

Hypertensive disorders of pregnancy increase the risk for chronic kidney disease

: a population-based retrospective study

(妊娠高血圧症候群は慢性腎臓病のリスクを増加させる——一般住民を対象とした後方視的検討——)

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Abstract

Hypertensive disorders of pregnancy (HDP) and chronic kidney disease (CKD) are well known risk factors for cardiovascular disease (CVD) in later life. However, few studies have investigated the association of HDP with CKD. Moreover, these studies utilized either registry based or clinical based data and did not include subclinical CKD patients. To address this gap in the literature, we investigated whether HDP is related to CKD, diagnosed based on the estimated glomerular filtration rate (eGFR), in later life.

We designed a population-based, retrospective study, and reviewed the results of blood and physiological examinations as well as the results of pregnancy data available in patients' Maternity Health Record Books for 312 women. We identified 15 women with a diagnosis of CKD based on the eGFR, and 14 women with HDP. We found that women who experienced HDP had a high risk of CKD in later life compared to women without HDP (odds ratio, [OR] 4.854; 95% confidence interval, [CI] 1.042-22.621). Compared to normotensive women, those who were hypertensive at the time of the examination were significantly associated with CKD (OR3.109, 95% CI 1.213-11.510).

Awareness regarding the risk for CKD and CVD in a relatively young age can enable women to prevent diseases effectively.

Keywords: Hypertensive disorders of pregnancy, cardiovascular disease, chronic kidney disease, hypertension, Maternity Health Record Book

Introduction

Hypertensive disorders of pregnancy (HDP) include cases of new-onset hypertension during pregnancy and affect 3-5% of all pregnancies. These disorders must be closely monitored as they can adversely affect maternal and fetal health. [1] It is well known that women who experience HDP develop cardiovascular disease at a high rate. [2-11] In addition, several studies have reported that HDP increase the risk for microalbuminuria [12-14] and kidney diseases in later life. [15-21]

Chronic kidney disease (CKD) is defined as the presence of an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73m^2 or albuminuria-induced end-stage kidney disease (ESKD). [22, 23] Worldwide, the incidence and economic medical burden of ESKD is increasing [24-27], therefore appropriate management of CKD is a priority in many countries. [28]

A few studies have reported that HDP increases the risk for CKD, but these were limited by the fact that they relied on data obtained from registries or clinically available data. [29-31] Since only a subset of patients with early stage CKD are symptomatic, it is

possible that the latter studies which relied on registry and clinical data did not account for the large proportion of patients with subclinical CKD. Furthermore, previous studies did not take into account the multitude of factors that influence the onset of CKD including hypertension and diabetes mellitus. [32, 33]

The aim of this study was to investigate whether a history of HDP was able to independently predict the risk for developing CKD in later life. To this end, we designed a population-based, cross-sectional study and examined multiple risk factors for CKD. We obtained data from Maternity Health Record Books regarding women's pregnancies and deliveries. Since 1942, all pregnant Japanese women have been receiving a Maternity Health Record Book from the local government, and since this book often serves the purpose of a public document for the child, most women hold on to these records for a long time after delivery. This book contains detailed information about the woman's pregnancy, including blood pressure measurements and the presence or absence of proteinuria, which is recorded by medical staff every 1-4 weeks depending on the gestational age. Importantly, Maternity Health Record Books have already been used for the purpose of epidemiologic research, thus validating their utility. [11, 34]

Methods

This study was performed as a part of the Iwaki Health Promotion Project, an ongoing observational study of adult residents living in the rural area of Iwaki that has been running since 2005. The project recruits were voluntary based and approximately 1000 participants participated every year, which was equivalent to 10% of all the inhabitants of the Iwaki area, and 60% of them were women. During this project, various examinations have been performed, including physical and physiological examinations, laboratory investigations, and detailed medical history interviews conducted by trained medical professionals. In addition, we asked the participants to bring their Maternity Health Record Books. We collected 361 Books of 952 multiparas from May 2011 to June 2015 and obtained information regarding patients' past pregnancies and deliveries. The prevalence of CKD and HDP were determined by calculating the eGFR and reviewing Maternity Health Record Books, respectively. Multiple risk factors for CKD were analyzed simultaneously, including hypertension, diabetes mellitus, and lipid profiles. We subsequently evaluated whether a history of HDP was an independent risk factor for CKD in later life.

We selected 312 women who 1) were over 35 years old, 2) had a complete antenatal record for their first singleton pregnancy, and 3) had at least five blood pressure

measurements during the pregnancy. In this study, we analyzed the data available for the women's first pregnancies, since HDP often develop at the time of the first pregnancy.

Using the Maternity Health Record Book, we diagnosed 14 women with HDP using the criteria developed by the Japan Society for the Study of Hypertension in Pregnancy (2015). [35] HDP were defined as hypertension (blood pressure $\geq 140/90$ mmHg) with or without proteinuria emerging after 20 weeks gestation, but normalizing by 12 weeks postpartum.

CKD, the main outcome in this study, was determined by calculating the eGFR using the following equation: $194 \times \text{sCr}^{-1.094} \times \text{age}^{-0.287} \times 0.739$, where sCr is the serum creatinine level. An eGFR < 60 mL/min/1.73m² was diagnostic of CKD.

Secondary outcomes (hypertension, dyslipidemia, and diabetes mellitus) were evaluated through a medical history interview and a blood test performed at the time of the medical examination. Hypertension was defined as blood pressure $> 140/90$ mmHg or use of anti-hypertensive drugs at the time of study participation. Dyslipidemia was defined as low-density lipoprotein cholesterol (LDL-C) level > 140 mg/dL, high-density lipoprotein cholesterol (HDL-C) level < 40 mg/dL, or triglycerides level (TG) > 150 mg/dL, or if the patient was on lipid-lowering drug therapy. Diabetes mellitus was diagnosed based on fasting blood glucose level > 126 mg/dL and hemoglobin A1c

(HbA1c) level > 6.5%, or if the patient was on anti-diabetic medication. All blood samples were collected in the early morning after an overnight fast. Serum glucose, HbA1c (standardized according to the National Glycohemoglobin Standardization Program), total cholesterol, LDL-C, HDL-C, TG, blood urea nitrogen, and creatinine were measured. Pulse wave velocity (PWV) and ankle-brachial index (ABI) were recorded by the form[®] PWV/ABI device (Nippon Colin Co, Aichi Japan). Information regarding past medical history, current illness, use of medications for hypertension/dyslipidemia/diabetes mellitus, and smoking and alcohol status were collected through interviews conducted by trained medical professionals.

Statistical analysis

Differences between the HDP group and the non-HDP group were analyzed using Student's t test or Mann-Whitney U test, Chi-square test or Fisher's exact test, as appropriate. Logistic regression analysis was used to calculate the odds ratios for the association between HDP and CKD. We adjusted for current age, body mass index, age at delivery, hypertension, dyslipidemia, and diabetes mellitus as the confounding factors in multivariate analysis. All results were considered statistically significant at a level of

P<0.05. All statistical analyses were performed using the SPSS, version 22.0 (SPSS Inc., Chicago, IL, U.S.A.)

Results

The average age of our patient cohort and the average age at first childbirth were 53.8 years old and 26.1 years old, respectively. Patients were followed up for an average of 30.7 years from HDP onset. As shown in Table 1, current blood pressure levels, as well as the incidence of hypertension, use of hypertensive medication and CKD were significantly higher in subjects who had a history of HDP than in women with normotensive pregnancies. Fourteen women (4.5%) had a history of HDP as identified from the corresponding Maternal Health Record Books; among them, 7 had preeclampsia, 5 had gestational hypertension and 2 had superimposed preeclampsia. Among the women with a history of HDP, three (21.4%) developed CKD, while only 12 (4.0%) women without HDP developed CKD in later life.

Table 2 shows the comparison between HDP and non-HDP groups with respect to biomarker and physiological test results. Although the PWV value, which is an indirect marker of arterial stiffness, tended to be higher in the HDP group than the non-HDP group, this difference was not statistically significant.

Table 3 shows the results of logistic regression analysis of CKD risk. After multivariate adjustment, HDP was identified as a significant risk factor for CKD (OR 4.854, 95% CI 1.042-22.621). Hypertension at the time of examination was also significantly associated with CKD (OR 3.109, 95% CI 1.213-11.510). Due to a low number of participants with diabetes mellitus, the odds ratio for diabetes mellitus could not be calculated. Analysis by subtypes of HDP was also not performed due to the small number of subjects in each group.

Discussion

This is the first population-based study to report a significant relationship between HDP and CKD diagnosed based on eGFR. Even after adjustment for CKD risk factors, our results indicated that women who experienced HDP had a 4.9 times increased risk for developing CKD.

It is well established that CKD is an important risk factor for CVD. Among the multiple theories that have been proposed to explain this association is the theory that CKD aggravates arteriosclerosis, which is an essential factor for the development of CVD.[36] Investigating the relationship between CKD and CVD is particularly important in light of the fact that the cardiovascular complications of CKD may lead to

death before kidney failure. [37, 38] The prevalence of CVD and ESKD has been increasing in many countries, bringing vast economic burden to society. As a result, the prevention of ESKD and CVD through early detection and medical intervention in the early stages of CKD is a clinical priority among medical professionals. [39]

Several epidemiologic studies conducted to date have confirmed that women who experienced HDP have an increased risk for CVD in later life. [2, 3, 5-11] Although the mechanisms contributing to this relationship remain unclear, some researchers have hypothesized that pregnancy itself acts as a “stress test” that increases the risk for CVD. [4, 34]

The fact that relatively young people are predisposed to CVD is important when thinking about how to prevent the onset of this chronic disease. Several guidelines recommend that medical professionals should inform women who developed HDP of their risk for future CVD. [40-42] However, in many cases, this useful information is not passed on to patients, and even if it is, medical professionals may fail to perform effective interventions such as regular physical check-ups and counseling regarding lifestyle interventions to reduce the risk of CVD.

A few studies have reported that a history of HDP also increases the risk of future CKD. [29-31] However, these results were obtained through clinical based or registry

based studies. Since CKD is usually asymptomatic in the early stages, thereby delaying the clinical detection of disease and therefore timely medical intervention, these studies were limited by the fact that patients with early stage CKD were not included in the study cohort.

In this study, we evaluated a cohort of women from a rural area and defined CKD according to eGFR stages. This allowed us to include patients with even mild or subclinical CKD, which were not included in the previous clinical based or registry based studies. In addition, women with HDP were accurately diagnosed through a review of the Maternity Health Record Books. Therefore, to our knowledge, this is the first population based study to include women with subclinical CKD. Our finding that HDP is an independent risk factor for CKD later in life will be invaluable to improving women's health through early and effective prevention of both CKD and CVD.

This study has three limitations worth noting. First, the number of patients with HDP and CKD was small, and we did not analyze the subclasses of HDP. Since the three subclasses of HDP, preeclampsia, gestational hypertension and superimposed preeclampsia, differ slightly in etiology, they may have differentially influenced the overall risk for CKD. Therefore, it is necessary to recruit more participants and continue the study in order to confirm our findings. Second, since all patients volunteered to

participate in the study, we cannot exclude the effect of sampling bias. However, 38% of multipara women brought their Maternity Health Record Books, we could analyze the some adult residents living in a rural area. Finally, we did not diagnose CKD based on the presence of proteinuria and not followed up for the required three months period, which may have resulted in an over estimation of CKD prevalence. However, since the eGFR forms the basis of CKD diagnosis, our results would not have been significantly affected by the inclusion of urine protein analysis.

In conclusion, we found that women who experienced HDP had a 4.9 times higher risk of developing CKD in later life compared with women without HDP. This information should be communicated to patients to increase their awareness regarding risk for CKD and CVD in an effort to prevent diseases in later life.

Conflicts of interest

The authors declare no conflict of interest.

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Table 1. Characteristics of participants (N=312)

	Hypertensive disorders of pregnancy		
	No (N=298)	Yes (N=14)	P value
Data at the time of study participation			
Age (years)	53.6±11.0	56.0±10.3	0.380
Body mass index (kg/m ²)	22.3±3.3	24.6±5.2	0.066
Levels of blood pressure at surveys			
systolic blood pressure (mmHg)	122.1±18.2	132.8±20.5	0.045
diastolic blood pressure (mmHg)	73.8±11.5	80.7±11.5	0.041
Current smoking	13 (4.4%)	2 (14.3%)	0.141
Hypertension	71 (23.8%)	8 (57.1%)	0.010
Use of hypertensive medication	60(20.1%)	8(57.1)	0.003
Dyslipidemia	34 (11.4%)	3 (21.4%)	0.225
Use of dyslipidemia medication	23(7.7%)	3(21.4%)	0.101
Diabetes mellitus	5 (1.7%)	0	0.793
Use of diabetes mellitus medication	5(1.7%)	0	0.793
Chronic kidney disease	12 (4.0%)	3 (21.4%)	0.024
Data at pregnancy			
Number of deliveries	2.17±0.693	1.93±0.917	0.350
Age at delivery (years)	26.04±4.356	26.57±4.345	0.663

Gestational age (week)			0.512
< 37	11 (3.7%)	1 (7.1%)	
≥ 37	287 (96.3%)	13 (92.9%)	
Birth weight (g)			0.677
< 2500	14 (4.7%)	1 (7.1%)	
≥ 2500	284 (95.3%)	13 (92.9%)	
Classification of hypertensive disorders in pregnancy			
preeclampsia		7 (50%)	
gestational hypertension		5 (35.7%)	
superimposed preeclampsia		2 (14.3%)	

Values are presented as the mean±standard deviation or as number (percentage).

Table 2. Biochemical markers and physiological examination

	Hypertensive disorders of pregnancy		
	No (N=298)	Yes (N=14)	P value
Total cholesterol (mg/dL)	209.6±34.6	218.6±37.6	0.426
Triglycerides (mg/dL)	76.9±36.8	91.2±49.2	0.286
Low-density lipoprotein cholesterol (mg/dL)	117.2±30.5	125.5±31.1	0.350
High-density lipoprotein cholesterol (mg/dL)	73.4±19.6	70.5±19.8	0.412
HbA1c (%)	5.7±0.4	5.7±0.3	0.587
Fasting blood glucose (mg/dL)	81.0±11.1	84.1±9.6	0.143
BUN (mg/dL)	14.3±3.7	14.4±2.8	0.609
Serum creatinine (mg/dL)	0.6±0.1	0.6±0.1	0.227
eGFR (mL/min per 1.73m ²)	79.6±12.4	73.9±14.7	0.158
Pulse wave velocity (cm/s)	1407.7±308.6	1551.7±311.9	0.074

Values are presented as the mean±standard deviation.

Abbreviations: BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c

Table 3. Unadjusted and multivariable-adjusted odds ratios for chronic kidney disease

	Unadjusted odds ratios (95%CI)	P value	Multivariable-adjusted odds ratios (95%CI)*	P value
Current age (years)	1.060 (1.008-1.114)	0.024	1.046 (0.983-1.113)	0.157
Body mass index (kg/m ²)	1.016 (0.878-1.175)	0.829	0.941 (0.788-1.12)	0.501
Age at delivery (years)	0.956 (0.833-1.097)	0.522	1.003 (0.862-1.166)	0.974
Hypertensive disorders of pregnancy				
No	1.0		1.0	
Yes	6.477 (1.595-26.298)	0.009	4.854 (1.042-22.621)	0.027
Hypertension				
No	1.0		1.0	
Yes	4.843 (1.666-14.079)	0.004	3.109 (1.213-11.510)	0.044
Dyslipidemia				
No	1.0		1.0	
Yes	1.178 (0.408-3.398)	0.762	1.088 (0.250-4.731)	0.911
Diabetes mellitus	Not estimated			

*adjusted for current age, body mass index, age at delivery, smoking, hypertension, dyslipidemia, diabetes mellitus