Review
Epidemiology of Venous Thromboembolism (VTE) Associated with Pregnancy

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This review is focused on the epidemiology of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), associated with pregnancy. Superficial vein thrombosis, a less hazardous and less studied type of thrombosis in pregnant women, is beyond the scope of this review. This study discusses the VTE incidence rate in women from developed countries for both antepartum and postpartum periods and for subpopulations of women affected by additional risk factors, such as thrombophilias, circulatory diseases, preeclampsia of varying degrees of severity, and Caesarean section. To minimize bias due to historical changes in medical and obstetric practices, lifestyle, diet, etc., this review is generally limited to relatively recent studies, i.e., those that cover the last 35 years. The absolute risk or incidence rate was used to ascertain risk of VTE associated with pregnancy. For the studies where the direct incidence rates of VTE were not reported, we calculated an estimate of the observed but not reported absolute incidence rates using the data presented in respective articles.

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Key words: venous thromboembolism; deep vein thrombosis; pulmonary embolism; pregnancy; pregnant women

Introduction

A major cause of maternal death during pregnancy in developed countries is thromboembolism (TE) and the percentage of deaths due to TE is about 15% (Khan et al., 2006). Approximately 20% of TE events are arterial, and the other 80% are venous (VTE) (James et al., 2006), giving 10 to 12% (James, 2009) of maternal death associated with VTE. It is known that normal pregnancy alters the state of hemostasis (Chan and Ginsberg, 2009; Ibeh et al., 2015). Pelvic vasculature is stressed by compression from the gravid uterus (Marik and Plante, 2008). Concentrations of coagulation factors VII, TF, X, and VIII increase, while the levels of anticoagulants (particularly of soluble protein S) and activators of fibrinolysis decrease (Hellgren and Blomback, 1981; Stirling et al., 1984; Alving and Comp, 1992; Bremme, 2003). This combination of factors, particularly when supported by additional genetic (e.g., Factor V Leiden) and acquired risk factors (obesity, trauma, history of VTE, cancer, etc.), leads to an increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), and other sequelae during pregnancy.

In addition to the physiological changes during pregnancy, an increased risk of VTE may be caused by complications or states directly related to pregnancy, such as multiple pregnancy, pre-eclampsia, and eclampsia (Lindqvist et al., 1999; Liu et al., 2009). For example, multiple pregnancy is associated with additional compression of blood vessels of pelvis, leading to more abnormal blood flow. In pre-eclampsia and eclampsia, damage to the vessel wall is suspected as an underlying factor for the increase in the risk of VTE.

SCOPE, METHODS, AND LIMITATIONS OF THE REVIEW

This review is focused on the epidemiology of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), associated with pregnancy. Superficial vein thrombosis, a less hazardous and less studied type of thrombosis in pregnant women, is beyond the scope of this review. This study discusses the VTE incidence rate in women from developed countries for both antepartum and postpartum periods and for subpopulations of women affected by additional risk factors such as thrombophilias, circulatory diseases, preeclampsia of varying degrees of severity, and Caesarean section. To minimize bias due to historical changes in medical and obstetric practices, lifestyle, diet, etc., this review is generally limited to relatively recent studies, i.e., those that cover the last 35 years.

The absolute risk or incidence rate (IR) was used to ascertain risk of VTE associated with pregnancy because this endpoint is the most intuitive, understandable, and

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TABLE 1. *Risk of VTE During Antepartum Period in Developed Countries*

Reference	Absolute risk of VTE per 10,000 deliveries (95% CI)	Region	Study period	Sample size	Comments
Sultan et al. (2012)	4.6‡[V]	UK			DVT and/or PE
Jacobsen et al. (2008b)	4.9 (4.6–5.2)	Norway	1990–2003		DVT and/or PE
McColl et al. (1997)	5.7‡[VI]	UK	1985–1996	72,201	DVT and/or PE
Heit et al. (2005)	7.1‡[VII] (2.0–11.2)	Olmsted county, MN, USA	1984–1995		DVT (no PE was observed)
Chan et al. (2001)	4.7‡[VIII]	Hong Kong, China	1998–2000	16,993	DVT and/or PE
James et al. (1996)	2.7‡[IX]	Cincinnati, USA	1989–1994	30,040	DVT
Virkus et al. (2011)	8.8‡[X]	Denmark	1995–2005	819,751	
Lindqvist et al. (1999)	6.4‡[XI]	Sweden	1990–1993	479,422	DVT and/or PE
James et al. (2006)	8.6‡[XII]	USA	2000–2001	8,330,927	DVT and/or PE
Gherman et al. (1999)	4‡[XIII]	Los Angeles, USA	1978–1996	268,525	DVT and/or PE
Andersen et al. (1998)	7.5 (4.7–11.2)	Denmark	1990–1994	30,772	DVT and/or PE
Macklon and Greer (1996)	6.6‡[XIV]	Scotland	1983–1992	645,663	DVT
Simpson et al. (2001)	2.8	London, UK	1988–1997	395,335	DVT and/or PE
Kane et al. (2013)	12.2[a](10.8–13.7)	Scotland	2001–2005	238,627	DVT
Liu et al. (2009)	5.4	Canada	1991–2006	3,852,569	DVT and/or PE
Median across studies (Q1; Q3)	5.7‡[b] (4.6; 7.5)				

Study selection was based on a coverage period, i.e. data for the last 35 years were chosen to minimize biases due to historical changes in medical and obstetric practices, lifestyle, diet, etc.

‡The value was not reported but was estimated using the data in respective publication.

[a]Only for the most recently studied period (2001–2005).

[b]Median (or second quartile), first and third quartiles are estimated for dataset from the same column as median provided.

DVT, deep vein thrombosis; PE, pulmonary embolism; Q1, first quartile; Q3, third quartile.

useful index for "daily" clinical (i.e., not statistical) practice. For the studies where the direct incidence rates of VTE were not reported, we calculated (if possible) an estimate of the observed but not reported absolute IRs using the data presented in respective articles. For example, because the incidence rate of pregnancy-associated VTE is low in the majority of pregnant women (excluding those with severe pregnancy complications), we considered published odds ratios to be approximately equal to the relative risk. For some published studies, the incidence rate was estimated as the number of VTE cases divided by the number of women in the subpopulation of interest. Because published values from different studies may vary by several multiples, depending on the studied populations, inherent lifestyle factors, and development of medical practices in the studied area, we believe that our approximate assessment would not compromise the overall conclusion about the order of magnitude of the average IRs. The values that were not provided by the sources but were estimated in this review, are marked with a "‡" symbol. Roman numerals formatted as a superscript (e.g., [XXIV]) indicate the reference to Supporting Information with details on performed assessments.

VTE DURING PREGNANCY

The risk of VTE in female population. The incidence rate of VTE in women independent of their pregnancy status declined considerably during 1960 to 1985 (Coon et al., 1973; Gillum, 1987; Lilienfeld et al., 1990). In 1959 to 1960, the VTE incidence rate in women of fertile age (20–49 years old) amounted to 28‡[I] cases per 10,000 persons per year; and pregnancy-associated (antepartum and postpartum) VTE occurred 59 times per 10,000 pregnancies (Coon et al., 1973). Modern (1987–2004) incidence rates of VTE are considered to be much lower. A large population-based cohort study of Sultan et al. (2012)

TABLE 2. *Risk of VTE at Different Trimesters of Pregnancy*

	First trimester		Second trimester		Third trimester				
Reference	IR[a]	Fraction of antepartum VTEs (%)	IR[a]	Fraction of antepartum VTEs (%)	IR[a]	Fraction of antepartum VTEs (%)	Region	Study period	Sample size
Sultan et al. (2012)	0.75‡[XV]	16‡[XVI]	1‡[XV]	22‡[XVI]	2.85‡[XV]	62‡[XVI]	UK	1987–2004	207,327
Jacobsen et al. (2008b)	1.0‡[XVII]	20.5‡[XVIII]	1.0‡[XVII]	21‡[XVIII]	2.9‡[XVII]	58‡[XVIII]	Norway	1990–2003	
McColl et al. (1997)	1.1‡[XIX]	22‡[XIX]	1.0‡[XIX]	19.5‡[XIX]	2.9‡[XIX]	58‡[XIX]	UK	1985–1996	72,201
Chan et al. (2001)	1.8‡[XX]	37.5‡[XX]	1.8‡[XX]	37.5‡[XX]	1.2‡[XX]	25‡[XX]	Hong Kong, China	1998–2000	16,993
James et al. (1996)	1.0‡[XXI]	37.5‡[XXI]	0.7‡[XXI]	25‡[XXI]	1.0‡[XXI]	37.5‡[XXI]	Cincinnati, USA	1989–1994	30,040
Virkus et al. (2011)	0.86‡[XXII]	12.4	2.2‡[XXII]	15.3	5.7‡[XXII]	72.3	Denmark	1995–2005	819,751
Blanco-Molina et al. (2007)		40		18		42	Spain	2001–2005	11,630
Pomp et al. (2008)						78‡[XXIII]	Netherlands	1999–2004	1,142
Gerhardt et al. (2000		22.5		21		56.5	Dusseldorf, Germany	1991–1998	119
Median across studies (Q1; Q3)	1‡[b] (0.86; 1.1)	22.3‡[b] (18.3; 37.5)	1‡[b] (1; 1.8)	21‡[b] (18.8; 23.5)	2.9‡[b] (1.2; 5.7)	57.3‡[b] (37.5; 62)			

Study selection was based on coverage period. Data for last 35 years was chosen to minimize bias due to historical changes in medical and obstetric practices, lifestyle, diet, etc.

‡The value was not reported but was estimated using the data in respective publication.

[a]Per 10,000 women.

[b]Median (or second quartile), first and third quartiles are estimated for dataset from the same column as median provided.

VTE, venous thromboembolism; Q1, first quartile; Q3, third quartile.

assessed the absolute risk of VTE outside of pregnancy (before the date of conception or after 3 months following delivery) as 2 per 10,000 persons per year (for reproductive-aged female population).

In the general female population, only about 2 to 2.4% VTE cases have been associated with pregnancy (women were pregnant or postpartum) (Samama, 2000; James et al., 2005). Assuming that distribution of VTE among males and females is equal (50%/50%), Blanco-Molina et al.'s study (2007) would also suggest an estimation of pregnancy-associated VTE of 2.3%‡[II] of total VTE cases in women. The low fraction of pregnancy-associated VTE is not surprising, if one considers that VTE is predominantly a disease of the elderly: the mean age of patients with VTE is around 59 to 76 years (Nordstrom et al., 1992; Oger, 2000; Samama, 2000; Ho et al., 2008). However, in the female population of childbearing age (<47 years), 16%‡[III] of registered VTEs were associated with pregnancy, i.e., were recorded either ante- or postpartum (Blanco-Molina et al., 2007).

TABLE 3. *Approximate Risk of VTE in the Early Postpartum Period*

	Absolute risk per 10,000 deliveries/births							
Reference	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Region**	**Study period**	**Sample size**
Virkus et al. (2011)	1.2‡[XXIV]	0.9‡[XXIV]	0.7‡[XXIV]	0.3‡[XXIV]	0.2‡[XXIV]	Denmark	1995–2005	819,751
Sultan et al. (2012)	1.3‡[XXV]	1.1‡[XXV]	1.2‡[XXV]	0.7‡[XXV]	0.6‡[XXV]	UK	1987–2004	207,327
Heit et al. (2005)	6.8‡[XXVI]	2.8‡[XXVI]	1.2‡[XXVI]	0.6‡[XXVI]	0.4‡[XXVI]	Olmsted county, MN, USA	1966–1995	50,080

‡The value was not reported but was estimated using the data in respective publication.

The risk of VTE during pregnancy. On average, the risk of thrombosis is considered to be 4 to 4.6 times higher in pregnant women during the antepartum period than in nonpregnant women of the same age (Heit et al., 2005; Pomp et al., 2008). Taking these numbers and the incidence rate for VTE in nonpregnant women into account, the absolute risk of antepartum VTE could be estimated as 8 to 9‡[IV] per 10,000 deliveries. This assessment is in good agreement with the range of reported absolute VTE risk in pregnant women, which varies from 2.7 to 12.2 per 10,000 deliveries, with a median around 5.7 per 10,000 deliveries (Table 1). Overall, the incidence rate of VTE during the antepartum period is calculated to be in single digits and rarely exceeds 10 per 10,000 (one exception is provided by Kane et al. (2013) and only for period of 2001–2005).

The risks of VTE shown in Table 1 consider statistics for all pregnancies observed in the respective studies without distinguishing uncomplicated from complicated pregnancies. However, complications are often associated with higher risk of VTE; therefore the estimates of risk in Table 1 might be overstated, relative to a subgroup of women without any complications and other risk factors. Furthermore, most of the studies in Table 1 were conducted in developed regions (North America, Europe, and Hong Kong, China). This fact might limit the generalizability of the reported absolute risk values, which do not include developing countries or regions.

The risk of VTE by trimesters. A woman's body is undergoing considerable changes during normal pregnancy, some of which have clear correlation with the risk of thrombotic events. Although the peak procoagulant state may be viewed as an adaptation to the trauma accompanying childbirth, an increased incidence of VTE events has been reported, also in the first and second trimesters of pregnancy. At these stages of pregnancy, it has been found that, compared with nonpregnant women, VTE IRR (incidence rate ratio) is 2.1 (Sultan et al., 2012) (95% confidence interval [CI] of 1.3–3.4), and OR (odds ratio) is 1.6 (Pomp et al., 2008) (95% CI 0.7–3.7). Although the data on distribution of risks during the antepartum period are occasionally inconsistent, there is general consensus that the risk of VTE increases in the third trimester. The risk of VTE during the third trimester was reportedly six to nine times higher than in nonpregnant women (IRR 6.1 and 95% CI 4.7–7.9 (Sultan et al., 2012), OR 8.8 and 95% CI 4.5–17.3 (Pomp et al., 2008)). Jacobsen et al. (1997) also found increased risk of VTE in the third trimester (Heit et al., 2005; Jacobsen et al., 2008b). A meta-analysis of older studies covering a period between 1967 and 1997 revealed that 22%, 34%, and 47% of antepartum DVTs occurred in the first, second, and third trimesters, respectively (Ray and Chan, 1999). Interestingly, some studies have reported an evenly distributed risk of VTE (James et al., 1996; Chan et al., 2001; Blanco-Molina et al., 2007) throughout the antepartum period, while one study found the highest risk in the first trimester (James et al., 2005). These findings of even risk are probably related to temporal trends in whether or not women at increased risk receive thromboprophylaxis during pregnancy. Note, however, that some of these studies (James et al., 1996; Chan et al., 2001) registered a very low number of VTEs, and therefore conclusions regarding the distribution of risk across trimesters may need to be taken with caution.

As shown in Table 2, the median incidence rate of VTE is 1, 1.4, and around 3 per 10,000 pregnant women for the first, second, and third trimesters, respectively. On average, about 20% of antepartum VTEs occurs in the first trimester, 20% in the second trimester, and around 50% in the third trimester. Increased risk of VTE during the antepartum period could be attributed to a gradual addition of new factors. In early pregnancy, hypercoagulability is most likely caused by hormonal changes. Later, the growing uterus adds physical pressure on pelvic veins, suppressing blood circulation and causing venous stasis. In late pregnancy, additionally reduced mobility or immobilization may facilitate VTE development.

VTE IN POSTPARTUM PERIOD

Dynamics of VTE frequency in early postpartum. Because of the vascular damage during labor and delivery, after delivery the VTE risk is dramatically increased (Gherman et al., 1999; Brown and Hiett, 2010). The highest rate of thrombosis is observed in the early postpartum period. In the first 3 months after delivery, the risk of thrombosis is up to 60

TABLE 4. *The Absolute Incidence Rate of Thrombosis During Postnatal Periods*

Reference	Absolute risk of thrombosis per 10,000 deliveries (95% CI)	Region	Study period	Sample size	Period of observation, weeks	Comments
Sultan et al. (2012)	5.2‡[XXVII]	UK			6	
Jacobsen et al. (2008b)	5.1 (4.8–5.4)	Norway	1990–2003		6	DVT and/or PE
McColl et al. (1997)	2.9‡[XXVIII]	UK	1985–1996	72,201	6	DVT and/or PE
Heit et al. (2005)	7.9‡[XXIX] (3.4–12.3)	Olmsted County, Minnesota, USA	1984–1995	–	4	DVT and/or PE
Chan et al. (2001)	14‡[XXX]	Hong Kong, China	1998–2000	16,993	6	DVT and/or PE
James et al. (1996)	1.7‡[XXXI]	Cincinnati, USA	1989–1994	30,040	Early postpartum period	DVT
Virkus et al. (2011)	3.8‡[XXXII]	Denmark	1995–2005	819,751	6	DVT and/or PE
Lindqvist et al. (1999)	6.3‡[XXXIII]	Sweden	1990–1993	479,422	6	DVT and/or PE
James et al. (2006)	8.6‡[XXXIV]	USA	2000–2001	8,330,927	NA	DVT and/or PE
Gherman et al. (1999)	2.1‡[XXXV]	Los Angeles, USA	1978–1996	268,525	6	DVT and/or PE
Andersen et al. (1998)	4.9 (2.7–8.0)	Denmark	1990–1994	30,772	8	DVT and/or PE
Macklon and Greer (1996)	3.3‡[XXXVI]	Scotland	1983–1992	645,663	8	DVT
Simpson et al. (2001)	6.5	London, Great Britain	1988–1997	395,335	NA	DVT and/or PE
Kane et al. (2013)	2.7[a](2.1–3.4)	Scotland	2001–2005	238,627	6	DVT
Liu et al. (2009	11.5‡[XXXVII]	Canada	1991–2006	3,852,569	NA	DVT and/or PE
Median across studies (Q1; Q3)	5.1‡[b] (2.9; 7.9)					

Study selection was based on coverage period. Data for the last 35 years was chosen to minimize biases due to historical changes in medical and obstetric practices, lifestyle, diet, etc.

‡The value was not reported but was estimated using the data in respective publication.

[a]Only for most recent studied period (2001–2005).

[b]Median (or second quartile), first and third quartiles are estimated for dataset from the same column as median provided.

DVT, deep vein thrombosis; PE, pulmonary embolism; CI, confidence interval; NA, not available; Q1, first quartile; Q3, third quartile.

fold higher (OR, 60.1; 95% CI 26.5–135.9) than in non-pregnant women; and during the first 2 to 6 weeks the risk is up to 84-fold higher (OR, 84.0; 95% CI 31.7–222.6) (Pomp et al., 2008). The elevated risk of the postpartum period is supported by several studies, which identified the occurrence of one-half of postpartum VTEs within the first (Chan et al., 2001; Heit et al., 2005) or the first 2 weeks (Jacobsen et al., 2008a; Virkus et al., 2011) after delivery.

Table 3 summarizes the data from several studies that evaluated weekly risks for thrombosis in early postpartum period (Heit et al., 2005; Pomp et al., 2008; Virkus et al., 2011). In all studies, the rate of VTE was considerably higher within the first couple of weeks after delivery and declined over time. According to Virkus et al. (2011), the VTE rate decreases linearly during an early postpartum period. Sultan et al. (2012) found that the risk of VTE did not change for weeks 1 to 3 after delivery, while after that

it decreased. Heit et al. (2005) observed a substantial risk reduction within the first five weeks postpartum, with a much higher VTE rate during the first two weeks after delivery than in similar studies. This higher than typical risk may be an overestimation possibly caused by two aspects of the Heit et al.'s study. First, the study counted as VTE all cases of confirmed VTE, as well as those classified in medical records as "possible VTE" or "with signs and symptoms consistent with VTE". Secondly, Heit analysis of weekly VTE rates was likely influenced by the inclusion of an early period 1966 to 1975, when postpartum VTE occurred almost two times more often than in 1986 to 1995 (Heit et al., 2005). Although, we were unable to extract the weekly VTE incidence rate for the recent 35 years from this study, we are including it in this summary for completeness, because it is the only study performed in North America.

General occurrence of VTE in postpartum period. Although the risk of VTE is not constant after delivery, most studies chose to report an overall (average) risk for the postpartum period (usually first 4–8 weeks), which is shown in Table 4. Consequently, even though the IRR for VTE in the early postpartum period is considerably increased compared with the antepartum period (Sultan et al., 2012), the median obtained from all studies gives comparable absolute IRs to develop a VTE before and after childbirth, 5.7‡ versus 5.1‡ per 10,000 pregnancies, respectively (compare Table 1 and Table 4). This may be explained by a long antepartum period (40 weeks) associated with low specific risk of VTE and a much shorter postpartum period (4–8 weeks) with a higher specific risk. Further, in the late postpartum period (7–12 weeks after delivery), the risk of VTE decreases considerably, but remains higher than in women who have not been pregnant recently. For example, Sultan et al. (2012) reported a decrease in the IRR from 22 (IRR 22.1; 95% CI 18.1–27.1; data collected during the first 6 weeks after delivery) down to just 2 (IRR 1.8; 95% CI 0.9–3.5; >6 weeks after delivery) times of nonpregnant women.

Since the postpartum period as defined by Liu et al. (2009) differs from the definition used in other studies of Table 4, for consistency, we recalculated the incidence reported by Liu et al. (2009) to include the rates of VTE for a period starting with hospital discharge (designated as postpartum by authors, IR 4.3 per 10,000 pregnancies) and the period from childbirth to discharge (IR of 7.2 per 10,000 pregnancies). The total combined incidence of VTE after delivery could then be estimated to have an upper limit to of 11.5‡[XXXVII] per 10,000 pregnancies.

RISK FACTORS FOR VTE ASSOCIATED WITH PREGNANCY

The same risk factors that are associated with higher incidence of VTE in the nonpregnant population are also in effect during pregnancy. For example, in pregnant women, the risk of VTE is increased with age, in the presence of anemia, obesity, smoking, and other risk factors (Jacobsen et al., 2008a; Liu et al., 2009; Sultan et al., 2012, 2013; Lindqvist and von, 2015). It is also well established that the risk of VTE during and after pregnancy is increased by the presence of certain prothrombotic conditions (e.g., thrombophilia, cardiac issues), history of previous VTE episodes, pregnancy complications, and Caesarean section. The most studied and relevant risk factors are described in detail below.

Thrombophilia. Hereditary thrombophilia is one of the most significant contributors to the elevated risk of VTEs. The incidence of hereditary thrombophilias in a general Western population is about 15% (Greer, 1999; Rosendaal, 1999). Congenital thrombophilia may be caused by deficiencies or defects of coagulation inhibitors, such as antithrombin (AT-III), Protein S, Protein C, and mutations causing elevated prothrombin (FII20210A variant) or resistance of Factor V (FV) to inactivation by activated protein C (e.g., FV Leiden variant). The risk of either DVT or PE or both during the peripartum hospitalization (including labor, delivery, and the period before hospital discharge) in women with thrombophilia is considerably increased, compared with other pregnant women (adjusted OR 15.4, 95% CI 10.8–22.0). The reported absolute risk of DVT and PE separately in women with thrombophilia was as high as 146 and 43 per 10,000 deliveries, respectively ((Liu et al., 2009), the study did not specify whether thromboprophylaxis was given). The estimated combined incidence rate of either DVT or PE or both is 184‡[XXXVIII] per 10,000 during the peripartum hospitalization.

In the studies where data were stratified by the individual thrombophilia-causing defect, the highest risk of VTE was observed in carriers of homozygous FV Leiden, OR 34.4, (95% CI 9.9–120), compared with pregnant women without thrombophilia. Compared with homozygotes, a heterozygous FV Leiden mutation was associated with a fourfold lower odds ratio—8.3 (Robertson et al., 2006). In another study of Factor V Leiden carriers (either homo- or heterozygous), the observed VTE incidence rate was 300‡[XXXIX] per 10,000 pregnancies (antepartum and postpartum periods combined) (Tormene et al., 2001). Homozygous carriers of FV Leiden mutation and heterozygous individuals had risks of pregnancy-associated VTE around 700 and 270‡[XL] per 10,000 pregnancies, respectively (Tormene et al., 2001).

The risk for VTE in pregnant carriers of the prothrombin FII20210A mutation is lower than FV Leiden, but is still higher compared with pregnant women without thrombophilia, OR 26.4 (95% CI 1.2–559) for homozygous, and 6.8 (95% CI 2.5–18.8) for heterozygous individuals (Robertson et al., 2006). Deficiencies of Protein C, AT-III, and Protein S are associated with increased risk of DVT,

TABLE 5. *The Risk of Pregnancy Related VTE (DVT and/or PE) in Population of Women with a History of VTE*

	Incidence rate of VTE per 10,000 deliveries/pregnancies, (95% CI)				Period of observation, weeks (95% CI)			
Reference	Antepartum	Postpartum (after delivery/end of pregnancy)	Pregnancy associated	Region	Study period	Sample size	Antepartum	Postpartum (after delivery/ end of pregnancy)
Without thromboprophylaxis								
De et al. (2006)	580 (300–1,060)	830 (450–1,460)	1,220 (790–1,830)	Rome and Milan, Italy	1995–2005	155 antepartum 120 postpartum	40	6
Pabinger et al. (2005)	620 (160–1,060)	510‡[XLVII]	910‡[XLVIII]	Vienna, Austria	1985–1998	87	40	6
Badaracco and Vessey (1974)[a]	–	–	1250	Massachusets USA	–	–	–	–
Brill-Edwards et al. (2000)	240 (20–690) or 400‡[b][XLIX]	–	–	Multi regional	1994–1998	125	25[c]	–
Pabinger et al. (2002)	444‡[L]	–	–	Vienna, Austria	1985–1998	180	21[d]	–
With thromboprophylaxis								
Pabinger et al. (2005)	No TE registered	575‡[LI]	575‡[LI]	Vienna, Austria	1985–1998	197	40	6
Roeters van Lennep et al. (2011)	160	400	560[LII]	Rotterdam, the Netherlands	1996–2009	126	–	12
Sanson et al. (1999)	200‡[LIII]	–	–	Multi regional pooled study	1992–1998	149	–	–
Lepercq et al. (2001)	280‡[e][LIV]	–		–	1988–1997	180	–	–

‡The value was not reported but was estimated using the data in a respective publication.

[a]This older study was included in the table because it shows rates in the absence of thromboprophylaxis.

[b]Rough estimation corrected to compensate for missed the first 15 weeks of gestation.

[c]Mean date of pregnancy at enrollment was 15 ± 6 weeks.

[d]Mean duration of the follow up without thromboprophylaxis was 21 weeks during pregnancy.

[e]Recurrent thrombosis happened after the first incidence one of thrombosis within the same pregnancy.

TE, thromboembolism; VTE, venous thromboembolism; CI, confidence interval.

but only by about 4.8, 4.8, and 3.2-fold, respectively (Robertson et al., 2006).

The risk of VTE in thrombophilic women is high for the entire duration of pregnancy-related period. In carriers of FV Leiden (both homo- and heterozygous), 37% of VTEs occurred in the antepartum period and 63% of VTEs—in the postpartum period (Tormene et al., 2001), giving a rough incidence rates of 110‡[XLI] and 190‡[XLII] VTEs per 10,000 pregnancies antepartum and postpartum, respectively. Risk estimations by Middeldorp et al. (1998) and Middeldorp and Van (2008) have similar trends: the incidence rates for the first episode of VTE were 40 (95% CI 10–240) per 10,000 in the antepartum and 170 (95% CI 70–430) per 10,000 during postpartum for carriers of FV Leiden. For women carrying prothrombin FII20210A mutation, the incidence rate was also lower in the antepartum period (50 per 10,000 pregnancies) than in postpartum period (190 per 10,000) (Bank et al., 2004; Middeldorp and Van, 2008). The incidence rates for patients with AT-III, Protein C, or Protein S deficiencies

TABLE 6. *Risks of VTE (or DVT only) in Women with Preeclampsia in Comparison with Pregnant Women Without Preeclampsia*

Reference	The relative risk of VTE antepartum (95% CI)	The risk of VTE postpartum (95% CI)	The risk of VTE during peripartum hospitalization (95% CI)	The risk of pregnancy associated VTE (95% CI)	Comment
Kane et al. (2013)	IRR 1.03 (0.76–1.39)	IRR 1.6 (1.01–2.53)	–	–	For DVT only; for any preeclampsia
Jacobsen et al. (2008a)	OR 0.5 (0.2–1.2)	OR 3.1 (1.8–5.3)	–	–	Preeclampsia without intrauterine growth restriction
	OR 1.0 (0.3–4.0)	OR 5.8 (2.1–16)	–	–	Preeclampsia with intrauterine growth restriction
Lindqvist et al. (1999)	OR 0.8 (0.4–1.6)	OR 2.9 (2.1–3.9)	–	–	Any preeclampsia
Liu et al. (2009)	–	–	OR 0.8 (0.6–1.1)	–	for DVT only
James et al. (2006)	–	–	–	OR 0.9 (0.7–1.0)	Preeclampsia and gestationalhypertension

DVT, deep vein thrombosis; VTE, venous thromboembolism; OR, odds ratio; CI, confidence interval.

TABLE 7. *Upper Bound Estimation for the Postpartum VTE Incidence Rate in Women with Preeclampsia*

Reference	The relative risk of VTE postpartum for women with preeclampsia	Rate of VTE postpartum in whole population of pregnant women (per 10,000)	The upper estimation of VTE rate in women with preeclampsia per 10,000
Kane et al. (2013)	1.6	2.7	1.6×2.7 = 4.3‡
Jacobsen et al. (2008a)	3.9‡[LIX]	5.1	3.9×5.1 = 20‡
Lindqvist et al. (1999)	4.8	6.3	6.3×4.8 = 30‡

‡The value was not reported but was estimated using the data in respective publication.
VTE, venous thromboembolism.

were reported as 120 versus 300 VTE events per 10,000 pregnancies, for ante- versus postpartum periods, respectively (Middeldorp and Van, 2008).

Therefore, the absolute VTE risk for thrombophilic women during pregnancy is exceptionally high and presents starting with the first trimester (Tormene et al., 2001). The absolute risk in the postpartum increases even further by two to threefold, compared with the antepartum.

Past history of VTE. Past history of thrombosis is another risk factor that leads to a significantly increase in the probability of pregnancy-associated recurrent VTE. In a population of women who did not receive thromboprophylaxis, the incidence rate of antepartum VTE was found to be approximately 600 (Table 5) per 10,000 (Pabinger et al., 2005; De et al., 2006). Brill-Edwards et al., however, found a substantially lower incidence rate of recurrent VTE of 240 per 10,000 women (95% CI 20–690) (Brill-Edwards et al., 2000). However, the Brill-Edwards et al.'s study was of shorter duration (starting on the 15th week of gestation) and excluded women with thrombophilias, who, according to the experience reported by Simioni et al. (2001), have incidence rates of antepartum VTE up to 20%‡[XLIII], and therefore may contribute considerably to the overall incidence of recurrent VTE in pregnancy. For consistency in the duration of the period analyzed, the IR observed in the Brill-Edwards et al.'s study (2000) may be increased proportionally to roughly 400‡[XLIV] per 10,000 women, to account for the first 15 weeks of gestation that were excluded.

TABLE 8. *Risk of VTE in Women with Severe Preeclampsia/Eclampsia*

Reference	Risk of thrombosis per 10,000 deliveries	Odds ratio (95% CI)	Region	Study period	Type of study	Sample size	Period of observation (wk)	Comments
Kuklina et al. (2009)	12.7	3.3 (2.6–4.2)	USA	1998–2006	Retrospective	394,596	Peripartum hospitalization	PE
Tuffnell et al. (2005)	28‡[LX]		Yorkshire UK	1999–2003	Prospective	1,087	During hospitalization associated with the severe state	PE
Zanette et al. (2014)	20		Brazil	1998–2006	Prospective	6,706	during hospitalization	DVT and/or PE

‡The value was not reported but was estimated using the data in respective publication.
DVT, deep vein thrombosis; PE, pulmonary embolism; CI, confidence interval.

Antepartum and postpartum VTE incidence rate was not different in women with a history of VTE who had not received thromboprophylaxis (Pabinger et al., 2005; De et al., 2006) (Table 5). For the antepartum and postpartum periods combined, the incidence was identified as 1220 cases of recurrent VTE per 10,000 pregnancies in women who had a single previous episode of VTE (De et al., 2006). This is consistent with the observations in an earlier study by Badaracco and Vessey (1974), who found recurrent VTE in 1250‡[XLV] cases per 10,000 women in 1974, i.e., when no thromboprophylaxis in pregnant women was used. On the other hand, older studies before the advent of diagnostic ultrasound in the early 1980s most likely over-diagnosed VTEs (Greer et al., 1990).

When women with a history of VTE were treated with anticoagulants, the incidence rate of VTE in the antepartum period was shown to decrease. Pabinger et al. (2005) did not observe any recurrent VTEs with thromboprophylaxis in antepartum period. Another study (Roeters van Lennep et al., 2011) reported risk of 160 VTE per 10,000 pregnancies. In a systematic review, Sanson et al. (1999) found only three thromboembolic complications in pregnancies of at-risk women on thromboprophylaxis. These cases were found in women with previous VTE ($n = 149$), resulting in an incidence rate of 200‡ per 10,000 (Table 5). Lepercq et al. (2001) identified 180 patients with VTE history, with five of them experiencing recurrent VTE during the same pregnancy, giving an incidence rate of 280‡ per 10,000.

In the postpartum period in women with thromboprophylaxis, the incidence rate was reported to be as high as 575‡**[LI]** per 10,000 (Pabinger et al., 2005), which is close to what was reported for the population without any thromboprophylaxis (Pabinger et al., 2005). Another study (Roeters van Lennep et al., 2011) observed slightly lower incidence rate of 400 per 10,000 deliveries in postpartum period in women, who receive or received thromboprophylaxis. It might be concluded that usual prophylactic dosage regimens are not fully effective during the period of very high risk in postpartum period.

A systematic review by Greer and Nelson-Piercy (2005) (not shown in Table 5) reported a considerably lower risk of pregnancy-associated VTE in women receiving heparin. Only 115 recurrent VTE events were found per 10,000 women in pregnancy who received treatment doses of low molecular weight heparin (LMWH) (Greer and Nelson-Piercy, 2005). In addition, when LMWH was used at lower doses, only 84 VTE cases per 10,000 were registered in a mixed subpopulation with acute VTE, previous VTE, thrombophilia, and/or additional risk factors (Greer and Nelson-Piercy, 2005). The difference in doses and subpopulations makes it difficult to compare the results of the Greer review study with the data extracted from the original articles listed in Table 5. Using data from another study (Kane et al., 2013) (also not shown in Table 5), the DVT incidence rate in women with previous VTE could be estimated as 62‡[XLVI] antepartum and 20‡[XLVI] postpartum cases per 10,000; however, no information about PE and thromboprophylaxis in that study was provided.

Thus the risk of VTE in women with a history of VTE exists throughout the whole pregnancy-related period (antepartum and postpartum combined). The risk in such a subpopulation of women appears to be higher than in women with thrombophilia as a sole risk factor.

Past history of circulatory diseases. A history of circulatory diseases also significantly increases the risk of VTE during the peripartum hospitalization (labor, delivery, and a period before hospital discharge). Compared with pregnant women, without such a history, the unadjusted OR for VTE in pregnant women with a history of cardiovascular

TABLE 9. *Risk of VTE in Women with Eclampsia*

Reference	Risk of thrombosis per 10,000 deliveries	Region	Study period	Type of study	Sample size	Period of observation	Comments
Liu et al. (2011)	47	Canada	2003–2009	retrospective	1,481	in pregnancy, in labor, in the postpartum	DVT and/or PE
Fong et al. (2013)	42	California, USA	2001-2007	retrospective	1,888	peripartum	DVT and/or PE
Douglas and Redman (1994)	130	UK	1992	prospective	382	antepartum, intrapartum and early postpartum (from one week to two) periods	PE
Jacobsen et al. (2008b)	106‡[LVIII]	Norway	1990-2003	retrospective		postpartum	DVT and/or PE
Median across studies (Q1; Q3)	76.5‡[a] (44.5; 118)						

‡The value was not reported but was estimated using the data in respective publication.

[a]Median (or second quartile), first and third quartiles are estimated for dataset from the same column as median provided.

DVT, deep vein thrombosis; PE, pulmonary embolism; Q1, first quartile; Q3, third quartile.

problems was 18.5 (95% CI 12.1–28.2) (Liu et al., 2009). The incidence rate of DVT and PE in these women was reported by Liu et al. (2009) as 100 and 58 per 10,000, respectively. Thus, for this sub-population, the rate of VTE (either DVT or PE) is around 150‡[LV] per 10,000 during the peripartum hospitalization.

Preeclampsia. Preeclampsia is one of the most common medical disorders of pregnancy. This pregnancy complication is defined by high blood pressure on 2 occasions ($\geq$140 mm Hg systolic or $\geq$90 mm Hg diastolic) combined with proteinuria ($\geq$0.3 g protein in a 24-h urine specimen) during the second half of pregnancy (ACOG Practice Bulletin, 2002). In the US, preeclampsia occurs in 2.6 to 3.4% (Saftlas et al., 1990; Wallis et al., 2008; Berg et al., 2009) of pregnancies. Preeclampsia and eclampsia (preeclampsia complicated with convulsions) are other serious risk factors for VTE.

From the study of Kane et al. (2013) the incidence rate of DVT in women with preeclampsia could be estimated as 9.9‡[LVI] and 5.6‡[LVI] per 10,000 for the ante- and postpartum periods, respectively. These assessments do not include cases of PE. According to Kane et al. (2013), preeclampsia did not significantly increase the risk of DVT during the antenatal period, compared with noncomplicated pregnancy (IRR ratio 1.03; 95% CI 0.76–1.39), but it increased the risk in the postpartum period by 1.6-fold (IRR ratio 1.6; 95% CI 1.01–2.53). Two additional studies, by Jacobsen et al. (2008a) and Lindqvist (Lindqvist et al., 1999), analyzed the incidence of VTE, and reported slightly different odds ratios (Table 6), but similar trends—no increase of VTE risk during pregnancy but elevated risk in the postpartum period.

Two more studies, however, did not find any considerable changes in frequency of VTE in women with preeclampsia. One of the studies, James et al. (2006), analyzed the association of preeclampsia with VTE during the whole pregnancy period, without division into antepartum and postpartum. This approach could have masked the increased postpartum VTE risk that was observed in other studies (Lindqvist et al., 1999; Jacobsen et al., 2008a; Kane et al., 2013) over the whole pregnancy-related period, potentially explaining the lack of association of VTE with preeclampsia reported by James (2006) (OR 0.9; 95% CI 0.7–1.0; compared with women without preeclampsia). The second study in women with preeclampsia estimated the relative risk, but only for DVT, and found no correlation (OR 0.8;95% CI 0.6–1.1) (Liu et al., 2009); however, the analysis included only the peripartum period.

None of the reviewed studies discussed here (Table 6) provided absolute incidence rates, but, instead reported the calculated odds ratios. However, the absolute rates of VTE events can be estimated for the subpopulation of women

TABLE 10. *Primary Data on the Prevalence of DVT and PE in the Postpartum Period after Caesarean Section*

Reference	Risk of thrombosis per 10,000	Region	Study Period	Sample size	Period of postpartum observation	Comments
Chan et al. (2001)	60‡[LXI]	Hong Kong, China	1998-2000	3,311	6 weeks	
Jacobsen et al. (2004)	47	Norway	2002-2003	1,067	6 weeks	PE only, DVT was not found
Jacobsen et al. (2008b)	16‡[LXIII]	Norway	1990-2003		6 weeks	DVT and/or PE
Kane et al. (2013)	5.8‡[LXIV]	Scotland, UK	1980-2005	242,165	6 weeks	DVT only
Macklon and Greer (1996)	7.8‡[LXV]	Scotland, UK	1981-1992	89,618	8 weeks	DVT and/or PE
Simpson et al. (2001)	17.8 (95% CI 14.3-21.2)	London, UK	1988-1997			DVT and/or PE
Liu et al. (2009)	14.3‡[LXVI]	Canada	1991-2006	3,852,569	Peripartum hospitalization	DVT and/or PE
Gherman et al. (1999)	8.5‡[LXVII]	Los Angeles, USA	1978-1996	268,525	6 weeks	DVT and/or PE
Median across studies (Q1; Q3)	16‡[a] (7.8; 47)					

‡The value was not reported but was estimated using the data in respective publication.

[a]Median (or second quartile), first and third quartiles are estimated for dataset from the same column as median provided.

DVT, deep vein thrombosis; PE, pulmonary embolism; CI, confidence interval; Q1, first quartile; Q3, third quartile.

with preeclampsia from these articles using several considerations described below. The reported odds ratios for the antepartum period are typically close to 1 (Table 6), which indicates that chances of getting a VTE for patients with preeclampsia are approximately equal to getting a VTE during pregnancy without preeclampsia. Therefore the absolute incidence rate of VTE in a subpopulation of women with preeclampsia during the antepartum period may be expected to be comparable to what was observed in a general population of pregnant women for the same period (Table 1). Based on the data from the two Jacobsen et al.'s studies (2008a,b), which were based on the same registry, we were able to calculate the incidence of VTE in women with preeclampsia. For the hospital-based case–control study (Jacobsen et al., 2008a), the estimated incidence was 4‡[LVII] and 20‡[LVII] VTE events per 10,000 preeclamptic pregnancies for the ante- and postpartum periods, respectively. For the register-based case-control study (Jacobsen et al., 2008b), a very similar incidence rate of preeclampsia-associated postnatal VTE was found, 25‡[LVIII] per 10,000 women with preeclampsia.

Another assessment could be made from the study of Liu et al. (2009). The absolute crude rates of DVT and PE cases as observed in this study were estimated as 8.6 and 6.4 per 10,000 pregnancies with preeclampsia. Taking into the account that the majority of DVT and PE cases in the studied population was recorded during the peripartum hospitalization, while only a small number of PE events (11%) occurred in combination with DVT, and assuming the same would be approximately true for women with preeclampsia, the absolute crude VTE rate could be estimated as a sum of incidence rates for DVT and PE, or 14 to 15‡ per 10,000 preeclampsias.

We used a complementary approach to estimate postpartum VTE rates in women with preeclampsia using published odds ratios (Table 6), which can be considered approximately equal to the relative risks because of the low incidence of VTE. Because the subpopulation of women with preeclampsia corresponds to only about 3% of the total population of pregnant women in developed countries (Saftlas et al., 1990; Wallis et al., 2008; Berg et al., 2009), the risk of VTE in this subgroup increases slightly, i.e., only 2 to 14 per 10,000 (Table 4) (not by 30 to 40-fold). This allows one to make an upper-bound estimation of the VTE rate in women with preeclampsia as a product of relative risk and the VTE rate in a general population (from the Table 4). This calculation gives 20 to 30‡ VTEs per 10,000 preeclamptic pregnancies for Jacobsen et al.'s (2008a) and Lindqvist et al.'s (1999) studies. These estimates are considerably higher than the

assessment based on the study of Kane et al. (2013) of 4.3‡ per 10,000 (Tables 7), partially due to the relatively low postpartum VTE incidence rate in the general population of pregnant women in Kane's data (Table 1). Our analysis suggests the possibility of an initial bias in Kane's study that could have spread out to our estimations, calculated on the basis of this work, and made them considerably lower compared with others.

Severe preeclampsia and eclampsia. Severe preeclampsia is characterized by higher blood pressure than preeclampsia (≥160 mm Hg systolic or ≥110 mm Hg diastolic) and/or more severe proteinuria (≥5 g protein in a 24-h urine specimen) than preeclampsia (ACOG Practice Bulletin, 2002). Moreover, other complications might present in severe preeclampsia: oliguria, cerebral or visual disturbances, pulmonary edema or cyanosis, impaired liver function, thrombocytopenia, and intrauterine growth restriction of the fetus (ACOG Practice Bulletin, 2002). A higher incidence of VTE might be expected in women with severe preeclampsia and eclampsia, because of the severity of their condition. Due to wide access to diagnostic and preventive measures, the incidence of severe preeclampsia in developed countries is quite low, i.e., on the scale of 10 to 60 per 10,000 deliveries (Zhang et al., 2003, 2005; Catov et al., 2007; Kuklina et al., 2009). The incidence of severe preeclampsia in developing countries could be substantially higher, ranging from 40 (Rojas-Suarez and Vigil-De, 2012) to as high as 570 (Abuladze and Asatiani, 2006) per 10,000 deliveries.

Because of the low incidence of severe preeclampsia and eclampsia, data on the incidence of VTE cases associated with these severe conditions is limited. Two studies found about 12.7 (Kuklina et al., 2009) and 28‡[LX] (Tuffnell et al., 2005) PE events per 10,000 pregnancies complicated by severe preeclampsia (Table 8), but no data on DVT or total VTE have been reported to date. One study conducted in Brazil reported about 20 VTE cases per 10,000 (0.2%) pregnancies with severe preeclampsia (Zanette et al., 2014).

Eclampsia. Eclampsia is characterized by occurrence of seizure in association with preeclampsia during pregnancy or postpartum. Eclamptic seizures are relatively rare and occur in approximately 1% of women with preeclampsia. The incidence of eclampsia was low in developed countries, from 2.4 (Ekholm et al., 1999) to 10 (Zhang et al., 2003) cases per 10,000 mothers, whereas in developing countries much higher rates were found, from 50 (Adam et al., 2009) to as high as 390 (Noor et al., 2004) per 10,000 deliveries. Because of the low incidence of eclampsia, the data on the incidence of eclampsia-associated VTE are very limited (Table 9) and mostly retrospective in nature.

Based on the data from the two Jacobsen et al.'s studies (2008a,b) from Norway, we could estimate the incidence of VTE as 106‡[LVIII] per 10,000 eclamptic pregnancies for the postpartum period. The incidence of VTE associated with eclampsia in North America was reported to be 2.3 times less than in Norway, and was reported as 47 and 42 per 10,000 in Canada (Liu et al., 2009) and the USA (Fong et al., 2013), respectively (Table 9).

Caesarean section. Current data indicates that in developed countries, from 11 to 25% of pregnancies culminate in a Caesarean section (Gherman et al., 1999; Lindqvist et al., 1999; Jacobsen et al., 2004; James et al., 2006; Kane et al., 2013). As an invasive procedure, Caesarean section is associated with increased risk of VTE compared with vaginal delivery (OR 4.9; 95% CI 3.8–6.3) (Lindqvist et al., 1999); during the peripartum period, the risk of PE (OR 2.9, 95% CI 2.4–3.5) associated with Caesarean section is higher than that of DVT (OR 1.8, 95% CI 1.6–2.0) (Liu et al., 2009). In the study by Jacobsen et al. (2008b), emergency Caesarean procedure was associated with a higher risk of VTE (OR 4.0; 95% CI 3.0–5.3) than was a planned surgical delivery (OR 2.7; 95% CI 1.8–4.0). A similar relationship was found by Kane et al. (2013): the probability of suffering from a DVT after the emergency Caesarean section was 2.1 times higher (IRR 2.06; 95% CI 1.63–2.61) than after vaginal delivery, compared with only a 1.4-fold increase vs. elective procedure (IRR 1.39; 95% CI 1.0–1.94). Thus, data from these studies suggest that emergency Caesarean section results in thrombosis approximately 1.5 times more often than in elective surgery, that is likely related to several factors, including sicker patients and lack of prophylaxis. Surprisingly, in Chinese women, an equal association of VTE with elective and emergency Caesarean sections was reported (Chan et al., 2001); however, the results were confounded by a small sample size and should be taken with caution.

The absolute IR of VTE after Caesarean section varies widely and depends on the population studied and obstetric practices. In Hong Kong, China, the incidence of VTE after Caesarean section was found to be up to 60‡[LXI] cases per 10,000 (Chan et al., 2001), whereas several studies from the UK have reported considerably lower numbers of 5.8 to 17.8 VTEs per 10,000 Caesarean sections (Table 10). Some of the reviewed studies, however, provided retrospective data spanning to as late as 1980s, i.e., when thromboprophylaxis after Caesarean section was not widely used. After the thromboprophylaxis guidelines in pregnancy were introduced in the UK in 1996, the crude rate of DVT after emergency Caesarean section decreased by 1.9‡ times (from 8.4‡[LXII] to 4.3‡[LXII] per 10,000), whereas the rate of DVT after elective surgery has not changed (4.6‡[LXII] and 4.3‡[LXII] per 10,000 before and after guidelines, respectively). Taken together, for any Caesarean sections, after introducing the guidelines (Kane et al., 2013), the risk of DVT decreased roughly by 1.6 times (from 6.9‡[LXII] to 4.3‡[LXII] per 10,000 any

TABLE 11. *Association of Postpartum VTE with Various Causes (Risk Factors)*

Reference (region, period of observation)	Comment	No. registered DVT and/or PE	Caesarean section (%)			Pre-eclampsia (%)	Eclampsia (%)	History of VTEs (%)	Thrombophilia (%)	Immobilization (%)
			Planned (elective)	emergency	Planned + emergency					
Lindqvist et al. (1999) (Sweden, 1990–1993)		308	–	–	41	13		–	–	–
Sultan et al. (2013) (Great Britain, 1995–2009)	not tested for thrombophilia, excluded women with previous DVT	285	–	–	29	4.6		–	–	–
Jacobsen et al. (2008a) (Norway 1990–2003)		291	8.6 (without infection)	25.8 (without infection)	34 (without infection) (43 any Caesarean)	18.5		–	–	–
Jacobsen et al. (2008b) (Norway 1990–2003)		314	10.2	30.9	41	18.2	1			
Blanco-Molina et al. (2007) (Spain, 2001–2005)	Included pregnant women with DVT only.	64	–	–	64	–		6.2	50	11
Martinelli et al. (2002) (Italy, 1995–2000)		68	–	–	–	–		–	39.5	–
Kane et al. (2013) (Scotland 1980–2005)	1,475,301; 91,621 (6.2%) from that of planned Caesarean sections, 150,544 (10.2%) emergency Caesarean section	498	8.2	19.9	28	8		5.2	–	–
Chan et al. (2001) (China, 1998–2000)					83				–	
Gerhardt et al. (2000) (Germany, 1991–1998)		119			33					
Gherman et al. (1999) (USA, 1978–1996)		165			19			14		

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Caesarean sections). This suggests that the data from older studies are not generalizable to the current time, and would most likely overestimate the current incidence rates of VTE after Caesarean section.

Estimations of VTE incidence rates after Caesarean section derived from the Liu et al. (2009) and Jacobsen et al. (2008b) studies gave 14.3‡ and 16‡ per 10,000, respectively (Table 10). An older publication by Jacobsen et al. (2004) reported a higher VTE rate—47 per 10,000. The difference in the results of the two Jacobsen studies may be explained by the different scope of the studies. Whereas the data from the Jacobsen et al. (2004) publication were based on a single hospital for a short observation period, the more recent Jacobsen et al. (2008b) study reflects the statistics on a countrywide scale for a period of 14 years.

VTE DISTRIBUTION AMONG DIFFERENT RISK FACTORS IN POSTPARTUM PERIOD

The one of the largest fractions of postpartum VTE (ranging from 19% (Gherman et al., 1999) to 64% (Blanco-Molina et al., 2007) has been associated with Caesarean section (Table 11). A comparable proportion of VTE was related to thrombophilia, amounting to 40 to 50% (Martinelli et al., 2002; Blanco-Molina et al., 2007). In contrast, a history of VTE was associated with only 5 to 6% of postpartum VTE (Blanco-Molina et al., 2007; Kane et al., 2013), despite the generally high risk of VTE in this population. This is likely explained by the low prevalence of young women who have a history of VTE. Preeclampsia was associated with 5 to 18% of DVT cases (Table 11). Similarly, despite a high risk of VTE in women with eclampsia, eclampsia contributed only 1% to an overall VTE, probably due to the low incidence of eclampsia in developed countries. Finally, immobilization (in nonsurgical patients who had been immobilized for $\geq$4 days in the two-month period prior to VTE diagnosis) was associated with only 11% of total pregnancy-associated DVTs.

SUMMARY AND CONCLUSIONS

Although the risk of thrombotic events in pregnancy is relatively low, the severity of the condition and adverse impact on the health of women and outcomes of pregnancy is substantial. The great number of studies reviewed in this article, although occasionally reporting discordant results, provides a generally consistent and logical picture that can be summarized in terms of crude incidence rates.

The risk of VTE in nonpregnant women is around 2 per 10,000. During pregnancy and the first 6 weeks after delivery, women are at a higher risk of VTE compared to nonpregnant women. The risk increases gradually during the course of pregnancy, with the highest risk evident during a short period of time (1–2 weeks) immediately after childbirth, and then the risk decreases gradually and falls considerably around the 6th week postdelivery. In general, the absolute risk of VTE appears to be similar for the whole duration of antepartum period and the period of the first 6 weeks of postpartum; and it is usually estimated as an order of single digits per 10,000 deliveries, rarely exceeding 10 per 10,000.

The prominent risk factors for VTE are thrombophilia, history of circulatory disease and previous venous thromboembolism, preeclampsia and related disorders, and Caesarean section. An extremely high VTE risk was observed in women with a history of VTE who did not receive thromboprophylaxis. In general, the incidence of pregnancy-associated VTE (for antepartum and postpartum periods combined) for these women is close to 1000 per 10,000 (10%). Separately for the antepartum period, VTE rate is about 400 to 600 per 10,000 women with a history of VTE. Thromboprophylaxis considerably decreases the chances of thrombosis in women with previous VTE, down to 100 to 300 per 10,000 in the antepartum period. The second most important factor is thrombophilia. The IR of VTE during the whole pregnancy-related period (antepartum and postpartum combined) ranges from 200 to as high as 400 per 10,000. The third important factor is a history of circulatory diseases, which gives incidence rates on the order of 100 to 200 per 10,000 women during the peripartum hospitalization. Fourth, eclampsia is related to VTE with the incidence rate of 40 to 130 per 10,000 women during peripartum hospitalization. The fifth factor, preeclampsia, was associated with an increased VTE rate of 15 to 30 per 10,000 in the postpartum period. Severe preeclampsia does not change this rate during peripartum hospitalization. This observation probably indicates that more severe preeclampsia is not associated with additional risk. The sixth factor, Caesarean section, could not be placed into this hierarchy unambiguously, because is associated with a wide range of VTE risk, from 6 to 60 per 10,000. The high variation in risk after Caesarean section probably reflects the differences in thromboprophylaxis in different countries, suggesting that the importance of Caesarean section as risk factor of VTE may depend on the geographic region studied.

We can also consider the risk factors by looking at the periods of pregnancy they affect. The VTE risk in women with a history of VTE exists throughout the whole pregnancy-related period if thromboprophylaxis was not administered; and according to reviewed data the absolute risk is slightly lower during antepartum (400–600 VTE per 10,000 pregnancies), compared with the postpartum (500–800 VTE per 10,000 pregnancies) period. Thrombophilia, in contrast to the history of VTE, increases pregnancy-related VTE rate differently before and after childbirth. During pregnancy, the absolute risk of VTE in women with thrombophilia is 40 to 120 per 10,000. In the postpartum period, the IR of VTE increases two to threefold further (compared with antepartum period) and reaches 170 to 300 cases per 10,000 women with thrombophilia. Likewise, the risk for VTE in women with

preeclampsia is distributed unevenly. The studies discussed in this review provide evidence that preeclampsia, in and of itself, does not affect the VTE risk during the antepartum period, whereas in the postpartum period, preeclampsia is associated with an increased VTE rate. Caesarean section, for obvious reasons, is associated with the increased rates of VTE events only in the postdelivery period.

If we discuss the risk factors from the perspective of their attributable risk for VTE, we would find that a major fraction of VTE cases in the postpartum period is associated with thrombophilia (about 40–50%). Although the risks of VTE for preeclampsia and the Caesarean section are considerably lower, these factors may contribute, respectively, to up to 60 and 18% (Table 11), because of the high incidence rate of Caesarean section and preeclampsia in a population of pregnant women. History of VTE, due to the low incidence rate in pregnant women and the prophylactic treatment with anticoagulants, contributes only 5 to 15% to the total number of VTE cases. Eclampsia is a minor contributor as it associated only with 1% of overall VTEs, probably due to the low incidence of eclampsia in developed countries.

In the published guidelines for preventing VTE in pregnancy (Royal College of Obstetricians and Gynaecologists, 2009; Queensland Clinical Guidelines, 2014; Bates et al., 2012), preeclampsia is considered a low risk factor for both antepartum and postpartum periods. However, three studies discussed in this review provided evidence that preeclampsia itself does not affect the VTE risk during the antepartum period. This conclusion may need to be addressed in the next revisions of the guidelines. However, it must be taken into account that preeclampsia is not diagnosed until the second trimester, with the most common diagnosis occurring towards the end of pregnancy. This might confound the true VTE risk when data is analyzed over the whole antepartum period.

We analyzed published studies of varied design, population, and criteria with some common limitations that are relevant for the interpretation of the results and the application of these findings to the design of future clinical trials. The study of the epidemiology of VTE in pregnant women, or any clinical trial using VTE as an endpoint, faces a number of challenges. The low incidence rate of VTE in a general subpopulation imposes a requirement for a large cohort of patients to be followed for a period of time. On the other hand, VTE rates are relatively high in extremely rare subgroups (e.g., women with eclampsia), limiting the number of patients who could be recruited during the finite time of a typical prospective study. These factors often justify the use of inferior designs, e.g., a retrospective approach. Differences in nationalities, lifestyle factors (including, for example, dietary practices and smoking), and other factors, such as body mass, and parity, and the availability of medical practices (i.e., VTE prevention and management), may account for the variability in results of different studies. Moreover well-defined VTE case definition and (ideally) objective medical confirmation of events is needed. Not every study follows this recommendation. An additional variability is brought by the uncertainty in diagnosis of risk factors that may exist for severe conditions. Since the severity and morbidity is a continuum, a sharp definitive division into mild and severe conditions may be a problem in the first stages of prospective study, i.e., during the recruitment phase. Furthermore, several definition requirements may be available for severe condition diagnostic coding in a database. On the other hand, it may be possible to extract those coded data and to re-assess the assignment of the severity grading in the initial diagnosis. All these successive data processing steps may lead to high variability in the VTE incidence rates in pregnant women with rare severe conditions.

The VTE risk for women with severe conditions is usually reported for the peripartum period, which may include the last month of antepartum and the first few months of the postpartum period. This complicates making a direct comparison of results obtained for the overall peripartum period to those estimated for the antepartum and postpartum periods separately. Besides that, the limited amount of data on severe conditions together with the differences in chosen end points (DVT only, PE only or both DVT and/or PE) complicates the comparison of results for rare subgroups. Additional research is needed for the subpopulations with severe preeclampsia and eclampsia. For such rare subpopulations, standardization of VTE cases for registration and reporting of data on both DVT and PE cases is recommended, which would be helpful for comparison of results in future.

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