CLINICAL RESEARCH STUDY

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Hypertensive Disorders in Pregnancy and Subsequent Diabetes Mellitus: A Retrospective Cohort Study

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ABSTRACT

BACKGROUND: Cohort study on the association between hypertensive disorders in pregnancy (HDP) and postpartum diabetes is limited. This retrospective cohort study investigated the incidence of diabetes mellitus after delivery among women with HDP using claims data of a universal insurance system.

METHODS: We defined the HDP group as women aged 19-40 years with their first HDP in 2003, excluding those with a history of gestational diabetes mellitus, diabetes mellitus, or hypertension before the date of diagnosis with HDP. Women who had normal pregnancy without HDP were randomly chosen as our comparison group, frequency matched with age and index year of the HDP group. Both groups were followed until December 31, 2008 to evaluate the occurrence of diabetes.

RESULTS: This study consisted of 1139 women with HDP cases and 4527 non-HDP pregnant women. Overall, the subsequent incidence of diabetes mellitus was 5.08-fold higher in the HDP group than in the non-HDP group, with an adjusted hazard ratio of 3.42 (95% confidence interval [CI], 2.07-5.64) after controlling for age, occupation, income, and comorbidity. The hazard ratio of developing diabetes increased to 39.5 (95% CI, 13.0-120.6) for women having HDP, hyperlipidemia, and obesity simultaneously.

CONCLUSIONS: Women with HDP have a high risk of subsequent diabetes. HDP women with obesity and hyperlipidemia are at an extremely high risk of diabetes mellitus. Early identification of women with HDP is needed for prevention, particularly those with other comorbidities.

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KEYWORDS: Diabetes; Eclampsia; Gestational hypertension; Preeclampsia; Pregnancy

Gestational hypertension and preeclampsia are hypertensive disorders in pregnancy (HDP).[1] Gestational hypertension is defined as the onset of hypertension (≥140/90 mm Hg) without proteinuria after 20 weeks of gestation, while preeclampsia is referred to as the onset of hypertension (≥140/90 mm Hg) with proteinuria (≥0.3 g/24 hours), also after 20 weeks of gestation. HDP may complicate 5%-10% of all pregnancies.[2] Gestational hypertension evolves into preeclampsia in 10%-20% of cases.[3] Preeclampsia is one of the common causes of maternal and fetal morbidity and mortality.[4] Both case-control and cohort studies have reported that women with HDP are at an elevated risk of later metabolism disorders and cardiovascular disease.[5-7] Metabolic abnormalities, including obesity, insulin resistance, and dyslipidemia, featuring metabolic syndrome, are risk factors for both HDP and cardiovascular disease.[8-12] On the other hand, HDP may lead to an exaggeration of insulin resistance and is associated with abnormal metabolic change during preg-

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nancy.[13] Vascular and metabolic abnormalities occurring in HDP may persist through postpartum.[14-16] Therefore, it is likely that women predisposed to insulin resistance are more likely to develop HDP and more likely to have subsequent hypertension, atherosclerosis, and type 2 diabetes mellitus in later life, which eventually lead to cardiovascular disease.

Limited cohort studies have reported the association between HDP and subsequent diabetes mellitus (DM) for Western populations.[6,17-19] The Danish National Patient Registry study found that preeclampsia is associated with 3.12-3.68–fold risk of developing type 2 diabetes.[6] The risk of diabetes is much greater for women with preeclampsia who undergo preterm delivery and deliver infants who are small for gestational age. However, no study has investigated the interaction of pregnant hypertensive disorders with other metabolic abnormalities for the subsequent DM. This retrospective cohort study investigated the risk of DM after delivery for Asian women with HDP and interaction with other metabolism abnormalities, using population-based universal insurance claims data.

CLINICAL SIGNIFICANCE

- The postpartum incidence of diabetes mellitus is approximately 5-fold higher in women with hypertensive disorders in pregnancy (HDP) than in women without HDP.
- Among women with HDP, those with preeclampsia/eclampsia are more likely to develop diabetes mellitus than women with only gestational hypertension.
- The hazard ratio of developing diabetes mellitus increased to approximately 40-fold higher for women with HDP, hyperlipidemia, and obesity simultaneously.

MATERIALS AND METHODS

Data Source

Data used in this study were extracted from National Health Insurance Research Database, an electronic claims database of the Taiwan National Health Insurance (NHI) program. Details of the NHI have been described elsewhere.[20] Briefly, NHI is a universal health insurance program reformed in providing health care services to 99% of the population of Taiwan. More than 90% of health care institutions have contracted with the NHI. For this study, we used a subset of the National Health Insurance Research Database containing comprehensive health care data including files of inpatient claims, ambulatory care claims, and prescriptions for one million people randomly selected from the entire 23 million beneficiaries of NHI. We linked these files using the encrypted unique personal identifiers to obtain longitudinal medical history of each individual. Diagnoses were based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The scrambled personal identifications secured the individual's confidentiality, preventing ethical violation of the claims data.

Study Subjects

We conducted the retrospective cohort analysis to determine the association between HDP (ICD-9 code 642) and DM (ICD-9 code 250 or A-code A181). From the 1997-2003 claims data, we identified 1520 women aged 19-40 years with their first HDP. Exclusions were those with a baseline history of gestational DM (n = 280; ICD-9 code 648.0 and 648.8), and those with DM (n = 55) or hypertension (n = 146) identified before the date of diagnosis with HDP. The remaining 1139 women with the first HDP were considered as the HDP cohort. Women who had normal pregnancy (ICD-9 code 650 or A-code A41) without HDP were randomly chosen as our comparison group, frequency matched on age (every 5 years) and the index year of HDP group, using the inclusion criteria similar to the HDP group. The HDP and non-HDP groups were selected in a 1:4 ratio in order to enhance the power of statistical tests. All subjects were followed-up to evaluate the occurrence of diabetes until December 31, 2008 or censored because of death, withdrawal from the insurance program, or loss to follow-up. Comorbidities including obesity (ICD-9 code 278.0 or A-code A183), hyperlipidemia (ICD-9 code 272 or A-code A182), preterm delivery (ICD-9 code 644), and abruption (ICD-9 code 641.2) were considered in data analyses.

Statistical Analysis

Data analyses first calculated the incidences of DM developed in both HDP and non-HDP groups and the HDP-to-non-HDP rate ratios by demographic status and comorbidities such as obesity, hyperlipidemia, preterm delivery, and placenta abruption. The Cox proportional hazardous regression analyses measured corresponding hazard ratios (HRs) with 95% confidence intervals (95% CIs). Both crude HRs and multivariable adjusted HRs were measured. Simple linear regression was used to evaluate trends of rate ratios for diabetes in HDP vs non-HDP groups for age, occupation, and income. Logistic regression model was used to measure odds ratios with 95% CIs to evaluate the associations between HDP and baseline comorbidities, including obesity, hyperlipidemia, and the history of preterm delivery or placenta abruption. We plotted the Kaplan-Meier curves to compare the probability of diabetes developing between women with HDP and without HDP during the study period and used the log-rank test to examine the significance of difference between the 2 groups. To differentiate how the risk of diabetes was associated with age between the HDP

Table 1 Comparisons of Diabetic Incidences Between Women With and Without Hypertensive Disorders of Pregnancy and Associated Hazard Ratios by Sociodemographic Status and Comorbidity

	Non-HDP				HDP								
Variables	n	Cases	PY	Rate*	n	Cases	PY	Rate*	Rate Ratio	Crude HR (95% CI)		Adjusted† HR (95% CI)	
All	4527	31	37,155	8.34	1139	39	9204	42.4	5.08	5.1	(3.19-8.18)‡	4.99	(3.11-8.00)‡
Age, years													
19-24	804	3	6686	4.5	201	2	1669	12.0	2.67	1.00	(Reference)	1.00	(Reference)
25-29	1540	9	12,562	7.2	385	8	3124	25.6	3.57	1.84	(0.68-5.00)	1.94	(0.71-5.27)
30-34	1520	14	12,385	11.3	380	17	3036	56.0	4.95	3.35	(1.30-8.62)	3.52	(1.36-9.13)§
35-40	663	5	5522	9.1	173	12	1375	87.3	9.64	4.06	(1.50-10.99)§	4.15	(1.52-11.35)§
Occupation													
White collar	2988	20	24,176	8.3	745	18	5989	30.1	3.63	1.00	(Reference)	1.00	(Reference)
Blue collar	949	7	8320	8.4	250	12	2081	57.7	6.85	1.38	(0.80-2.40)	1.42	(0.80-2.51)
Unemployed‖	590	4	4659	8.6	144	9	1134	79.4	9.25	1.81	(0.96-3.39)	2.14	(0.97-4.70)
Income													
<15,000	1462	8	12,186	6.6	378	18	3085	58.3	8.89	1.00	(Reference)	1.00	(Reference)
15,000-29,999	2361	13	19,235	6.8	578	18	4622	38.9	5.76	0.77	(0.46-1.30)	0.89	(0.48-1.62)
≥30,000	704	10	5734	17.4	183	3	1497	20.0	1.15	1.07	(0.55-2.09)	1.23	(0.54-2.77)
Co-morbidities													
Obesity													
No	4472	28	36,684	7.6	1086	34	8771	38.8	5.08	1.00	(Reference)	1.00	(Reference)
Yes	55	3	471	63.6	53	5	433	115.4	1.81	6.33	(3.03-13.2)	6.61	(3.17-13.8)
Hyperlipidemia													
No	4156	14	34,015	4.1	959	13	7694	16.9	4.11	1.00	(Reference)	1.00	(Reference)
Yes	371	17	3140	54.1	180	26	1510	172.1	3.18	13.8	(8.53-22.4)	12.2	(7.47-19.9)
Preterm delivery													
No	4502	26	36,942	7.0	1057	27	8471	31.9	4.53	1.00	(Reference)	1.00	(Reference)
Yes	25	5	213	234.7	82	12	733	163.7	0.70	2.02	(0.63-6.42)	1.84	(0.58-5.85)
Abruption													
No	4527	31	37,155	8.3	1133	39	9150	42.6	5.11	1.00	(Reference)	1.00	(Reference)
Yes	0	0	0	–	6	0	54	0.0	–	–		–	

CI = confidence interval; HDP = hypertensive disorders in pregnancy; HR = hazard ratio; PY = person-years.
*Per 10,000 person-years.
†Adjusted for age, occupation, and income.
‡P <.0001.
§P <.01.
‖Unemployed: retired, low income.

and non-HDP cohorts, we measured the HR for each age group, compared with non-HDP subjects aged 19-24 years. Interactions between HDP and baseline metabolism abnormalities in association with developing diabetes also were measured. Information on metabolism abnormalities in terms of obesity and hyperlipidemia is available in the claims data. For the HDP group, we further classified them into 2 groups: women with only gestational hypertension (ICD-9 code 642.3) and women with preeclampsia/eclampsia (ICD-9 codes 642.4-642.6) to examine whether the severity of the hypertensive disorder correlated with the HR of developing diabetes. We used SAS software (version 9.1 for windows; SAS Institute Inc., Cary, NC) for all statistical analyses. All significant levels were set at a 2-tailed P value of <.05. Kaplan-Meier curves were plotted using R (version 2.11.1; R Development Core Team, Vienna, Austria, 2010).

RESULTS

This study consisted of 1139 women with HDP and 4527 non-HDP women for data analyses after excluding ineligible subjects. The mean ages were similar in the HDP and non-HDP groups (29 ± 4.8 years). The mean follow-up periods were 8.1 ± 2.1 years in the HDP cohort and 8.2 ± 2.0 years in the non-HDP cohort (data not shown).

Table 1 demonstrates the incidences of DM in both cohorts, HDP-to-non-HDP rate ratios, and HRs of DM by socioeconomic status and comorbidity. The incidence of diabetes was 5.08-fold greater in the HDP women than in non-HDP women (42.4 vs 8.34 per 10,000 person-years); it increased with age in both groups. The age-specific incidence of diabetes increased much more in the HDP group than in the non-HDP group (P for trend <.0001). The incidence rate ratio also increased with age, from 2.67 for women aged 19-24 years to 9.64 for those aged 35-40 years, with an HR of 4.15 (95% CI, 1.52-11.4) for the oldest women compared with the youngest women. The incidence of diabetes was 87.3 per 10,000 person-years in the oldest HDP women, nearly 10-fold greater than their counterpart non-HDP women. Among the comorbidities, the risk of developing diabetes had strong association with hyperlipidemia (adjusted HR 12.2; 95% CI, 7.47-19.9) and obesity (adjusted HR 6.61; 95% CI, 3.17-13.8) but not with preterm

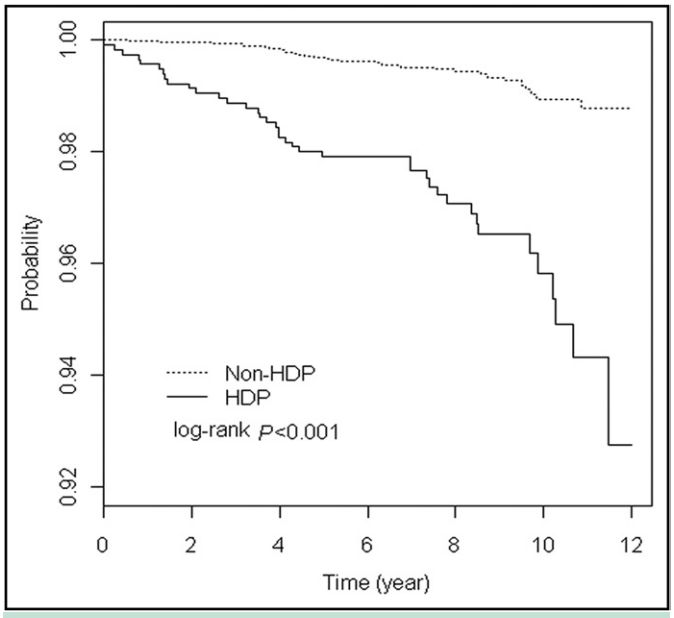

Figure The Kaplan-Meier model measured the diabetes-free proportions in the study cohorts with and without hypertensive disorders in pregnancy (HDP) during the follow-up period.

delivery and abruption. The Kaplan-Meier analysis shows that the cumulative incidence of diabetes was 6% greater in the HDP group than in the non-HDP group, more prominent after the 7-year follow-up ($P < .001$) (**Figure**).

Table 2 shows the prevalence of selected morbidities in association with HDP in the study subjects. Patients with HDP were more prevalent with obesity (4.7% vs 1.2%, $P < .001$), hyperlipidemia (15.8% vs 8.2%, $P < .001$), and preterm delivery (7.2% vs 0.6%, $P < .001$).

Table 3 shows the age-specific hazard of diabetic development for HDP and non-HDP groups separately, comparing with 19- to 24-year-old women in the non-HDP group, after controlling for occupation, obesity, hyperlipidemia, and abruption. Age interacted with HDP. The increase of diabetic risk in the HDP group was particularly strong for patients aged 30-34 years and above with an adjusted HR of 8.87 (95% CI, 2.46-32.0) (P for trend .0004). Overall, the HDP cohort had a higher risk of diabetes than the non-HDP cohort, with an adjusted HR of 3.42 (95% CI, 2.07-5.64) after controlling for age, occupation, income, and comorbidity.

The HDP women were further stratified into 2 subgroups by the severity of hypertensive disorders. Women with preeclampsia/eclampsia had a higher risk of developing diabetes (adjusted HR 4.15; 95% CI, 2.48-6.95) (**Table 4**), while women with only gestational hypertension were less likely to develop diabetes (adjusted HR 1.73; 95% CI, 0.78-3.81).

Data analyses further observed whether comorbidity interacted with HDP in the subsequent development of DM. The incidences of DM associated with HDP and preterm delivery or placenta abruption were not large enough to observe the effect. However, hyperlipidemia interacted strongly with HDP and obesity. The HR of developing diabetes increased to 39.5 (95% CI, 13.0-120.6) for women with HDP, hyperlipidemia, and obesity simultaneously (**Table 5**).

DISCUSSION

To the best of our knowledge, this study is the first one observing a high risk of subsequent DM associated with HDP for Asian women. The pathogenesis of preeclampsia is likely related to both maternal and fetal/placental factors.[21-23] It is likely that preeclampsia develops when abnormal placentation, through the release of anti-angiogenic factors, interacts with maternal constitutional metabolic

Table 2 Odds Ratio of HDP in Association with Comorbidities in Univariate and Multivariate Logistic Regression Models

	HDP Cases	Model 1		Model 2	
Variables	Yes/No	OR	(95% CI)	OR	(95% CI)
Obesity					
No	1086/4472	1	(Reference)	1	(Reference)
Yes	53/55	3.97	(2.71-5.82)*	3.98	(2.71-5.83)*
Hyperlipidemia					
No	959/4156	1	(Reference)	1	(Reference)
Yes	180/371	2.1	(1.74-2.55)*	2.09	(1.72-2.53)*
Preterm delivery					
No	1057/4502	1	(Reference)	1	(Reference)
Yes	82/25	14	(8.88-22.0)*	13.9	(8.82-21.8)*
Abruption					
No	1133/4527	1	(Reference)	1	(Reference)
Yes	6/0	–		–	

CI = confidence interval; HDP = hypertensive disorders in pregnancy; OR = odds ratio. Model 1: Unadjusted; Model 2: Adjusted for age and occupation.

*$P < .001$.

Table 3 Age-specific Incidence of Diabetes in Women With and Without HDP and Cox Proportional Hazard Regression Measured Age-specific Hazard Ratio Compared With 19-24 Years Group in Non-HDP Group

	Non-HDP					HDP				
Variables	DM	PY	Incidence*	HR	(95% CI)	DM	PY	Incidence*	HR	(95% CI)
All†	31	37,155	8.34	1	(Reference)	39	9204	42.4	3.42	(2.07-5.64)
Age, years‡										
19-24	3	6686	4.49	1.00	(Reference)	2	1669	12.0	2.24	(0.37-13.43)
25-29	9	12,562	7.16	1.57	(0.42-5.81)	8	3124	25.6	3.43	(0.90-13.09)
30-34	14	12,385	11.3	2.12	(0.61-7.40)	17	3036	56.0	7.00	(2.02-24.26)
35-40	5	5522	9.05	1.49	(0.36-6.27)	12	1375	87.3	8.87	(2.46-31.98)
P for trend					.15					.0004

CI = confidence interval; DM = diabetes mellitus; HDP = hypertensive disorders in pregnancy; HR = hazard ratio; PY = person-years.
*Per 10,000 person-years.
†Adjusted for age, occupation, obesity, and hyperlipidemia.
‡Adjusted for occupation, obesity, and hyperlipidemia.

syndrome.[24] Gestational hypertension may share the same pathophysiological effect as preeclampsia.

Several cohort studies have demonstrated that insulin resistance in early pregnancy predisposes to HDP.[9,11-12] Cross-sectional studies also have shown that HDP is associated with increased insulin resistance and metabolic syndrome in the third trimester (relative to normal pregnancy).[13,25] Insulin resistance and associated metabolic syndrome may still persist after delivery.[14-16] These studies have clearly indicated an important relationship of potentially predisposing insulin resistance to HDP. Moreover, insulin resistance is exaggerated in HDP and persists after delivery in women with a history of HDP. In our study, obesity and hyperlipidemia, components of metabolic syndrome, interact strongly with HDP for developing DM.

Several other recent studies also have demonstrated that HDP is associated with developing subsequent DM.[6,17-19] A cohort study by Libby et al[19] found that mothers with preeclampsia had an adjusted odds ratio of 1.40 (95% CI, 1.12-1.75) for developing type 2 DM. But they did not exclude women with preexisting or gestational diabetes for their study. Callaway et al[17] performed a survey and found that HDP was associated with subsequent diabetes 21 years after the pregnancy, with an adjusted odds ratio of 1.76 (95% CI, 1.21-2.56). However, that study also did not exclude women with gestational diabetes. Carr et al[18] reported that preeclampsia was associated with a high risk of subsequent diabetes, with an HR of 1.86 (95% CI, 1.22-2.84).[18] But their study did not adjust for confounding variables such as obesity and lifestyle. A Denmark registry-based study showed that the HRs of subsequent type 2 DM were 3.12 (95% CI, 2.63-3.70) for women with gestational hypertension and 3.63 (95% CI, 3.34-3.93) for women with preeclampsia. For women with preterm delivery and preeclampsia, the HR increased to 6.59 (95% CI, 5.34-8.13).[6] They also found that women with 2 episodes of preeclampsia had increased risk of subsequent type 2 diabetes, compared with women with only 1 episode of preeclampsia. But this study also failed to exclude gestational diabetes and adjust for the confounding effect of obesity and hyperlipidemia.

In our study, we excluded women with preexisting hypertension, diabetes, or gestational diabetes at the baseline to reduce the confounding effect of gestational diabetes and preexisting hypertension. HDP was associated with subsequent diabetes with an HR of 3.42 after controlling for age, occupation, and comorbidities. The risk is significantly increased with maternal age, and much stronger than in women without HDP. Among women with HDP, those with preeclampsia/eclampsia have more severe hypertensive dis-

Table 4 Multivariable Cox Proportional Hazard Regression Analysis for Risk of Diabetes in Women With and Without Hypertensive Disorders in Pregnancy

Group	n	DM	PY	Incidence*	HR	(95% CI)
Non-HDP	4527	31	37,155	8.34	1.00	(Reference)
GHT only	488	8	3864	20.70	1.73	(0.78-3.81)
Preeclampsia/eclampsia	651	31	5340	58.05	4.15	(2.48-6.95)†

CI = confidence interval; DM = diabetes mellitus; GHT = gestational hypertension; HDP = hypertensive disorders in pregnancy; HR = hazard ratio; PY = person-years. Adjusted for age, occupation, obesity, hyperlipidemia.
*Per 10,000 person-years.
†$P < .001$.

Table 5 Interaction between HDP and Preterm Delivery Associated with Diabetes in Cox Regression Analysis Controlling for Sociodemographic Factors and Other Comorbidities

Variables							Model 1		Model 2	
HDP	Obesity	Hyperlipidemia	n	DM	PY	Incidence*	HR	(95% CI)	HR	(95% CI)
No	No	No	4180	14	34,240	0.41	1	(Reference)	1	(Reference)
No	Yes	No	40	0	341	0.00	–		–	
No	No	Yes	354	14	2992	4.68	11.2	(5.31-23.4)	10.1	(4.78-21.2)
No	Yes	Yes	17	3	148	20.2	46.4	(13.3-161.5)	40.9	(11.7-142.6)
Yes	No	No	946	12	795	1.58	3.90	(1.81-8.44)	3.94	(1.82-8.51)
Yes	Yes	No	27	1	221	4.52	11.0	(1.44-83.3)	12.6	(1.66-96.3)
Yes	No	Yes	155	22	1306	16.8	39.5	(20.2-77.3)	33.0	(16.7-65.1)
Yes	Yes	Yes	27	4	218	18.3	44.9	(14.8-136.3)	39.5	(13.0-120.6)

CI = confidence interval; DM = diabetes mellitus; HDP = hypertensive disorders in pregnancy; HR = hazard ratio; PY = person-years. Model 1: Unadjusted; Model 2: Adjusted for age, occupation.

*Per 1,000 person-years.

orders. Most diabetes cases developed subsequently were in women who had experienced preeclampsia/eclampsia.

Another important finding in this study is that the women simultaneously having HDP, hyperlipidemia, and obesity are at extremely high risk of subsequent development of DM. This interaction term has not been reported previously. However, the interaction between preterm delivery and HDP was not significant in this study ($P = .99$; data not shown). Because there was only 1 woman who had HDP twice (data not shown), we also failed to observe a significant trend in the development of diabetes associated with multiple HDP episodes.

Limitations

Our study has several limitations. First, the National Health Insurance Research Database provided limited information on sociodemographic characteristics, with information unavailable on marital status, educational level, smoking habit, and laboratory data. These variables could not be adjusted in the analysis. However, controlling for smoking habit and parity resulted in only a small change in odds ratio according to a previous study.[17] Moreover, we were able to use occupation and income for adjustment. Second, some information on chronic conditions, such as hyperlipidemia and obesity, was unavailable for a few individuals. However, this situation happened in both groups. Finally, prenatal care may be different between medical centers, regional hospitals, local hospitals, and obstetrician clinics. The prenatal care at clinics has been standardized to adhere to the insurance system. Insurance claims are subject to be reviewed and validated by auditors of medical records to insure the accuracy of the claims. It is not likely that the prenatal care diagnosis of HDP will vary. Most women receive their prenatal care at hospitals. Our further data analysis showed that women in the HDP group and the non-HDP group had made 140 and 120 clinic visits on average, respectively, during the study period. Examination for DM was likely included in the routine clinic check-up.

CONCLUSIONS

In conclusion, our study results can be generalized to pregnant women in Taiwan for the association between HDP and diabetes risk because we used a representative pregnant population data. The risk of subsequent diabetes in women with HDP was 3.4 times more than in those with uncomplicated pregnancy. The risk doesn't increase further for women with both HDP and preterm delivery, but increases drastically for women with HDP and comorbidities of hyperlipidemia and obesity. Moreover, older pregnant women with HDP may have a much higher risk of subsequent diabetes than younger pregnant women with HDP. Close surveillance for diabetes should be considered for women with HDP, particularly for those with a history of preeclampsia/eclampsia. Lifestyle or pharmacological interventions also should be considered for these high-risk women.

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