**Temporal trends in pregnancy-associated stroke and its outcomes among women with hypertensive disorders of pregnancy**

Wu. Stroke and hypertensive disorders of pregnancy

Pensée Wu, MD(Res)1,2; Kelvin P. Jordan, PhD3; Carolyn A. Chew-Graham, MD3,4; Thais Coutinho, MD5; Gina P. Lundberg, MD6,7; Ki E. Park, MD8; Lucy C. Chappell, PhD9; Phyo K. Myint, MD10; Angela H.E.M. Maas, PhD11; Mamas A. Mamas, DPhil1,12

1Keele Cardiovascular Research Group, School of Primary, Community and Social Care, Keele University, Staffordshire, UK.

2Academic Unit of Obstetrics and Gynaecology, University Hospital of North Midlands, Stoke-on-Trent, UK.

3School of Primary, Community and Social Care, Keele University, Staffordshire, UK.

4National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West Midlands, Keele University, Staffordshire, UK.

5Division of Cardiac Prevention and Rehabilitation, Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Canada.

6Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia, USA.

7Emory Women’s Heart Center, Atlanta, Georgia, USA.

8Division of Cardiovascular Medicine, University of Florida College of Medicine, Gainesville, Florida, USA.

9Women’s Health Academic Centre, King’s College London, London, UK.

10Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK.

11Department of Cardiology, Women's Cardiac Health, Radboud University Medical Center, Nijmegen, The Netherlands.

12The Heart Centre, University Hospital of North Midlands, Stoke-on-Trent, UK.

**Corresponding author**

Pensée Wu

School of Primary, Community and Social Care

Keele University

Staffordshire

UK

Email: p.wu@keele.ac.uk

Tel: +44 (0)1782 732913

Fax: +44 (0)1782 734719

Subject term: epidemiology

**Abstract**

*Background*

Stroke is a serious complication of hypertensive disorders of pregnancy (HDP), with potentially severe and long-term sequelae. However, the temporal trends, predictors and outcomes of stroke in women with HDP at delivery remain unknown.

*Methods and Results*

All HDP delivery hospitalisations with or without stroke event (ischaemic, haemorrhagic, or unspecified) between 2004 and 2014 in the United States National Inpatient Sample were analysed to examine incidence, predictors and prognostic impact of stroke. Of 4,240,284 HDP delivery hospitalisations, 3,391 (0.08%) women had stroke. While the prevalence of HDP increased over time, incident stroke rates decreased from 10 to 6 per 10,000 HDP delivery hospitalisations between 2004 and 2014. Women with stroke were increasingly multimorbid with some risk factors being more strongly associated with ischaemic strokes, including congenital heart disease, peripheral vascular disease, dyslipidaemia and sickle cell disease. Delivery complications were also associated with stroke, including Caesarean section (OR 1.58, 95% CI 1.33, 1.86), postpartum haemorrhage (OR 1.91, 95% CI 1.33, 1.86) and maternal mortality (OR 99.78, 95% CI 59.15, 168.31), independently of potential confounders. Women with stroke had longer hospital stays (median 6 vs. 3 days), higher hospital charges (median $14,655 vs. $4,762) and a higher proportion of non-routine discharge locations (38% vs. 4%).

*Conclusions*

The incidence of stroke in women with HDP has declined over time. While a relatively rare event, identification of women at highest risk of ischaemic or haemorrhagic stroke on admission for delivery is important to reduce long-term sequelae.

Key words: preeclampsia/pregnancy, pregnancy, stroke in young adults

**Introduction**

Hypertensive disorders of pregnancy (HDP) are a leading cause of maternal morbidity and mortality worldwide,1-4 affecting almost 10% of all pregnancies.5 Chronic hypertension is defined as hypertension diagnosed before pregnancy or before 20 weeks of gestation; gestational hypertension is hypertension diagnosed during pregnancy at or after 20 weeks of gestation, delivery, or postpartum; while preeclampsia or eclampsia is hypertension diagnosed during pregnancy at or after 20 weeks of gestation, delivery, or postpartum with proteinuria or multisystem organ failure.6 Women with HDP are at increased risk of stroke long-term,7 while during the pregnancy almost 50% of pregnancy-associated strokes are associated with preeclampsia or eclampsia.8

Pregnancy-associated stroke is the most common cause of serious long-term disability following pregnancy,9 and accounts for 7.7% of maternal deaths in the United States (U.S.). Furthermore, maternal deaths from stroke in women with HDP may be underestimated as they may be categorised as deaths due to HDP.10 In the U.S., 6.9% of maternal mortality is due to HDP.10 Although there are known risk factors for peripartum strokes in preeclampsia, including older age, black race, infections, and prothrombotic or inflammatory disorders,11 pregnancy-associated strokes continue to be difficult to predict and prevent.

Approximately 40% of pregnancy-associated strokes occur during hospital admissions for delivery,1, 12, 13 with the highest risk occurring in the day before or 2 days after delivery.14 Most of the literature has not assessed the risk of stroke in women with HDP during this high-risk period,15 when it may be possible to implement preventative strategies for these devastating events. The few larger studies in the context of HDP delivery outcomes are limited by the fact that they reported outcomes from selected preeclampsia cohorts,11, 16 lacked specific delivery admissions data,1 included only selected risk factors and comorbidities,1, 16 were derived from limited geographic areas,11, 16 and lacked stroke subtype comparisons.11, 16 A nationally representative database, such as the National Inpatient Sample (NIS) containing discharge data from U.S. hospitals, offers the opportunity to study rare events such as pregnancy-associated strokes during hospital delivery and fill current knowledge gaps in order to accelerate the progress in peripartum stroke prevention.

The current study used a national cohort of over 4 million delivery hospitalisation episodes with HDP which occurred between 2004 and 2014. We aimed to assess the temporal trends in the incidence of stroke, patient characteristics and comorbidities, as well as the associations of stroke with delivery complications, stratified by type of stroke.

**Methods**

We conducted a cross-sectional study using the nationally representative NIS database, the largest all-payer inpatient health care database within the U.S. sponsored by the Agency for Healthcare Research and Quality (AHRQ) as a part of the Healthcare Cost and Utilization Project (HCUP).17 It contains information on 7 to 8 million hospital discharges per year.

We identified all women with a delivery hospitalisation over 11 calendar years between January 2004 and December 2014 using a validated protocol that has been previously published (Supplemental Methods).18 Following this, we established delivery hospitalisations that also had diagnosis codes for HDP using codes from previous publications on the NIS (Supplemental Table IA).19-22 Within these hospitalisations, we extracted records of a stroke event during the admission episode. This was stratified into ischaemic (acute ischaemic stroke, cerebral venous thrombosis, and transient ischaemic attack), haemorrhagic (acute haemorrhagic stroke) and unspecified (stroke in puerperium or iatrogenic stroke, unspecific in nature) stroke (Supplemental Table IB). In parallel, we also stratified the hospitalisations into HDP subgroups (chronic hypertension, gestational hypertension, preeclampsia and superimposed preeclampsia on chronic hypertension).

Relevant treatments (angiography, thrombolysis and thrombectomy), delivery complications (maternal mortality, preterm birth, stillbirth, Caesarean section, postpartum haemorrhage) and cost outcomes (length of stay and total hospital charge) were determined from the dataset using ICD-9-CM codes from previous studies (Supplemental Table IC).19-21, 23-28 We grouped the years (2004-2007, 2008-2011, and 2012-2014) in the temporal trend analyses.

Covariates on patient demographics, obstetric factors and all AHRQ Elixhauser comorbidity measures were extracted, except for weight loss, metastatic cancer, solid tumour without metastasis, lymphoma and blood loss, which are deemed either too uncommon in pregnancy or too common in our delivery cohort (Supplemental Methods). Neurological disorders included multiple sclerosis and epilepsy. Cardiovascular disease (CVD) was defined as a composite of arrhythmia, valvular disease, ischaemic heart disease, peripheral vascular disease, heart failure or peripartum cardiomyopathy. The ICD-9-CM codes used were based on previous publications and presented in Supplemental Table ID.26, 27, 29, 30 This study involved the analysis of de-identified data, and therefore did not require IRB review in accordance with the Code of Federal Regulations, 45 CFR 46.

Stata/MP version 14.0 statistical package was used to perform all analyses. Continuous variables are presented as medians and interquartile ranges, and categorical data are presented as numbers and percentages. As recommended by AHRQ, to account for the survey design of the NIS database, the survey estimation commands were used (*svy* prefix in Stata) for all analyses.

We conducted binary logistic regression analyses to determine the association of potential risk factors with pregnancy-associated stroke, as well as the association between stroke and delivery complications of interest. The following potential risk factors were adjusted for in all fully adjusted analyses: year of admission, age, weekday/weekend admission, race and ethnicity, median ZIP code income quartile, hospital region, smoking, congenital heart disease, dyslipidaemia, ischaemic heart disease, peripartum cardiomyopathy, arrhythmias, previous stroke, sickle cell disease, obstetric factors associated with gestational hypertension or coagulopathy (gestational diabetes, fetal growth restriction, placenta praevia, and multiple pregnancy) and selected AHRQ Elixhauser comorbidity measures (obesity, heart failure, diabetes, valvular disease, pulmonary circulation disorders, peripheral vascular disease, neurological disorders, chronic pulmonary disease, hypothyroidism, renal failure, liver disease, HIV and AIDS, rheumatoid arthritis/collagen vascular diseases, fluid and electrolyte disorders, deficiency anaemias, alcohol abuse, drug abuse, depression, psychosis, coagulopathy, paralysis and peptic ulcer). All odds ratios (OR) were presented with the corresponding 95% confidence intervals (CI). We ensured our study adhered to the recommended methodology standards31 and an extension of the STROBE checklist, the RECORD checklist,32 is shown in Supplemental Table II.

**Results**

A total of 4,240,284 delivery hospitalisation episodes with HDP, including 3,391 (0.08%) women with stroke, between 2004 and 2014 were included (Figure 1). There was an increase in the proportion of HDP delivery hospitalisation episodes from 8.4 to 10.9% out of a total of 44,801,002 hospitalisations between 2004 and 2014 (Figure 2A). However, the proportion of HDP delivery hospitalisations with a recorded stroke diagnosis decreased from 10 per 10,000 HDP delivery hospitalisations in 2004 to 6 per 10,000 HDP delivery hospitalisations in 2008 then remained stable until 2014 (Figure 2B). Next, we examined the temporal trends of demographic factors that may affect HDP women with stroke, such as age, race and ethnicity, median income and prevalent CVD. In both the HDP population and its stroke subpopulation, the median age and the composition of race groups remained relatively constant over time (Supplemental Table III). Although median income (Supplemental Figure IA) and prevalent CVD (Figure 2C) within the HDP population have remained unchanged over the decade, there was a proportional increase of women in the wealthiest income quartile (6 to 17%; Supplemental Figure IB) and with CVD (6 to 18%; Figure 2D) in HDP women with stroke during this study period.

Supplemental Table IV shows the characteristics of our study population. Women with stroke comprised 0.08% of the HDP delivery population. They were older (median age 30 vs. 28) and had a higher proportion of black ethnicity (24% vs. 17%). These women had more comorbidities, such as congenital heart disease, ischaemic heart disease, peripheral vascular disease, heart failure, peripartum cardiomyopathy, coagulopathy, dyslipidaemia and previous stroke. Longer hospital stays (median 6 vs. 3 days) and higher hospital charges (median $14,655 vs. $4,762), compared to women without stroke, were evident in women within the stroke group.

More women with stroke had ischaemic or haemorrhagic strokes (36% or 35% of all stroke population), whilst the remaining 28% had unspecified strokes. The ischaemic stroke group had a higher proportion of Hispanic women, and women with ischaemic heart disease, peripheral vascular disease, heart failure, peripartum cardiomyopathy, previous stroke, dyslipidaemia, sickle cell disease and obesity. Conversely, the prevalences of valvular disease and coagulopathy, were higher in the haemorrhagic compared with the ischaemic group.

The temporal changes in the prevalences of recorded stroke risk factors and comorbidities in the HDP delivery hospitalisation episodes within the stroke and no stroke groups showed increased recorded prevalences of all risk factors and comorbidities over time in women with stroke (Supplemental Table V), except for valvular disease, ischaemic heart disease, renal failure and rheumatoid arthritis or collagen vascular diseases. No obvious differences in stroke risk factors or comorbidities were found between the stroke subgroups.

Angiography was most commonly conducted in haemorrhagic strokes, while for ischaemic strokes, thrombolysis was performed more frequently than thrombectomy (Supplemental Table VI). The prevalences of all delivery complications were higher in women with strokes compared to women without strokes (Supplemental Table VI). Maternal mortality, stillbirth and postpartum haemorrhage occurred most frequently in haemorrhagic strokes, whereas preterm birth occurred most frequently in ischaemic strokes. No obvious temporal patterns were detected for treatments and delivery complications both overall and in the stroke subgroups (Supplemental Table V).

Multivariable analyses were conducted to examine the independent association of risk factors and stroke subgroups (ischaemic, haemorrhagic and unspecified) (Table 1). Pre-existing neurological disorders (adjusted odds ratio (OR) 17.35 (95% CI 13.42, 22.43)), peripheral vascular disease (OR 10.03 (95% CI 3.98, 25.25)), congenital heart disease (OR 7.38 (95% CI 3.85, 14.16), fluid and electrolyte disorder (OR 5.90 (95% CI 4.65, 7.49), and previous stroke (OR 4.77 (95% CI 2.09, 10.87) had the highest odds ratios in association with all stroke. We performed a separate analysis to study the independent predictors of ischaemic and haemorrhagic strokes. Generally, the risk factors associated with stroke were the same for ischaemic and haemorrhagic strokes, although congenital heart disease, peripheral vascular disease, dyslipidaemia and sickle cell disease were more strongly associated with ischaemic stroke.

We also examined the association of stroke with delivery complications (Table 2). This showed that all stroke was associated with a 100-fold increase in risk of maternal mortality (OR 99.78 (95% CI 59.15, 168.31)), which was even greater in the case of haemorrhagic stroke (OR 260.80 (95% CI 138.10, 492.51)). There was an almost double risk of postpartum haemorrhage (OR 1.91 (95% CI 1.54, 2.37)) and 1.5-fold risk for Caesarean section (OR 1.58 (95% CI 1.33, 1.86)) for women with strokes. Over the 11-year study period, there was no change in the association between stroke and delivery complications (Supplemental Figure II).

Women with stroke had longer lengths of hospital stays (6 days (interquartile range (IQR) 3-10)) compared to women without stroke (3 days (IQR 2-4)), with haemorrhagic stroke being associated with the longest duration (7 days (IQR 3-12)) out of all stroke subgroups (ischaemic, haemorrhagic, unspecified) (Supplemental Table IV). Similarly, the total charge was higher for women with stroke ($14,655 (IQR $8,494-$27,895)) compared to women without stroke ($4,762 (IQR $3,278-$7,036)), with the highest charge seen in haemorrhagic stroke ($20,532 (IQR $10,256-$41,042)) (Supplemental Table IV). No temporal changes were detected in the length of stay and total charge outcomes (Supplemental Table V). Additional sensitivity analyses on delivery complications and cost outcomes were conducted to examine for the effects of excluding records with missing data (Supplemental Table VII). This showed no important changes in the ORs.

As a surrogate of disability following stroke, we examined the discharge locations following delivery hospitalisations (Supplemental Table IV, Figure 3). Women with stroke (Figure 3B) had a higher proportion of discharges to facilities other than routine at own home compared to women without stroke (Figure 3A). The haemorrhagic stroke population (Figure 3D) had a greater proportion of discharges to short-term hospitals and other care facilities, compared with ischaemic (Figure 3C) and unspecified (Figure 3E) stroke populations. In contrast, there was a greater proportion of discharges to home care in women with ischaemic (Figure 3C) and unspecified (Figure 3E) compared with haemorrhagic strokes (Figure 3D).

We also stratified the data according to subgroups of HDP (chronic hypertension, gestational hypertension, preeclampsia and superimposed preeclampsia). Over a half of the strokes (52.5%) occurred in women with preeclampsia (Supplemental Table VIII). We then reassessed the prognostic association of stroke risk factors with stroke and the delivery complications associated with strokes for each HDP subgroup (Supplemental Table IX). The gestational hypertension subgroup had the highest increase in risk of maternal mortality and preterm birth following stroke; while for the preeclampsia group, the highest increase in risk occurred in postpartum haemorrhage and Caesarean section.

**Discussion**

Our study is the first to consider the temporal trends of the clinical profile and delivery complications of HDP women with stroke during hospital admissions for delivery, a time of increased stroke risk. Our analysis of over 4.2 million HDP delivery hospitalisations show that while the prevalence of HDP has increased over time, incident stroke rates have declined but remain important predictors of delivery complications, including mortality and Caesarean section. Women with stroke are increasingly multimorbid with distinctive risk profiles for ischaemic and haemorrhagic complications. Congenital heart disease, peripheral vascular disease, dyslipidaemia and sickle cell disease were more strongly associated with ischaemic stroke compared with haemorrhagic stroke.

Previous studies have suggested the incidence of peripartum stroke is increasing over time but without considering the effects of concurrent increase in the incidence of HDP. We are the first to compare the temporal trends in the characteristics of HDP population with its stroke subpopulation. Our analysis shows that the proportion of incident stroke within the HDP delivery population is actually decreasing. This finding is consistent with previous research showing a decline in overall stroke hospitalisations in general population over time, which was more pronounced in women.33, 34 This may be due to improvements in CVD prevention efforts. However, this downward trend in stroke incidence is at risk of being lost due to other emerging patterns such as increasing sedentary lifestyle, substance abuse and social isolation, as well as the obesity/metabolic syndrome epidemic.

We comprehensively assessed comorbidities using Elixhauser comorbidity measures and showed an increasing proportion of multimorbid HDP women suffer strokes, despite the reduction in overall incident stroke in HDP over time. However, this may simply reflect the general trend of more multimorbid women conceiving successfully.22 There was an increase in HDP pregnancy admissions in women who reside in wealthier zip codes over the years, this may be related to increasing access to fertility treatments as HDP is associated with fertility treatments.35, 36

There is limited literature on peripartum outcomes of HDP women with stroke as the majority have studied stroke in the wider pregnant population.15, 37, 38 A previous study using the 1994-2011 NIS database examined hospitalisations with HDP and stroke during the whole pregnancy, rather than the delivery period that we have studied, and showed an event rate of 0.02% for stroke.1 In contrast to our study, they found that stroke in HDP pregnancy hospitalisations increased over their study period.1 This discrepancy may be due to the different study population. Furthermore, different clinical outcomes were examined, with ours focusing on delivery complications while the other study assessed stroke-related outcomes, such as mechanical ventilation, pneumonia and seizure.1 Other national studies on HDP delivery hospitalisations only evaluated women with preeclampsia without other HDP subgroups.11, 16, 39, 40 These focused on stroke risk factors and did not consider adverse outcomes following stroke. A regional study on HDP delivery hospitalisations in New York showed an incidence rate of 0.13% for stroke.41 However, most of the analyses in this study only included stroke in a composite cardiovascular morbidity outcome.

Traditional stroke risk factors have been shown to increase the risk for any stroke in women with HDP during pregnancy.1 We demonstrated that there are some risk factors that are more strongly associated with ischaemic than haemorrhagic strokes. A previous study on the whole pregnancy period also identified sickle cell disease as a risk factor for ischaemic stroke.1 Consistent with our findings, diabetes was not found to increase the risk for pregnancy-associated stroke in this study on HDP pregnancy hospitalisations.1 Unique to our study, we are the first to stratify stroke predictors by specific HDP subgroups.

There are some possible mechanisms for the stroke predictors we identified. The most common mechanism of stroke associated with congenital heart disease is paradoxical embolism, where right to left shunts allows thromboemboli to reach into the arterial circulation without traversing the lungs.42 Moreover, while pregnancy increases the risk of thromboembolism by 6-fold, this risk is further increased in women with HDP.43, 44 Peripheral vascular disease and dyslipidaemia both increase the risk of atherosclerosis which in turn causes ischaemic stroke. In addition to the physiological hyperlipidaemia of pregnancy,45 women with dyslipidaemia have increased risk of preeclampsia.46 Therefore, women with HDP is a particularly high-risk group for ischaemic stroke. Women with sickle cell disease are at high risk for HDP and stroke. Moreover, the stress of delivery can precipitate vaso-occlusive crisis, a cause of stroke in sickle cell disease.47

We are the first to show peripartum stroke is independently associated with increased odds of Caesarean section and excessive in-hospital mortality risk in the HDP population at 1.5-fold and 100-fold, respectively. It is worth noting that pregnant women suffering stroke are usually delivered by Caesarean sections. Comparable to our findings, prior research that examined stroke in pregnancy admissions showed a 1.8-fold risk for postpartum haemorrhage.13 It is possible that postpartum haemorrhage is caused by stroke treatment, however as there is no data on chronicity in our dataset, we can only speculate. In a longer term setting, the adjusted incident rate ratio for death from stroke for pre-eclampsia/eclampsia was 3.59 (95% CI 1.04-12.4).48

Stroke is often misdiagnosed in pregnant women as representing more benign conditions, such as migraines or seizures.49 Compounded with clinicians’ general reluctance to give medication and/or perform non-obstetric surgery in pregnant women, these patients may miss the chance to receive timely effective treatment. Prior research has shown that for even for minor symptoms of nausea and vomiting, general practitioners were reluctant to start antiemetic treatment in pregnancy unless the symptoms have progressed to a severe stage.50 Therefore, clinicians should be encouraged to actively investigate and treat pregnant women with features suggestive of stroke, especially in the high-risk HDP population.

The strengths of this study include the large number of HDP hospital admission episodes, the comprehensive capture of delivery hospitalisations and the diversity of the HDP population in terms of geography and race or ethnicity. This allows us to have statistical power to examine disease patterns of rare events such as stroke. With 3,391 stroke events in our population, we were also able to examine the temporal trends in the prevalence, comorbidities, and associated delivery complications.

A limitation of our study is that our results are national estimates based on sampling weights. As the unweighted events for stroke subtype are low, some of the calculated odds ratios in the subgroup analyses have wide confidence intervals. Another limitation is the lack of information relevant to patient prognosis after stroke, for example time-to-diagnosis, imaging modality, and pharmacotherapy. However, other available data could provide further information. For example, the arrhythmia comorbidity may be a surrogate for warfarin use. We only captured data on women admitted to hospital without considering stroke in the community. Similarly, we have not captured births in the community. However, U.S. national statistics show that >98% of births occur in hospitals.51 Due to the design of NIS, we were unable to track patients over the years and could only consider in-hospital outcomes. Therefore, one woman could have had multiple deliveries during the study period. As there was no information on timing of events, we could not conduct analyses on time to events, such as delivery complications, nor effects of chronicity on comorbidities. In addition to mortality, we examined other delivery complications, such as Caesarean section and postpartum haemorrhage, which could have contributed to the cause of mortality. However, we did not consider mortality as a competing risk for other delivery complications. Since we did not adjust for multiple testing, some of the statistically significant results may be due to chance. Errors may arise from inaccurate physician and administrative reporting of ICD codes. Furthermore, chronic conditions are usually under coded in administrative datasets with low to moderate sensitivity for the majority of conditions. Finally, for the temporal analyses, the accuracy may have improved over time because of improved diagnosis or better coding from changes in guidelines or incentives.

In conclusion, our analysis showed that over a decade, the incidence of stroke reduced in an increasingly complex HDP delivery population. HDP women with ischaemic versus haemorrhagic strokes had moderately different clinical profiles whereby some stroke predictors were more strongly associated with ischaemic than haemorrhagic strokes, and therefore represent underlying differences in the populations at risk. The assessment of HDP women for their risk of ischaemic or haemorrhagic stroke on admission for delivery is needed so that measures, such as closer blood pressure monitoring, may be instigated to improve their intrapartum care.

**Funding**

PW is funded by a NIHR Transitional Research Fellowship. CCG is part-funded by West Midlands ARC. LCC is funded by a NIHR Professorship (RP-2014-05-019). This paper presents independent research funded by the NIHR. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. The funders had no involvement in the conduct of this research.

**Disclosures**

None.

**References**

1. Leffert LR, Clancy CR, Bateman BT, Bryant AS and Kuklina EV. Hypertensive disorders and pregnancy-related stroke: Frequency, trends, risk factors, and outcomes. *Obstet Gynecol*. 2015;125:124-131.

2. Grear KE and Bushnell CD. Stroke and pregnancy: clinical presentation, evaluation, treatment, and epidemiology. *Clin Obstet Gynecol*. 2013;56:350-359.

3. McClure JH, Cooper GM and Clutton-Brock TH. Saving mothers’ lives: reviewing maternal deaths to make motherhood safer: 2006–8: a review. *Br J Anaesth*. 2011;107:127-132.

4. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J, Gulmezoglu AM, Temmerman M and Alkema L. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. 2014;2:e323-333.

5. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. *Obstet Gynecol*. 2003;102:181-192.

6. ACOG. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on hypertension in pregnancy. *Obstet Gynecol*. 2013;122:1122-1131.

7. Callaghan WM, Mackay AP and Berg CJ. Identification of severe maternal morbidity during delivery hospitalizations, United States, 1991-2003. *Am J Obstet Gynecol*. 2008;199:133.e1-8.

8. Sharshar T, Lamy C and Mas JL. Incidence and causes of strokes associated with pregnancy and puerperium. A study in public hospitals of Ile de France. Stroke in Pregnancy Study Group. *Stroke*. 1995;26:930-936.

9. Treadwell SD, Thanvi B and Robinson TG. Stroke in pregnancy and the puerperium. *Postgrad Med J*. 2008;84:238-245.

10. Centers for Disease Control and Prevention. Pregnancy Mortality Surveillance System: Causes of pregnancy-related death in the United States: 2011-2016. https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm. Accessed May 5 2020.

11. Miller EC, Gatollari HJ, Too G, Boehme AK, Leffert L, Marshall RS, Elkind MSV and Willey JZ. Risk factors for pregnancy-associated stroke in women with preeclampsia. *Stroke*. 2017;48:1752-1759.

12. Liu S, Chan W-S, Ray JG, Kramer MS and Joseph KS. Stroke and cerebrovascular disease in pregnancy. *Stroke*. 2019;50:13-20.

13. James AH, Bushnell CD, Jamison MG and Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. *Obstet Gynecol*. 2005;106:509-516.

14. Salonen Ros H, Lichtenstein P, Bellocco R, Petersson G and Cnattingius S. Increased risks of circulatory diseases in late pregnancy and puerperium. *Epidemiology*. 2001;12:456-460.

15. Swartz RH, Cayley ML, Foley N, Ladhani NNN, Leffert L, Bushnell C, McClure JA and Lindsay MP. The incidence of pregnancy-related stroke: A systematic review and meta-analysis. *Int J Stroke*. 2017;12:687-697.

16. Miller EC, Gallo M, Kulick ER, Friedman AM, Elkind MSV and Boehme AK. Infections and risk of peripartum stroke during delivery admissions. *Stroke*. 2018;49:1129-1134.

17. Healthcare Cost and Utilization Project. National Inpatient Sample. https://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed September 22, 2019.

18. Kuklina E, K Whiteman M, Hillis S, J Jamieson D, F Meikle S, Posner S and A Marchbanks P. An enhanced method for identifying obstetric deliveries: Implications for estimating maternal morbidity. *Matern Child Health J*. 2008;12:469-477.

19. Lima FV, Parikh PB, Zhu J, Yang J and Stergiopoulos K. Association of cardiomyopathy with adverse cardiac events in pregnant women at the time of delivery. *JACC Heart failure*. 2015;3:257-266.

20. Stevens W, Shih T, Incerti D, Ton TGN, Lee HC, Peneva D, Macones GA, Sibai BM and Jena AB. Short-term costs of preeclampsia to the United States health care system. *Am J Obstet Gynecol*. 2017;217:237-248.e16.

21. Bateman BT, Bansil P, Hernandez-Diaz S, Mhyre JM, Callaghan WM and Kuklina EV. Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. *Am J Obstet Gynecol*. 2012;206:134.e1-8.

22. Fingar K, Mabry-Hernandez I, Ngo-Metzger Q, Wolff T, Steiner C and Elixhauser A. Delivery hospitalizations involving preeclampsia and eclampsia, 2005-2014. HCUP Statistical Brief #222. 2017.

23. Kuklina EV and Callaghan WM. Cardiomyopathy and other myocardial disorders among hospitalizations for pregnancy in the United States: 2004-2006. *Obstet Gynecol*. 2010;115:93-100.

24. Collins RT, 2nd, Chang D, Sandlin A, Goudie A and Robbins JM. National in-hospital outcomes of pregnancy in women with single ventricle congenital heart disease. *Am J Cardiol*. 2017;119:1106-1110.

25. Vaidya VR, Arora S, Patel N, Badheka AO, Patel N, Agnihotri K, Billimoria Z, Turakhia MP, Friedman PA, Madhavan M, Kapa S, Noseworthy PA, Cha YM, Gersh B, Asirvatham SJ and Deshmukh AJ. Burden of arrhythmia in pregnancy. *Circulation*. 2017;135:619-621.

26. Zhong Q-Y, Gelaye B, Smoller JW, Avillach P, Cai T and Williams MA. Adverse obstetric outcomes during delivery hospitalizations complicated by suicidal behavior among US pregnant women. *PLOS ONE*. 2018;13:e0192943.

27. Mogos MF, Piano MR, McFarlin BL, Salemi JL, Liese KL and Briller JE. Heart failure in pregnant women: A concern across the pregnancy continuum. *Circ Heart Fail*. 2018;11:e004005.

28. Rougerie M, Czuzoj-Shulman N and Abenhaim HA. Diabetic ketoacidosis among pregnant and non-pregnant women: a comparison of morbidity and mortality. *J Matern Fetal Neonatal Med*. 2018:1-4.

29. Agarwal MA, Garg L, Lavie CJ, Reed GL and Khouzam RN. Impact of family history of coronary artery disease on in-hospital clinical outcomes in ST-segment myocardial infarction. *Ann Transl Med*. 2018;6:3.

30. Smilowitz NR, Gupta N, Guo Y, Beckman JA, Bangalore S and Berger JS. Trends in cardiovascular risk factor and disease prevalence in patients undergoing non-cardiac surgery. *Heart*. 2018; 104:1180-1186.

31. Khera R, Angraal S, Couch T, Welsh JW, Nallamothu BK, Girotra S, Chan PS and Krumholz HM. Adherence to methodological standards in research using the National Inpatient Sample. *JAMA*. 2017;318:2011-2018.

32. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM and Committee RW. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLOS Medicine*. 2015;12:e1001885.

33. Ramirez L, Kim‐Tenser MA, Sanossian N, Cen S, Wen G, He S, Mack WJ and Towfighi A. Trends in acute ischemic stroke hospitalizations in the United States. *J Am Heart Assoc*. 2016;5:e003233.

34. Tong X, George MG, Gillespie C and Merritt R. Trends in hospitalizations and cost associated with stroke by age, United States 2003–2012. *Int J Stroke*. 2016;11:874-881.

35. Thomopoulos C, Salamalekis G, Kintis K, Andrianopoulou I, Michalopoulou H, Skalis G, Archontakis S, Argyri O, Tsioufis C, Makris TK and Salamalekis E. Risk of hypertensive disorders in pregnancy following assisted reproductive technology: overview and meta-analysis. *J Clin Hypertens (Greenwich)*. 2017;19:173-183.

36. Pandey S, Shetty A, Hamilton M, Bhattacharya S and Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. *Hum Reprod Update*. 2012;18:485-503.

37. Kuklina EV, Tong X, Bansil P, George MG and Callaghan WM. Trends in pregnancy hospitalizations that included a stroke in the United States from 1994 to 2007: reasons for concern? *Stroke*. 2011;42:2564-2570.

38. Miller EC and Leffert L. Stroke in Pregnancy: A Focused Update. *Anesth Analg*. 2020;130:1085-1096.

39. Tang CH, Wu CS, Lee TH, Hung ST, Yang CY, Lee CH and Chu PH. Preeclampsia-eclampsia and the risk of stroke among peripartum in Taiwan. *Stroke*. 2009;40:1162-1168.

40. Park Y, Cho GJ, Kim LY, Lee TS, Oh MJ and Kim YH. Preeclampsia increases the incidence of postpartum cerebrovascular disease in Korean population. *J Korean Med Sci*. 2018;33:e35.

41. Ackerman CM, Platner MH, Spatz ES, Illuzzi JL, Xu X, Campbell KH, Smith GN, Paidas MJ and Lipkind HS. Severe cardiovascular morbidity in women with hypertensive diseases during delivery hospitalization. *Am J Obstet Gynecol*. 2019;220:582.e1-582.e11.

42. Attar H, Sachdeva A and Sundararajan S. Cardioembolic stroke in adults with a history of congenital heart disease. *Stroke*. 2016;47:e79-e81.

43. Kane EV, Calderwood C, Dobbie R, Morris C, Roman E and Greer IA. A population-based study of venous thrombosis in pregnancy in Scotland 1980-2005. *Euro J Obstet Gynecol Reprod Biol*. 2013;169:223-229.

44. Won HS, Kim DY, Yang MS, Lee SJ, Shin H-H and Park JB. Pregnancy-induced hypertension, but not gestational diabetes mellitus, is a risk factor for venous thromboembolism in pregnancy. *Korean Circ J*. 2011;41:23-27.

45. Grimes SB and Wild R. Effect of Pregnancy on Lipid Metabolism and Lipoprotein Levels. In: Feingold KR et al, eds. *Endotext.* South Darthmouth: MDText.com Inc; 2018.

46. Baumfeld Y, Novack L, Wiznitzer A, Sheiner E, Henkin Y, Sherf M and Novack V. Pre-conception dyslipidemia is associated with development of preeclampsia and gestational diabetes mellitus. *PLOS ONE*. 2015;10:e0139164.

47. Yale SH, Nagib N and Guthrie T. Approach to the vaso-occlusive crisis in adults with sickle cell disease. *Am Fam Physician*. 2000;61:1349-56, 1363-4.

48. Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P and Smith WC. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ*. 2003;326:845.

49. Kuruvilla A, Bhattacharya P, Rajamani K and Chaturvedi S. Factors associated with misdiagnosis of acute stroke in young adults. *J Stroke Cerebrovasc Dis*. 2011;20:523-527.

50. Heitmann K, Svendsen HC, Sporsheim IH and Holst L. Nausea in pregnancy: attitudes among pregnant women and general practitioners on treatment and pregnancy care. *Scand J Prim Health*. 2016;34:13-20.

51. MacDorman MF, Matthews TJ and Declercq E. Trends in out-of-hospital births in the United States, 1990–2012. *NCHS data brief, no 144.* Hyattsville, MD: National Center for Health Statistics; 2014.

**Figure Legends**

Figure 1. Flow diagram of included/excluded records.

Figure 2. Comparison of hypertensive disorders of pregnancy (HDP) population in the delivery hospitalisations and stroke subpopulation in the HDP delivery hospitalisations over one decade. (A) Percentage of HDP diagnosis in delivery hospitalisations. (B) Percentage of stroke (CVA) diagnosis within the HDP delivery hospitalisation population. A comparison of cardiovascular disease (CVD) diagnosis was also made between (C) HDP and (D) stroke populations.

Figure 3. Discharge locations of women with hypertensive disorders of pregnancy and (A) no stroke (B) any stroke (C) ischaemic stroke (D) haemorrhagic stroke (E) unspecified stroke.

Table 1. Association between stroke risk factors and comorbidities with subgroups of stroke.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All stroke**  *n=3,391* | **Stroke** | | | **No Stroke**  *n=4,236,893* |
| **Ischaemic**  *n=1,229* | **Haemorrhagic**  *n=1,187* | **Unspecified**  *n=975* |
| OR (95% CI); *n* | | | | |
| Neurological disorders | 17.35  (13.42, 22.43)  *n=730* | 15.99  (10.82, 23.62)  *n=255* | 18.94  (12.87, 27.86)  *n=276* | 17.23  (10.63, 27.92)  *n=199* | 1.00  (reference)  *n=34,319* |
| Peripheral vascular disease | 10.03  (3.98, 25.25)  *n=54* | 24.16  (8.47, 68.90)  *n=40* | 6.26  (1.18, 33.18)  *n=10* | 1.40  (0.09, 21.21)  *n=4* | 1.00  (reference)  *n=1,695* |
| Congenital heart disease | 7.38  (3.85, 14.16)  *n=81* | 7.70  (2.90, 20.43)  *n=29* | 3.49  (0.93, 13.05)  *n=14* | 12.31  (4.46, 33.96)  *n=38* | 1.00  (reference)  *n=6,779* |
| Fluid and electrolyte disorders | 5.90  (4.65, 7.49)  *n=661* | 6.66  (4.39, 10.09)  *n=269* | 8.50  (6.03, 11.96)  *n=291* | 2.46  (1.41, 4.30)  *n=101* | 1.00  (reference)  *n=72,875* |
| Previous stroke | 4.77  (2.09, 10.87)  *n=55* | 3.67  (0.96, 14.03)  *n=20* | \*  *n=0* | 14.09  (5.20, 38.18)  *n=35* | 1.00  (reference)  *n=36* |
| Coagulopathy | 4.71  (3.80, 5.84)  *n=639* | 3.92  (2.74, 5.61)  *n=210* | 6.71  (4.83, 9.31)  *n=300* | 3.45  (2.18, 5.46)  *n=129* | 1.00  (reference)  *n=129,225* |
| Arrhythmia | 2.86  (1.94, 4.21)  *n=203* | 2.58  (1.41, 4.72)  *n=77* | 2.77  (1.50, 5.14)  *n=67* | 3.39  (1.57, 7.29)  *n=59* | 1.00  (reference)  *n=30,082* |
| Ischaemic heart disease | 2.84  (1.25, 6.46)  *n=53* | 3.21  (0.84, 12.26)  *n=29* | 2.61  (0.65, 10.48)  *n=9* | 2.54  (0.58, 11.09)  *n=15* | 1.00  (reference)  *n=3,813* |
| Drug abuse | 1.99  (1.35, 2.94)  *n=173* | 1.87  (0.92, 3.79)  *n=63* | 1.94  (1.07, 3.53)  *n=57* | 2.23  (1.09, 4.54)  *n=53* | 1.00  (reference)  *n=72,451* |
| Sickle cell disease | 1.94  (0.68, 5.50)  *n=23* | 6.81  (2.21, 20.99)  *n=23* | \*  *n=0* | \*  *n=0* | 1.00  (reference)  *n=4,237* |
| Peripartum cardiomyopathy | 1.89  (0.70, 5.06)  *n=82* | 2.54  (0.64, 10.14)  *n=44* | 0.55  (0.03, 9.95)  *n=9* | 2.30  (0.43, 12.23)  *n=29* | 1.00  (reference)  *n=11,016* |
| Heart failure | 1.66  (0.74, 3.69)  *n=91* | 2.51  (0.79, 7.94)  *n=49* | 0.48  (0.01, 15.22)  *n=9* | 1.80  (0.51, 6.40)  *n=33* | 1.00  (reference)  *n=12,287* |
| Renal failure | 1.36  (0.68, 2.73)  *n=65* | 0.94  (0.26, 3.44)  *n=20* | 0.89  (0.25, 3.15)  *n=15* | 2.86  (0.99, 8.25)  *n=30* | 1.00  (reference)  *n=13,558* |
| Rheumatoid arthritis / collagen vascular diseases | 1.23  (0.64, 2.36)  *n=55* | 0.30  (0.04, 2.27)  *n=5* | 0.96  (0.29, 3.21)  *n=14* | 2.85  (1.25, 6.51)  *n=36* | 1.00  (reference)  *n=20,761* |
| Depression | 1.02  (0.68, 1.52)  *n=147* | 0.63  (0.29, 1.38)  *n=35* | 1.12  (0.56, 2.25)  *n=54* | 1.44  (0.77, 2.69)  *n=58* | 1.00  (reference)  *n=117,362* |
| Obesity | 0.87  (0.67, 1.13)  *n=342* | 1.01  (0.67, 1.54)  *n=153* | 0.75  (0.47, 1.20)  *n=98* | 0.82  (0.48, 1.40)  *n=91* | 1.00  (reference)  *n=469,024* |
| Smoking | 0.87  (0.62, 1.21)  *n=259* | 1.01  (0.63, 1.64)  *n=111* | 0.78  (0.43, 1.40)  *n=75* | 0.78  (0.41, 1.46)  *n=73* | 1.00  (reference)  *n=286,838* |
| Valvular disease | 0.87  (0.39, 1.94)  *n=69* | 0.33  (0.06, 1.68)  *n=15* | 1.81  (0.62, 5.28)  *n=26* | 1.03  (0.31, 3.42)  *n=28* | 1.00  (reference)  *n=26,269* |
| Diabetes | 0.57  (0.38, 0.86)  *n=152* | 0.54  (0.26, 1.10)  *n=59* | 0.38  (0.18, 0.82)  *n=34* | 0.85  (0.42, 1.73)  *n=59* | 1.00  (reference)  *n=165,239* |
| Gestational diabetes | 0.49  (0.36, 0.68)  *n=192* | 0.53  (0.32, 0.88)  *n=73* | 0.38  (0.20, 0.70)  *n=52* | 0.60  (0.34, 1.06)  *n=67* | 1.00  (reference)  *n=446,145* |
| Alcohol abuse | 0.16  (0.02, 1.51)  *n=5* | \*  *n=0* | \*  *n=0* | 0.63  (0.08, 5.07)  *n=5* | 1.00  (reference)  *n=6,355* |

Data expressed as odds ratios (OR) and 95% confidence intervals (CI). *n*, weighted number of cases. \*An odds ratio could not be calculated due to lack of cases in subgroup.

Table 2. Association between subgroups of stroke and delivery complications.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All stroke**  *n=3,391* | **Stroke** | | | **No Stroke**  *n=4,236,893* |
| **Ischaemic**  *n=1,229* | **Haemorrhagic**  *n=1,187* | **Unspecified**  *n=975* |
| OR (95% CI); *n* | | | | |
| Maternal mortality | 99.78  (59.15, 168.31)  *n=297* | 30.34  (12.32, 74.73)  *n=59* | 260.80  (138.10, 492.51)  *n=193* | 40.34  (14.16, 114.87)  *n=45* | 1.00  (reference)  *n=847* |
| Postpartum haemorrhage | 1.91  (1.54, 2.37)  *n=531* | 1.98  (1.38, 2.83)  *n=194* | 2.03  (1.46, 2.82)  *n=223* | 1.65  (1.01, 2.68)  *n=114* | 1.00  (reference)  *n=205,913* |
| Stillbirth | 1.68  (1.00, 2.82)  *n=96* | 0.93  (0.34, 2.69)  *n=21* | 1.67  (0.70, 4.00)  *n=35* | 2.84  (1.33, 6.07)  *n=40* | 1.00  (reference)  *n=37,285* |
| Caesarean section | 1.58  (1.33, 1.86)  *n=2,084* | 1.62  (1.22, 2.16)  *n=761* | 1.44  (1.08, 1.91)  *n=708* | 1.71  (1.26, 2.30)  *n=615* | 1.00  (reference)  *n=1,961,258* |
| Preterm birth | 1.22  (0.99, 1.49)  *n=797* | 1.34  (0.98, 1.82)  *n=303* | 1.25  (0.91, 1.73)  *n=283* | 1.02  (0.68, 1.54)  *n=211* | 1.00  (reference)  *n=637,229* |

Data expressed as odds ratios (OR) and 95% confidence intervals (CI). *n*, weighted number of cases.