Synergistic Effect of Gestational Hypertension and Postpartum Incident Hypertension on Cardiovascular Health: A Nationwide Population Study

Jong Shiuan Yeh, MD,* Hao-Min Cheng, MD, PhD;* Pai-Feng Hsu, MD; Shih-Hsien Sung, MD; Wen-Ling Liu, MS; Hsin-Ling Fang, MS; Shao-Yuan Chuang, PhD

**Background**—Gestational hypertension (GH) is a common complication of pregnancy and is associated with increased risk of incident hypertension in later life (IH) and cardiovascular events. However, the interactive effect of GH and IH on postpartum cardiovascular health remains unclear.

**Methods and Results**—A nationwide population-based study was conducted using 1 million individuals from the Taiwan National Health Insurance database. Records from 1998 to 2009 were used to identify 1260 pregnant women with GH and without previous cardiovascular disease. The control group comprised 5040 pregnant women without GH, matched for age and date of delivery. During the follow-up period (median duration, 5.8 years), 182 cardiovascular events developed. Women with GH had significantly higher risk of cardiovascular events (hazard ratio [95% CI], 2.44 [1.80 to 3.31]) and IH (8.29 [6.30 to 10.91]) than controls. Compared with women without GH and IH, there was a significantly higher risk of cardiovascular events for women without GH but with IH (relative risk [95% CI], 2.89 [1.27–6.58]), women with GH but without IH (1.66 [1.16–2.39]), and women with GH and IH (8.11 [5.36–12.30]). The synergy index was 2.91 (95% CI 1.11 to 7.59), suggesting a positive interaction between GH and IH.

**Conclusions**—GH increased the risk of subsequent IH. Women with both GH and IH were at a substantially higher cardiovascular risk than were women with either GH or IH. The synergistic adverse effect of GH and IH on postpartum cardiovascular health indicates that more attention should be paid to this special population. (J Am Heart Assoc. 2014;3:e001008 doi: 10.1161/JAHA.114.001008)

**Key Words:** cardiovascular events • gestational hypertension • incident hypertension

Hypertensive disorders in pregnancy are common, affecting 5% to 10% of pregnancies, and range widely in severity from gestational hypertension (GH) to preeclampsia and eclampsia. In recent decades, the incidence of GH has increased, along with the level of obesity and maternal age.

New-onset hypertension during pregnancy has been associated with increased risk of subsequent cardiovascular disease (CVD) and incident hypertension in later life. Previous cohort studies have demonstrated the influence of hypertensive disorders during pregnancy on long-term maternal cardiovascular risk. Compared with women with normotensive pregnancies, women with GH are at increased risk of developing hypertension in the following decades. However, little is known about the long-term prognosis of women with GH who later develop hypertension. We conducted a nationwide population-based cohort study to investigate whether there is an additive or a synergistic effect of GH and incident hypertension in later life on postpartum cardiovascular health. Improved risk stratification of this common complication during pregnancy may result in better management of this clinical population.
The database includes patient demographics, diagnosis, prescriptions during hospital stays, and outpatient claims. Currently, the National Health Research Institutes in Miaoli, Taiwan, is in charge of the National Health Insurance Research Database (NHIRD; www.nhri.org.tw/nhird/), and this is one of the largest nationwide population-based databases in the world. The complete National Health Insurance claims database, along with several dozen extracted datasets, is available to researchers. The information is managed with a double-scrambling protocol, whereby the original identification number for each individual is encrypted to protect privacy while maintaining consistency. Therefore, it is possible to follow patients by linking claims belonging to the same patient across the extracted datasets noted above. For this analysis, a nationally representative group of 1 million individuals was randomly selected from all insured persons in the NHIRD. The medical records of all selected individuals from 1996 to 2009 were included in the dataset used for this analysis. Because the National Health Insurance program was initiated in 1996, the claims data for that year were not complete. We thus included data from individuals who were enrolled between January 1, 1997, and December 31, 2009.

### Study Design

We conducted a cohort study of pregnant women with and without GH in this nationally representative sample of 1 million individuals. All diagnoses were made based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. From this nationally representative sample of 1 million individuals, we identified 1260 women with GH (ICD-9-CM code 642), including preeclampsia (642.4 to 642.5) and eclampsia (642.6, 642.7), from January 1, 1998, who had no history of any CVD requiring hospitalization (ICD-9-CM code 390-459) and no history of hypertension (ICD-9-CM code 401-405) in the 12 months before delivery. The control group was 5040 pregnant women (a ratio of 1 case to 4 controls) without GH, who were matched for age and date of delivery. Each matched case and controls had the same delivery date, which signaled the start of the follow-up period.

A history of diabetes or dyslipidemia was identified from medical records in the 12 months before the delivery. Diabetes was defined as ≥3 outpatient claims with ICD-9-CM code 250. Dyslipidemia was defined as ≥3 outpatient claims with ICD-9-CM code 272. Cardiovascular events after pregnancy were identified from medical records as hospitalization because of CVD. The incidence of hypertension (ICD-9-CM code 401-405), diabetes (ICD-9-CM code 250), or dyslipidemia (ICD-9-CM code 272) after pregnancy was identified from medical records submitted after the date of delivery to the date of a cardiovascular event or the end of the study (December 31, 2009). The cardiovascular events were defined with hospitalization claim data (ICD-9-CM: 390-459). All women who developed hypertension in the follow-up period classified as having GH. The study project was reviewed and approved by the institutional review committee of National Health Research Institutes, Miaoli, Taiwan.

### Statistical Methods

Parametric continuous data were compared across groups using the unpaired Student t test and categorical data were compared across groups using the $\chi^2$ test. Survival times were calculated from the date of delivery to the onset date of the cardiovascular event or to the end of the study (December 31, 2009). The Kaplan–Meier method was used to estimate survival curves for each group, and the log-rank test was used to test the homogeneity between survival curves. The hazard ratios (HRs) and 95% CIs were estimated for IH and for cardiovascular events using the Cox proportional hazards model. In addition, because the postpartum IH may be an intermediate variable in the temporal pathway between GH and cardiovascular events, we therefore also considered postpartum IH as a time-dependent variable in our multivariate survival model.

To evaluate whether there is any subgroup of women with GH carrying a substantially different risk of IH and CVD, we carried out a stratified analysis by the onset time of GH before or after 36th week of pregnancy, birth order (first, second, and others), frequency of occurrence of GH (signal and multiple), and types of GH.

Participants were further classified into 4 groups: (1) without GH and IH (GH−/IH−), (2) with GH but without IH (GH+/IH−), (3) without GH but with IH (GH−/IH+), and (4) with GH and IH (GH+/IH+). Logistic regression was used to evaluate the risk of cardiovascular events in each group relative to the GH−/IH− group. The relative risk of cardiovascular events in each group was used to estimate the synergy index, which is the ratio between the combined effect and the individual effects of GH and IH, and indicates the interaction on an additive scale. The synergy index was calculated using the following formula based on the analytic framework proposed by Rothman and Hosmer:

\[
\text{Synergy index} = \frac{RR_{GH+/IH+} - 1}{(RR_{GH+/IH+} - 1) + (RR_{GH+/IH+} - 1)}
\]

where $RR_{GH+/IH+}$, $RR_{GH+/IH+}$, and $RR_{GH+/IH+}$ are the relative risk of cardiovascular events in the GH+/IH+, GH+/IH−, and GH−/IH+ groups, respectively. Synergy index values can range from 0 to infinity. The CIs of the synergy index was also estimated. A value of 1 indicates no interaction or exact additivity, a value >1 indicates a positive interaction or more than additivity, and a value <1 indicates a negative interaction or less than additivity.
Moreover, because the information of potential confounders (eg, body mass index or smoking) is not comprehensively collected in the NHIRD and may cause false associations between GH, IH, and cardiovascular risk, a bias analysis was carried out to quantify the potential impact of unmeasured confounding factors.

**Results**

**Characteristics of the Study Population**

Table 1 presents the characteristics of the study population. The prevalence of diabetes and dyslipidemia at baseline was significantly higher in women with GH than in controls (Table 1), suggesting that an abnormal metabolic profile may have an effect on the development of GH. The percentage of women with diabetes, dyslipidemia, and hypertension during the follow-up period was significantly higher in women with GH than in controls (all \( P < 0.001 \), Table 1).

**GH and the Risk of IH and Cardiovascular Disease**

The median follow-up duration was 5.8 years (interquartiles 2.9 to 8.7 years). During the follow-up period, 68 of 1260 women with GH and 114 of 5040 age-matched controls experienced cardiovascular events (Table 2). The incidence of cardiovascular events was significantly greater in women with GH than in controls (9.74 versus 3.99 per 1000 person-years, \( P < 0.001 \), Table 2). GH increased the risk of cardiovascular events (HR 2.44, 95% CI 1.80 to 3.31, Table 2 and Figure 1A).

During the follow-up period, 158 of 1260 women with GH and 95 of 5040 age-matched controls developed IH (Table 2). The incidence of IH was greater for women with GH than in controls (24.93 versus 3.36 per 1000 person-years, \( P < 0.0001 \), Table 2). GH increased the risk of IH (HR 8.29, 95% CI 6.30 to 10.91, Table 2 and Figure 1B).

As for the stratified analysis, the HRs (adjusted for baseline diabetes and dyslipidemia) of women with GH that occurred before and after the 36th week were 6.43 (4.28 to 9.65) and 8.32 (5.98 to 11.57) for IH and 2.21 (1.35 to 3.62) and 2.57 (1.76 to 3.76), respectively, for CVD events. Women with GH were at significantly increased risk for IH and CVD. Stratified by the birth order, the HRs of GH for predicting IH was 6.76 (5.01 to 9.13), 11.01 (6.26 to 19.34), and 6.51 (2.40 to 17.66) for first, second, and other parity of delivery. In addition, the HRs of GH for CVD was 2.47 (1.74 to 3.51), 2.31 (1.20 to 4.45), and 3.31 (0.89 to 12.34) stratified by first, second, and other parity of delivery, respectively. Furthermore, within the subgroups of woman with different occurrence frequency and various types of GH, comparable and significantly increased HRs for IH and for CVD were still noted (Table 3).

**Table 1. Characteristics of the Study Population**

| Characteristics at baseline | Women With GH (n=1260) | Age-Matched Controls (n=5040) | \( P \) Value |
|----------------------------|------------------------|-------------------------------|----------------|
| GH occurred after 36 wk    | 640 (50.79%)           |                                |                |
| GH occurred at 1st delivery| 876 (69.52%)           |                                |                |
| 2nd delivery               | 324 (25.71%)           |                                |                |
| 3rd delivery or beyond     | 60 (4.77%)             |                                |                |

**Table 2. Association of GH and Age-Matched Controls With the Incidence of IH and Cardiovascular Events**

|                              | Women With GH | Age-Matched Controls |
|------------------------------|---------------|----------------------|
| IH                           |               |                      |
| No. of events                | 158           | 95                   |
| Duration from delivery to event, d | 1837±1234   | 2051±1259            |
| Incidence per 1000 person-y  | 24.93         | 3.36                 |
| Hazard ratio (95% CI)        | 8.29 (6.30 to 10.91) | Reference |
| Cardiovascular events        |               |                      |
| No. of events                | 68            | 114                  |
| Duration from delivery to event, d | 2023±1243   | 2071±1266            |
| Incidence per 1000 person-y  | 9.74          | 3.99                 |
| Hazard ratio (95% CI)        | 2.44 (1.80 to 3.31) | Reference |

Data are the mean±SD or n (%). GH indicates gestational hypertension; IH, incident hypertension in later life.

DOI: 10.1161/JAHA.114.001008
Figure 1. Survival curves for the development of cardiovascular events (A) and IH (B) in women with (blue) and without (red) GH. The P-value of the log-rank test for homogeneity between the 2 survival curves was <0.05 for both outcomes. GH indicates gestational hypertension; IH, incident hypertension in later life.

Table 3. Stratified Analysis for the Risk of IH and Cardiovascular Diseases (CVD) in Different Subgroups of GH

| Stratification Factors                        | Diabetes, β (P Value) | Dyslipidemia, β (P Value) | GH, β (P Value) | Hazard Ratio of GH |
|-----------------------------------------------|-----------------------|---------------------------|-----------------|-------------------|
| Model 1 IH as Dependent Variable              |                       |                           |                 |                   |
| GH occurred before 36 wk                      | 1.37 (0.18)           | −12.17 (0.98)             | 1.86 (<0.01)    | 6.43 (4.28 to 9.65) |
| GH occurred after 36 wk                       | −10.43 (0.98)         | 0.17 (0.87)               | 2.12 (<0.01)    | 8.32 (5.98 to 11.57) |
| Occurrence of GH stratified by birth order    |                       |                           |                 |                   |
| First delivery                                | 0.81 (0.43)           | 0.17 (0.87)               | 1.91 (<0.01)    | 6.76 (5.01 to 9.13) |
| Second delivery                               | −10.17 (0.99)         | −12.27 (0.99)             | 2.40 (<0.01)    | 11.01 (6.26 to 19.34) |
| Third delivery or beyond                      | −11.32 (0.99)         | −11.28 (1.00)             | 1.87 (<0.01)    | 6.51 (2.40 to 17.66) |
| Frequency of occurrence of GH                 |                       |                           |                 |                   |
| Once                                          | 0.63 (0.55)           | −0.32 (0.76)              | 2.02 (<0.01)    | 7.56 (5.77 to 9.91) |
| More than once                                | −11.35 (0.99)         | −0.02 (1.00)              | 1.93 (<0.01)    | 6.90 (3.20 to 14.89) |
| Types of GH                                   |                       |                           |                 |                   |
| GH without preeclampsia or eclampsia          | 1.51 (0.13)           | −12.12 (0.98)             | 2.00 (<0.01)    | 7.40 (4.95 to 11.06) |
| Preeclampsia                                  | −11.04 (0.98)         | 0.24 (0.81)               | 2.03 (<0.01)    | 7.65 (5.40 to 10.83) |
| Eclampsia                                     | −1.86 (<0.01)         | −11.12 (1.00)             | 1.93 (<0.01)    | 6.90 (3.20 to 14.89) |
| Model 2 CVD as dependent variable             |                       |                           |                 |                   |
| GH occurred before 36 wk                      | 1.80 (0.08)           | −12.56 (0.98)             | 0.79 (<0.01)    | 2.21 (1.35 to 3.62) |
| GH occurred after 36 wk                       | −11.52 (0.99)         | −12.29 (0.99)             | 0.94 (<0.01)    | 2.57 (1.76 to 3.76) |
| Occurrence of GH stratified by birth order    |                       |                           |                 |                   |
| First delivery                                | −11.61 (0.98)         | −11.90 (0.99)             | 0.91 (<0.01)    | 2.47 (1.74 to 3.51) |
| Second delivery                               | 3.27 (<0.01)          | −13.49 (0.98)             | 0.84 (<0.01)    | 2.31 (1.20 to 4.45) |
| Third delivery or beyond                      | −10.91 (1.00)         | −10.91 (1.00)             | 1.20 (0.07)     | 3.31 (0.89 to 12.34) |
| Frequency of occurrence of GH                 |                       |                           |                 |                   |
| Once                                          | 1.18 (0.24)           | −11.31 (0.97)             | 0.82 (<0.01)    | 2.28 (1.66 to 3.14) |
| More than once                                | −11.01 (0.99)         | −0.00 (1.00)              | 1.54 (<0.01)    | 4.68 (1.81 to 12.13) |
| Types of GH                                   |                       |                           |                 |                   |
| GH without preeclampsia or eclampsia          | 1.60 (0.11)           | −12.24 (0.98)             | 0.70 (<0.01)    | 2.00 (1.26 to 3.18) |
| Preeclampsia                                  | −11.40 (0.99)         | −12.25 (0.99)             | 1.11 (<0.01)    | 3.02 (2.00 to 4.56) |
| Eclampsia                                     | −0.32 (0.69)          | −11.12 (1.00)             | 0.82 (<0.01)    | 2.28 (1.66 to 3.14) |

Control variables: diabetes and dyslipidemia at baseline. GH indicates gestational hypertension; IH, incident hypertension in later life.
Multivariate analysis revealed that GH and IH were independent risk factors for cardiovascular events (Table 4). GH increased the risk of cardiovascular events (HR 2.45, 95% CI 1.81 to 3.32) in the model that accounted for baseline diabetes and dyslipidemia, and IH during the follow-up period (Model 2, Table 4). IH (as a time-dependent variable) was also associated with increased risk of cardiovascular events in this model (HR 7.57, 95% CI 3.67 to 15.63).

To further evaluate the impact and interaction of GH and IH on postpartum cardiovascular health, study subjects were classified into 4 groups: GH−/IH− (n=4945), GH+/IH− (n=1102), GH−/IH+ (n=95), and GH+/IH+ (n=158). The risk of cardiovascular events was 2.18%, 3.63%, 6.32%, and 17.72%, respectively (Figure 2 and Figure 3A). Compared with the GH−/IH− group, the relative risk (95% CI) of cardiovascular events was 1.66 (1.16 to 2.39), 2.89 (1.27 to 6.58), and 10.72, respectively (Table 4).
8.11 (5.36 to 12.30) for the GH+/IH−, GH−/IH+, and GH+/IH+ groups, respectively (Table 5 and Figure 3).

The synergy index was used to evaluate whether there was an additive or a synergistic effect of GH and IH on future cardiovascular events. The synergy index was 2.91 (95% CI 1.11 to 7.59), suggesting that there was a positive, or more than additive, interaction between GH and IH. In other words, women with GH and IH had a higher cardiovascular risk than did those with either GH or IH alone. Moreover, the combined effects of GH and IH on cardiovascular health may be more pronounced than the mere summation of the individual risk resulting from GH and IH.

Figure 4 shows the bias-adjusted relative risks of CVD for women with GH plus IH. It could be argued that the risk imposed by GH and IH could be related to confounding parameters that could not be measured with the current study design. However, with the assumed prevalence of an unmeasured confounder in women with GH plus IH changing from 0.2 to 0.8 and RR (Relative Risk) of CVD for unmeasured confounder ranging from 3 to 9, the bias-adjusted RR of cardiovascular events for women with GH plus IH was 2.4 to 7.5, which indicated that the significant association between cardiovascular events and GH plus IH cannot be explained by the impact of other unmeasured confounding factors.

**Discussion**

New-onset hypertension is a common complication during pregnancy. Our findings are in line with previous reports that GH increases the risk of future cardiovascular events and incident hypertension in later life. In this large, nationwide cohort study, we found that women with GH had a higher risk of IH than did age-matched pregnant women without GH. In addition, as shown in Table 3, these findings were consistent in different subgroups of GH. More important, women with both GH and IH had a significantly higher cardiovascular risk than did women with either GH or IH alone, indicating a positive interaction or synergistic effect. The independent prognostic significance of GH and IH suggests that these 2 risk factors may impose adverse impacts on postpartum cardiovascular health through complex interactions and mechanisms. As a result, while treating women with hypertension, clinicians should be reminded of the importance of the past history of GH because it may be an easily unheeded risk factor for CVD and the risk of GH combined with IH is synergistic rather than additive. Indeed, women with GH who later developed IH had an ≈3-fold risk of CVD compared with hypertensive women without the past history of GH (RR 2.806, 95% CI 1.206 to 6.527, Table 5).

We found a link between GH, IH, and the risk of cardiovascular events. Part of our findings are consistent with previous reports on the association between GH or preeclampsia and cardiovascular risk. Hermes et al showed that women with a history of GH or preeclampsia at term had higher predicted 10- and 30-year cardiovascular risk than did women with a history of uncomplicated pregnancies. In a Japanese cohort study, GH was identified as a risk factor for hypertension, hypercholesterolemia, and diabetes in later life. However, these studies failed to provide information about the cardiovascular risk of women with GH who later also developed hypertension. We demonstrated for the first time that women with GH who develop new-onset hypertension postpartum may have a higher-than-expected cardiovascular risk. Using the synergy index, we clearly demonstrated...
that GH and IH were 2 independent risk factors for postpartum cardiovascular health that interacted with each other synergistically.

The mechanisms underlying these findings remain to be elucidated. The reasons why women with GH are more prone to the development of hypertension in later life and the mechanisms by which GH synergistically interacts with IH to affect long-term cardiovascular health are not clear. It has been proposed that abnormal cytotrophoblastic invasion and spiral artery remodeling may lead to ischemia/hypoxia–mediated increases in inflammatory cytokines during pregnancy.17–19 These effects might or might not resolve after placental delivery. An observational study reported that hypertension in later life after preeclampsia in pregnancy was preceded by increased left ventricular mass and diastolic blood pressure at postpartum screening.20 More studies are needed to clarify the possible underlying mechanisms. A previous study, conducted with a novel experimental model resembling human preeclampsia, demonstrated that placental soluble fms-like tyrosine kinase 1, an antagonist of vascular endothelial growth factor and placental growth factor, is upregulated in preeclampsia, leading to increased systemic levels of soluble fms-like tyrosine kinase 1 that fall after delivery. More important, the administration of soluble fms-like tyrosine kinase 1 to pregnant rats can induce hypertension, proteinuria, and glomerular endotheliosis, the classic lesion of preeclampsia.21 Whether soluble fms-like tyrosine kinase 1 plays a central role in the mechanism linking GH and IH with long-term postpartum cardiovascular health should be further explored.

It has been speculated that women with GH may have a clustering of metabolic syndrome traits before and after pregnancy along with subclinical vascular damage and endothelial dysfunction, all of which may increase the risk of CVD later in life.5,22 Such a hypothesis might partly explain the observed synergistic effects shown in our study. However, although the incidence of diabetes and dyslipidemia during follow-up was higher in women with GH than in age-matched controls, the overall prevalence of abnormal metabolic profiles was relatively low. As suggested in an analysis of women with GH but without other known risk factors, GH probably has an independent effect on long-term cardiovascular risk.3 Women with both GH and IH might have an underlying genetic predisposition, with their vulnerability being revealed by pregnancy as a stressor.3

Table 5. The Relative Risk of Cardiovascular Events in Women With and Without GH and IH

| GH   | IH   | Number of Subjects | Age, y   | Number of Cardiovascular Events | Relative Risk (Control by Age) | 95% CI (Control by Age) | P Value Compared With Reference Group (Control by Age) | Diabetes During the Follow-up Period | Dyslipidemia During the Follow-up Period |
|------|------|--------------------|---------|--------------------------------|--------------------------------|--------------------------|--------------------------------------------------------|-------------------------------------|---------------------------------------|
| No   | No   | 4945               | 29.80±4.18 | 108                           | Reference                       | Reference                | Reference                                              | 58 (1.17%)                          | 121 (2.45%)                          |
| Yes  | No   | 1102               | 29.69±4.16 | 40                            | 1.66 (1.66)                     | 1.16 to 2.39             | 0.0061 (0.0064)                                        | 34 (3.09%)                          | 34 (3.09%)                           |
| No   | Yes  | 95                 | 31.94±3.78 | 6                             | 2.89 (3.05)                     | 1.27 to 6.58             | 0.0113 (0.0080)                                        | 13 (13.68%)                         | 19 (20.00%)                          |
| Yes  | Yes  | 158                | 30.92±4.18 | 28                            | 8.11 (8.35)                     | 5.36 to 12.30            | <0.0001 (<0.0001)                                      | 20 (12.66%)                         | 35 (22.15%)                          |

GH indicates gestational hypertension; IH, incident hypertension in later life.

Figure 4. Bias analysis to evaluate the impact of unmeasured confounders on the association between GH plus IH and cardiovascular disease. The calculated relative risk (RR) of cardiovascular disease (CVD) for women with GH plus IH was 11.49 and the assumed prevalence of unmeasured confounders in the women without GH plus IH was 15%. With the assumed prevalence of unmeasured confounder in women with GI plus IH changing from 0.2 to 0.8 (different horizontal lines) and RR of CVD for unmeasured confounder ranging from 3 to 9 (x-axis), there were still significant bias adjusted RRs (y-axis) of CVD for women with GH plus IH. GH indicates gestational hypertension; IH, incident hypertension in later life.
For assessing the interactions of public health importance, for >30 years, it is the general consensus in the epidemiologic community that measuring interaction on the additive scale is most appropriate.\textsuperscript{10,23} As elegantly illustrated in a review article by Knol et al,\textsuperscript{23} there have been 3 most popular indices proposed to presenting analyses of effect modification and interaction: relative excess risk due to interaction, synergy index, and proportion attributable to the interaction.

For women with GH and/or IH, we also calculated these indices to quantify the effect of interaction of these 2 major exposures. Besides the synergy index, the relative excess risk due to interaction of GH and IH for cardiovascular mortality is 6.102 (95% CI 1.377 to 10.823, \( P=0.0113 \)), and the proportion attributable to the interaction is 0.633 (95% CI 0.339 to 0.926, \( P=0.0001 \)), which further confirmed the synergistic effect of GH and IH on postpartum cardiovascular health.

There are limitations to the present study. Although we controlled for most cardiovascular risk factors, it is possible that there remain some unmeasured confounders that may bias our findings. Other possible confounders such as body mass index and smoking habit could not be faithfully retrieved from the nationwide registry data to allow for appropriate adjustment. However, the prevalence of smoking in women in Taiwan aged >16 years is very low (2% to 5%) and has remained at this low level for a long time (1974–1996). Moreover, significant associations between GH plus IH and cardiovascular risk were still demonstrated with the bias-adjusted analysis (Figure 4); therefore, we do not anticipate that this had a large confounding effect on our results.\textsuperscript{24}

Conclusions

Women with GH had a higher incidence of arterial hypertension later in life than did age-matched pregnant women without GH. Women with both GH and IH after childbirth were at a higher risk of cardiovascular events than were women with either GH or IH alone. There may be a synergetic effect of GH and IH on the risk future cardiovascular events. The long-term cardiovascular health of this special population of pregnant women merits more attention.

Sources of Funding

This study was supported by Taipei Medical University (TMU102-AE1-B14) and by a grant from the National Health Research Institutes (no. PH-103-PP-19 and PH-103-PP-23). This study was conducted in part using data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health, or National Health Research Institutes.

Disclosures

None.

References

1. Hutchison JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. \textit{Best Pract Res Clin Obstet Gynaecol}. 2011;25:391–403.
2. Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1988–2004. \textit{Am J Hypertens}. 2008;21:521–526.
3. Mannisto T, Mendola P, Vaarasmaki M, Jarvelainen AL, Pouta A, Suvanto E. Elevated blood pressure in pregnancy and subsequent chronic disease risk. \textit{Circulation}. 2013;127:681–690.
4. Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P, Smith WC. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. \textit{BMJ}. 2003;326:845.
5. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Pajaud MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. \textit{Hypertension}. 2009;53:944–951.
6. Marin R, Gorostidi M, Portal CG, Sanchez M, Sanchez E, Alvarez J. Long-term prognosis of hypertension in pregnancy. \textit{Hypertens Pregnancy}. 2000;19:199–209.
7. Haukkamaa L, Salminen M, Lauvuori H, Leironen H, Hillemaa V, Kaaja R. Risk for subsequent coronary artery disease after preeclampsia. \textit{Am J Cardiol}. 2004;93:805–808.
8. Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. \textit{Lancet}. 2001;357:2002–2006.
9. Knol MJ, VanderWeele TJ, Groenwold RH, Klungel OH, Middel MA, Grobbee DE. Estimating measures of interaction on an additive scale for preventive exposures. \textit{Eur J Epidemiol}. 2011;26:433–438.
10. Rothman KJ, Greenland S, Walker AM. Concepts of interaction. \textit{Am J Epidemiol}. 1980;112:467–470.
11. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. \textit{Epidemiology}. 1992;3:452–456.
12. Lash TL, Fox MP, Fink AK. \textit{Applying Quantitative Bias Analysis to Epidemiologic Data}. New York: Springer; 2010.
13. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. \textit{BMJ}. 2013;347:f4533.
14. Young B, Hacker MR, Rana S. Physicians’ knowledge of future vascular disease in women with preeclampsia. \textit{Hypertens. Pregnancy}. 2012;31:50–58.
15. Hermes W, Tamsma JT, Grootendorst DC, Franx A, van der Post J, van Pampus MG, Bloemenkamp KW, Porath M, Mol BW, de Groot CJ. Cardiovascular risk estimation in women with a history of hypertensive pregnancy disorders at term: a longitudinal follow-up study. \textit{BMC Pregnancy Childbirth}. 2015;13:126.
16. Kurabayashi T, Mizunuma H, Kubota T, Kiyohara Y, Nagai K, Hayashi K. Pregnancy-induced hypertension is associated with maternal history and a risk of cardiovascular disease in later life: Japanese cross-sectional study. \textit{Maturitas}. 2013;75:227–231.
17. Warrington JP, George EM, Palei AC, Spadley FT, Granger JP. Recent advances in the understanding of the pathophysiology of preeclampsia. \textit{Hypertension}. 2013;62:666–673.
18. Shibata E, Rajakumar A, Powers RW, Larkin RW, Gilmore C, Bodnar LM, Crombleholme WR, Ness RB, Roberts JM, Hubel CA. Soluble fms-like tyrosine kinase 1 is increased in preeclampsia but not in normotensive pregnancies with small-for-gestational-age neonates: relationship to circulating placental growth factor. \textit{J Clin Endocrinol Metab}. 2005;90:4895–4903.
19. Rajakumar A, Cerdeira AS, Rana S, Zengelller Z, Edmunds L, Jeyabalan A, Hubel CA, Stillman IE, Parikh SM, Karumanchi SA. Transcriptionally active spondylic aggregates in the maternal circulation may contribute to circulating soluble fms-like tyrosine kinase 1 in preeclampsia. \textit{Hypertension}. 2012;59:256–264.

DOI: 10.1161/JAHA.114.001008
20. Ghossein-Doha C, Peeters L, van Heijster S, van Kuijk S, Spaan J, Delhaas T, Spaanderman M. Hypertension after preeclampsia is preceded by changes in cardiac structure and function. Hypertension. 2013;62:382–390.

21. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, Libermann TA, Morgan JP, Sellke FW, Stillman IE, Epstein FH, Sukhatme VP, Karumanchi SA. Excess placental soluble fms-like tyrosine kinase 1 (sflt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest. 2003;111:649–658.

22. Fraser A, Nelson SM, Macdonald-Wallis C, Cherry L, Butler E, Sattar N, Lawlor DA. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the Avon Longitudinal Study of Parents and Children. Circulation. 2012;125:1367–1380.

23. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. Int J Epidemiol. 2012;41:514–520.

24. Annual Report of Tobacco, Alcohol Consumption Investigation in Taiwan Area. Taiwan: Bureau of Tobacco and Alcohol Monopoly; 1997.