Research Article

Preeclampsia and the Risk of Pancreatitis: A Nationwide, Population-Based Cohort Study

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Background. Preeclampsia is a multiple organ dysfunction during pregnancy, including hepatic, renal, and neurological dysfunction, and is defined as hypertension and proteinuria occurring after 20 weeks of pregnancy. Clinical features seen in preeclampsia are due to relatively poorly perfused placenta and maternal endothelial dysfunction. Some studies have found that preeclampsia may cause acute pancreatitis due to microvascular abnormalities and visceral ischemia. This retrospective cohort study used the Taiwanese National Health Insurance Research Databases (NHIRD) to study the relationship between preeclampsia and the risk of pancreatitis.

Methods. In total, 606,538 pregnant women were selected from the NHIRD between January 1, 1998 and December 31, 2010. They were divided into a preeclampsia cohort (n = 485,211) and a nonpreeclampsia cohort (n = 121,327). After adjusting for comorbidities that may induce pancreatitis, we analyzed and compared the incidence of pancreatitis in the two cohorts.

Results. The overall incidence of pancreatitis in the preeclampsia cohort was significantly higher than that in the control cohort (4.29 vs. 2.33 per 10,000 person-years). The adjusted HR of developing pancreatitis increased 1.68-fold (95% CI: 1.19-2.36) in the preeclampsia cohort. In addition, pregnant women with preeclampsia without comorbidities had a significantly high risk of pancreatitis (aHR = 1.83, 95% CI 1.27-2.63). The combined effect of preeclampsia and alcohol-related diseases resulted in the highest risk of pancreatitis (aHR = 43.4, 95% CI: 6.06-311.3). Conclusion. Compared with patients without preeclampsia, the risk of pancreatitis in patients with preeclampsia is significantly increased after adjusting for demographics and comorbidities. The risk of pancreatitis is greatly increased when preeclampsia is accompanied by alcohol-related diseases, hepatitis C, gallstones, diabetes, or age of 26–35 years. Early identification and effective control of preeclampsia and the associated comorbidities can reduce the risk of pancreatitis and the associated morbidity and mortality.

1. Introduction

Preeclampsia is defined as the presence of de novo hypertension (>140 mmHg systolic or >90 mmHg diastolic) after 20 weeks of gestation combined with proteinuria or other maternal organ dysfunction (renal, hepatic, and neurologic diseases) [1–3]. It occurs in 3%-5% of pregnancies worldwide [4]. Risk factors associated with preeclampsia include a past history of preeclampsia, preexisting hypertension, preexisting diabetes, obesity, multifetal pregnancy, chronic kidney disease, advanced maternal age, antiphospholipid syndrome, and systemic lupus erythematosus [5].

The increased systemic inflammatory response plays a critical role in the pathogenesis of preeclampsia, leading to edema, extravasation, and increased damage to the vascular bed of the placenta, kidneys, and other organs [6]. This leads
to poorly perfused placenta and maternal endothelial dysfunc-
tion [7]. These changes make preeclampsia a multiorgan 
syndrome dysfunction, with increased risks of various 
disorders, including chronic hypertension, diabetes mellitus, 
ischemic heart disease, cerebrovascular disease, kidney dis-
ease, thromboembolism, hypothyroidism, and even memory 
impairment [8]. Women with preeclampsia have an 
increased risk of life-threatening obstetric or medical complica-
tions. Globally, 10%–15% of maternal deaths due to 
pregnancy complications are directly related to preeclamp-
sia/eclampsia [9].

Pancreatitis is the inflammation of the pancreatic glandu-
lar parenchyma, usually accompanied by abdominal pain 
and elevated serum pancreatic enzymes. Acute pancreatitis 
is the most common cause of hospitalization for gastrointes-
tinal diseases in the United States [10]. Several conditions are 
related to acute pancreatitis, among which gallstones and 
chronic alcoholism account for approximately two thirds 
[11]. Systemic inflammatory response syndrome and organ 
failure are the main causes of death in the first two weeks of 
acute pancreatitis, and sepsis is the main cause of death after 
two weeks [12]. In a systematic review of studies of acute 
pancreatitis, the overall mortality rate is approximately 5% 
[13].

Severe preeclampsia can cause various systemic abnor-
malities, such as refractory abdominal pain, impaired liver 
function, severe hypertension, cerebral or visual disturb-
ances, progressive renal insufficiency, and thrombocytope-
nia [14, 15]. Some case reports have indicated a link 
between the development of pancreatic diseases and pre-
eclampsia [16–20], but studies with a higher level of evidence 
examining this link are lacking. Therefore, this retrospective 
cohort study explored the relationship between preeclampsia 
and pancreatitis by using the Taiwanese National Health 
Insurance Research Database (NHIRD).

2. Materials and Methods

2.1. Data Source. This retrospective population-based study 
used data from the Taiwan NHIRD which covers medical 
benefit claims for over 23 million people (approximately 
99% of Taiwan’s population) [21]. The NHIRD contains 
the registry of beneficiaries and all medical service data. 
These claim files record the disease based on the Interna-
tional Classification of Diseases, Ninth Revision, Clinical 
Modification (ICD-9-CM). For each beneficiary, a unique 
encrypted identification number is used to link all insurance 
information and health care records. This study was 
approved by the Ethics Review Board of China Medical 
University, Taichung (CMUH104-REC2-115).

2.2. Variables and Participants. We identified all preeclamp-
sia patients from the NHIRD corresponding to the Interna-
tional Classification of Disease, the Ninth Revision (ICD-9) 
codes 642.4–642.7 from 1998 to 2010. The date of preeclamp-
sia diagnosis was assigned as the index date. For each woman 
with preeclampsia, we identified a pregnant woman without 
the history of preeclampsia for the comparison cohort, fre-
cuency matched by age (every 5 years span), and pregnancy 
year. Patients were excluded if they were <18 or >45 years 
of age and had a history of pancreatitis (ICD-9 code 577) 
before the index date. The confirmation of pancreatitis events 
was based on the database from 1998 to 2011 as the study 
endpoint. All study participants were followed up from the 
index date to the occurrence of endpoint, death, withdrawal 
from the database, or the end of 2011, whichever came first. 
We evaluated several comorbidities, which were defined as 
the history before the endpoint. They could be related to pan-
creatitis, namely, alcohol-related diseases (ICD-9 codes 291, 
303, 305.00, 305.01, 305.02, 305.03, 790.3, and V11.3), biliary 
stone (ICD-9 code 574), diabetes mellitus (ICD-9 code 250), 
hyperlipidemia (ICD-9 code 272), hypertension (ICD-9 
codes 401–405), hepatitis B virus (ICD-9 codes V02.61, 
070.20, 070.22, 070.30, and 070.32), and hepatitis C virus 
(ICD-9 codes V02.62, 070.41, 070.44, 070.51, and 070.54).

2.3. Statistical Analysis. Distributions of age and comorbid-
ties were compared between cohorts with and without pre-
eclampsia and then tested using the chi-square test for 
categorical variables and Student’s t-test for continuous 
variables. The cumulative incidence curve for pancreatitis 
was assessed using the Kaplan–Meier method, and intergroup 
differences were estimated using the log-rank test. We esti-
mated the incidence densities of pancreatitis during follow-
up in both cohorts. We evaluated the risk of pancreatitis for 
preeclampsia patients compared with the comparison cohort 
by using univariable and multivariable Cox proportional 
hazards models and presented by hazard ratios (HRs) and 
corresponding 95% confidence intervals (CIs). Multivariable 
models were adjusted for age and comorbidities. All statisti-
cal analyses were performed using SAS 9.4 (SAS Institute, 
Cary, NC, USA). We set the significant level at p < 0.05 for 
two-sided testing.

3. Results

The eligible study participants consisted of 17 263 patients in 
the preeclampsia cohort and 69 052 individuals in the non-
preeclampsia cohort. The baseline characteristics of all 
patients are summarized in Table 1. The mean age of patients 
with and without preeclampsia was 31.2 ± 5.19 and 31.0 ± 
5.22 years, respectively, and 64.0% of the study participants 
were aged 26–35 years. Compared with patients without pre-
eclampsia, those with preeclampsia were more likely to have 
biliary stones (1.74%), diabetes mellitus (5.02%), hyperlipid-
emia (1.81%), hypertension (3.85%), hepatitis B virus 
(0.74%), and hepatitis C virus (0.27%). The average follow-
up duration was 7.03 ± 3.90 years for the preeclampsia 
cohort and 7.03 ± 3.92 years for the comparison cohort.

The overall incidence of pancreatitis was greater in the 
preeclampsia cohort than in the comparison cohort (4.29 
vs. 2.33 per 10,000 person-years, crude HR = 1.84, 95% CI 
1.32–2.55), and after adjusting for age and comorbidities of 
alcohol-related disease, biliary stone, diabetes mellitus, 
hyperlipidemia, hypertension, hepatitis B virus, and hepatitis 
C virus, the adjusted HR (aHR) was 1.68 (95% CI 1.55–1.78) 
(Table 2). The pancreatitis incidence increased with age. The 
risk of pancreatitis was higher in patients with preeclampsia
than the comparison cohort for the 26–35 age group (aHR = 2.22, 95% CI 1.43–3.44). Moreover, among patients without comorbidities, the risk of pancreatitis was higher in the preeclampsia cohort than in the comparison cohort (aHR = 1.83, 95% CI 1.27–2.63). Patients with preeclampsia had a higher pancreatitis rate than did the comparison cohort after 14 years of follow-up (log-rank p < 0.001, Figure 1).

Table 3 reveals the combined effect of preeclampsia with specific comorbidities. Compared with nonpreeclampsia patients without alcohol-related diseases, a significantly increased risk of pancreatitis was observed in preeclampsia patients with alcohol-related diseases (aHR = 43.4, 95% CI 6.06–311.3), followed by preeclampsia patients without alcohol-related diseases (aHR = 1.80, 95% CI 1.29–2.50) (Table 3). A significantly high pancreatitis risk was observed in patients with both preeclampsia and hepatitis C virus (aHR = 11.0, 95% CI 1.54–78.9) compared with those without either disease. Preeclampsia coexisting with diabetes mellitus (aHR = 5.89, 95% CI 1.87–18.6) or biliary stone (aHR = 3.63, 95% CI 1.59–8.27) was also associated with a high risk of pancreatitis.

4. Discussion

This is the first nationwide, population-based study to investigate the incidence of pancreatitis after preeclampsia. Our results revealed that patients with a history of preeclampsia exhibited a 1.68-fold risk of pancreatitis than did those without preeclampsia, after adjusting for demographic characteristics and comorbidities.

Preeclampsia is a common pregnancy-specific disease with potential adverse maternal and neonatal outcomes affecting 3%-5% of all pregnancies [4]. Preeclampsia is an obstetric emergency; in the United States, preeclampsia/eclampsia is one of the four leading causes of death among pregnant women, along with bleeding, cardiovascular disease, and thromboembolism [22–24]. Women with preeclampsia are more likely to suffer from systemic diseases in the future, including hypertension, coronary heart disease, stroke, diabetes, and renal disease [25, 26]. Our study found that women with preeclampsia are more likely to develop comorbidities such as gallstones, diabetes, hyperlipidemia, hypertension, and hepatitis B and C infection than pregnant women without preeclampsia (Table 1), which is consistent with some existing studies [27–30]. In fact, these comorbidities are also risk factors for pancreatitis [31–34]. Pancreatitis may affect surrounding tissues or may cause dysfunction of the distal organ system. A small proportion of patients may have pancreatic necrosis, inflammation of surrounding tissues, and organ failure [35, 36]. The pathophysiology of pancreatitis has not been fully elucidated [37, 38]. The most common factors associated with acute pancreatitis are gallstones (35%-75%) and alcohol consumption (25%-35%), followed by idiopathic causes (10%-20%), hypertriglyceridemia (1%-4%), endoscopic retrograde cholangiopancreatography, and drugs (1.4%-2%) [31–34, 39]. Preeclampsia and pancreatitis seem to have common risk factors, including diabetes, hyperlipidemia, and hepatitis [8, 29–34, 39, 40].

The overall incidence of pancreatitis in the preeclampsia cohort was higher than that in the control cohort, even after adjusting for comorbidities associated with pancreatitis and even when only preeclampsia patients without comorbidities were considered (Table 2). Compared with the control cohort, the incidence of pancreatitis in patients with preeclampsia increased with age, especially in the 26–35 age group; this finding is consistent with studies indicating that advanced maternal age is prone to preeclampsia or pancreatitis [41, 42].

The present study revealed that preeclampsia was an independent risk factor for pancreatitis. However, specific diseases, such as alcohol-related diseases, gallstones, or diabetes, were more influential than preeclampsia. Preeclampsia patients with a single specific comorbidity had a higher risk of pancreatitis than did nonpreeclampsia patients with that comorbidity (aHRs = 1.78–1.89) (Table 3), but the combined effects of preeclampsia and the specific comorbidity further increased the risk of pancreatitis. The risk was especially high for preeclampsia combined with alcohol-related diseases, as well as with hepatitis C, diabetes mellitus, and biliary stone.

The prevalence of pancreatitis in pregnancy is low and ranges between 1 in 1000 and 1 in 3000 deliveries [43], but maternal mortality with severe pancreatitis is high [44]. The incidence of fetal distress and fetal loss increases with the severity of pancreatitis [45]. Fortunately, early diagnosis of pancreatitis during pregnancy and improved maternal–infant intensive care has led to a declined in maternal and infant mortality rates [44]. The most common causes of acute pancreatitis in pregnancy are gallstones (67%-100% of pregnancy cases) [43], alcoholism, and hypertriglyceridemia [44]. Other causes include idio-pathic pancreatitis, gestational hypertension, drug-induced pancreatitis, traumatic pancreatitis, and inherited diseases [42, 44, 46].
This study explored the relationship between preeclampsia and pancreatitis. Although no direct link was seen between preeclampsia and the pathology of pancreatitis, preeclampsia has been shown to cause global vascular endothelial dysfunction, which can lead to pancreatitis \[7\]. The pathophysiology of preeclampsia likely involves both maternal and placental factors, such as abnormalities in the uterine and placental circulations. The resultant ischemic placenta seems to introduce complex factors into the maternal circulation; this leads to maternal vascular endothelial dysfunction and eventually gives rise to the clinical manifestations of preeclampsia \[4, 47–50\]. Preeclampsia is associated with microvascular abnormalities, which may involve the cerebral, placental, hepatic, renal, and visceral circulation. Thus, the pancreatic vasculature may also get affected and cause acute pancreatitis, which leads to organized pancreatic necrosis \[20\]. Ramin et al. \[43\] investigated 9 cases of pancreatitis related to preeclampsia and found microthrombosis, intra-vascular coagulation, and vasculitis during preeclampsia, probably resulting in neurological, renal, hepatic, and placental diseases \[43\]. Another study reported that preeclampsia can cause acute edematous pancreatitis likely related to microvascular abnormalities and visceral ischemia \[51\]. Taken together, these findings indicate that maternal vascular endothelial dysfunction in patients with preeclampsia may increase pancreatic vascular system damage, eventually leading to pancreatitis. Further research is warranted to elucidate underlying biological mechanisms.

The difference in the cumulative incidence between patients with preeclampsia and control cohorts increased over time (Figure 1), indicating that the risk of pancreatitis in patients with a history of preeclampsia is long lasting. Because other comorbidities, such as alcoholism, gallstones, hypertension, dyslipidemia, diabetes, and overweight, further increase the risk of pancreatitis, both preeclampsia and comorbidities should be identified as soon as possible and treated effectively to reduce the patient’s long-term morbidity and mortality.

### 5. Limitations

The strength of our research was its population-based design. However, the use of an observational database (i.e., NHIRD) has some inherent limitations.

First, the diagnostic accuracy was based on administrative data, making potential misjudging of preeclampsia and pancreatitis results inevitable. However, the Bureau of National Health Insurance randomly cross-checks medical records in all medical institutions to reduce error codes and misclassification bias. We identified hypertensive disorders during pregnancy and other comorbidities by using ICD-9-CM codes. In Taiwan, since the implementation of the National Health Insurance Program, prenatal care has been very well delivered \[52\]. The program includes 10 routine

### Table 2: Incidence densities of the pancreatitis hazard ratio in women with and without preeclampsia stratified by age and presence of comorbidity.

| Variables | Preeclampsia | Crude HR* (95% CI) | Adjusted HR† (95% CI) |
|-----------|--------------|---------------------|----------------------|
| All       | Event | No PY | Rate* | Event | Yes PY | Rate* | 1.84 (1.32, 2.55)** | 1.68 (1.19, 2.36)** |
| Stratify age | ≤25 | 19 | 66230 | 2.87 | 3 | 16945 | 1.77 | 0.61 (0.18, 2.08) | 0.58 (0.17, 1.99) |
|           | 26-35 | 57 | 311988 | 1.83 | 34 | 77967 | 4.36 | 2.39 (1.56, 3.65)** | 2.22 (1.43, 3.44)** |
|           | 36-45 | 37 | 106993 | 3.46 | 15 | 26416 | 5.68 | 1.63 (0.90, 2.97) | 1.40 (0.74, 2.64) |
| Comorbidity‡ | No | 99 | 469860 | 2.11 | 41 | 106185 | 3.86 | 1.83 (1.27, 2.63)** | 1.83 (1.27, 2.63)** |
|           | Yes | 14 | 15351 | 9.12 | 11 | 15143 | 7.26 | 0.80 (0.36, 1.75) | 0.80 (0.36, 1.76) |

Rate*: incidence rate per 10000 person-years; crude HR*: relative hazard ratio; adjusted HR†: multivariable analysis including age, alcohol-related diseases, biliary stone, diabetes mellitus, hyperlipidemia, hypertension, hepatitis B, and hepatitis C; comorbidity‡: patients with any one of the comorbidities alcohol-related diseases, biliary stone, diabetes mellitus, hyperlipidemia, hypertension, hepatitis B, and hepatitis C were classified as the comorbidity group. *p < 0.05, **p < 0.01, ***p < 0.001.
Antenatal checkups, which involve blood pressure measurement and urinary protein tests, allowing accurate and timely diagnosis of preeclampsia by obstetricians. Although we could not calculate the validity of diagnostic codes for hypertensive disorders in pregnancy, the high validity of the diagnostic codes of the NHIRD has been reported [53, 54]. In addition, we used univariable and multivariable Cox proportional hazards models to assess the risk of pancreatitis and expressed them as HRs. Multivariable models were adjusted for age and comorbidities, including the exclusion of only hypertensive patients. The diagnosis of pancreatitis is typically based on clear guidelines involving characteristic symptoms and signs, blood biochemistry results, and imaging findings [55] and is thus not prone to error.

Second, the NHIRD does not include details of high alcohol consumption, body mass index, tobacco use, or other lifestyle-related factors that may be potential confounders. We tried to reduce these confounders by, for example, including alcohol-related diseases as a proxy of alcohol consumption and metabolic syndrome parameters (such as hyperlipidemia and diabetes) as an alternative indicator of body mass index. In general, the smoking rate among

| Variables                  | Event | PY      | Rate† | Adjusted HR† (95% CI) |
|----------------------------|-------|---------|-------|-----------------------|
| Preeclampsia               | Alcohol-related disease | -     | 113   | 484731                | 2.33 | 1 (reference) |
| -                         | -     | 0       | 480   | 0.00                  | —    | —             |
| +                         | -     | 51      | 121225| 4.21                  | 1.80 (1.29, 2.50)*** |
| +                         | +     | 1       | 102   | 97.7                  | 43.4 (6.06, 311.3)*** |
| Preeclampsia              | Biliary stone | -     | 109   | 482191                | 2.26 | 1 (reference) |
| -                         | -     | 4       | 3020  | 13.2                  | 5.45 (2.01, 14.8)*** |
| +                         | -     | 46      | 114489| 4.02                  | 1.78 (1.26, 2.51)** |
| +                         | +     | 6       | 6838  | 8.77                  | 3.63 (1.59, 8.27)** |
| Preeclampsia              | Diabetes mellitus | -     | 104   | 479566                | 2.17 | 1 (reference) |
| -                         | -     | 9       | 5645  | 15.9                  | 7.13 (3.61, 14.1)*** |
| +                         | -     | 49      | 119078| 4.11                  | 1.89 (1.35, 2.66)*** |
| +                         | +     | 3       | 2249  | 13.3                  | 5.89 (1.87, 18.6)*** |
| Preeclampsia              | Hyperlipidemia | -     | 112   | 483311                | 2.32 | 1 (reference) |
| -                         | -     | 1       | 1900  | 5.26                  | 2.12 (0.30, 15.2)  |
| +                         | -     | 51      | 118648| 4.30                  | 1.85 (1.33, 2.57)*** |
| +                         | +     | 1       | 2679  | 3.73                  | 1.51 (0.21, 10.9)  |
| Preeclampsia              | Hypertension | -     | 113   | 482869                | 2.34 | 1 (reference) |
| -                         | -     | 0       | 2341  | 0.00                  | —    | —             |
| +                         | -     | 51      | 116693| 4.37                  | 1.86 (1.34, 2.59)*** |
| +                         | +     | 1       | 4635  | 2.16                  | 0.91 (0.13, 6.52)  |
| Preeclampsia              | Hepatitis B virus | -     | 113   | 482353                | 2.34 | 1 (reference) |
| -                         | -     | 0       | 2858  | 0.00                  | —    | —             |
| +                         | -     | 51      | 120381| 4.24                  | 1.80 (1.29, 2.51)*** |
| +                         | +     | 1       | 946   | 10.6                  | 4.58 (0.64, 32.8)  |
| Preeclampsia              | Hepatitis C virus | -     | 112   | 484455                | 2.31 | 1 (reference) |
| -                         | -     | 1       | 756   | 13.2                  | 5.55 (0.78, 39.8)  |
| +                         | -     | 51      | 120965| 4.22                  | 1.82 (1.30, 2.53)*** |
| +                         | +     | 1       | 363   | 27.6                  | 11.5 (1.54, 78.9)** |

Rate†: incidence rate per 10000 person-years; adjusted HR†: multivariable analysis including age; **p < 0.01, ***p < 0.001.
Taiwanese women is low, being <2.5% among pregnant women [56]. Moreover, such a large population-based study may have neutralized this effect.

6. Conclusions

Compared with patients without preeclampsia, the risk of pancreatitis in patients with preeclampsia was found to be significantly high even after adjusting for certain demographic characteristics and comorbidities. Preeclampsia is an independent risk factor for pancreatitis, and the risk is further increased when accompanied by alcohol-related diseases, gallstones, diabetes, hepatitis C infection, or age of 26–35 years. Thus, timely identification and effective management of preeclampsia and the aforementioned comorbidities can reduce the risk of pancreatitis and the associated morbidity and mortality.

Abbreviations

aHR: Adjusted hazard ratio  
CI: Confidence interval  
HR: Hazard ratio  
ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification  
NHIRD: National Health Insurance Research Databases.

Data Availability

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). The Ministry of Health and Welfare must approve our application to access this data. Any researcher interested in accessing this dataset can apply form to the Ministry of Health and Welfare requesting access. Please contact the staff of MOHW (email: scarol-wu@mohw.gov.tw) for further assistance: Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan. Phone: +886-2-8590-6848. All relevant data are within the paper.

Additional Points

Reporting Checklist. The authors have completed the STROBE reporting checklist. Data Sharing Statement. The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). The Ministry of Health and Welfare must approve our application to access this data. Any researcher interested in accessing this dataset can apply form to the Ministry of Health and Welfare requesting access. Please contact the staff of MOHW (Email: scarol-wu@mohw.gov.tw) for further assistance: Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan. Phone: +886-2-8590-6848. All relevant data are within the paper.

Ethical Approval

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work which are appropriately investigated and resolved. This study was exempted from a full ethical review by the China Medical University and Hospital Research Ethics Committee (IRB permit number: CMUH104-REC2-115-R4).

Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

Authors’ Contributions

(I) Jia-Lun Huang and Hong-Mo Shih performed the conception and design. (II) Wei-Kung Chen and Chia-Hung Kao contributed to the administrative support. (III) Jia-Lun Huang, Cheng-Li Lin, and Hong-Mo Shih contributed to the provision of study, materials, or patients. (IV) Cheng-Li Lin and Wei-Kung Chen performed the collection and assembly of data. (V) Jia-Lun Huang, Cheng-Li Lin, and Hong-Mo Shih contributed to the data analysis and interpretation. (VI) All authors contributed to the manuscript writing. (VII) All authors have approved the final manuscript.

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References

[1] M. E. Helewa, R. F. Burrows, J. Smith, K. Williams, P. Brain, and S. W. Rabkin, "Report of the Canadian Hypertension Society Consensus Conference: 1. Definitions, evaluation and classification of hypertensive disorders in pregnancy," CMAJ: Canadian Medical Association Journal = journal de l’Association medicale canadienne, vol. 157, pp. 715–725, 1997.
[2] B. W. J. Mol, C. T. Roberts, S. Thangaratinam, L. A. Magee, C. J. M. de Groot, and G. J. Hofmeyr, “Pre-eclampsia,” Lancet, vol. 387, pp. 999–1011, 2016.
[3] J. M. Pauli and J. T. Repke, “Preeclampsia: short-term and long-term implications,” Obstetrics and Gynecology Clinics of North America, vol. 42, no. 2, pp. 299–313, 2015.
[4] J. M. Roberts and C. W. Redman, “Pre-eclampsia: more than pregnancy-induced hypertension,” Lancet, vol. 341, no. 8858, pp. 1447–1451, 1993.
[5] K. Duckitt and D. Harrington, “Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies,” BMJ, vol. 330, p. 565, 2005.
[6] D. Mihu, C. Razvan, A. Malutan, and C. Mihaela, “Evaluation of maternal systemic inflammatory response in preeclampsia,” Taiwanese Journal of Obstetrics & Gynecology, vol. 54, no. 2, pp. 160–166, 2015.
[7] J. M. Roberts, “Endothelial dysfunction in preeclampsia,” Seminars in Reproductive Endocrinology, vol. 16, no. 1, pp. 5–15, 1998.
[8] R. J. Levine, L. J. Vatten, G. L. Horowitz et al, "Pre-eclampsia, soluble fms-like tyrosine kinase 1, and the risk of reduced
[42] O. Igbinosa, S. Poddar, and C. Pitchumoni, "Pregnancy associated pancreatitis revisited," *Clinics and Research in Hepatology and Gastroenterology*, vol. 37, no. 2, pp. 177–181, 2013.

[43] K. D. Ramin, S. M. Ramin, S. D. Richey, and F. G. Cunningham, "Acute pancreatitis in pregnancy," *American Journal of Obstetrics and Gynecology*, vol. 173, no. 1, pp. 187–191, 1995.

[44] G. Ducarme, F. Maire, P. Chatel, D. Luton, and P. Hammel, "Acute pancreatitis during pregnancy: a review," *Journal of Perinatology*, vol. 34, no. 2, pp. 87–94, 2014.

[45] M. Tang, J. M. Xu, S. S. Song, Q. Mei, and L. I. Zhang, "What may cause fetus loss from acute pancreatitis in pregnancy: analysis of 54 cases," *Medicine*, vol. 97, article e9755, 2018.

[46] J. J. Eddy, M. D. Gideonsen, J. Y. Song, W. A. Grobman, and P. O’Halloran, "Pancreatitis in pregnancy," *Obstetrics and Gynecology*, vol. 112, no. 5, pp. 1075–1081, 2008.

[47] J. W. Meekins, R. Pijnenborg, M. Hanssens, I. R. McFadyen, and A. van Asshe, "A study of placental bed spiral arteries and trophoblast invasion in normal and severe pre-eclamptic pregnancies," *British Journal of Obstetrics and Gynaecology*, vol. 101, pp. 669–674, 2005.

[48] I. P. Webster, "Vascular biology of preeclampsia," *Journal of thrombosis and haemostasis: JTH*, vol. 7, no. 3, pp. 375–384, 2009.

[49] S. E. Maynard and S. A. Karumanchi, "Angiogenic factors and preeclampsia," *Seminars in Nephrology*, vol. 31, no. 1, pp. 33–46, 2011.

[50] C. W. Redman, G. P. Sacks, and I. L. Sargent, "Preeclampsia: an excessive maternal inflammatory response to pregnancy," *American Journal of Obstetrics and Gynecology*, vol. 180, no. 2, pp. 499–506, 1999.

[51] N. Badja, G. Troché, J. F. Zazzo, and D. Benhamou, "Acute pancreatitis and preeclampsia-eclampsia: a case report," *American Journal of Obstetrics and Gynecology*, vol. 176, no. 3, pp. 707–709, 1997.

[52] T. C. Liu and C. S. Chen, "The role of Taiwan’s National Health Insurance program in influencing adequate prenatal care," *The International Journal of Health Planning and Management*, vol. 19, no. 2, pp. 113–130, 2004.

[53] C. L. Cheng, Y. H. Kao, S. J. Lin, C. H. Lee, and M. L. Lai, "Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan," *Pharmacoepidemiology and Drug Safety*, vol. 20, no. 3, pp. 236–242, 2011.

[54] C. C. Lin, M. S. Lai, C. Y. Syu, S. C. Chang, and F. Y. Tseng, "Accuracy of diabetes diagnosis in health insurance claims data in Taiwan," *Taiwan yi zhi*, vol. 104, no. 3, pp. 157–163, 2005.

[55] P. A. Banks, T. L. Bollen, C. Dervenis et al., "Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus," *Gut*, vol. 62, pp. 102–111, 2012.

[56] C. P. Wen, T. Y. Cheng, C. L. Lin et al., "The health benefits of smoking cessation for adult smokers and for pregnant women in Taiwan," *Tobacco Control*, vol. 14, suppl_1, pp. i56–i61, 2005.