDL = high-density lipoprotein, HDP = hypertensive disorders of pregnancy, MS = metabolic syndrome, NHIS = National Health Insurance System, ORs = odds ratios, SBP = systolic blood pressure, TG = triglyceride.

Keywords: hypertensive disorders of pregnancy, Korea, metabolic syndrome, NHIS data registry

1.Introduction

Hypertensive disorders of pregnancy (HDP) affect 5% to 10% of all pregnancies worldwide.[1] Compared with women who maintain a normal blood pressure during pregnancy, those with a history of HDP have an increased risk of future cardiovascular disease (CVD).[2] The most serious form of this disorder is preeclampsia. Other forms of HDP include gestational hypertension (hypertension alone without evidence of end-organ damage or proteinuria), chronic hypertension, and preeclampsia superimposed on chronic hypertension.[3]

HDP is strongly associated with the future development of hypertension, as previously reported.[4,5] Recent data have demonstrated that elevated blood pressure during pregnancy, irrespective of the type and risk factors, foreshadows a high risk of the development of CVD, chronic kidney disease, and diabetes mellitus in the future.[2,5,6] Women with a history of preeclampsia are also at a higher risk for future development of diabetes mellitus, CVD, stroke, and overall increased mortality.[6–8]

Metabolic syndrome (MS) is a cluster of metabolic abnormalities that increase the risk for these conditions.[9–11] Most studies have reported that women with preeclampsia have an increased risk of developing MS after delivery, suggesting a role in the pathophysiology of conditions ranging from preeclampsia to long-term CVD.[12,13] A previous genomic cohort study in South Korea showed that preeclampsia increases the risk of MS later in life, and older age at first pregnancy can further exacerbate this risk.[14] There were different reports in prevalence rates of metabolic syndrome following HDP, with values ranging from 13.9% in the Netherlands Netherlands (median of 8 months postpartum) and 14.5% in the United States of America.[15,16] However, no longitudinal studies comparing MS prevalence between women with a normal delivery and those with HDP and monitoring the time until MS development have been performed in Korean population using a customized database (DB) of the National Health Insurance System (NHIS) registry.

Therefore, the aim of the current study was to examine the prevalence and time interval of MS development among women with hypertension during pregnancy compared to women with

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

The authors have no conflicts of interest to disclose.

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a normal delivery using big data analysis of a customized DB from the NHIS data registry. In addition, this study sought to compare the prevalence of MS components between the HDP group and the normal delivery group.

2.Methods

2.1 Study population

Koreans enact national health examination programs in accordance with the National Health Insurance Acts administered by the NHIS at least every 2 years.[17,18] NHIS targets can include local households and job applicants regardless of age, and those eligible for the national health examination can receive benefits from local households, workers, dependents, and medical benefits starting at the age of 40 years or older. Tests are generally conducted every other year, and nonoffice workers are required to undergo annual health examinations. Additionally, since 2008, people aged between 40 and 66 years have undergone life-changing health checkups regardless of their qualifications. These widespread checkups create a group of subjects representative of the entire population, and the data obtained include disease- and death-related information as well as demographic and socioeconomic information. For all subjects undergoing national health examination, the results of the basic examination, including health behaviors and physical health data, were also included. From 2002 to 2012, the National Health Insurance Research Database compared the data of women diagnosed with hypertensive disorders during pregnancy with those of women with normal singleton pregnancies. Using these data, we created a customized database called the National Health Insurance Service-National Women HDP Cohort. Women who underwent medical checkups between 2009 and 2016 were assessed for MS given the lack of data sources on MS components before 2009. We investigated an eligibility database and a health examination database (results of general health examinations and questionnaires on lifestyle and behavior). We categorized our data registry into 2 groups: the HDP and normal delivery groups. The flow chart in Figure 1 shows the study population and design using our customized database.

This research followed the guidelines of the Declaration of Helsinki, and the NHIS-2018-1-315 project was approved by the Institutional Review Board of the Korean National Health Insurance Service. This study received ethical approval from the Gangneung Asan Hospital ethical committee of Ulsan University (reference GNAH 2018-05-003). Only anonymized and deidentified data were used for the analyses. Thus, informed consent was not necessary, and the requirement was waived.

2.2 Diagnosis of hypertensive disorders in pregnancy

The Task Force of the American College of Obstetricians and Gynecologists provided evidence-based recommendations for clinical practice to diagnose hypertensive disorders in pregnancy.[19] Data from individuals with hypertension during pregnancy were collected according to the International Classification of Disease 10th revision (ICD-10) standards using NHIS data. Patients with gestational hypertension, chronic hypertension of any etiology, preeclampsia superimposed on chronic hypertension, preeclampsia and eclampsia were included.

2.3 Diagnosis of MS

The diagnostic criteria of the National Cholesterol Education Program Adult Treatment Panel III published in 2005 were used to diagnose MS. A waist circumference of 88 cm or greater, a systolic blood pressure (SBP) of 130 mm Hg or higher, a diastolic blood pressure of 85 mm Hg or higher, a fasting blood sugar (FBS) level of 100 mg/dL or higher, a high-density lipoprotein cholesterol (HDL) level of less than 50 mg/dL, or a triglyceride (TG) level greater than 150 mg/dL were the criteria used to diagnose MS. A person who met 3 or more diagnostic criteria was defined as having MS.[20]

2.4 Statistical analysis

The prevalence of MS and the odds ratios (ORs) for developing MS were compared between the HDP and normal delivery groups. The chi-square test and Student's t test were used to compare the basic characteristics of women who had experienced a pregnancy complicated by HDP and those who had a normal pregnancy. All results with a P value < 0.05 were considered statistically significant as the data were normally distributed, and the data are expressed as the mean (±standard deviation). To investigate whether HDP was independently associated with the risk of subsequent MS and its individual components, binary logistic regression models were used to estimate ORs and 95% confidence intervals (CIs). All statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC).

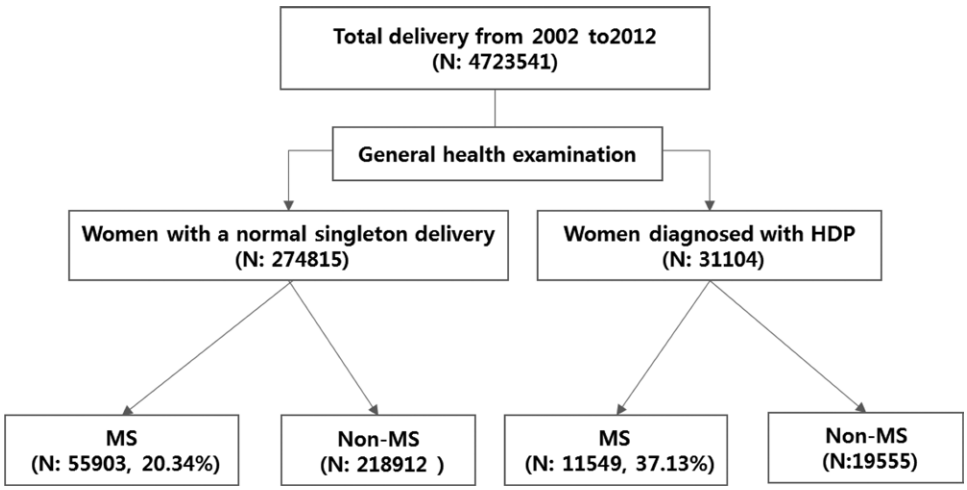

Figure 1. Flow chart of the study population. HDP = hypertensive disorders of pregnancy, MS = metabolic syndrome.

3.Results

3.1 Study population characteristics and MS development comparison between the normal delivery and HDP groups

Figure 1 shows the total number of deliveries in Korea, HDP prevalence and MS prevalence in both groups. A total of 4723,541 women delivered between 2002 and 2012, of whom 305,919 women received national health checkups registered in the NHIS registry data. Based on NHIS registry data, HDP was diagnosed in 31,104 (10.16%) women, whereas 274,815 (89.84%) women remained normotensive during pregnancy. Compared to the prevalence of MS (n = 58,903, 20.3%) among women with a normal delivery, the prevalence of MS among women with a history of HDP was significantly higher (n = 11,549, 37.1%). Therefore, women diagnosed with HDP had significantly higher odds of developing MS (OR 1.23; 95% CI, 1.12–1.35), as shown in Table 1. Table 1 also shows the age at delivery, age at MS development, and time interval from delivery to MS development in both groups. Women diagnosed with HDP were significantly older (33.1 ± 4 years vs 31 ± 4 years, $P < .0001$). The age of women at the time of MS development in the HDP group was 39.5 ± 4.9 years, which was significantly older than that of the women in the normal delivery group (38.9 ± 4.9 years, $P < .0001$). The time to MS development in women who had experienced pregnancy complicated by HDP was significantly shorter than that of the women who did not have HDP (6.6 ± 3.4 years vs 8.2 ± 3.4 years, $P < .0001$).

The lifestyle, laboratory findings, and anthropometric data of the study population diagnosed with MS are summarized in Table 2. Women diagnosed with HDP tended to be older during pregnancy (31 years vs 33.1 years, $P < .0001$). When all putative confounders were considered, women diagnosed with HDP were found to have significantly higher blood pressure, TG level, waist circumference, and body mass index (BMI) ($P < .0001$). However, fasting glucose levels were significantly reduced ($P = .0139$) and HDL levels were significantly increased ($P < .0001$) in the HDP group.

3.2 Future metabolic syndrome component development according to the presence of hypertension during pregnancy

The prevalence of MS and its components among women diagnosed with MS is shown in Table 3. Three components of MS (SBP ≥ 130 mm Hg, TGs ≥ 150 mg/dL, and waist circumference ≥ 88 cm) were significantly more prevalent. However, low HDL levels and high FBS levels were less prevalent in patients with MS. Figure 2 shows the risk of developing MS and its components in women with and without a history of HDP. As shown in Figure 3, women diagnosed with HDP had significantly higher odds of central obesity (OR 1.0376; 95% CI, 1.018–1.057), elevated TG levels (OR 1.026; 95% CI, 1.006–1.046), and elevated SBP (OR 1.644; 95% CI, 1.610–1.678) as part of their MS diagnosis. In other words, women with a normal delivery had increased odds of elevated fasting glucose levels (OR 1.13; 95% CI, 1.03–1.25) and low HDL levels (OR 1.031; 95% CI, 1.012–1.050). To analyze additional lifestyle effects on MS development, we compared drinking habits, smoking habits, physical activity, and weight effects (Fig. 4). Women diagnosed with HDP had a significantly increased risk for smoking (OR 1.143; 95% CI, 1.026–1.273), weight gain (OR 1.143; 95% CI, 1.026–1.273), and reduced physical activity (OR 1.0553; 95% CI, 1.012-1.100). Alcohol consumption had a neutral effect on the development of MS (OR 1.003; 95% CI, 0.945–1.063).

4.Discussion

In our study, MS development exhibited a shorter time period (average of 1.6 years) in women with HDP compared with the normal delivery group. A history of HDP appeared to be independently associated with the future development of MS in the HDP group 1.2 times more than the normal group. In addition, a history of HDP appears to be associated with 3 MS components: hypertension, high TG levels, and abdominal obesity. However, HDP was not associated with high FBS levels or reduced HDL levels. In our study, we constructed a customized DB and performed big data analysis using the NHIS data registry to confirm the findings described above. Our study was a longitudinal analysis of MS development in women who had experienced pregnancy complicated by HDP among the study population undergoing medical health examination during the follow-up period.

Preeclampsia, the most serious form of HDP, may contribute to the subsequent risk of pathophysiological abnormalities linked to CVD, which occur due to disturbances in various metabolic pathways. Preeclamptic women are predicted to be at a greater risk of poor health as they age because MS is a critical risk factor for CVD incidence and mortality, and the prevalence of MS is thought to increase linearly with age due to multiple age-related physiological mechanisms.[21,22] Previous genomic cohort studies conducted in South Korea showed that preeclamptic patients were significantly more prone to developing metabolic disorders, such as central obesity, elevated blood pressure, and elevated fasting glucose levels, later in life simply by having a pregnancy complicated by preeclampsia.[14] The authors noted that further longitudinal follow-up studies are needed.

Our study had several strengths. First, we used the NHIS data registry cohort and constructed a customized DB to confirm the long-term follow-up study and longitudinal analysis of the future risk of MS in women with a history of HDP. The NHIS in Korea is recognized as an example of a good health insurance system worldwide. The NIHS sample cohort data is considered a big data source of health information because the subjects are representative of the entire population, and the data contain disease- and death-related information as well as demographic and socioeconomic information. Among all national health examination recipients, the results of the basic examination, including health behaviors and physical parameters, were also included. The representative quality of the national health information data serves as another strength of this study

Table 1

Comparison of MS developlment between normal delivery group and HDP group.

	Normal group (n = 55,903)	HDP group (n = 11,549)	*P* value
The age at delivery (yrs)	31 ± 4.49	33.11 ± 4.49	**<.0001**
The age of MS (yrs)	38.99 ± 4.96	39.52 ± 4.81	**<.0001**
Time interval from delivery to MS development (yrs)	8.18 ± 3.39	6.64 ± 3.38	**<.0001**
Prevalence of MS	20.34%	37.13%	**<.001**

Data, if appropriate, are presented as mean ± SD. Significant values presented in bold.

HDP = hypertensive disorders of pregnancy, MS = metabolic syndrome.

Table 2

Comparison of lifestyle factors, laboratory findings, and anthropometry between normal delivery group and HDP group who diagnosed as MS.

	Normal group (n = 55,903)	HDP group (n = 11,549)	*P* value
Lifestyle factors			
Maternal age at delivery (years)	31 ± 4.49	33.11 ± 4.49	**<.0001**
Drinking history	7917/55,878 (14.1%)	1624/11,542 (14.1%)	*NS*
Smoking history	2296/55,895 (4.1%)	426/11,547 (3.7%)	*NS*
Laboratory findings			*NS*
Urine-prot (mg/dL)	1.21 ± 0.52	1.19 ± 0.67	
Hg (mg/dL)	12.86 ± 1.39	12.85 ± 1.47	
SGOT (mg/dL)	22.92 ± 26.12	23.99 ± 23.67	
SGPT (mg/dL)	23.49 ± 30.94	25.45 ± 53.51	
GGT (mg/dL)	26.07 ± 33.06	27.91 ± 36.71	
LDL (calculated) (mg/dL)	114.2 ± 72.61	114.9 ± 57.29	
Cr (mg/dL)	0.78 ± 0.58	0.82 ± 0.71	
GFR (mL/min/1.73 m^2)	98.86 ± 28.13	97.57 ± 31.42	
Anthropometry			
Systolic BP (mm Hg)	123.32 ± 14.85	131.4 ± 16.57	**<.0001**
Diastolic BP (mm Hg)	77.75 ± 10.61	83.31 ± 11.63	**<.0001**
Fasting blood glucose(mg/dL)	110.6 ± 37.13	107.4 ± 36.58	**.0139**
Triglyceride (mg/dL)	120.5 ± 90.12	128.9 ± 99.91	**<.0001**
HDL-cholesterol(mg/dL)	52.26 ± 15.77	53.53 ± 18.22	**<.0001**
Waist(cm)	81.97 ± 13.48	83.22 ± 11.07	**<.0001**
BMI (kg/m^2)	25.44 ± 4.26	26.38 ± 4.71	**<.0001**

Data, if appropriate, are presented as mean ± SD. Significant values presented in bold. BMI = body mass index, BP = blood pressure, Cr = creatinine, GFR = glomerular filtration rate, GGT = gamma-glutamyl transpeptidase, HDL = high-density lipoprotein, HGB = hemoglobin, LDL = low density lipoprotein, prot = protein, SGOT = serum glutamic-oxaloacetic transaminase, SGPT = serum glutamic-pyruric transaminase.

Table 3

Risk of the development of MS and its components in women with a normal delivery group and HDP group.

	Normal group (n = 55,903)	HDP group (n = 11,549)	Odds Ratio (95% CI)
MS	20.34%	37.13%	1.23 (1.12–1.35)
Individual components of MS			
SBP ≥ 130 mm Hg	19,657 (35.16%)	6207 (53.74%)	1.644 (1.610-1.678)
TG ≥ 150 mg/dL	9655 (17.27%)	2648 (22.93%)	1.026 (1.006–1.046)
HDL < 50 mg/dL	29,991 (53.65%)	5437 (47.08%)	0.969 (0.950–0.988)
FBS ≥ 100 mg/dL	32,383 (57.93%)	5495 (47.58%)	0.87 (0.75–0.97)
Waist ≥ 88 cm	21,757 (38.92%)	4799 (41.55%)	1.0376 (1.018–1.057)

FBS = Fasting blood glucose, HDL = high-density lipoprotein cholesterol, HDP = hypertensive disorders of pregnancy, MS = metabolic syndrome, SBP = systolic blood pressure, TG = Triglyceride.

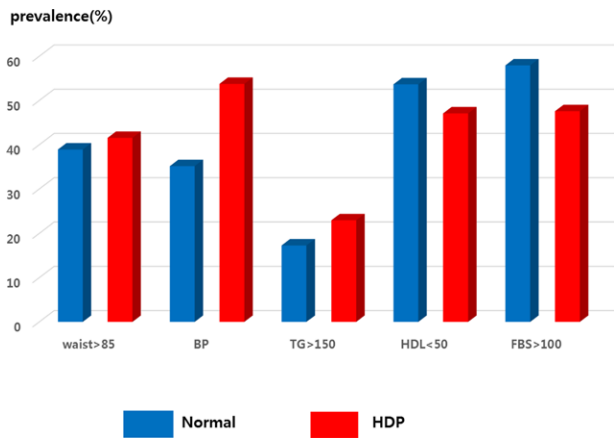

Figure 2. Comparison of the risk of developing MS and its components in women with and without a history of HDP. HDL = high-density lipoprotein cholesterol, FBS = fasting blood glucose, HDP = hypertensive disorders of pregnancy, MS = metabolic syndrome, SBP = systolic blood pressure, TG = triglyceride.

assessing the longitudinal risk of MS development in women who experienced HDP. In addition, our cohort enrolled all pregnant women between 2009 and 2016 in Korea and sampled the NHIS database between 2009 and 2016 given the lack of MS component data before 2009. As previously noted, we constructed a customized DB using the NHIS registry data of pregnant women and performed a longitudinal analysis of the risk of MS development.

The present results were similar to those of previous studies reporting that women experiencing HDP during pregnancy tended to have higher blood pressure, unfavorable lipid profiles and higher BMI, which are known risk factors for CVD in later life; moreover, the prevalence of MS was significantly increased in women who had experienced a pregnancy complicated by preeclampsia.[23–26] Additionally, a previous meta-analysis reported that women diagnosed with HDP were at a higher risk of developing worse biochemical CVD indicators (i.e., levels of TGs, HDL, glucose, insulin, and microalbumin) than those with normotensive pregnancies.[27] This finding indicates that abnormal metabolic changes activated and/or induced by a pregnancy complicated by HDP may influence the development of CVD in the future.

However, our study demonstrated that our cohort of women in their mid-30s exhibits an increased tendency to develop MS based on the meta-analysis results. Thus, in Korea, older pregnant women should be intensively monitored for MS components using heath checkups before reaching 40 years of age.

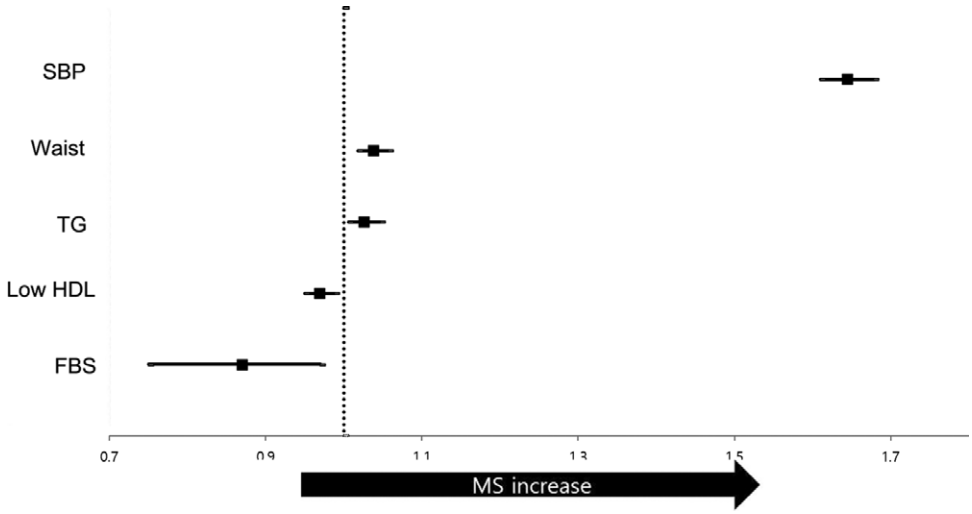

Figure 3. Risk estimates for metabolic syndrome and components of metabolic syndrome in women with a history of hypertensive disorder of pregnancy. FBS = fasting blood glucose, HDL = high-density lipoprotein cholesterol, SBP = systolic blood pressure, TG = triglyceride.

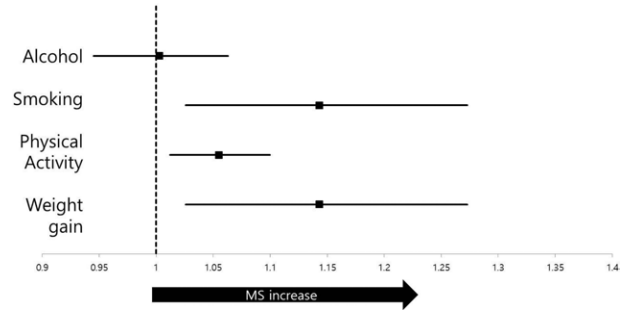

Figure 4. Risk estimates for metabolic syndrome based on lifestyle factors.

Regarding lifestyle factors, modifiable factors, such as BMI, central obesity, high TGs, smoking and physical exercise, can delay MS development in pregnant women with HDP. Although limited data were available, alcohol intake was not significantly associated with the development of MS in our cohort.

A certain number of vascular and metabolic changes typically occur during placental and fetal development; however, preeclamptic women who also have endothelial injury and dysfunction are likely to experience high levels of metabolic stress.[28] Moreover, the characteristics of preeclampsia, including insulin resistance, hypertension, and unfavorable lipid profiles, overlap with those of MS. This overlap suggests that preeclampsia is associated with metabolic deregulation and that the high levels of metabolic stress that occur during gestation could be maintained and/or could develop into MS after pregnancy. Based on a literature review and the present results, it is possible to posit that metabolic stress associated with pregnancy seems to be an apparent precursor of MS in later life. Metabolic stress during pregnancy in women who become pregnant at older than 30 years of age is more likely to have a serious influence on future metabolic health, and women with a history of preeclampsia and pregnancy at an older age may be vulnerable to the future development of MS.[22,25,28–32]

This study had several limitations. First, the study population consisted of women who underwent delivery and health examinations registered in the NHIS database; thus, selection bias could occur, which is often inevitable in observational NHIS registry studies. Additionally, an important limitation is that the diagnoses of HDP, including preeclampsia, severe preeclampsia, superimposed hypertension of pregnancy, and pregnancy-induced hypertension, were defined based on the Korean Classification of Disease codes, which may be inaccurate compared with the diagnoses obtained from a medical chart. In addition, underreporting or misclassification is also possible. Additionally, we could not assess family history or medical history. The NHIS-NSC 2018 data did not include information obtained before 2009 because the factors needed for the diagnosis of MS were missing. In addition, because this was a longitudinal observational study, it was not possible to demonstrate the causal relationship between HDP and future MS syndrome development.

Despite these limitations, our findings suggest that to promote the cardiovascular and metabolic health of women in the future, women with HDP should be considered a group at increased risk who should be targeted for both closer surveillance and personalized interventions for risk modification rather than following the standard health checkup programs conducted for the general population.

5.Conclusion

Our longitudinal analysis findings suggest that HDP increases the risk of MS development later in life and results in a shorter time interval to MS development than that noted in women with normal delivery. Women with HDP should undergo intensive examinations of their metabolic components.

Acknowledgments

Database and statistical analysis

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Statistical analysis: Hyeyoun Lee.
Study conception: Da-Hye Ju.
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