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Risk of a Thrombotic Event after the 6-Week Postpartum Period

Hooman Kamel, M.D., **Babak B. Navi, M.D.**, **Nandita Sriram, B.S.**, **Dominic A. Hovsepian, B.S.**, **Richard B. Devereux, M.D.**, and **Mitchell S.V. Elkind, M.D.**
Department of Neurology (H.K., B.B.N., N.S., D.A.H.), Feil Family Brain and Mind Research Institute (H.K., B.B.N.), and Division of Cardiology (R.B.D.), Weill Cornell Medical College, the Department of Neurology, Columbia College of Phy sicians and Surgeons (M.S.V.E.), and the Department of Epidemiology, Mailman School of Public Health, Columbia University (M.S.V.E.) — all in New York.

Abstract

Background—The postpartum state is associated with a substantially increased risk of thrombosis. It is uncertain to what extent this heightened risk persists beyond the conventionally defined 6-week postpartum period.

Methods—Using claims data on all discharges from nonfederal emergency departments and acute care hospitals in California, we identified women who were hospitalized for labor and delivery between January 1, 2005, and June 30, 2010. We used validated diagnosis codes to identify a composite primary outcome of ischemic stroke, acute myocardial infarction, or venous thromboembolism. We then used conditional logistic regression to assess each patient's likelihood of a first thrombotic event during sequential 6-week periods after delivery, as compared with the corresponding 6-week period 1 year later.

Results—Among the 1,687,930 women with a first recorded delivery, 1015 had a thrombotic event (248 cases of stroke, 47 cases of myocardial infarction, and 720 cases of venous thromboembolism) in the period of 1 year plus up to 24 weeks after delivery. The risk of primary thrombotic events was markedly higher within 6 weeks after delivery than in the same period 1 year later, with 411 events versus 38 events, for an absolute risk difference of 22.1 events (95% confidence interval [CI], 19.6 to 24.6) per 100,000 deliveries and an odds ratio of 10.8 (95% CI, 7.8 to 15.1). There was also a modest but significant increase in risk during the period of 7 to 12 weeks after delivery as compared with the same period 1 year later, with 95 versus 44 events, for an absolute risk difference of 3.0 events (95% CI, 1.6 to 4.5) per 100,000 deliveries and an odds ratio of 2.2 (95% CI, 1.5 to 3.1). Risks of thrombotic events were not significantly increased beyond the first 12 weeks after delivery.

Conclusions—Among patients in our study, an elevated risk of thrombosis persisted until at least 12 weeks after delivery. However, the absolute increase in risk beyond 6 weeks after delivery was low. (Funded by the National Institute of Neurological Disorders and Stroke.)

Address reprint requests to Dr. Kamel at 407 E. 61st St., 5th Fl., New York, NY 10065, or at hok9010@med.cornell.edu..

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Pregnancy significantly increases the risk of thrombosis. This heightened thrombotic risk rises further during the postpartum period, which is conventionally defined as the 6 weeks after delivery.[1] As compared with the nonpregnant state, the 6-week postpartum period is associated with increases by a factor of 3 to 9 in the risk of stroke, by a factor of 3 to 6 in the risk of myocardial infarction, and by a factor of 9 to 22 in the risk of venous thromboembolism.[2-8] It is unknown whether these risks remain increased after the conventionally defined 6-week postpartum period. Guidelines for the treatment of thrombotic disorders during pregnancy advise the discontinuation of prophylactic therapy at 6 weeks after delivery in women at high risk for venous thromboembolism.[1] However, previous studies and isolated case reports have suggested that an increased thrombotic risk may persist beyond 6 weeks after delivery.[5,8-10] Therefore, more data are needed to rigorously assess the risk after the 6-week postpartum period. We designed this study to assess the duration of an increased postpartum thrombotic risk in a large population-based cohort of women.

Methods

Study Design

We performed a retrospective crossover-cohort study (a study design in which each patient serves as his or her own control), using administrative claims data on all discharges from nonfederal emergency departments and acute care hospitals in California. We compared each patient's likelihood of a first thrombotic event during sequential 6-week periods after delivery with the likelihood of an event during the corresponding 6-week period 1 year later. Since exposure to pregnancy varies discretely over time, this design allowed each patient to serve as her own control, thereby minimizing unmeasured confounding.[11,12] California was chosen because it is a large and demographically heterogeneous state[13] with administrative data that allow tracking of individual patients across visits over numerous years,[14] thereby providing sufficient statistical power to detect associations among conditions with low absolute event rates. Analysts at each facility used detailed reporting and formatting specifications and automated online-reporting software to provide uniform data on all discharges to the California Office of Statewide Health Planning and Develop ment.[15] After a multistep quality-assurance process to flag invalid or inconsistent entries, these data were provided in a deidentified format to the Healthcare Cost and Utilization Project.[14] The institutional review boards at Weill Cornell Medical College and Columbia University Medical Center certified that this analysis of publicly available, deidentified data was exempt from review and from the need for informed consent. All authors take responsibility for the integrity of the data and analyses.

Study Patients

We identified all women who had been hospitalized for labor and delivery, using standard codes from the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) for vaginal delivery (72, 73, 75, V27, or 650–659) and cesarean delivery (74).[16] To maximize longitudinal follow-up, we excluded non-California residents. We included patients 12 years of age or older, given the infrequency of births among patients younger than 12 years of age (<0.1% of all births[17]). Post hoc sensitivity analyses that

included patients regardless of age or included only patients 18 years of age or older did not substantially alter our findings.

For women with multiple labor-related hospitalizations during a single 40-week period, we excluded cases of false labor by identifying delivery as the latest hospitalization during that time. Since women who have had a thrombotic event may be less likely to subsequently become pregnant, we included only the first pregnancy captured in our database for each patient. To focus on incident outcomes, we excluded patients who had had any thrombosis diagnoses before their first recorded delivery (see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org, for definitions).

To compare thrombotic risk during the post-partum period with the risk during nonpregnant periods, we excluded patients with a second delivery during the follow-up period. We included hospitalizations for labor starting on January 1, 2005, when patient-specific longitudinal tracking identifiers were introduced in these databases.[14] Data were available through December 31, 2011,[14] so to accommodate analyses of the 24 weeks after delivery and the same 24-week period 1 year later, we included patients with a hospitalization for a first labor through June 30, 2010.

Study Outcomes and Measurements

The primary outcome was a composite of ischemic stroke, acute myocardial infarction, or venous thromboembolism. We identified these outcomes using validated diagnosis-code algorithms that were previously shown to have a positive predictive value of 90% or more (see the Supplementary Appendix).[18-20] To maximize accuracy, we limited our case ascertainment to stroke and myocardial infarction resulting in hospitalization but included discharges from the emergency department as well as hospitalizations for venous thromboembolism, since this condition is now often managed in the outpatient setting.[21] To focus on incident outcomes and avoid bias from the effects of antithrombotic therapy prescribed after the initial thrombotic event, we included a maximum of one thrombosis diagnosis for each patient; however, in a sensitivity analysis, we also included thrombosis diagnoses subsequent to the index event.

In addition to the primary composite outcome, we separately assessed arterial events (stroke or myocardial infarction) as compared with venous thromboembolism. The definition of venous thromboembolism in our primary analysis did not include cerebral venous thrombosis because that condition lacks rigorously validated ICD-9-CM diagnosis codes, but it was included among secondary outcomes, which consisted of the primary outcome plus a broader set of other thrombosis diagnoses (see the Supplementary Appendix for definitions).

We performed subgroup analyses stratified according to thrombotic risk, using ICD-9-CM codes to identify consistently reported risk factors for postpartum thrombosis: maternal age of more than 35 years, primary hypercoagulable state, eclampsia or preeclampsia, smoking, and cesarean delivery (see the Supplementary Appendix for definitions).[1,3,22,23]

Statistical Analysis

For each patient, we compared the likelihood of a first-ever recorded thrombosis during postpartum days 0 through 41 versus the same period exactly 1 year later. We repeated this crossover-cohort analysis for postpartum days 42 through 83, 84 through 125, and 126 through 167. We used conditional logistic regression to calculate odds ratios for each interval because each patient was matched to her own crossover period 1 year later.[11] Our a priori hypothesis was that the risk would progressively decrease across sequential 6-week periods but remain significantly elevated at least through the period of 7 to 12 weeks after delivery. To help ensure that visits that were related to venous thromboembolism did not represent the sequelae of previous outpatient diagnoses, we performed a sensitivity analysis that excluded diagnoses of venous thromboembolism with a concomitant bleeding-related diagnosis,[24] since the event may have represented a complication of preexisting anticoagulant therapy.

To assess the sensitivity of our results to our baseline model structure, we inverted the model and performed a case-crossover analysis. We identified all women who were 12 years of age or older in whom the primary outcome had been diagnosed from July 1, 2006, to December 31, 2011. We compared the likelihood of a first recorded labor and delivery during days 0 through 41 before the thrombotic event versus the same 6-week period exactly 1 year earlier. We repeated this case-crossover analysis for postpartum days 42 to 83, 84 to 125, and 126 to 167 before the thrombotic event. In a sensitivity analysis, we included only cases that occurred beyond 1 year 24 weeks after a first documented delivery. This nested design ensured that all patients were alive and under observation throughout the entire study period, while also allowing us to assess the effects of the inclusion of pregnancies subsequent to the first.

We performed a separate post hoc case–control analysis to confirm whether any heightened risk of postpartum thrombosis was associated with labor and delivery specifically, rather than with hospitalization in general. We defined cases and controls on the basis of the presence or absence of the primary outcome. The exposure variable was a preceding hospitalization for delivery versus for any other diagnosis. To account for potential confounders, these analyses were adjusted for age, race, insurance type, the presence or absence of a primary hypercoagulable state, smoking, and the Elixhauser comorbidity index.[25]

Results

Study Population

We identified 1,687,930 California residents with a first recorded hospitalization for labor and delivery between January 1, 2005, and June 30, 2010. This number was within 6% of the expected number on the basis of birth certificates issued during that time.[17] In the 1 year 24 weeks after delivery, 1015 women had a thrombotic event (248 cases of stroke, 47 cases of myocardial infarction, and 720 cases of venous thromboembolism). As compared with patients without post-partum thrombosis, those with postpartum thrombotic events were

older, were more likely to be white or black than Hispanic or Asian, were less often privately insured, and were more likely to have risk factors for thrombosis (Table 1).

Risk of Thrombotic Events

Significantly more thrombotic events occurred within 6 weeks after delivery than during the same period 1 year later (411 events, or 24.4 events per 100,000 deliveries, vs. 38 events, or 2.3 events per 100,000 deliveries), corresponding to an absolute risk difference of 22.1 (95% confidence interval [CI], 19.6 to 24.6) per 100,000 deliveries and an odds ratio of 10.8 (95% CI, 7.8 to 15.1). In the period of 7 to 12 weeks after delivery, there was a modest but still significant increase in the number of thrombotic events, as compared with the same period 1 year later (95 events, or 5.6 events per 100,000 deliveries, vs. 44 events, or 2.6 events per 100,000 deliveries), corresponding to an absolute risk difference of 3.0 (95% CI, 1.6 to 4.5) per 100,000 deliveries and an odds ratio of 2.2 (95% CI, 1.5 to 3.1).

The risk was no longer significantly elevated after 12 weeks, with an odds ratio of 1.4 (95% CI, 0.9 to 2.1) for the period of 13 to 18 weeks after delivery and an odds ratio of 1.0 (95% CI, 0.7 to 1.4) for the period of 19 to 24 weeks after delivery (Table 2). In post hoc exploratory analyses, the thrombotic risk was increased during the period of 13 to 15 weeks after delivery (odds ratio, 2.0; 95% CI, 1.1 to 3.6) but was no longer elevated in the period of 16 to 18 weeks (odds ratio, 1.0; 95% CI, 0.6 to 1.8) (Fig. 1, and Table S1 in the Supplementary Appendix).

The risk of thrombosis during the period of 7 to 12 weeks after delivery appeared to be similarly elevated for arterial events (odds ratio, 2.1; 95% CI, 1.0 to 4.3) and venous events (odds ratio, 2.2; 95% CI, 1.4 to 3.3), although the absolute risk difference was especially low for arterial events. We found a similar temporal pattern of thrombotic risk in the secondary analysis, which included a broader set of thrombosis diagnoses, including cerebral venous thrombosis (Table 2).

The period during which thrombotic risk was significantly increased was also materially unchanged in sensitivity analyses that excluded diagnoses of venous thromboembolism with accompanying bleeding codes or that included thrombosis diagnoses subsequent to the first recorded event. Except for a significantly higher risk within 6 weeks after delivery among women who had undergone cesarean section than among those who had undergone vaginal delivery, we found no significant variation in thrombotic risk over the different time periods across subgroups with or without thrombotic risk factors (Tables S2 and S3 in the Supplementary Appendix).

Case-Crossover and Case–Control Analyses

In a case-crossover analysis of the likelihood of labor and delivery before a first thrombotic event versus the same periods 1 year earlier, we found that the odds of a first delivery were markedly elevated in the period of 0 to 6 weeks before a thrombotic event (odds ratio, 9.8; 95% CI, 7.0 to 13.9), significantly elevated in the period of 7 to 12 weeks before a thrombotic event (odds ratio, 2.2; 95% CI, 1.5 to 3.2), and not significantly different in the periods of 13 to 18 weeks or 19 to 24 weeks before a thrombotic event (Table 3). This pattern was essentially unchanged in a nested analysis that included only patients who were

known to be alive and under observation for the entire 1 year 24 weeks before the thrombotic event. In a separate case–control analysis, women with a thrombotic event were more likely to have been hospitalized for labor and delivery within the previous 7 to 12 weeks than to have been hospitalized for another diagnosis (odds ratio, 1.9; 95% CI, 1.4 to 2.5) (data not shown).

Discussion

Using administrative claims data from a large state population, we found that the risk of a thrombotic event remained elevated beyond the 6-week postpartum period, as compared with a similar time period 1 year later, although absolute risk increases were small after 6 weeks. As compared with the absolute increase in risk during the period within 6 weeks after delivery (22.1 cases per 100,000 deliveries), the absolute increase during the postpartum period of 7 to 12 weeks was much smaller (3.0 cases per 100,000 deliveries). During the latter period, odds ratios for thrombosis were similar for women with recognized risk factors for thrombosis and those without those risk factors, so the increased relative risk would be expected to be especially important among high-risk patients (e.g., those with an inherited primary hypercoagulable state or previous thrombosis).

To our knowledge, previous studies have not reliably determined the relative risk of thrombosis beyond 6 weeks after delivery. A population-based analysis of pregnancy-related venous thromboembolism over several decades included events up to 3 months after delivery, but only two cases were captured beyond 6 weeks, and relative risks for this period were not reported.[5] In a population-based study of venous thromboembolism after in vitro fertilization, thrombosis rates between 7 weeks and 1 year after delivery were reported, but the study lacked suitable nonpregnant control patients or intervals.[26] In another population-based study, there was no significantly elevated risk of thrombosis between 7 weeks and 1 year after delivery, but investigators did not assess risks across discrete intervals during that time.[4] Two other studies suggested a possibly heightened risk of venous thromboembolism between 7 and 12 weeks after delivery but lacked sufficient statistical power[8] or had imbalances between cases and controls, which probably resulted in an overestimation of post-partum risks.[9]

Despite this limited prior evidence, our finding that increased risk for thrombosis persists beyond 6 weeks after delivery has face validity. The magnitude of increased risk is high throughout the 6 weeks after delivery,[2,5] and it is unlikely that this prothrombotic state would resolve suddenly. Our findings are consistent with a more biologically plausible tapering of risk through at least 12 weeks after delivery (Fig. 1). This pattern is concordant with data on laboratory coagulation markers after delivery; most of these markers normalize by 6 weeks after delivery, but some remain abnormal through at least 8 to 12 weeks after delivery.[27-29]

The validity of our study is buttressed by its crossover-cohort design, which allowed each patient to serve as her own control and thus reduced the unmeasured confounding that can occur with traditional case–control or cohort studies.[12] The validity of our study is further supported by the consistency of our findings in a confirmatory case-crossover analysis. Our

study fully meets the assumptions of these crossover designs, in that we modeled a transient, discrete exposure with stable prevalence over time and an outcome that was defined by an acute event.[30]

Limitations of our study require consideration, however. First, in the absence of prospective case ascertainment and detailed clinical information, some outcome events may have represented delayed sequelae of previous thrombotic events. For example, an outpatient in whom venous thromboembolism is diagnosed at 2 weeks after delivery who is then hospitalized with symptoms of venous thromboembolism 8 weeks later would have incorrectly appeared to have had a first thrombotic event at 10 weeks after delivery. This scenario would have artificially increased the apparent length of time between delivery and outcome, thereby upwardly biasing our estimates for later postpartum periods. However, we think that this possibility is unlikely to have substantially affected our results. Although we may not have captured some cases of venous thromboembolism that were diagnosed entirely in the outpatient setting, almost all diagnoses of ischemic stroke and acute myocardial infarction are made in the emergency department and result in hospitalization,[31,32] and our analysis of these arterial events alone was consistent with our overall analysis. Furthermore, our estimates of the magnitude of thrombotic risk within 6 weeks after delivery closely overlap with those of previous studies that incorporated detailed clinical information,[2,5] suggesting that we did not often miss thrombotic events and incorrectly ascribe them to later periods. Second, patients may have been progressively lost to follow-up during the 1 year 24 weeks after delivery owing to unre-corded out-of-hospital deaths or emigration from California, and this would also have upwardly biased our estimates. However, we think that this is unlikely because we found the same results in a nested case-crossover analysis that was limited to patients who were known to be alive and under observation throughout the entire study period. Third, the sensitivities of the diagnosis codes that we used to determine risk factors for thrombosis have not been validated, and therefore our subgroup analyses may not have detected true interactions between specific risk factors — especially between the presence of a primary hypercoagulable state and smoking — and the duration of thrombotic risk after delivery. Fourth, we lacked data from federal health care facilities, which comprise 3.1% of the facilities in California.[33]

Current guidelines advise that high-risk patients receive prophylactic anticoagulant therapy until 6 weeks after delivery, but these recommendations are based largely on expert opinion.[1] The duration of therapy that best balances the risk of thrombosis with the risk of bleeding[34,35] remains uncertain.[36] Our findings suggest that the risks and benefits of continuing treatment for high-risk women beyond 6 weeks after delivery should be investigated. In addition, clinicians who are evaluating possible symptoms of thrombosis in postpartum women should recognize that risk remains increased for at least 12 weeks after delivery, although the absolute risk of thrombotic events beyond 6 weeks after delivery is low.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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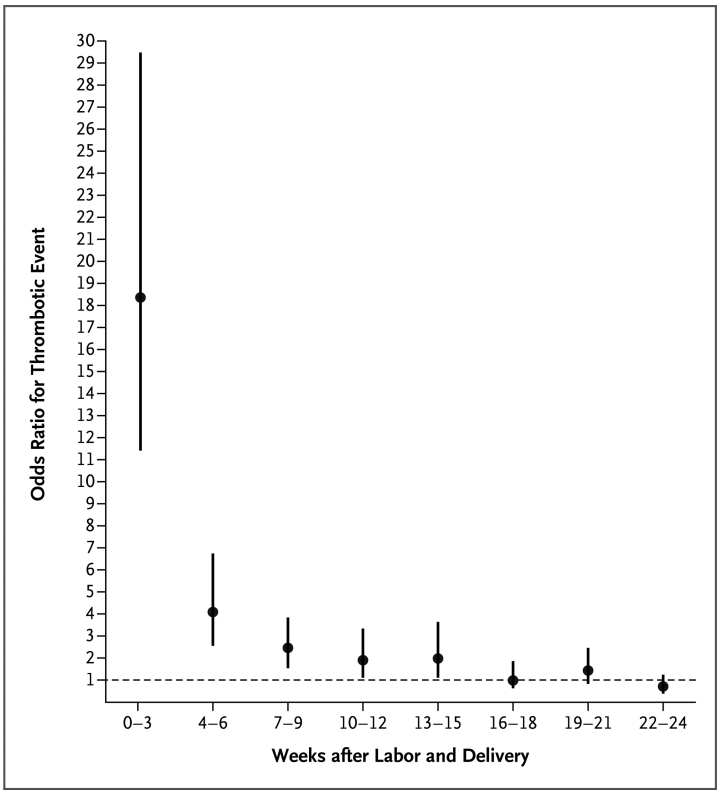

Figure 1. Risk of a Thrombotic Event, According to the Interval after Delivery.

Shown are the results of a post hoc exploratory analysis of the risk of a composite primary outcome of ischemic stroke, acute myocardial infarction, or venous thromboembolism across sequential 3-week periods after labor and delivery, as compared with each patient's risk during the same period 1 year later. The thrombotic risk was still increased during the period of 13 to 15 weeks after delivery (odds ratio, 2.0; 95% CI, 1.1 to 3.6) but was no longer elevated in the period of 16 to 18 weeks after delivery (odds ratio, 1.0; 95% CI, 0.6 to 1.8). The vertical lines indicate 95% confidence intervals.

Table 1

Baseline Characteristics of the Patients, According to the Presence or Absence of a Postpartum Thrombotic Event.*

Characteristic	Thrombotic Event (N = 1015)	No Thrombotic Event (N = 1,686,915)
Age — yr	29.5±7.2	28.0±6.7
Race or ethnic group — no. (%)†		
White	430 (42.4)	635,852 (37.7)
Black	135 (13.3)	99,486 (5.9)
Hispanic	293 (28.9)	593,790 (35.2)
Asian or Pacific Islander	66 (6.5)	188,125 (11.2)
Native American	2 (0.2)	2,208 (0.1)
Other	24 (2.4)	49,024 (2.9)
Missing data	65 (6.4)	118,430 (7.0)
Payment source — no. (%)		
Medicare	9 (0.9)	6,764 (0.4)
Medicaid	344 (33.9)	500,534 (29.7)
Private insurance	516 (50.8)	1,021,579 (60.6)
Self-pay	93 (9.2)	104,111 (6.2)
Other	53 (5.2)	53,526 (3.2)
Missing data	0	401 (<0.1)
Thrombotic risk factors — no. (%)		
Age >35 yr	264 (26.0)	271,729 (16.1)
Eclampsia or preeclampsia	240 (23.6)	131,527 (7.8)
Primary hypercoagulable state‡	8 (0.8)	1,495 (0.1)
Smoking	45 (4.4)	29,853 (1.8)
Cesarean delivery	490 (48.3)	548,217 (32.5)

* Plus–minus values are means ±SD. Between-group differences for all baseline characteristics were significant (P<0.001). Percentages may not total 100 because of rounding.

† Race or ethnic group was reported by patients or their surrogates.

‡ Primary hypercoagulable state was defined according to diagnosis code 289.81 in the *International Classification of Diseases, 9th Revision, Clinical Modification.*

Table 2

Number and Rate of Postpartum Thrombotic Events during Sequential 6-Week Intervals after Labor and Delivery.*

Time Interval after Labor and Delivery and Outcome	Case Period	Crossover Period	Absolute Risk Difference (95% CI)†	Odds Ratio (95% CI) ‡
no. of events (rate per 100,000 deliveries)				
Weeks 0–6				
Stroke, myocardial infarction, or venous thromboembolism§	411 (24.4)	38 (2.3)	22.1 (19.6 to 24.6)	10.8 (7.8 to 15.1)
Stroke	119 (7.1)	14 (0.8)	6.2 (4.8 to 7.6)	8.5 (4.9 to 14.8)
Myocardial infarction	13 (0.8)	1 (01)	0.7 (0.2 to 1.2)	13.0 (1.7 to 99.4)
Venous thromboembolism	279 (16.5)	23 (1.4)	15.2 (13.1 to 17.2)	12.1 (7.9 to 18.6)
Stroke, myocardial infarction, venous thromboembolism, or other¶	2253 (133.5)	99 (5.9)	127.6 (121.9 to 133.3)	22.8 (18.6 to 27.8)
Weeks 7–12				
Stroke, myocardial infarction, or venous thromboembolism	95 (5.6)	44 (2.6)	3.0 (1.6 to 4.5)	2.2 (1.5 to 3.1)
Stroke	15 (0.9)	9 (0.5)	0.4 (–0.3 to 1.0)	1.7 (0.7 to 3.8)
Myocardial infarction	8 (0.5)	2 (0.1)	0.4 (–0.1 to 0.8)	4.0 (0.8 to 18.8)
Venous thromboembolism	72 (4.3)	33 (2.0)	2.3 (1.1 to 3.6)	2.2 (1.4 to 3.3)
Stroke, myocardial infarction, venous thromboembolism, or other	197 (11.7)	94 (5.6)	6.1 (4.1 to 8.1)	2.1 (1.6 to 2.7)
Weeks 13–18				
Stroke, myocardial infarction, or venous thromboembolism	55 (3.3)	39 (2.3)	0.9 (–0.2 to 2.1)	1.4 (0.9 to 2.1)
Stroke	9 (0.5)	9 (0.5)	0 (–0.6 to 0.6)	1.0 (0.4 to 2.5)
Myocardial infarction	2 (0.1)	2 (0.1)	0 (–0.3 to 0.3)	1.0 (0.1 to 7.1)
Venous thromboembolism	44 (2.6)	28 (1.7)	0.9 (–0.1 to 2.0)	1.6 (1.0 to 2.5)
Stroke, myocardial infarction, venous thromboembolism, or other	99 (5.9)	95 (5.6)	0.2 (–1.4 to 1.9)	1.0 (0.8 to 1.4)
Weeks 19–24				
Stroke, myocardial infarction, or venous thromboembolism	52 (3.1)	53 (3.1)	–0.1 (–1.3 to 1.2)	1.0 (0.7 to 1.4)
Stroke	16 (0.9)	15 (0.9)	0.1 (–0.6 to 0.8)	1.1 (0.5 to 2.2)
Myocardial infarction	5 (0.3)	2 (0.1)	0.2 (–0.2 to 0.5)	2.5 (0.5 to 12.9)
Venous thromboembolism	31 (1.8)	36 (2.1)	–0.3 (–1.3 to 0.7)	0.9 (0.5 to 1.4)
Stroke, myocardial infarction, venous thromboembolism, or other	98 (5.8)	113 (6.7)	–0.9 (–2.6 to 0.9)	0.9 (0.7 to 1.1)

*Data for the case period are for the indicated interval after labor and delivery. Data for the crossover period are for the indicated interval plus 1 year after labor and delivery. Discrepancies between the reported risks for individual and composite end points or for different periods are due to rounding.

†Listed are the absolute differences in rate per 100,000 deliveries between the case period and the crossover period.

‡Odds ratios are for the case period versus the crossover period, as calculated with the use of conditional logistic regression.

§The composite of ischemic stroke, acute myocardial infarction, or venous thromboembolism was the primary outcome.

¶The secondary outcome consisted of the primary outcome plus a broader set of thrombosis diagnoses, including cerebral venous thrombosis (see the Methods section in the Supplementary Appendix for diagnosis definitions).

Table 3

Number and Rate of Deliveries during Sequential 6-Week Intervals Preceding a Thrombotic Event (Case-Crossover Analysis).*

Time Interval after Labor and Delivery and Outcome	Case Period	Crossover Period	Absolute Risk Difference (95% CI)	Odds Ratio (95% CI)
no. of events (rate per 100,000 deliveries)				
Weeks 0–6				
Stroke, myocardial infarction, or venous thromboembolism	354 (22.8)	36 (2.3)	20.4 (17.9 to 23.0)	9.8 (7.0 to 13.9)
Stroke	96 (6.2)	13 (0.8)	5.3 (4.0 to 6.7)	7.4 (4.1 to 13.2)
Myocardial infarction	19 (1.2)	1 (0.1)	1.2 (0.5 to 1.8)	19.0 (2.5 to 141.9)
Venous thromboembolism	239 (15.4)	22 (1.4)	14.0 (11.9 to 16.1)	10.9 (7.0 to 16.8)
Stroke, myocardial infarction, venous thromboembolism, or other	2013 (129.4)	92 (5.9)	123.5 (117.6 to 129.3)	21.9 (17.8 to 27.0)
Weeks 7–12				
Stroke, myocardial infarction, or venous thromboembolism	76 (4.9)	35 (2.2)	2.6 (1.2 to 4.0)	2.2 (1.5 to 3.2)
Stroke	12 (0.8)	8 (0.5)	0.3 (–0.4 to 0.9)	1.5 (0.6 to 3.7)
Myocardial infarction	7 (0.5)	2 (0.1)	0.3 (–0.1 to 0.8)	3.5 (0.7 to 16.8)
Venous thromboembolism	57 (3.7)	25 (1.6)	2.1 (0.9 to 3.3)	2.3 (1.4 to 3.6)
Stroke, myocardial infarction, venous thromboembolism, or other	182 (11.7)	74 (4.8)	6.9 (4.9 to 9.0)	2.5 (1.9 to 3.2)
Weeks 13–18				
Stroke, myocardial infarction, or venous thromboembolism	48 (3.1)	36 (2.3)	0.8 (–0.4 to 2.0)	1.3 (0.9 to 2.1)
Stroke	11 (0.7)	9 (0.6)	0.1 (–0.5 to 0.8)	1.2 (0.5 to 2.9)
Myocardial infarction	2 (0.1)	2 (0.1)	0 (–0.3 to 0.3)	1.0 (0.1 to 7.1)
Venous thromboembolism	35 (2.3)	25 (1.6)	0.6 (–0.4 to 1.7)	1.4 (0.8 to 2.3)
Stroke, myocardial infarction, venous thromboembolism, or other	94 (6.0)	81 (5.2)	0.8 (–0.9 to 2.6)	1.2 (0.9 to 1.6)
Weeks 19–24				
Stroke, myocardial infarction, or venous thromboembolism	46 (3.0)	53 (3.4)	–0.4 (–1.8 to 0.9)	0.9 (0.6 to 1.3)
Stroke	15 (1.0)	15 (1.0)	0 (–0.8 to 0.8)	1.0 (0.5 to 2.0)
Myocardial infarction	4 (0.3)	2 (0.1)	0.1 (–0.2 to 0.5)	2.0 (0.4 to 10.9)
Venous thromboembolism	27 (1.7)	36 (2.3)	–0.6 (–1.6 to 0.5)	0.8 (0.5 to 1.2)
Stroke, myocardial infarction, venous thromboembolism, or other	86 (5.5)	105 (6.7)	–1.2 (–3.0 to 0.6)	0.8 (0.6 to 1.1)

*Data for the case period are for the indicated interval before a first thrombotic event. Data for the crossover period are for the indicated interval plus 1 year before a first thrombotic event.