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## Venous thromboembolism as a cause of severe maternal morbidity and mortality in the United States

Karon Abe<sup>a,\*</sup>, Elena V. Kuklina<sup>b</sup>, W. Craig Hooper<sup>a</sup>, William M. Callaghan<sup>b</sup>

<sup>a</sup>Division of Blood Disorders, National Center on Birth Defects and Development Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA

<sup>b</sup>Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA

### Abstract

In the U.S., deaths due to pulmonary embolism (PE) account for 9.2% of all pregnancy related deaths or approximately 1.5 deaths per 100,000 live births. Maternal deaths and maternal morbidity due to PE are more common among women who deliver by cesarean section. In the past decade, the clinical community has increasingly adopted venous thromboembolism (VTE) guidelines and thromboprophylaxis recommendations for pregnant women. Although deep vein thrombosis rates have decreased during this time-period, PE rates have remained relatively unchanged in pregnancy hospitalizations and as a cause of maternal mortality. Changes in the health profile of women who become pregnant, particularly due to maternal age and co-morbidities, needs more attention to better understand the impact of VTE risk during pregnancy and the postpartum period.

### Keywords

Venous thromboembolism; pregnancy; maternal morbidity; maternal mortality

### Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is both a morbidity during pregnancy and a cause of pregnancy-related mortality. Pregnant women have a 4.0–4.6 higher risk of a VTE compared to similarly age non-pregnant women.<sup>1,2</sup> The median absolute VTE risk during pregnancy is reported to be 5.7 per 10,000 deliveries, with the preponderance of studies showing an increased risk of VTE through each passing trimester of pregnancy, a peak one to three weeks postpartum and then a decline in risk equivalent to a non-pregnant state by 12 weeks postpartum.<sup>1–8</sup> The increased hypercoagulable state brought on by the physiological changes during pregnancy is likely an evolutionary protective mechanism against hemorrhaging

\*Correspondence to: Centers for Disease Control and Prevention, 4770 Buford Highway, MS E-64, Atlanta, GA 30341, United States. kga4@cdc.gov (K. Abe).

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during childbirth, but it also marks pregnancy as a strong risk factor for VTE.<sup>1,9–11</sup> Other pregnancy-related VTE risk factors are decreased venous outflow in the pelvic vasculature due to uterine compression, decreased mobility, and vascular injury from maternal complications such as preeclampsia and eclampsia.<sup>5,9,11–13</sup> Risk factors for VTE in the general population such as older age, black race, chronic diseases, obesity, trauma, cancer, a history of VTEs, thrombophilia, and recent surgery including cesarean delivery can impart additional risk of VTE during pregnancy and the postpartum period.<sup>3,9,11,13,14</sup>

### **Pregnancy-related VTE morbidities**

Morbidities associated with pregnancy-related VTE such as swelling, pain, ulceration, skin discoloration, recurrence of a thromboses, and post-thrombotic syndrome can be acute or within months or years of the VTE event.<sup>15,16</sup> The morbidities associated with VTE are serious and can reduce the quality of life for the affected individual.<sup>11,15</sup> Chronic thrombotic pulmonary hypertension is a reported complication among 4% of PE patients up to 2 years after the diagnosis.<sup>17</sup> Longterm pregnancy-related VTE morbidities come from two follow-up studies conducted outside the U.S. In a study of 104 Swedish women surveyed 7–27 years after the VTE event, leg ulceration was the most severe outcome among women with DVT during pregnancy. A study conducted in Norway demonstrated that up to 42% of women with pregnancy-related DVT and 24% with pregnancy-related PE developed post-thrombotic syndrome 316 years after the initial diagnosis.

Two studies using the Nationwide Inpatient Sample (NIS), the largest database of all-payer U.S. inpatient hospital stays derived from billing data, showed overall increases since the mid-1990s in rates of recorded pregnancy-associated VTE, although stable after 2004.<sup>9,18</sup> From 1994–2009, VTE-associated pregnancy hospitalizations increased 14% (1.74 to 1.99 per 1000 deliveries), and increased 17% (0.57 to 0.67 per 1000 deliveries) and 47% (0.40 to 0.59 per 1000 deliveries) for antepartum and postpartum hospitalizations, respectively.<sup>18</sup> From 1998–2009, thrombotic PE recorded as a severe maternal morbidity among pregnant women increased approximately 72% during delivery (0.81 to 1.39 per 10,000 delivery hospitalizations) and 169% during postpartum hospitalizations (1.33 to 3.57 per 10,000 delivery hospitalizations).<sup>19</sup> Indeed these increases are alarming, though it is not clear to what extent the increases in VTE rates among pregnant women through the mid-2000s were due to a true rise in VTE or due to greater detection of PE through use of computed tomographic pulmonary angiography (CTPA). After the introduction of CTPA in 1998, there was a 2.7 fold increase in PE incidence among obstetric admissions, with little change in mortality based on NIS data from 1998–2006.<sup>20</sup>

### **VTE maternal mortality**

PE has accounted for about 9–11% of U.S. pregnancy-related deaths over the past 20 years, and has remained among the top ten causes based on national data from the CDC Pregnancy Mortality Surveillance System (PMSS).<sup>21</sup> Over the past two decades, the proportionate contribution of PE among other causes of pregnancy-related death has decreased (11.2 to 9.2%), outpaced by deaths due to cardiovascular diseases.<sup>21</sup> For this article, we pooled PMSS data for the period 1998–2013 and report 985 pregnancy-related PE deaths with a pregnancy-related death rate of 1.5 deaths per 100,000 live births due to PE. Previous reports

regarding maternal deaths from PE observed a calculated rate of 1.6 deaths per 100,000 live births (2011–2013) and a second study reporting 1.1 deaths per 100,000 deliveries (2000–2001) using NIS data.<sup>21–23</sup> The risk of maternal death from a PE is higher during the postpartum period. A study using NIS data found that from 1998–2009, PE accounted for 8.8% of maternal deaths during postpartum hospitalizations compared to 6.7% of maternal deaths during delivery hospitalizations.<sup>19</sup> Among the PE deaths in PMSS for 1998–2013, 26% were during pregnancy and just over 60% were after delivery, the majority of which were within 42 days of delivery (Fig. 1).<sup>21,24,25</sup> We also evaluated PMSS data by mode of delivery since past studies have demonstrated that cesarean delivery can increase the risk of a pregnancy-associated VTE up four-fold.<sup>9,11,26</sup> There were 586 deaths due to PE for the period 1998–2013 with known modes of delivery; 69% of the women had a cesarean delivery and 31% had a vaginal delivery.

### Current VTE trends, 2004–2014

We conducted analyses using NIS data to observe VTE, DVT, and PE prevalence rates in pregnancy hospitalizations during the time when VTE prevention guidelines and recommendations were adopted and patient safety initiatives and quality measures implemented. Similar methodologies were used for identifying pregnancy hospitalizations and for International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) coding for VTE, DVT, and PE.<sup>18,19</sup> However, two nonspecific pregnancy codes were excluded from this analysis, which in turn resulted in lower rates of DVT and VTE reported in this review. We did not stratify on risk factors, such as race/ethnicity due to high proportions of missing data. According to previous studies, PE rates among delivery hospitalizations had been increasing since the 90s.<sup>18,19</sup> Here we show that after 2004, PE rates began to stabilize, consistent with prior analyses,<sup>18</sup> and by 2014 the rate was 1.04 PEs per 10,000 delivery hospitalizations (Table 1). DVT rates showed a 16% decrease (5.3 to 4.4 DVTs per 10,000 delivery hospitalizations) from 2004–2014, similar to decreases described in Ghaji et al.<sup>18</sup>

Among postpartum hospitalizations (Table 1), overall VTE rates remained unchanged from 2004 to 2014. The trend was the primary result of a small decrease (10%) in the DVT rates (3.2 in 2004 to 2.9 in 2014 per 10,000 postpartum hospitalizations), as PE rates increased 36% (1.4 to 1.9 per 10,000 postpartum hospitalizations) from 2004 to 2009 and decreased 12% from (1.9 to 1.6 per 10,000 postpartum hospitalizations) from 2009 to 2014. DVTs occur three to four times more often than PEs among pregnancy-associated VTEs, and a high-risk period for a PE is after delivery.<sup>1,2,8,9,11</sup> The estimated number of PE cases in 2014 was at least one and half times more frequently associated with postpartum hospitalizations ( $n = 626$ ) compared to delivery hospitalizations ( $n = 394$ ). In contrast, the estimated number of DVT cases were at least one and half times higher during delivery hospitalizations ( $n = 1680$ ) compared to those associated with postpartum hospitalizations ( $n = 1080$ ). The lower DVT rates associated with postpartum hospitalizations may be due to in part to outpatient treatment of the women at risk for VTE after delivery.

We also stratified by mode of delivery among delivery hospitalizations and observed prevalence rates of VTE, DVT, and PE. Fig. 2 shows that among cesarean deliveries from

2004, VTE rates decreased overall by 31%, primarily due to decreasing DVT rates. PE rates leveled off from 2011 to 2014 reaching 2.3 PEs per 10,000 delivery hospitalizations. We saw a 40% decrease in DVT rates by cesarean section (9.4 to 5.6 DVTs per 10,000 delivery hospitalizations). For vaginal deliveries (Fig. 3), however, we did not observe decreases in rates of either of VTE, DVT, or PE. Unfortunately, we could not conduct analyses by mode of delivery among postpartum hospitalizations because of a lack of information regarding mode of delivery.

## Conclusion

Adoption of system-wide patient safety initiatives that adhere to VTE prevention guidelines and recommendations may have helped reduce DVT rates in the US and overall VTE rates among pregnant women from 2004–2014. Similar to other studies, we show continued decreases in VTE rates to 2014 among overall delivery hospitalizations.<sup>1,9,18</sup> The decreases in DVT rates were greatest among women delivering by cesarean section. PE rates during delivery and postpartum hospitalizations as well as its relative contribution to maternal deaths remained unchanged. Our results among vaginal deliveries possibly reflect an absence of well-defined recommendations for prevention of VTE among women delivering vaginally except for women with prior events and/or thrombophilias.<sup>27</sup> Today, developing evidence on how to provide thromboprophylaxis among women who delivery vaginally represents an opportunity to prevent thromboembolic events and to reduce morbidity among these women. Furthermore, risk factors for cardiovascular disease such as older age, obesity, and hypertension, the latter of which can impart complications such as preeclampsia or eclampsia, are also risk factors for pregnancy-associated VTE.<sup>9</sup> These risk factors are increasing among pregnant women.<sup>18,21</sup> Providers should continue to discuss with their patients the different morbidities that put them at greater risk of a pregnancy-associated VTE and opportunities to reduce their risk.

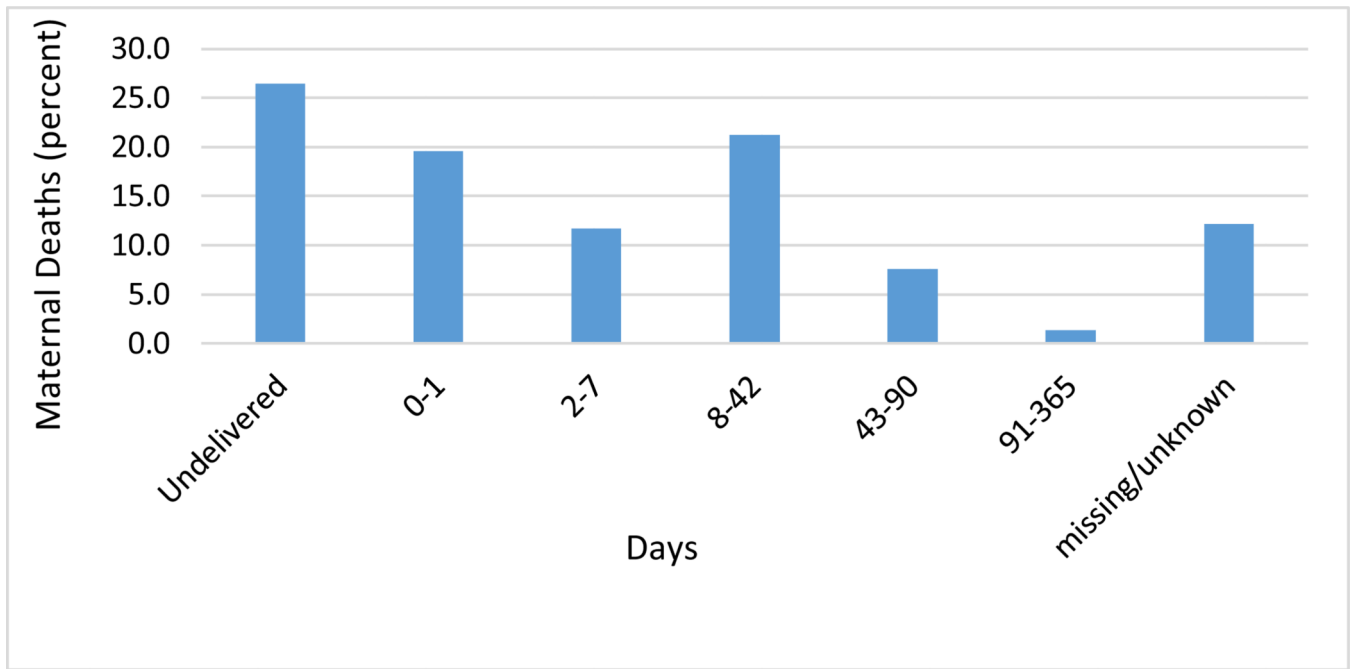
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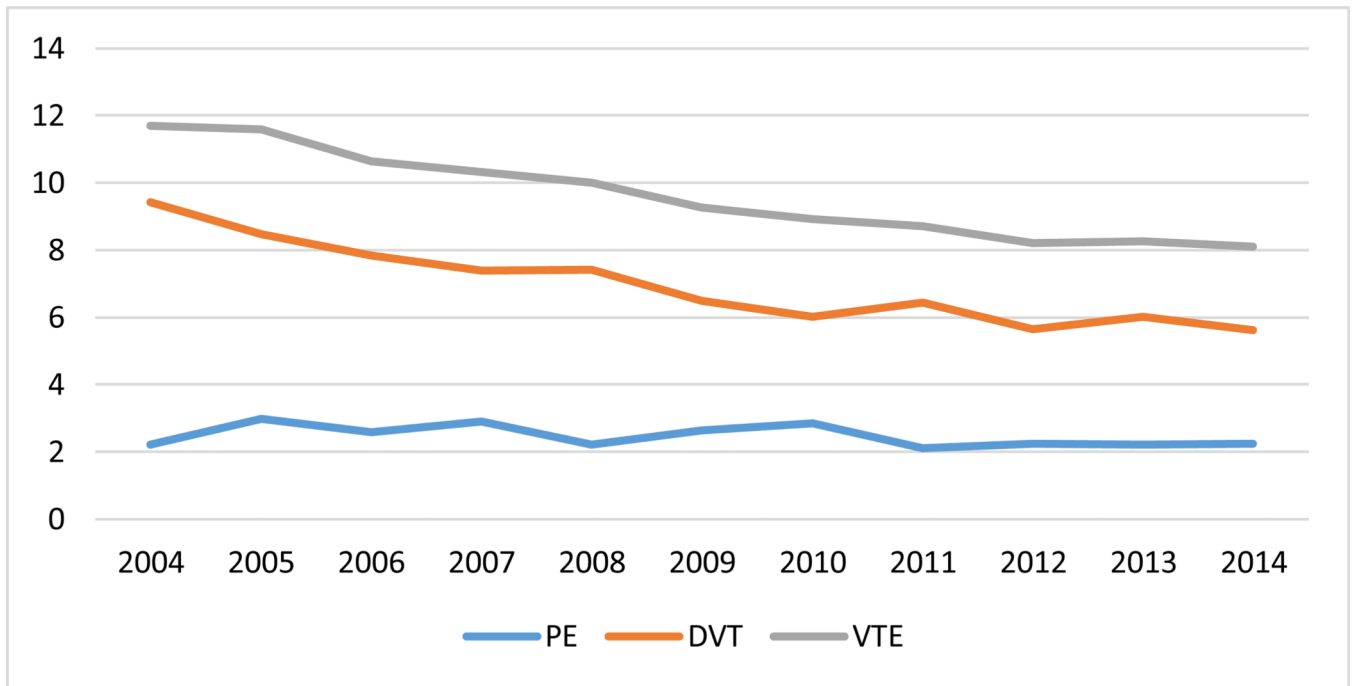
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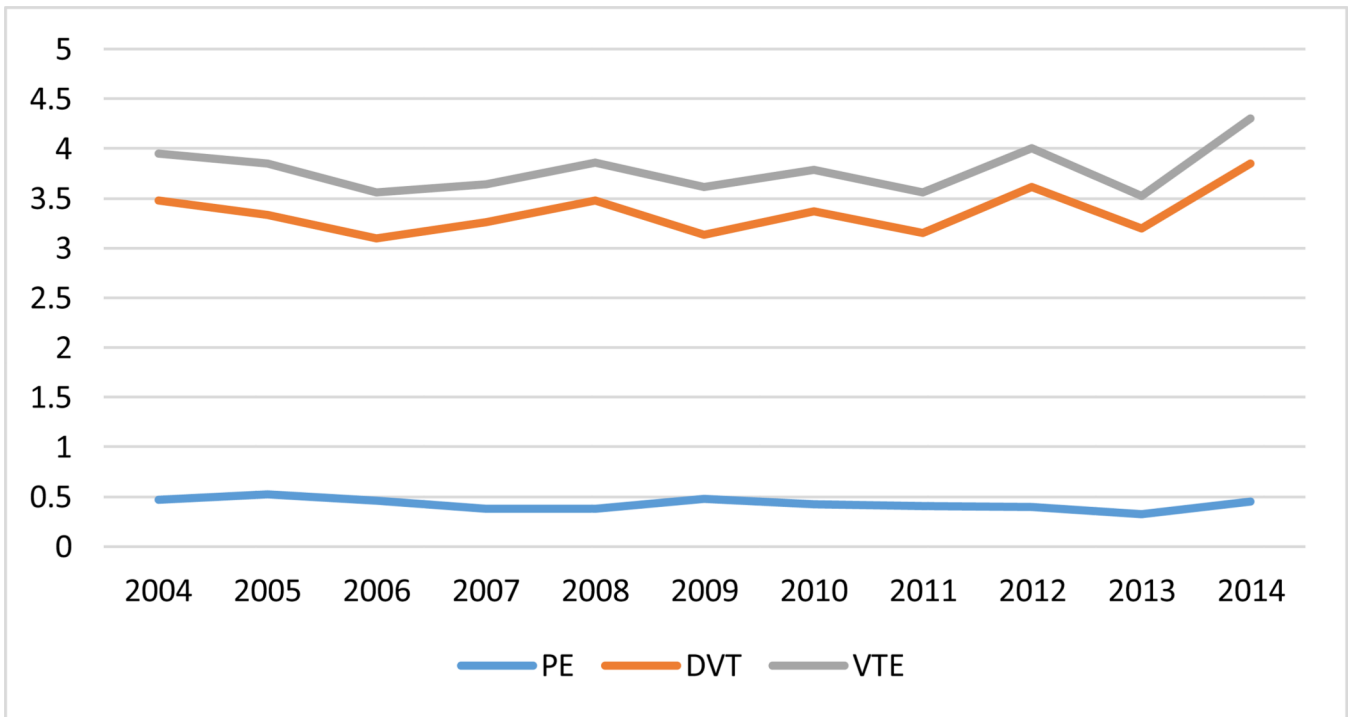
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**Fig. 1-**  
Timing of maternal deaths from pulmonary embolism, PMSS 1998–2013.



**Fig. 2-** Rates of venous thromboembolism per 10,000 delivery hospitalizations among cesarean deliveries, nationwide inpatient sample, 2004–2014.



**Fig. 3-** Rates of venous thromboembolism per 10,000 delivery hospitalizations among vaginal deliveries, nationwide inpatient sample, 2004–2014.



**Table 1-**

Rates of venous thromboembolism in the United States during delivery and postpartum hospitalizations, nationwide inpatient sample, 2004–2014.<sup>b</sup>

Delivery hospitalization	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
PE	Rate (CI) <sup>a</sup>	0.99 (0.75–1.23) 1.28 (0.99–1.57)	1.14 (0.90–1.37) 1.21 (0.97–1.44)	1.21 (0.90–1.44) 1.21 (0.92–1.49)	0.98 (0.78–1.19) 0.98 (0.78–1.19)	1.21 (0.92–1.49) 1.22 (0.96–1.48)	1.01 (0.78–1.24) 1.01 (0.78–1.24)	0.95 (0.71–1.18) 0.95 (0.71–1.18)	1.04 (0.80–1.27) 1.04 (0.80–1.27)		
DVT	N	408	516	468	396	480	456	360	384	360	396
DVT	Rate (CI) <sup>a</sup>	5.27 (4.63–5.91) 4.92 (4.35–5.50)	4.60 (4.03–5.17) 4.61 (3.96–5.27)	4.61 (3.96–5.27) 4.25 (3.69–4.80)	4.77 (4.16–5.38) 4.77 (4.16–5.38)	4.24 (3.67–4.80) 4.24 (3.69–4.80)	4.29 (3.83–4.75) 4.29 (3.83–4.75)	4.13 (3.65–4.61) 4.13 (3.65–4.61)	4.43 (3.93–4.94) 4.43 (3.93–4.94)		
VTE	N	2160	2004	1896	2016	1932	1572	1560	1620	1548	1680
VTE	Rate (CI) <sup>a</sup>	6.28 (5.55–7.00) 6.26 (5.56–6.95)	5.80 (5.11–6.48) 5.83 (5.07–6.59)	5.83 (5.07–6.59) 5.51 (4.88–6.14)	5.86 (5.21–6.51) 5.86 (5.21–6.51)	5.27 (4.59–5.94) 5.27 (4.59–5.94)	5.40 (4.88–5.93) 5.40 (4.88–5.93)	5.09 (4.55–5.63) 5.09 (4.55–5.63)	5.54 (4.98–6.10) 5.54 (4.98–6.10)		
Total	N	2568	2544	2400	2556	2376	2040	1932	2040	1908	2100
Postpartum hospitalization	N	4095132	4058250	4132026	4379064	4046358	3714024	3670998	3766200	3741612	3801564
PE	Rate (CI) <sup>a</sup>	1.38 (1.11–1.66) 1.57 (1.30–1.84)	1.61 (1.31–1.91) 1.49 (1.22–1.76)	1.61 (1.31–1.91) 1.49 (1.22–1.76)	1.41 (1.14–1.69) 1.41 (1.14–1.69)	1.87 (1.52–2.23) 1.87 (1.52–2.23)	1.72 (1.38–2.06) 1.72 (1.38–2.06)	1.68 (1.33–2.03) 1.68 (1.33–2.03)	1.74 (1.44–2.04) 1.74 (1.44–2.04)	1.55 (1.25–1.85) 1.55 (1.25–1.85)	1.64 (1.35–1.94) 1.64 (1.35–1.94)
DVT	N	564	636	660	660	576	636	612	660	576	624
DVT	Rate (CI) <sup>a</sup>	3.18 (2.75–3.61) 3.21 (2.79–3.63)	2.93 (2.54–3.33) 2.83 (2.44–3.23)	2.93 (2.54–3.33) 2.83 (2.44–3.23)	2.90 (2.50–3.30) 2.90 (2.50–3.30)	3.03 (2.63–3.43) 3.03 (2.63–3.43)	3.20 (2.71–3.70) 3.20 (2.71–3.70)	2.89 (2.45–3.32) 2.89 (2.45–3.32)	2.44 (2.07–2.82) 2.44 (2.07–2.82)	2.57 (2.19–2.94) 2.57 (2.19–2.94)	2.85 (2.45–3.25) 2.85 (2.45–3.25)
VTE	N	1296	1308	1212	1236	1176	1188	1056	924	960	1080
VTE	Rate (CI) <sup>a</sup>	4.56 (4.04–5.09) 4.78 (4.26–5.30)	4.54 (4.00–5.08) 4.33 (3.81–4.85)	4.54 (4.00–5.08) 4.33 (3.81–4.85)	4.32 (3.81–4.83) 4.32 (3.81–4.83)	4.90 (4.35–5.45) 4.90 (4.35–5.45)	4.92 (4.30–5.55) 4.92 (4.30–5.55)	4.57 (3.96–5.18) 4.57 (3.96–5.18)	4.18 (3.69–4.68) 4.18 (3.69–4.68)	4.12 (3.61–4.63) 4.12 (3.61–4.63)	4.50 (3.99–5.00) 4.50 (3.99–5.00)
	N	1872	1944	1872	1896	1752	1824	1680	1572	1536	1716

<sup>a</sup>Rate per 10,000 deliveries and 95% Confidence Intervals (CI)

<sup>b</sup>The set of ICD-9-CM codes for DVT differed from Ghajji et. al. in this analysis since two non-specific pregnancy codes were not included (671.5 and 671.9).