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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

Claire McLintock, MBChB, FRACP, FRCPA, Clinical Director, Obstetric Medicine *

National Women's Health, Auckland City Hospital, Auckland, New Zealand

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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.

* National Women's Health, Level 9 Clinical Support Building, Auckland City Hospital, Park Road, Grafton, Private Bag 92024, Auckland 1142, New Zealand. Tel.: +64 9 3670000; Fax: +64 9 3754344.
E-mail addresses: claire.mclintock@adhb.govt.nz, doctorclaire@redhealth.org.

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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.