HSV infection is associated with gestational hypertension: results from the US National inpatient sample

Lifeng Shi,[1] Yan Wu[2]

[1]Department of Obstetrics and Gynecology, NO.117 Center Military Hospital, Hangzhou, China
[2]Department of Endocrinology, NO.117 Center Military Hospital, Hangzhou, China

Correspondence to
Dr Lifeng Shi, Department of Obstetrics and Gynecology, Center Military Hospital, Hangzhou 310013, China; lifengshi@mca21cn.cn

LS and YW contributed equally.

Accepted 2 March 2018

ABSTRACT

The purpose of this study was to determine if there is an association between maternal herpes simplex virus (HSV) infection and pre-eclampsia/eclampsia or gestational hypertension. The US Nationwide Inpatient Sample database was searched for women aged 15–44 years who delivered in a hospital between 2005 and 2014. The patients were categorized into those with and without HSV and pre-eclampsia/eclampsia and gestational hypertension were compared between the groups. The analytic sample size (n=8 264 076) was equivalent to a population-based sample size of 40 653 030 patients. After adjusting for significant variables including age, race, income, insurance status, diabetes mellitus (DM), gestational DM, obesity, and multiple gestations, multivariate regression analysis indicated that HSV was associated with a higher OR for gestational hypertension (adjusted OR 1.038; 95% CI 1.004 to 1.072). However, HSV was not associated with pre-eclampsia/eclampsia (OR 1.001; 95% CI 0.968 to 1.035) in univariate regression analysis. The results of the current study suggest that HSV infection is associated with gestational hypertension but not pre-eclampsia. Given the prevalence of HSV infection and its potential association with hypertensive disorders of pregnancy, further study of HSV and hypertension in pregnancy is warranted.

Significance of this study

What is already known about this subject?

- Gestational hypertension occurred after 20 weeks' gestation in a previously normotensive woman.
- Aberrant activation of inflammatory cascades was associated with pregnancy complications.
- Maternal infections were associated with hypertensive disorders of pregnancy.

What are the new findings?

- The percentage of women who gave birth with HSV increased from 0.8% in 2005 to 2.4% in 2014.
- Maternal herpes simplex virus (HSV) infection was associated with gestational hypertension.
- But, HSV infection was not associated with pre-eclampsia/eclampsia.

How might these results change the focus of research or clinical practice?

- The risk of gestational hypertension in women with HSV should be examined in clinical practice.

INTRODUCTION

Pre-eclampsia is characterized by new onset hypertension (blood pressure >140/90 mm Hg) and proteinuria after 20 weeks' gestation in pregnant women who were previously normotensive.[1] Pre-eclampsia occurs in 2%–8% of all pregnancies and is a leading cause of maternal and neonatal morbidity and mortality worldwide.[2 3] Gestational hypertension, or pregnancy-induced hypertension (PIH), is also characterized by the development of new hypertension after 20 weeks' gestation in a previously normotensive woman without the presence of proteinuria or other signs of pre-eclampsia.[1]

Despite decades of research, the pathophysiology and causative factors of pre-eclampsia and PIH have remained elusive.[4–7] A number of mechanisms have been postulated, and it is now generally accepted that the etiology of pre-eclampsia and PIH is multifactorial and involves both maternal and placental contributions.[4–7]

An inflammatory response is required for proper embryo implantation and placentation.[7]. However, aberrant activation of inflammatory cascades has been shown to be associated with pregnancy complications.[4 5] Over the past 1–2 decades, a growing body of literature has suggested that maternal infections by bacteria, viruses, and parasites and the subsequent maternal inflammatory response play an important role in the development of pre-eclampsia.[8–10]

Herpes simplex virus (HSV) is a member of the herpes virus family that affects humans. HSV-1 primarily affects the orofacial region producing cold sores, while HSV-2 is a sexually transmitted disease that produces genital lesions.[11] Both are highly contagious and infections are lifelong. Although the exact prevalence

To cite: Shi L, Wu Y. *J Investig Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jim-2017-000687

of HSV infection is extremely difficult to estimate because a large number of cases go unreported, the WHO has estimated that 3.7 billion people under the age of 50 (67%) have HSV-1 infection, and 417 million people globally 15–49 years of age (11%) have HSV-2 infection.[11] A study has suggested an association between HSV infection and essential hypertension.[12] However, studies regarding HSV and hypertensive disorders of pregnancy are few.

Thus, the purpose of this study was to determine if there is an association between maternal HSV infection and pre-eclampsia and/or PIH using a nationwide, population-based US database, the Nationwide Inpatient Sample (NIS).

METHODS

Data source

The NIS is the largest all-payer US inpatient care database, and it contains over a hundred clinical and non-clinical data elements from approximately 8 million hospital stays each year. Included in these data elements are primary and secondary diagnoses, primary and secondary procedures, admission and discharge status, patient demographic data, expected payment source, length of stay, and hospital characteristics. All patients are considered for inclusion. The most recent NIS database contains data from about 1050 hospitals from 44 states in the US sampled to approximate a 20% stratified sample of US community hospitals as defined by the American Hospital Association. The NIS was developed as part of the Healthcare Cost and Utilization Project (HCUP), which is sponsored by the Agency for Healthcare Research and Quality.

This study obtained the certificate number, HCUP-74GZR8817, and conforms to the data-use agreement for the NIS from the HCUP Project.

Study population and definitions

The first step of this study was to identify patients who delivered an infant in a hospital between 2005 and 2014 in HCUP-NIS database. This was done by identifying records of women aged 15–44 years with a delivery hospitalization (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code V27, 65X.X, 66X.X). These codes are exclusive to births occurring during a hospital admission.

We then excluded women with chronic hypertension (women who had hypertension before pregnancy or before 20 weeks' gestation) by using ICD-9 code 401–405 to focus only on those who developed hypertension after 20 weeks' gestation. Finally, we identified women with a HSV infection who delivered an infant by identifying admissions containing the ICD-9 diagnostic code 054.XX. Patients without these codes were categorized as without HSV infection.

Variable definitions

The dependent variables were gestational hypertension, which was defined using ICD-9-CM codes 642.0, 642.2, 642.3, and pre-eclampsia/eclampsia, which was defined using ICD-9-CM codes 642.4, 642.5, and 642.6. The independent variables (covariates) were age, race, income status, insurance status, and hospital location. The following potential confounding variables were also examined: pre-gestational diabetes, gestational diabetes, obesity, alcohol abuse, history of smoking, and multiple gestations.

Statistical analysis

Differences in categorical variables between NIS discharges with and without HSV were examined using the Rao-Scott X^2 test, and data were expressed as unweighted counts (weighted %). Univariate and multivariate logistic regression models were used to determine whether HSV was associated with gestational hypertension or pre-eclampsia/eclampsia. Variables having a p value <0.05 in the univariate analysis were selected and evaluated by the multivariate logistic regression model. Since the NIS database is a 20% sample of the US yearly inpatient admissions, weighted samples (DISCWT), stratum (NIS_STRATUM), and cluster (HOSPID) were used to produce national estimates for all analyses. All statistical assessments were two-sided and evaluated at the 0.05 level of significance. Statistical analyses were performed using the statistical software package SPSS complex sample module V.22.0.

RESULTS

A total of 8 436 558 females aged between 15 and 44 years with a delivery hospitalization were identified in the NIS during the period 2005–2014. A total of 172 482 women with the history of hypertension were excluded. Using discharge weights, the analytic sample size (n=8 264 076) was equivalent to a population-based sample size of 40 653 030 patients in the USA.

The percentage of women who gave birth with HSV increased from 0.8% in 2005 to 2.4% in 2014 (p<0.001; figure 1). The characteristics of patients with and without HSV are shown in table 1. There were significant differences in age, race, insurance status, living location, and the comorbidities of DM, gestational DM, obesity, alcohol abuse, smoking, and multiple gestations between patients with and without HSV (all, p<0.001).

The ORs for the probability of gestational hypertension with point estimates and 95% CI are shown in table 2. Age, race, income, insurance status, DM, gestational DM, obesity, smoking, multiple gestation, and HSV were significantly associated with gestational hypertension according to univariate logistic regression. After adjusting for significant

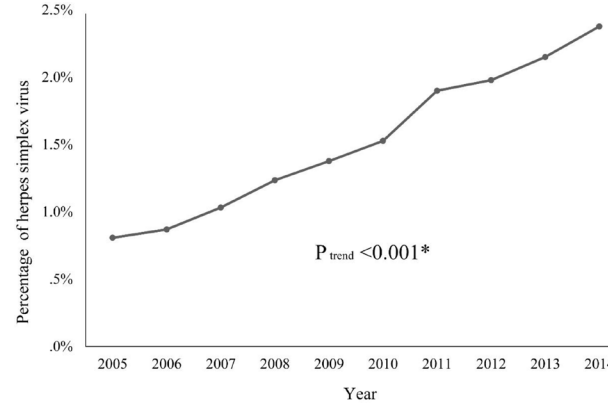

Figure 1 Yearly percentage of patients with herpes simplex virus from 2005 to 2014.

Table 1 Characteristics of patients with and without HSV (unweighted n=8 264 076, weighted n=40 653 030)*

Variable	Without HSV (n=8 140 845)	With HSV (n=123 231)	P values
Age, years			
15–19	749 284 (9.2)	7551 (6.1)	<0.001†
20–35	6 469 031 (79.5)	97 636 (79.2)	
>35	922 530 (11.4)	18 044 (14.6)	
Race			
White	3 566 655 (52.4)	58 751 (54.8)	<0.001
Black	918 059 (13.5)	26 618 (24.8)	
Hispanic	1 594 033 (23.2)	14 712 (13.7)	
Asian or Pacific Islander	357 045 (5.2)	2418 (2.2)	
Native American	56 508 (0.8)	617 (0.6)	
Others	335 393 (5.0)	4030 (3.8)	
Income			
US$1–US$38 999	2 179 616 (27.3)	33 965 (28.1)	0.063
US$39 000–US$47 999	2 025 955 (25.4)	29 538 (24.3)	
US$48 000– US$62 999	1 973 328 (24.7)	30 314 (25.0)	
US$63 000 or more	1 807 282 (22.6)	27 416 (22.6)	
Insurance			
Uninsured	505 763 (6.2)	5721 (4.6)	<0.001†
Insured	7 621 194 (93.8)	117 310 (95.4)	
Location			
Rural	891 349 (11.1)	9704 (7.9)	<0.001†
Urban	7 204 245 (88.9)	112 642 (92.1)	
Comorbidity			
DM	69 232 (0.9)	1438 (1.2)	<0.001†
Gestational DM	461 749 (5.7)	7322 (6.0)	<0.001†
Obesity	288 517 (3.6)	7157 (5.8)	<0.001†
Alcohol abuse	8874 (0.1)	379 (0.3)	<0.001†
Smoking	170 987 (2.1)	4915 (4.0)	<0.001†
Multiple gestation	154 040 (1.9)	2116 (1.7)	<0.001†

Data presented as unweighted count (weighted %).
*Data were weighted according to the National Inpatient Sample protocol.
†Significant difference between the two groups, p<0.05.
DM, diabetes mellitus; HSV, herpes simplex virus.

Table 2 OR for probability of gestational hypertension with point estimates and 95% CI

	Crude OR (95% CI)	Adjusted OR (95% CI)
Age		
15–19 years versus 20–35 years	1.004 (0.983 to 1.026)	**1.060 (1.039 to 1.082)**
>35 years versus 20–35 years	**1.194 (1.172 to 1.217)**	**1.188 (1.168 to 1.208)**
Race		
Black versus white	**1.186 (1.148,1.225)**	**1.115 (1.083 to 1.149)**
Hispanic versus white	**0.624 (0.602 to 0.646)**	**0.602 (0.581 to 0.623)**
Asian or Pacific Islander versus white	**0.497 (0.443 to 0.557)**	**0.502 (0.448 to 0.562)**
Native American versus white	**0.843 (0.778 to 0.914)**	**0.787 (0.726 to 0.852)**
Others versus white	**0.660 (0.627 to 0.693)**	**0.664 (0.632 to 0.696)**
Income		
Q2 versus Q1	**0.950 (0.924 to 0.976)**	**0.961 (0.939 to 0.985)**
Q3 versus Q1	**0.964 (0.932 to 0.997)**	**0.972 (0.947 to 0.997)**
Q4 versus Q1	**0.850 (0.815 to 0.887)**	**0.869 (0.839 to 0.900)**
Insurance		
Insured versus uninsured	**1.249 (1.207 to 1.292)**	**1.167 (1.134 to 1.201)**
Location		
Urban versus rural	0.964 (0.926 to 1.003)	
Diabetes mellitus		
Yes versus no	**2.206 (2.131 to 2.285)**	**1.897 (1.826 to 1.971)**
Gestational diabetes mellitus		
Yes versus no	**1.704 (1.675 to 1.732)**	**1.608 (1.581 to 1.637)**
Obesity		
Yes versus no	**6.945 (6.695 to 7.204)**	**2.872 (2.811 to 2.934)**
Alcohol abuse		
Yes versus no	0.895 (0.798 to 1.003)	
Smoking		
Yes versus no	**1.178 (1.137 to 1.221)**	1.025 (0.987 to 1.065)
Multiple gestation		
Yes versus no	**1.375 (1.336 to 1.415)**	**1.243 (1.203 to 1.283)**
Herpes simplex virus		
Yes versus no	**1.162 (1.124 to 1.202)**	**1.038 (1.004 to 1.072)**

Significant values in bold, p<0.05.
Income: Q1, US$1–US$38 999; Q2, US$39 000–US$47 999; Q3, US$48 000–US$62 999; Q4, US$63 000 or more.

variables including age, race, income, insurance status, DM, gestational DM, obesity, and multiple gestation, multivariate regression analysis indicated that HSV was still associated with a higher OR of gestational hypertension (adjusted OR 1.038; 95% CI 1.004 to 1.072).

Univariate logistic regression showed that age, race, income, living location, DM, gestational DM, obesity, smoking, and multiple gestations were significantly associated with pre-eclampsia/eclampsia (table 3). However, HSV was not associated with pre-eclampsia/eclampsia (OR 1.001; 95% CI 0.968 to 1.035) in univariate logistic regression analysis (table 3).

DISCUSSION

The main finding of this population-wide database study was that maternal HSV infection was associated with the development of gestational hypertension, but not with pre-eclampsia/eclampsia.

Decades of research have led to the identification of some risk factors for gestational hypertension and pre-eclampsia/eclampsia, and many causal models have been proposed, but the pathophysiological mechanism(s) have yet to be determined.[1 13] Studies in the past decade have suggested that the immune system and the inflammatory response play a leading role in the development of hypertension in pregnancy.[4 5 7] Some studies have suggested that the underlying cause of hypertension in pregnancy is an imbalance of angiogenic factors, and inflammation enhances this underlying pathology.[6] In any event, the possibility that inflammation involved in the development of gestational hypertension and pre-eclampsia/eclampsia has resulted in examining if infectious causes of inflammation are associated with hypertension in pregnancy.

Table 3 OR for probability of pre-eclampsia/eclampsia with point estimates and 95% CI

	Crude OR (95% CI)	Adjusted OR (95% CI)
Age		
15–19 years versus 20–35 years	**1.568 (1.542 to 1.595)**	**1.514 (1.490 to 1.539)**
>35 years versus 20–35 years	**1.157 (1.139 to 1.176)**	**1.118 (1.100 to 1.136)**
Race		
Black versus white	**1.463 (1.419 to 1.509)**	**1.300 (1.265 to 1.337)**
Hispanic versus white	1.052 (0.998 to 1.109)	0.977 (0.926 to 1.030)
Asian or Pacific Islander versus white	**0.642 (0.607 to 0.679)**	**0.649 (0.616 to 0.684)**
Native American versus white	**1.417 (1.257 to 1.598)**	**1.254 (1.141 to 1.379)**
Others versus white	1.015 (0.969 to 1.064)	0.965 (0.928 to 1.004)
Income		
Q2 versus Q1	**0.902 (0.881 to 0.924)**	**0.947 (0.925 to 0.970)**
Q3 versus Q1	**0.856 (0.833 to 0.880)**	**0.914 (0.888 to 0.940)**
Q4 versus Q1	**0.751 (0.722 to 0.780)**	**0.824 (0.790 to 0.859)**
Insurance		
Insured versus uninsured	1.036 (0.992 to 1.083)	
Location		
Urban versus rural	**1.126 (1.079 to 1.174)**	**1.161 (1.111 to 1.214)**
Diabetes mellitus		
Yes versus no	**3.753 (3.642 to 3.868)**	**3.351 (3.233 to 3.474)**
Gestational diabetes mellitus		
Yes versus no	**1.722 (1.694 to 1.751)**	**1.701 (1.671 to 1.732)**
Obesity		
Yes versus no	**4.506 (4.371 to 4.646)**	**2.307 (2.250 to 2.365)**
Alcohol abuse		
Yes versus no	1.085 (0.976 to 1.207)	
Smoking		
Yes versus no	**1.066 (1.030 to 1.102)**	1.019 (0.983 to 1.056)
Multiple gestation		
Yes versus no	**3.749 (3.656 to 3.845)**	**3.153 (3.068 to 3.239)**
Herpes simplex virus		
Yes versus no	1.001 (0.968 to 1.035)	

Significant values in bold, p<0.05.
Income: Q1, US$1–US$38 999; Q2, US$39 000–US$47 999; Q3, US$48 000–US$62 999; Q4, US$63 000 or more.

Few studies have explored the relationship between HSV infection and hypertension. An early study by Sun *et al*[12] investigated patients (male and female) with essential hypertension and normotensive controls and found that HSV-2 infection was an independent risk factor for essential hypertension after adjusting for covariates including age, male sex, smoking, body mass index, dyslipidemia, diabetes, and coronary heart disease. A recent case-controlled study reported that HSV-2 as well as rubella seropositivity was associated with pre-eclampsia.[14] Another population-based study reported that fetal exposure to herpes virus infection was associated with pregnancy-induced hypertensive disorders and preterm birth.[15] However, lack of association between HSV infection and pre-eclampsia has also been reported.[9 16] Furthermore, no significant differences in maternal plasma seropositivity for HSV-2 immunoglobulin (Ig)M and IgG between the pre-eclampsia and control groups were observed.[17] In agreement with the above studies,[9 15–17] the current NIS study found significant association between HSV with gestational hypertension, but not with pre-eclampsia/eclampsia.

Although the association between HSV and hypertensive disorders of pregnancy has not been extensively studied, studies have reported bacterial, viral, and parasitic infections are associated with increased risk of developing pre-eclampsia.[8–10] Some specific infections found to be associated with the development of pre-eclampsia include *Chlamydia trachomatis*,[16] *Helicobacter pylori*,[18] *Chlamydia pneumoniae*,[17 19] urinary tract infections,[20 21] infection associated with periodontal disease,[9] cytomegalovirus,[10] and parasitic infections including *Plasmodium* spp and *Toxoplasma gondii*.[10]

The current study has certain inherent strengths and limitations. The primary strength of this study is that it includes a large number of patients from all geographical regions in the USA. The NIS encompasses 20% of all discharges in the USA and is thus a respectable representative sample of the US population. With respect to limitations, the diagnoses were identified based on ICD codes only, and coding errors and misclassifications might exist.

The severity of comorbidities was unknown based on the ICD-coded system and might confound the results. The cross-sectional design of this study can only demonstrate associations; therefore, causation cannot be determined.

In conclusion, the results of the current study suggest that HSV infection is associated with gestational hypertension but not pre-eclampsia. Given the prevalence of HSV infection and its potential association with hypertensive disorders of pregnancy, further study of HSV and hypertension in pregnancy is warranted.

Contributors LS supervised the study, contributed to the critical revision of the manuscript and is the guarantor of integrity of the entire study. YW drafted the manuscript and did the statistical analysis. Both authors contributed to the conception and design; acquisition of data and analysis and interpretation of data. Both authors have read and approved the final version to be submitted.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 American College of Obstetricians and GynecologistsTask Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013;122:1122–31.
2 Kent MS, Wang T, Gangadharan SP, *et al*. What is the prevalence of a "nontherapeutic" thymectomy? *Ann Thorac Surg* 2014;97:276–82.
3 Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009;33:130–7.
4 Laresgoiti-Servitje E. A leading role for the immune system in the pathophysiology of preeclampsia. *J Leukoc Biol* 2013;94:247–57.

5 Cotechini T, Graham CH. Aberrant maternal inflammation as a cause of pregnancy complications: a potential therapeutic target? *Placenta* 2015;36:960–6.
6 Ramma W, Ahmed A. Is inflammation the cause of pre-eclampsia? *Biochem Soc Trans* 2011;39:1619–27.
7 Nadeau-Vallée M, Obari D, Palacios J, *et al*. Sterile inflammation and pregnancy complications: a review. *Reproduction* 2016;152:R277–R292.
8 Rustveld LO, Kelsey SF, Sharma R. Association between maternal infections and preeclampsia: a systematic review of epidemiologic studies. *Matern Child Health J* 2008;12:223–42.
9 Conde-Agudelo A, Villar J, Lindheimer M. Maternal infection and risk of preeclampsia: systematic review and metaanalysis. *Am J Obstet Gynecol* 2008;198:7–22.
10 Nourollahpour Shiadeh M, Behboodi Moghadam Z, Adam I, *et al*. Human infectious diseases and risk of preeclampsia: an updated review of the literature. *Infection* 2017;45:589–600.
11 World Health Organization. Media center. Herpes simplex virus. Updated Jan 2017 http://www.who.int/mediacentre/factsheets/fs400/en/ (accessed 20 Nov 2017).
12 Sun Y, Pei W, Wu Y, *et al*. Herpes simplex virus type 2 infection is a risk factor for hypertension. *Hypertens Res* 2004;27:541–4.
13 Trogstad L, Magnus P, Stoltenberg C. Pre-eclampsia: risk factors and causal models. *Best Pract Res Clin Obstet Gynaecol* 2011;25:329–42.
14 Alshareef SA, Eltom AM, Nasr AM, *et al*. Rubella, herpes simplex virus type 2 and preeclampsia. *Virol J* 2017;14:142.
15 Gibson CS, Goldwater PN, MacLennan AH, *et al*. Fetal exposure to herpesviruses may be associated with pregnancy-induced hypertensive disorders and preterm birth in a Caucasian population. *BJOG* 2008;115:492–500.
16 Haggerty CL, Panum I, Uldum SA, *et al*. Chlamydia trachomatis infection may increase the risk of preeclampsia. *Pregnancy Hypertens* 2013;3:28–33.
17 Soydinc HE, Kan I, Dal T, *et al*. Evaluation of the relationship between preeclampsia and seropositivity of infectious disease in maternal plasma. *Clin Ter* 2013;164:e199–202.
18 Nourollahpour Shiadeh M, Riahi SM, Adam I, *et al*. Helicobacter pylori infection and risk of preeclampsia: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2017:1–8.
19 Karinen L, Leinonen M, Bloigu A, *et al*. Maternal serum Chlamydia pneumoniae antibodies and CRP levels in women with preeclampsia and gestational hypertension. *Hypertens Pregnancy* 2008;27:143–58.
20 Minassian C, Thomas SL, Williams DJ, *et al*. Acute maternal infection and risk of pre-eclampsia: a population-based case-control study. *PLoS One* 2013;8:e73047.
21 Easter SR, Cantonwine DE, Zera CA, *et al*. Urinary tract infection during pregnancy, angiogenic factor profiles, and risk of preeclampsia. *Am J Obstet Gynecol* 2016;214:387.e1–7.