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5

Thromboembolism in pregnancy: Challenges and controversies in the prevention of pregnancy-associated venous thromboembolism and management of anticoagulation in women with mechanical prosthetic heart valves

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Thromboembolism in pregnancy is an important clinical issue. Despite identification of maternal and pregnancy-specific risk factors for development of pregnancy-associated venous thromboembolism, limited data are available to inform on optimal approaches for prevention. The relatively low overall prevalence of pregnancy-associated venous thromboembolism has prompted debate about the validity of recommendations, which are mainly based on expert opinion, and have resulted in an increased use of pharmacological thromboprophylaxis in pregnancy and postpartum. A pragmatic approach is required in the absence of more robust data. Anticoagulation management of pregnant women with mechanical prosthetic heart valves is particularly challenging. Continuation of therapeutic anticoagulation during pregnancy is essential to prevent valve thrombosis. Warfarin, the most effective anticoagulant, is associated with adverse fetal outcomes, including embryopathy and stillbirth. Fetal outcome is improved with therapeutic-dose low-molecular-weight heparin, but there may be more thromboembolic complications. More intensive anticoagulation, targeting higher trough anti-Xa levels, may reduce the risk of valve thrombosis.

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Pregnancy-associated venous thromboembolism

Venous thromboembolism (VTE) is an infrequent but potentially preventable cause of maternal morbidity and mortality. Maternal mortality associated with pregnancy-associated venous thromboembolism (PA-VTE) is reported to be between 0.4 and 1.6 per 100,000 pregnancies in developed countries, and is one of the most common causes of maternal death [1–5]. Deciding who would benefit from thromboprophylaxis requires an understanding of when thromboembolic events are likely to occur and which women are at risk of developing this complication. The relative infrequency of PA-VTE means that most clinicians have limited experience, and clinical trial data are insufficient to inform on best practice. Published guidelines [6–8] and recommendations [9,10] are 'eminence based' rather than 'evidence based'.

Epidemiology and risk factors for pregnancy-associated venous thromboembolism

The reported rate of PA-VTE from 15 epidemiological studies [11–25] ranges from 0.61 to 2.22 per 1000 deliveries (Table 1), which represents around 5–10-fold increase compared with the rate in non-pregnant women of the same age [26]. Across the studies [13–17,19–21,23–25,27], an average of 23.5% of events are diagnosed as pulmonary embolism, of which up to one in 30 are fatal.

Timing and presentation of venous thromboembolism in pregnancy and the postpartum period

The timing of presentation with PA-VTE in the antenatal and postpartum period shows some variation [11–16,18,19,21–25,27–31], (Table 2). The risk per day is higher in the shorter postpartum period. Over 95% (369 out of 383) of women with postpartum VTE presented in the first 6 weeks, with the remainder in weeks 7–12 [22,32]. Pulmonary embolism is more frequent in the postpartum period compared with the antenatal period: 0.22 out of 1000 *v* 0.06 out of 1000 deliveries, respectively [22]. A 15-fold increase in the observed incidence of pulmonary embolism was reported in the first 3 months postpartum compared with pregnancy [23]. Up to 50% of women who develop VTE during pregnancy present in the third trimester (Table 2), but a significant number occur in the first and second trimesters. Most women present with deep vein thrombosis (DVT) in the left leg (Table 3) [14–16,24,25,27,30–33], particularly proximal and iliofemoral DVT, although distal DVT present with equal frequency in either leg [27,30].

Table 1
Epidemiological studies reporting rate of pregnancy-associated venous thromboembolism.

Country	Study period	PA-VTE N	Deliveries N	Rate of VTE per 1000 deliveries	Pulmonary embolism N (%)
Hong Kong [25]	1998–2000	32	16,993	1.88	2 (6.3)
USA [24]	1978–1996	165	268,525	0.61	38 (23.0)
USA [23]	1966–1995	100	50,080	2.0	24 (24.0)
Norway [22]	1990–2003	615	613,232	1.0	Data not reported
USA [21]	2000–2001	14335	8,330,927	1.72	3009 (21.0)
Scotland [20]	1980–2005	2006	1,475,301	1.36	290 (14.5)
Denmark [19]	1980–2001	129	71,729	1.8	17 (13.2)
Sweden [18]	1990–1993	607	479,422	1.27	Data not reported
Canada [17]	1991–2006	6821	3,852,569	1.77	2144 (31.4)
UK [16]	1997–2007	82	82,000	1.00	24 (29.3)
USA [15]	2003–2008	74	33,311	2.22	37 (50.0)
Australia [14]	1999–2006	8	6987	1.14	0 (0)
UK [13]	1988–1997	336	395,335	1.33	42 (12.5)
UK [39]	1995–2009	500	376153[a]	1.33[a]	Data not reported
Denmark [11]	1995–2005	727	460464[a]	1.58[a]	Data not reported

[a] Pregnancy-years not deliveries; PA-VTE, pregnancy-associated venous thromboembolism; VTE – venous thromboembolism.

Table 2
Timing of presentation in women with pregnancy-associated venous thromboembolism: antenatal and postpartum incidence and trimester at presentation.

Study	All PA-VTE N	Antenatal VTE N (%)	First trimester N (%)	Second trimester N (%)	Third trimester N (%)	Postpartum VTE (N)
Chan et al. [25]	32	8 (25.0)	3 (37.5)	3 (37.5)	2 (25.0)	24 (75.0)
Chan et al. [30]	60	31 (51.7)	14 (45.2)	7 (22.6)	10 (32.3)	29 (48.3)
Heit et al. [23]	100	36 (36.0)	4 (11.1)	14 (38.9)	18 (50.0)	64 (64.0)
Jacobsen et al. [22]	615	301 (48.9)	62 (20.6)	64 (21.3)	175 (58.1)	314 (51.1)
Lyall and Myers [16]	82	56 (68.3)	13 (23.2)	21 (37.5)	22 (39.5)	26 (31.7)
James et al. [33]	53	34[a] (64.2)	15 (44.1)	8 (23.5)	9 (26.5)	19 (35.8)
Blanco-Molina et al. [31]	136	72 (52.9)	29 (40.3)	13 (18.1)	30 (41.7)	64 (47.1)
Virkus et al. [11]	709	491 (69.3)	61 (12.4)	75 (15.3)	355 (72.3)	218 (30.7)
Sharma and Monga [14]	8	7 (87.5)	5 (71.4)	0 (0)	2 (28.6)	1 (12.5)
Voke et al.[b] [27]	126	126	31 (24.6)	37 (29.4)	58 (46.0)	–
Gherman et al. [24]	165	109 (66.1)	–	–	–	56 (33.9)
James et al. [21]	14335	7177 (50.1)	–	–	–	7158 (49.9)
Larsen et al. [19]	129	61 (47.3)	–	–	–	68 (52.7)
Lindqvist et al. [18]	608	308 (50.7)	–	–	–	300 (49.3)
Morris et al. [28][c]	375	145 (38.7)	–	–	–	230 (61.3)
O'Connor et al. [15]	74	36 (48.6)	–	–	–	38 (51.4)
Simpson et al. [13]	336	109 (32.4)	–	–	–	256 (76.2)
Sultan et al. [12]	500	215 (43.0)	–	–	–	285 (57.0)
Trimester at presentation			**237 (20.4)**	**242 (20.9)**	**683 (58.7)**	
Antenatal *v* postpartum		**9196[d] (50.1)**	**–**	**–**	**–**	**9150 (49.9)**

PA-VTE, pregnancy-associated venous thromboembolism; VTE, venous thromboembolism.
[a] Trimester at presentation unknown in two cases.
[b] antenatal VTE only.
[c] pulmonary embolism only.
[d] Voke et al: not included as antenatal VTE only.

Risk factors for pregnancy-associated venous thromboembolism

All components of 'Virchow's triad' are present in pregnancy. Venous stasis is induced by venous dilation and obstruction to venous return [34], pro-coagulant factors are increased, natural anticoagulants reduced, and vessel wall injury occurs during labour and after caesarean section. Pregnancy is also a pro-inflammatory state with activation of endothelial cells [35]. Inherent maternal factors further increase the risk of VTE in pregnancy. A number of epidemiological studies [12,13,17–22,25,28,36–39] have explored risk factors for thrombosis (Table 4). The reported contribution of risk factors for developing PA-VTE, particularly in more recent studies, will be influenced by whether women received thromboprophylaxis. Information relating to use of thromboprophylaxis is not generally available in population studies, but can be assumed to have been given to women with

Table 3
Deep vein thrombosis in pregnancy: leg involved at presentation.

Study	Deep vein thrombosis (N)	Left leg N (%)	Right leg N (%)	Bilateral N (%)
Chan et al. [25]	32	15 (47)	13 (41)	4 (13)
Chan et al. [30]	44	29 (66)	12 (27)	3 (7)
Gherman et al. [24]	127	104 (82)	22 (17)	1 (1)
Lyall and Myers [16]	54	36 (67)	18 (33)	Not reported
James et al. [33]	53	35 (66)	11 (21)	6 (11)
O'Connor et al. [15]	40	23 (58)	14 (35)	3 (8)
Blanco-Molina et al. [31]	111	76 (68)	35 (32)	Not reported
Pomp et al. [32]	74	55 (74)	19 (26)	Not reported
Voke et al. [27]	76	54 (71)	22 (29)	Not reported
Sharma and Monga [14]	8	2 (25)	6 (75)	Not reported
Overall	**618**	**429 (69)**	**172 (28)**	**17 (3)**

Table 4
Risk factors for pregnancy-associated venous thromboembolism summarised from epidemiological studies.

Risk factor	Adjusted odds ratio for PA-VTE
Maternal characteristic	
Previous VTE	4.2–24.8 [20,21,28]
Age > 35 years	1.0–2.7 [12,13,17,18,20,22,28,36,38,39]
BMI > 30	1.5–5.3 [12,13,17,19,21,37,39]
Smoking	1.0–3.4 [12,17,19,21,28,36,37,39]
Antiphospholipid syndrome	5.1–15.8 [17,21]
Cardiac disease	3.2–7.1 [12,13,17,21,39]
Sickle cell disease	1.3–6.7 [17,21]
SLE	2.3–8.7 [12,17,21,28,39]
Varicose veins	2.7–3.8 [12,39]
Inflammatory bowel disease	3.5–4.6 [12,39]
Diabetes	1.4–2.0 [17,21]
Hypertension	0.9–1.8 [12,17,21,39]
Cancer (any past diagnosis)	1.2–2.0 [12,39]
Pregnancy-specific factors	
Assisted reproductive technology	2.2–4.4 [36]
Multiple gestation	0.8–2.7 [12,13,17,18,21,22,39]
Parity ≥ 3	0.8–2.8 [12,18,20,22,28,39]
Gestational diabetes	1.7–4.1 [12,22,39]
Caesarean section	
All	1.8–11.2 [12,13,17,18,21,25,39]
Planned	1.4–3.1 [20,22,28]
Emergency	2.2–4.0 [20,22,28]
Hypertensive disorders of pregnancy	0.5–5.8 [12,17,18,20–22,25,28,39]
Preterm delivery < 37 weeks	1.8–4.5 [12,17,21,25,37,39]
Placenta previa	3.6 [22]
Placental abruption	2.5 [22]
Stillbirth	6.0–6.2 [12,28,39]

PA-VTE, pregnancy-associated venous thromboembolism; VTE, venous thromboembolism.

clinical factors perceived to place them at higher risk of thrombosis, introducing a source of bias, with the effect of minimising the effect of that risk factor in the cohort studied.

Intrinsic maternal risk factors

Maternal age

The rate of VTE was 38% higher in women over the age of 35 years (2.27 out of 1000 deliveries) compared with younger women (1.64 out of 1000 deliveries) [21]. Heit et al. [23] reported a three-fold (95% CI 1.4 to 6.5) increased risk of pulmonary embolism for every 10 years of maternal age.

Body mass index

The contribution of increased body mass index (BMI) has been recently reviewed [40]. Increased (BMI ≥ 25 kg m^{-2}), combined with immobility, was associated with a major increase in the risk of antenatal and postpartum VTE, aOR 62.3 (95% CI 11.5 to 337.6) and aOR 40.1 (95% CI 8.0 to 201.5), respectively [36].

Racial factors

Background rates of VTE in a general population are lower in individuals of Asian descent [41], but published studies in pregnancy are limited. A study of ethnic Chinese women from Hong Kong [25] in a tertiary obstetric unit reported a rate of 18.8 out of 10,000 deliveries between 1998 and 2000, with only one DVT recorded between 1988 and 1992. The investigators postulate that a more westernised diet and affluent lifestyle might account for the increasing rate. Lower rates of PA-VTE were reported in Asian women (10.7 out of 10,000 deliveries) and Hispanic women (12.5 out of 10,000 deliveries) in a large US study [21] compared with white women (17.5 out of 10,000 deliveries), with higher rates in black women (26.4 out of 10,000 deliveries).

Prior history of venous thromboembolism

Previous VTE seems to be one of the more important risk factors for developing PA-VTE. The risk of recurrent PA-VTE is similar (2–10%) in women who have had a previous unprovoked VTE, and those who have had a previous hormonally provoked VTE (i.e. associated with pregnancy or oral contraception) [42–44]. Women who have had a previous VTE associated with a major (surgical or traumatic) provoking factor are at low risk of recurrence in pregnancy, with three separate studies reporting no recurrent events among this group of patients [43–45].

Hereditary thrombophilia

As in non-pregnant populations, laboratory markers of thrombophilia are found in 40–50% of cases compared with 6–15% of controls [46–48]. Racial differences in thrombophilias exist, with factor V Leiden (FVL) and the prothrombin gene mutation (PTM) found almost exclusively in white people, with deficiencies of antithrombin, protein C and S being relatively rare [49]; deficiencies of these natural anticoagulants are more common in individuals of Asian descent [50]. Studies have shown that the rate of VTE in relatives who share the thrombophilia is three to five-fold higher than in relatives without the thrombophilia [51,52]. Pregnancy is a critical risk period for development of VTE in affected relatives, and administration of thromboprophylaxis at periods of risk seems to reduce the risk of VTE [51,52]. Of note, family cohort studies also show increased rates of VTE even in unaffected relatives compared with the background population [52–54]. Screening asymptomatic women for thrombophilias is not recommended [55].

Family history with no thrombophilia

Venous thromboembolism is increasingly being recognised as a multigenic disease, and a positive family history alone (one or more affected first-degree relative) has been shown to increase the risk of VTE two-fold [56], with the strength of the association increased when younger relatives are affected (OR 2.7, 95% CI 2.2 to 3.4) and if more than one relative is affected (OR 3.9, 95% CI 2.7 to 5.7).

Pregnancy-specific factors

Mode of delivery

Caesarean section, especially emergency caesarean section, increases the risk of postpartum VTE (Table 4). It seems likely that increasing awareness of the risk of thrombosis after caesarean section has led to an increasing use of thromboprophylaxis, thus modifying the development of thrombosis. In the study by Jacobsen et al. [36], it was usual practice in all but one hospital to give pharmacological thromboprophylaxis to all women after caesarean section. Separate thromboprophylaxis guidelines published in 1995 in Scotland [57] and by the UK Royal College of Obstetricians and Gynaecologists [58] highlighted pregnancy as a risk factor for VTE, and recommended pharmacological thromboprophylaxis for women at risk (i.e. after emergency caesarean section) [20]. In the years after publication, the Scottish population study reported a 66% reduction in the rate of VTE after emergency caesarean section (12.3 out of 10,000 deliveries between 1980 and 1985, and 3.9 out of 10,000 deliveries between 2001 and 2005), whereas no change in the incidence of VTE after vaginal delivery or elective caesarean section was reported [20].

Assisted reproductive technology. Nearly 50% of thrombotic events occurring in women after assisted reproductive technology were in women who developed first-trimester ovarian hyperstimulation syndrome [36].

Obstetric haemorrhage. Women who required surgery after postpartum haemorrhage were three times more likely to develop thrombosis than those who did not require surgery [36].

Infection. The use of pharmacological thromboprophylaxis in most women delivering by caesarean section [36] may explain the observed greater risk of VTE with infection after vaginal delivery (aOR 20.2, 95% CI 6.4 to 63.5) compared with after caesarean section (aOR 6.2, 95% CI 2.4 to 16.2).

Pre-eclampsia and intrauterine growth restriction. Pre-eclampsia has been found to be a risk factor for VTE in some [18,20,22,25] but not all studies [17,21,39], and is particularly associated with postpartum events [18,36]. One study reported that postpartum VTE were more frequent in women who had both pre-eclampsia and intrauterine growth restriction than either complication alone [36].

Thromboprophylaxis

The overall low prevalence of PA-VTE means that universal prescription of thromboprophylaxis is unwarranted. A recurring theme in maternal mortality and morbidity reports is the apparent lack of appreciation of risk factors for thrombosis in women who develop PA-VTE [59]. Attempts to identify women at risk for PA-VTE who would merit antenatal, postpartum thromboprophylaxis, or both, is challenged by the lack of clinical data supporting benefit. A recent Cochrane review [60] confirmed what clinicians working in the field have long recognised, that there is 'insufficient evidence available from randomised-controlled trials to guide clinical decision-making' and 'practitioners must rely on consensus derived clinical practice guidelines'. An assessment of a woman's risk factors is key, but what determines the threshold for recommendation for thromboprophylaxis is unclear. Decisions should be made after a discussion of the available evidence with the woman, taking into consideration her perception of the balance of risk and benefit with thromboprophylaxis, an approach endorsed by the most recent American College of Chest Physicians guidelines [7].

Risk-factor assessment

Most guidelines [6–9] recognise that the threshold for recommending thromboprophylaxis in the postpartum period should be lower given a higher daily risk of thrombosis in the postpartum period. All pregnant women should have an assessment of risk of VTE at the earliest opportunity and, if the threshold for antenatal thromboprophylaxis is reached, it should be commenced as soon as pregnancy is recognised. Re-assessment should be carried out if any change occurs to a woman's health during pregnancy, such as admission to hospital and also after delivery.

Contribution of multiple risk factors

Some thromboprophylaxis guidelines [7,8] focus mainly on personal and family history of VTE and the presence of thrombophilias, whereas others [6,9] emphasise the importance of additional risk factors for thrombosis (Table 4). In the absence of data from clinical trials, decisions about how to implement risk assessment strategies is based only on expert opinion. A summary of recommendations from different guidelines is presented in Table 5. The overall low incidence of PA-VTE means that many women will need to be given thromboprophylaxis to prevent an event, and considerable resources are required to provide thromboprophylaxis as per current guidelines. Clinical studies are urgently required to inform clinical practice.

Inconsistencies in recommendations for thromboprophylaxis in women with inherited thrombophilia

Recommendations for women homozygous for factor V Leiden and the prothrombin gene mutation

Recommendations for thromboprophylaxis in women with inherited thrombophilias are inconsistent. The most recent American College of Chest Physicians guidelines (ACCP) [7] have modified the recommendations for thromboprophylaxis in women with inherited thrombophilias who have a family history of VTE but no personal history. Antenatal thromboprophylaxis is advised only for women who are homozygous for either FVL or prothrombin gene mutation (PTM) and not antithrombin deficiency as in the previous guidelines [61]. The recommendation for women who are homozygous for FVL seems reasonable as pregnancy-associated VTE was reported in 53 out of 501 (10.6%) pregnancies across six studies of women homozygous for FVL who did not receive thromboprophylaxis [53,62–66]. The recommendation for thromboprophylaxis in women homozygous for the prothrombin mutation is less robust, and is based on a single case-control study of inherited thrombophilias in women with PA-VTE, which reported that two out of 42 women were homozygous for PTM compared with none of the

Table 5
Comparison of recommendations for thromboprophylaxis in pregnancy and the postpartum for women not taking long-term anticoagulation.

	ACCP [6]		ACOG [7]		RCOG [5]		ASTH and SOMANZ [8]	
	Antenatal	Postpartum	Antenatal	Postpartum	Antenatal	Postpartum	Antenatal	Postpartum
Personal history VTE								
Idiopathic	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓
Pregnancy or related to combined oral contraceptives	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓
Temporary risk factor	✗	✓✓✓	✗	✓✓✓	✗	✓✓✓	✗	✓✓✓
Multiple VTE	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓
Family history VTE plus thrombophilia*								
Antithrombin deficiency	✗	✓✓✓	✓✓✓	✓✓✓	✓	✓✓	✓✓✓	✓✓✓
Protein C or S deficiency	✗	✓✓✓	✗ or ✓	✗ or ✓	✓	✓✓	✓	✓✓✓
Homozygous FVL or PTM	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓	✓✓	✓	✓✓✓
Heterozygous FVL or PTM	✗	✓✓✓	✗ or ✓	✗ or ✓	✓	✓✓	✗	✓
FVL/PTM comp heterozygous	✗	✓✓✓	✓✓✓	✓✓✓	✓	✓✓	✓	✓✓✓
No thrombophilia	NC	NC	NC	NC	NC	NC	✗	✓
Thrombophilia without personal or family history VTE*								
Antithrombin deficiency	✗	✗	✓✓✓	✓✓✓	✓	✓✓	✓	✓✓✓
Protein C or S deficiency	✗	✗	✗ or ✓	✗ or ✓	✓	✓✓	✓	✓✓✓
Homozygous FVL or PTM	✗	✓✓✓	✓✓✓	✓✓✓	✓	✓✓	✓	✓✓✓
Heterozygous FVL or PTM	✗	✗	✗ or ✓	✗ or ✓	✓	✓✓	✗	✗
FVL/PTM compound heterozygous	✗	✗	✓✓✓	✓✓✓	✓	✓✓	✓	✓✓✓
Family history VTE no thrombophilia	NC	NC	NC	NC	✗	✗	✗	✓

Key
✗ Thromboprophylaxis not recommended.
✓ Consider thromboprophylaxis.
✓✓ Short duration postpartum thromboprophylaxis (at least 7 days).
✓✓✓ Extended thromboprophylaxis recommended for all women (antenatal – throughout pregnancy; postpartum – 6 weeks).
NC – no specific recommendation made.
* ACOG recommendations made on basis of presence or absence of thrombophilia and personal history of VTE but not family history VTE.
ACCP, American College of Chest Physicians; ACOG, American College of Obstetricians Gynecologists; ASTH, Australasian Society Thrombosis and Haemostasis; FVL, factor V Leiden mutation; PTM, prothrombin mutation; RCOG, Royal College Obstetricians Gynaecologists UK; SOMANZ, Society Obstetric Medicine Australia and New Zealand.

213 control women [67]. These data lead to calculation an odds ratio for PA-VTE in women homozygous for PTM of 26.36 (95% CI 1.24 to 559.29) [68].

Risk of pregnancy-associated venous thromboembolism in women with deficiencies of antithrombin, protein C and protein S

The ACCP recommendation [7] against routine antenatal thromboprophylaxis for women with deficiencies of antithrombin, protein C, and protein S, appears to be based on data from a single familial VTE cohort study [69] of female relatives of individuals with VTE and either antithrombin, protein C, or protein S deficiency, who had undergone at least one pregnancy but had no personal history of VTE before pregnancy. Women were interviewed to determine if they had suffered VTE either antenatally or within 3 months postpartum. Pregnancy-associated venous thromboembolism was reported in one out of 33 (3.0%) pregnancies to 13 women with antithrombin deficiency; one out of 60 pregnancies (1.7%) to 19 women with protein C deficiency; and five out of 76 pregnancies (6.6%) to 28 women with protein S deficiency. In contrast, a single postpartum VTE, which developed after a pelvic fracture sustained during delivery, was reported in the 198 (0.5%) pregnancies to 69 women who did not have the inherited thrombophilia. Data from a second familial cohort study of similar design, however, which reported first episodes of VTE in women with deficiencies of the natural anticoagulants, was not considered [54]. In this study, PA-VTE was reported in eight out of 45 pregnancies (18%) to 18 women

with antithrombin deficiency, three out of 63 pregnancies (5%) to 19 women with protein C deficiency, and one out of 54 pregnancies (2%) to 17 women with protein S deficiency compared with one VTE in 245 (0.4%) pregnancies to 79 women who did not have the thrombophilia, suggesting that women with deficiencies of natural anticoagulants have a 70- to 140-fold increased risk of PA-VTE compared with background rates. These rates are not as high as those reported in previous cohort studies [70–72] of women with deficiencies of the natural anticoagulants that included women with a history of VTE before pregnancy and women with superficial venous thromboembolism, and reported rates of PA-VTE in 37–47% of women with antithrombin deficiency, 12–19% with protein C deficiency, and 13–27% with protein S deficiency. Concern has been expressed at the advice against giving routine antenatal thromboprophylaxis for women with these thrombophilias who have a family history of VTE but no personal history of thrombosis [73].

It seems prudent to consider the presence of a thrombophilia in the context of other risk factors for VTE, so that if, for example, heterozygosity for FVL is the only additional risk factor for thromboembolism in a woman who has a first-degree relative with a VTE, clinical observation during the antenatal period is a reasonable approach, whereas thromboprophylaxis may be justified if the woman is also a smoker and has a BMI of 40.

Options for thromboprophylaxis

The options for prophylaxis include mechanical methods (e.g. mobilisation, compression stockings, calf stimulation, or intermittent pneumatic compression) or pharmacologic agents (low molecular weight heparin [LMWH] and unfractionated heparin [UFH]). Mechanical methods are suitable for women who are at low-risk or for those in whom pharmacologic prophylaxis is contraindicated (e.g. acute haemorrhage or impending surgery). Low molecular weight heparin is used in preference to UFH for pharmacologic prophylaxis, and measurement of anti-Xa levels is not required. In the absence of compelling evidence, it seems premature to recommend an increased dose of LMWH for thromboprophylaxis in pregnancy for all women weighing more than 90 kg [6], but a reasonable threshold for considering higher doses is not clear.

Side-effects of low molecular weight heparin

Low molecular weight heparins are generally well tolerated and, at prophylactic doses, there does not seem to be a substantial increase in bleeding. A large review reported significant bleeding in around 56 out of 2777 (2%) pregnancies [74], including wound haematoma in 0.6% and bleeding at delivery owing to obstetric causes in 0.92%. A review of tinzaparin use in pregnancy [75] reported a higher rate of bleeding at 15.5%, with 3.4% of bleeds requiring intervention. Generalised or local allergic skin reactions have been described in 1–2% of women. Prophylactic dose LMWH is not associated with reductions in bone mineral density and osteoporosis [76], and heparin-induced thrombocytopaenia has not been described in this setting [74].

Anaesthesia and anticoagulation in pregnancy

The major concern with regional analgesia and anaesthesia in women taking anticoagulation medication is of spinal haematoma; however, the incidence in obstetric patients is extremely low, estimated to be around six cases per million [77]. Most cases occurred in women with coagulation disturbances such as HELLP (haemolysis elevated liver and low platelets), and most develop at the time of insertion or removal of a neuraxial catheter. Guidelines [78] are regularly reviewed, and timings for insertion and removal of neuraxial catheter and anticoagulant dosing are outlined in Table 6. Where this is not possible, alternatives during labour include intravenous patient-controlled analgesia, or general anaesthesia if caesarean delivery is required. After delivery, it is recommended that neuraxial catheters be removed before commencing therapeutic anticoagulation. Women should be educated about the potential signs of a neuraxial haematoma and be monitored closely for the development of such signs.

Table 6
Timing of administration of low molecular weight heparin, unfractionated heparin, and placement of catheters for regional anaesthesia, based on recommendations from the American Society of Regional Anesthesia and Pain Medicine [78]. Timings should be modified if multiple attempts to insert neuraxial block, traumatic insertion or bloody tap.

Heparin type	Dose	Timing of last dose	Timing of next dose	Timing of dose	Timing of dose
		Before placement of neuraxial block	After placement of neuraxial block	Before epidural catheter removal	After epidural catheter removal
Unfractionated heparin	Prophylactic	≥6 h	≥2 h	≥6 h	≥2 h
	Therapeutic	2–4 h; confirm normal APTT	≥1 h	2–4 h confirm normal APTT	2–4 h; confirm normal APTT
Low molecular weight heparin	Prophylactic	≥12 hours	≥2 h	≥12 h	≥2 h
	Therapeutic	≥24 hours	Avoid therapeutic doses while catheter *in situ*		≥24 h

APTT, Activated partial thromboplastin.

Management of anticoagulation in pregnant women with mechanical heart valves

Pregnancy presents a particular challenge for the management of anticoagulation in women with mechanical prosthetic heart valves (MPHV). Outside of pregnancy, people with MPHV have at least a 4% annual risk of developing valve thrombosis, which may be complicated by systemic thromboembolism or valve failure, if they discontinue anticoagulation. Factors that increase the risk of thromboembolic complications include older valve design (e.g. ball-cage valves) and position (mitral > aortic valve) atrial fibrillation, heart failure, and non-compliance with anticoagulation. Although the newer models of mechanical heart valves are likely to be less thrombogenic, the potential for thrombosis remains, and oral anticoagulation is considered to be standard care for all patients with MPHV.

Oral vitamin K antagonists: maternal and fetal issues

Outside of pregnancy, the oral vitamin K antagonists, such as warfarin (coumadin), phenprocoumon, and acenocoumarol, are the anticoagulant drugs of choice. The new oral anticoagulants are not recommended, with dabigatran having an increased risk of thromboembolic and bleeding complications compared with warfarin [79]. Vitamin K antagonists, however, cross the placenta and affect the fetus. Warfarin embryopathy, characterised by nasal hypoplasia, stippled epiphyses, or both, are reported in 5–12% of infants exposed between 6–9 weeks gestation. Warfarin fetopathy with central nervous system abnormalities or ocular abnormalities, fetal loss, and stillbirth, occurs in infants exposed at later gestations [80–83]. In addition, valve thrombosis occurs in as many as 1 out of 25 women prescribed vitamin K antagonists during pregnancy [84].

Is there a safe warfarin dose?

A perception of 'good fetal outcomes' with warfarin at low doses less than 5 mg has led to recommendations to continue oral anticoagulants either throughout pregnancy or in the second and third trimester [85,86]. A careful review of the data suggests that, although a dose-relationship exist for warfarin fetopathy, there is no clear evidence that warfarin embryopathy is dose-related.

Warfarin embryopathy

In studies [81–83,87] reporting outcomes in women who took warfarin during the first trimester, five cases of warfarin embryopathy were reported in women taking 5 mg or less of warfarin and seven cases in women taking over 5 mg.

Warfarin fetopathy

Warfarin fetopathy with central nervous system disorders and late fetal loss are likely to be secondary to bleeding in the fetus. Warfarin crosses the placenta and doses that provide a therapeutic level of maternal anticoagulation can be expected to induce significant over-anticoagulation in the

fetus, deficient in vitamin K and clotting factors [88], leading to an increased risk of fetal bleeding. Studies report increased rates of miscarriage (fetal loss less than 20 weeks gestation) and stillbirth (fetal loss greater than 20 weeks gestation) in women taking warfarin at doses over 5 mg, 63.6% ($n = 21$ out of 33) and 15% ($n = 5$ out of 33) compared with women 5.2% ($n = 2$ out of 38) and 0% ($n = 0$ out of 38) in women taking 5 mg warfarin or less, respectively [89]. Higher rates of miscarriage and stillbirth with increasing doses of warfarin were also reported in a separate study, occurring in 3.6% ($n = 1$) and 29% ($n = 8$) in 28 pregnancies to women taking 5 mg or less of warfarin; 24% ($n = 5$) and 14% ($n = 3$) in 21 women taking between 5.1 and 7.4 mg warfarin; 7.7% ($n = 1$) and 38.5% ($n = 5$) in 13 women on doses 7.5 mg or over [81].

Dose requirements in patients on warfarin

A fundamental clinical issue when considering the potential effect of dose on the risk of fetal complications is that women with MPHV cannot be arbitrarily assigned a low dose of warfarin. The dose must be adjusted to reach a target international normalised ratio (INR), and considerable inter-individual variability exists in the dose required to be within target, with the dose modified by age, diet, body weight, and also genetic differences in vitamin K epoxide reductase subunit 1, the drug target [90]. Many patients will require doses greater than 5 mg to be in the therapeutic range. One centre [91] has reported good maternal and fetal outcomes in women identified as requiring lower doses of warfarin to maintain a target INR before valve replacement and then continuing the drug throughout pregnancy. The group used a target INR of only 1.5–2.5, however, for women with a St Jude valve in the aortic position, which is lower than the level of 2.0–3.0 generally recommended for this valve type [92,93]. This approach also would not avoid the risk of embryopathy with first-trimester exposure.

Low molecular weight heparin: an alternative to warfarin?

Women's reluctance to take drugs that may be harmful to their unborn child has led many clinicians to seek alternative anticoagulant regimens during pregnancy for women with MPHV. Heparins do not cross the placenta and will not anticoagulate the fetus or cause embryopathy. The properties of LMWH make it a more appealing alternative than UFH for use in pregnancy, although it may be less effective than warfarin at preventing thromboembolic complications.

Clinical experience with low molecular weight heparin

Initial single case reports and small cases series have raised concerns about high rates of maternal thromboembolic events; however, intermediate doses of LMWH were often used and no anti-Xa monitoring was carried out. In an early review [94] of outcomes in 37 women who received LMWH in pregnancy, only one thromboembolic complication (2.7%) occurred in women who received therapeutic LMWH with anti-Xa directed dose-adjustment, whereas most events ($n = 9$) occurred where either lower LMWH doses were given or anti-Xa levels were not done.

Recent cohort studies with low molecular weight heparin in women with mechanical prosthetic heart valves

Maternal and fetal complications in women from five cohort studies [82,95–98] treated with twice-daily, dose-adjusted therapeutic level LMWH throughout pregnancy are presented in Table 7. In six of the nine reported episodes of thrombosis described in women prescribed LMWH, compliance issues with twice-daily injections, and testing of anti-Xa levels, or both, was considered to have been a contributory factor. Two other thromboembolic events developed in women had been prescribed suboptimal doses of LMWH [95]. The single thromboembolic event that was clearly a failure of LMWH [98] occurred in a woman with a Medtronic Hall aortic valve replacement who presented with a transient ischaemic attack at 24 weeks' gestation with anti-Xa levels of 0.99 IU/ml, having been compliant with treatment since 5 weeks gestation (anti-Xa levels ranged between 0.99–1.4 U/ml.) No valve thrombus was seen on echocardiography and, despite an increase in the LMWH, she had a fatal cardiac arrest caused by valve thrombosis 2 weeks later. No other maternal deaths were reported.

Fetal outcomes are reported in four out of the five studies. Two late fetal losses were described as being caused by placental insufficiency [98], one unexplained intrauterine fetal death occurred at 37

Table 7
Details of maternal and fetal outcomes in women anticoagulated with dose-adjusted therapeutic level low molecular weight heparin throughout pregnancy.

Study	Pregnancies (women) N	Maternal TEC N (%)	Valve thrombosis N	CVA/TIA N	Late fetal loss >20 weeks N(%)[a]	Live births N (%)[a]
Abildgaard [95]	12 (11)	2 (16.7)	1	0/1	0 (0)	12/12 (100)
Chitsike[b] [96]	15 (15)	0 (0)	0	0	–	–
McLintock[c] [82]	34 (23)	5 (14.7)	1	2/2	1 (3)	22/23 (95)
Quinn [97]	8 (7)	1 (12.5)	1	0	1 (13)	7/8 (88)
Yinon [98]	23 (17)	1 (4.3)	1	0	2 (10)	19/21 (91)
Total	92	9 (9.8)	4	5	4 (6)	60/64 (94)

CVA, cerebrovascular accident. TEC, thromboembolic complications; TIA, transient ischaemic attacks.
[a] Excluding spontaneous miscarriages and terminations of pregnancy.
[b] Fetal outcomes not reported in paper.
[c] Includes only women from cohort taking low molecular weight heparin throughout pregnancy;

weeks' gestation [97], and one spontaneous preterm delivery untreated to anticoagulant treatment was reported [82]. No fetal anomalies were reported.

The pros and cons for options for anticoagulation for women with MPHV are presented in Fig. 1. Both warfarin and LMWH are safe in breast-feeding [99,100].

The importance of trough anti-Xa levels

Dose adjustment of LMWH directed by measurement of peak anti-Xa levels has been recommended by most investigators [7], and has been carried out in centres reporting large case series. Some investigators [101,102] have suggested that measurement of trough anti-Xa levels is more important, as this will ensure that women maintain a baseline anticoagulant effect. Target trough anti-Xa levels of 0.6-0.7 IU/mL with peak anti-Xa levels of around 1.0–1.2 IU/mL or less than 1.5 IU/mL are recommended by these groups. A multicentre prospective cohort study would be a useful way to assess the efficacy of such an approach if a randomised-controlled trial was not logistically possible.

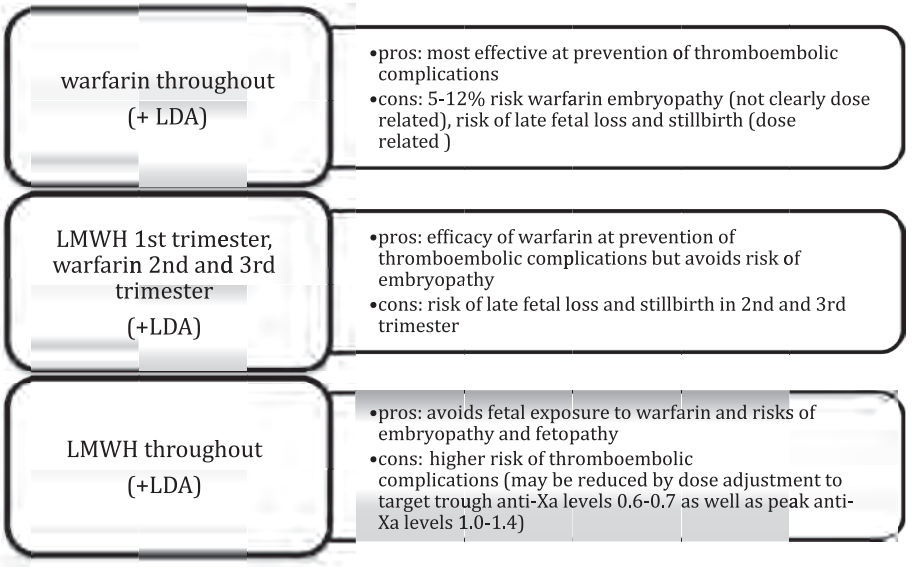

Fig. 1. Options for anticoagulant regimens during pregnancy in women with mechanical prosthetic heart valves. Warfarin (or other vitamin K antagonist) must be discontinued before 6 weeks gestation to avoid the risk of embryopathy and restarted after 12 weeks gestation. (LDA – low dose aspirin 100–150 mg, LMWH – low molecular weight heparin).

Low-dose aspirin: additional benefit?

Low dose aspirin (100–150 mg) has been recommended in addition to warfarin for patients with additional risk factors for thromboembolism, as it reduces the risk of major thromboembolism without causing an increase in the risk of major bleeding [103]. It seems reasonable to consider pregnancy as a risk factor, and it is given routinely in some centres [82,95,98].

Management of anticoagulation in the peri-delivery period

The need to minimise time off anticoagulation in these women at high risk of thromboembolism requires early reinstitution of anticoagulation postpartum, and this may contribute to the high risk of primary and secondary postpartum haemorrhage. Of particular concern are the high rates of secondary haemorrhage, including wound haemorrhage after caesarean section, but also vulval and perineal haemorrhage in women who have had normal vaginal delivery. Continuation of intravenous UFH instead of LMWH postpartum while waiting for oral contraceptives to become therapeutic allows more flexible control of anticoagulation if bleeding occurs, but does require women to remain inpatients for longer. Whichever method of anticoagulation is chosen, there is clearly a high risk of major haemorrhage if women are fully anticoagulated at the time of delivery. Planned delivery is essential, either induction of labour or elective caesarean section, as dictated by obstetric indications.

Women taking warfarin or other vitamin K antagonists

Warfarin will also anticoagulate the fetus, which is effectively vitamin K deficient and has low levels of clotting factors, hence the dose of warfarin that produces therapeutic anticoagulation of the mother will over-anticoagulate her unborn infant. Delivery while over-anticoagulated poses a severe haemorrhagic risk to the infant and, after stopping warfarin, the fetal INR will take much longer to normalise than the maternal INR. Warfarin should be discontinued 2–3 weeks before planned delivery (around 34 weeks gestation or before if earlier delivery is anticipated), and women should switch to either intravenous UFH or LMWH.

Women taking unfractionated heparin and low molecular weight heparin

Heparin does not anticoagulant the fetus, and only the mother is at risk of haemorrhage if she delivers on therapeutic dose anticoagulation. Suggested peripartum anticoagulation regimens for induction of labour or caesarean section are outlined in Fig. 2. Both warfarin and LMWH are safe in breast-feeding [99,100].

Rapid reversal of anticoagulation

Onset of labour is unpredictable, and women may go into preterm labour or require urgent delivery because of the development of other maternal or fetal complications. In women taking LMWH, the activated partial thromboplastin time will not provide an accurate indication of the degree of anticoagulation and risk of bleeding. Most laboratories do not provide urgent testing of anti-Xa levels. Protamine administration may partially reverse the anticoagulant effect of therapeutic dose LMWH [104], and should be given to women who have taken a dose within 24 h. Fresh frozen plasma has no role in reversal of UFH or LMWH.

Emergency reversal of anticoagulation

A plan for urgent reversal of anticoagulation using local guidelines should be in place. Management of women on LMWH is outlined above. For women taking oral contraceptives, coagulation factor complexes such as prothrombinex are increasingly been used, although fresh frozen plasma is also an option [105]. Reversal using oral or intravenous vitamin K takes at least 12 h. None of these manoeuvers will reverse the anticoagulant effect of oral contraceptives on the fetus, and an INR from the infant should be taken after delivery, before reversal using adult protocols adjusted for fetal weight. The nature of the emergency is likely to dictate the mode of delivery but, as infants born to mothers taking oral contraceptives will be over-anticoagulated, delivery should be as atraumatic as possible, and fetal scalp electrodes, forceps and ventouse are contraindicated.

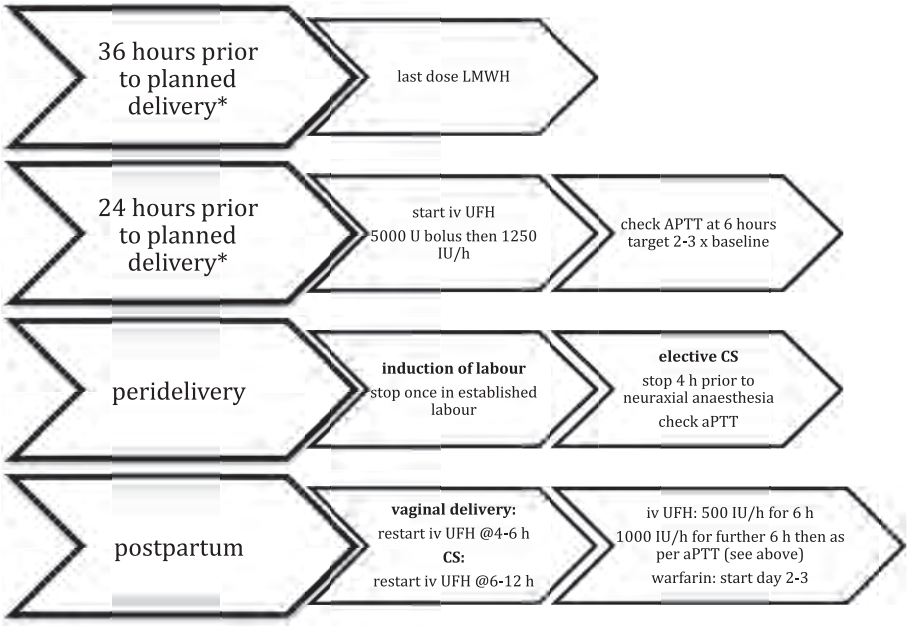

Fig. 2. Suggested approach to peri-delivery management in women who require therapeutic dose anticoagulation. Women requiring therapeutic doses of anticoagulation require a planned delivery* either by induction of labour (IOL) or caesarean section (CS) as per obstetric indications. In the postpartum period, anticoagulation should only be restarted if there are no concerns re bleeding. (LMWH – low molecular weight heparin, UFH – unfractionated heparin). Once INR therapeutic postpartum, iv UFH can be stopped.

Choosing the safest acceptable option

Pregnancy in women with MPHV is high risk, and the safest option is not to become pregnant at all; however, experience tells us that women will become pregnant. It is not uncommon for a woman to place the health and wellbeing of her unborn child above her own, and this may be at odds with the clinician's prime concern. Justifiable apprehension about fetal effects of warfarin will continue to drive women and clinicians to look for alternative anticoagulants. The role of the clinician is to discuss the pros and cons of the available options but, ultimately, the decision of which drug to take rests with the woman and her family; remembering that the most dangerous choice is to take no anticoagulation.

Summary

Thromboembolism is a relatively uncommon problem in pregnancy, which is likely to be one explanation for the paucity of data to guide clinical management. Risk factors for developing PA-VTE have been identified, but most women with these risk factors will not develop venous thrombosis, and VTE will also develop in some women with no risk factors. 'Eminence-based' recommendations for thromboprophylaxis against PA-VTE are all that are available at present. Efforts to develop clinical trials that would more clearly delineate at-risk populations and determine the efficacy and safety of thromboprophylaxis are urgently needed. The management of women with MPHV is particularly challenging as there is no anticoagulant regimen that is safe for both mother and infant. The adverse fetal outcomes with warfarin are unacceptable to many women, and justifiable attention is being given to efforts to explore regimens with therapeutic dose LMWH that provide improved safety against thromboembolic complications.

Conflict of interest

Dr McLintock has received support to attend conferences from Sanofi.

Practice points

Thromboprophylaxis

- No clinical data are available to inform the best approach to thromboprophylaxis in pregnancy or the postpartum, and all published recommendations are based on expert opinion.
- Women with previous idiopathic or hormonally related VTE are advised to take antenatal and postpartum extended thromboprophylaxis, whereas women with previous VTE related to other risk factors that are no longer present are generally recommended postpartum prophylaxis alone.
- Other maternal and pregnancy-related risk factors should also be taken into consideration when reviewing the risk of pregnancy-associated VTE.
- The decision for thromboprophylaxis must be taken in consultation with the woman taking into account her personal preference.

Labour in women on prophylactic doses of low molecular weight heparin

- Women taking prophylactic doses of LMWH can be allowed to go into spontaneous labour and should be counselled that they will require a 12-h gap between the last dose of LMWH and placement of a neuraxial catheter for analgesia or anaesthesia.
- Close to term, women can be advised that if they feel they might be going into labour, they should take no further doses of LMWH until they have been reviewed clinically.

Pre-pregnancy counselling

- Pre-pregnancy counselling for women with MPHV provides the opportunity to discuss the various options for anticoagulation during pregnancy and the risks associated with each option.

Research agenda

Prevention of venous thromboembolism in pregnancy

- Clinical studies to determine threshold for thromboprophylaxis in pregnant and postpartum women with risk factors for VTE.

Anticoagulation of pregnant women with mechanical prosthetic heart valves

- Clinical study to assess the safety and efficacy of therapeutic dose LMWH using peak and trough anti-Xa levels to determine LMWH dose as an alternative to warfarin in pregnant women with mechanical prosthetic heart valves.

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