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Review article

# Postpartum venous thromboembolism prophylaxis may cause more harm than benefit: a critical analysis of international guidelines through an evidence-based lens

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Based on prediction models and expert opinion, most obstetric venous thromboembolism guidelines recommend low-molecular-weight heparin for many postpartum women, including most delivering by caesarean. Scrutiny reveals major oversights: prediction models are based on studies that report asymptomatic deep vein thrombosis; risk estimates are not adjusted for time exposure; and harm caused by heparin has been overlooked. The benefits of heparin are exaggerated and its harms are under-appreciated. Estimates of the numbers-needed-to-treat and harm are universally lacking. This paper critically reviews the evidence and quantifies the benefit and harm from low-molecular-weight heparin in postpartum women with common risk factors.

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**Tweetable abstract** Randomised trials should demonstrate more benefit than harm before widespread postpartum low-molecular-weight heparin is recommended.

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## Introduction

Whether low molecular weight heparin (LMWH) benefits postpartum women with risk factors such as caesarean delivery (CD) is unknown. Prospective evidence is lacking and Cochrane reviewers have called for large randomised controlled trials (RCTs).[1] However, based on case–control studies and expert opinion, most national obstetric guidelines recommend LMWH prophylaxis in large numbers of postpartum women and most women after CD.[2]

Prothrombotic haemostatic changes make pregnant and postpartum women logical targets for venous thromboembolism (VTE) prophylaxis. A fatal pulmonary embolus (PE) in a healthy young woman is a tragedy, and deep vein thrombosis (DVT) can lead to post-thrombotic syndrome.[3] Although evidence is limited, a small subset of pregnant and postpartum women is at very high risk of VTE. Women with a personal history of VTE, potent thrombophilia, or prolonged immobilisation usually receive and very probably benefit from antenatal and postpartum LMWH prophylaxis.[4,5] This perception of benefit has spread to women with more common risk factors, in whom the risk of VTE is lower.

Since 1986, the American College of Chest Physicians (ACCP) has published VTE guidelines.[6] Early editions were based on studies that identified asymptomatic DVT on screening ultrasound.[6,7] In 2012, recognising that asymptomatic DVT are not clinically relevant, the ACCP published their ninth edition,[8,9] specifically acknowledging that:

- Prior editions of the guidelines failed to recognise the implications of asymptomatic, screening-detected thrombosis, the use of which markedly over-estimates the clinical benefit of prophylaxis;

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• Clinical rather than asymptomatic VTE should be used for estimates of VTE incidence and calculations of prophylaxis benefit;
• Financial and intellectual conflicts of interest of leading experts and previous authors were 'highly problematic'; and their involvement was restricted.

The evidence was thoroughly re-evaluated and many recommendations were scaled back. The use of scoring systems to estimate the post-surgical incidence of VTE was qualified and a minimum risk of 3% is now deemed necessary to warrant chemoprophylaxis in abdominal/pelvic surgical patients.[10–12] After orthopaedic surgery, less aggressive prophylaxis is now considered acceptable.[13–15] In medical patients, LMWH is still recommended according to the Padua Prediction Score; however, large RCTs show elevated risk of haemorrhage and minimal reduction in clinical VTE, calling into question the score's validity and the overall net benefit of liberal LMWH prophylaxis.[16–18]

Obstetric VTE guidelines from the ACCP, Australia, Canada, New Zealand, Sweden and the Royal College of Obstetricians and Gynaecologists (RCOG) are based on case–control studies reporting relative risks of VTE in women with various risk factors and screening studies that report asymptomatic DVT.[19–23] Risk-scoring systems based on these data have not been validated. The RCOG recommends LMWH after all CD in labour and for women birthing vaginally with any two risk factors, including such common attributes as body mass index (BMI) > 30 kg/m$^2$, age >35 years, parity >3, smoking or preterm delivery. Other guidelines recommend LMWH after CD in labour in the presence of one additional risk factor. However, estimates of absolute risk reduction (ARR), number-needed-to-treat (NNT) and number-needed-to-harm (NNH) – key components of evidence-based medicine, are lacking.

## Overestimating the incidence of VTE

Most observational data on VTE come from case–control studies of large databases. Odds ratios are calculated for various risk factors while the database as a whole is used as a denominator to calculate incidence.[24–28] Case–control studies are often used to investigate rare phenomena; however, they are designed to evaluate relative not absolute risks and they do not reliably determine the underlying frequency of events.[29] VTE are typically identified using unverified diagnostic codes, allowing women with suspected VTE and those receiving LMWH for prophylaxis rather than treatment to be inappropriately included. A Norwegian study that validated every episode of postpartum VTE found that half of coded diagnoses were inaccurate.[27] Also, similarity of codes for superficial, septic and deep venous thrombophlebitis and amniotic fluid and venous pulmonary embolism inflate the incidence of VTE.[30–32]

The incidence of clinical DVT in nonpregnant patients is estimated to be approximately one-tenth the incidence of asymptomatic DVT.[33] Left untreated, a large majority of asymptomatic DVT resolve without clinical sequelae. It is now accepted that screening studies that identify asymptomatic DVT overestimate the incidence of clinical VTE and the benefit of LMWH.[8,9,33] Although asymptomatic DVT has been reported in 10–40% of medical and surgical patients, symptomatic VTE occurs in fewer than 5%.[7,12,17,18] Yet screening studies of women after CD have found asymptomatic DVT in fewer than 1% (3/560).[34–38] These studies are still referenced in the ninth edition ACCP obstetric VTE guideline via a decision analysis by Blondon et al.[39] Although screening studies were removed from other sections of the ACCP guideline, the obstetric portion was overlooked. Therefore, estimates of the incidence of clinically relevant DVT after CD are markedly inflated: 0.5% and 4% for low-risk and high-risk women, respectively. These values are not plausible to experienced obstetricians, who rarely encounter women with clinical VTE.[19,40] It is not known whether postpartum women have an incidence of symptomatic DVT approximately one-tenth that of asymptomatic DVT.

## Adjusting VTE incidence for time

Postpartum VTE incidence is commonly reported as events per 100 000 births or person-years. As most women are only treated for the first 3–10 days after birth, these estimates exaggerate the benefit of LMWH. To improve clinical relevance, recent studies report the incidence per antenatal or postpartum week.[27,41–44] These studies provide the best estimates of absolute VTE risk for the period during which LMWH prophylaxis is typically given. They show that VTE risk is spread unevenly over the postpartum period. The highest risk is during the first 4 weeks, and almost one-quarter of postpartum VTE episodes occur during the first week: 680 out of 2870 per 100 000 person-years or a proportion of 0.24 (Figure 1)

## Preventive effectiveness of LMWH

The preventive effect of 1 week of postpartum LMWH is unknown. Although LMWH might be expected to inhibit small clots destined to become symptomatic, there is no evidence that LMWH prevents clinical VTE when it is no longer given. Initial benefit may be offset by transient hypercoagulability following heparin treatment.[4,45] In two small RCTs comprising the Cochrane review, 2/109 women receiving LMWH developed VTE compared with 0/108 women receiving placebo.[46,47] Both VTE episodes occurred


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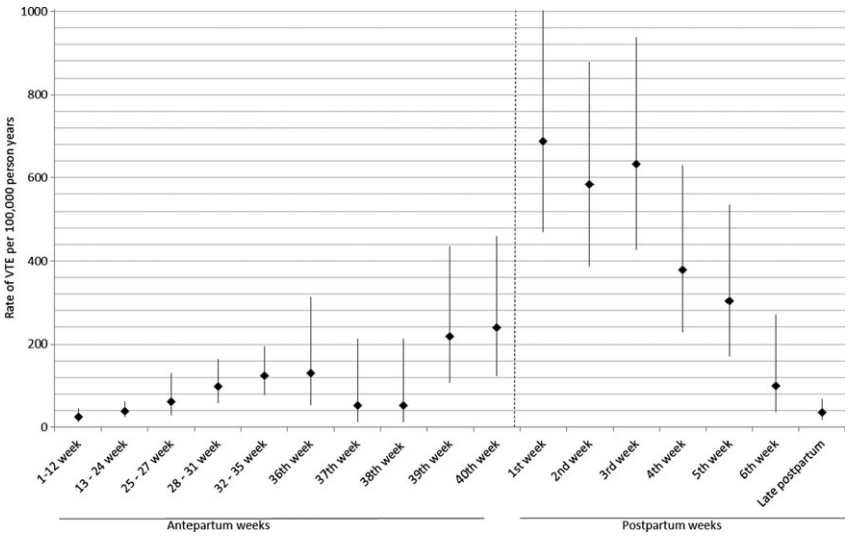


**Figure 1.** Rate of VTE per 100 000 person-years by antepartum and postpartum week. (From Sultan et al. *Br J Haematol* 2011, with permission.) Risk during the first postpartum week = 680/100,000. Total 12 postpartum weeks = 2870/100,000. Proportion of total postpartum risk during the first week = 680/2870 = 0.24.

2 weeks postpartum, after LMWH administration had ceased. In non-obstetric patients, LMWH prevents 60–70% of post-surgical VTE episodes.[48] Post-surgical patients tend to be older with age-related co-morbidities including neoplastic conditions. Pregnant and postpartum women are generally younger and mobilise quickly after birth. Without data specific to pregnant and postpartum women, it is reasonable to estimate that LMWH given for 1 week postpartum might reduce VTE during that week by 70%.

## Evidence-based medicine analysis

ARR, NNT and NNH are critical tools for evaluating the clinical utility of LMWH prophylaxis; however, they are missing from obstetric VTE guidelines. Without large RCTs, they cannot be measured and must be inferred from estimates of the incidence of VTE, the protective effect of LMWH, and the harm caused by LMWH.

Arguably the best estimates of the incidence of postpartum VTE come from two studies of a large primary-care database from the UK.[41,42] Sultan et al. reported VTE incidence and incidence risk ratios for clinical factors by postpartum week. After CD, they found a postpartum VTE incidence of 637 episodes per 100 000 person-years. This equates to 147 VTE during the 12-week postpartum period. As seen in Figure 1, almost one-quarter of all postpartum VTE episodes occur during the first week, so the incidence of VTE in the first postpartum week is $0.24 \times 147 = 35$ events per 100 000 women.

If LMWH given for the first week reduces this incidence by 70%, then $35 \times 0.7 = 25$ VTE would be avoided per 100 000 women. Correspondingly, 4000 women would need to be treated to prevent one VTE. This is the NNT. If one assumes double the incidence for a high-risk woman compared with an average woman after CD, the NNT would be 2000. Table 1 shows the VTE incidence, risk ratio and NNT for other risk factors.

A postpartum VTE prediction tool later developed by Sultan et al. corroborates these estimates. Based on a large English database and validated using a large Swedish database, they calculate a VTE risk of 1.1/1000 during six postpartum weeks for a 20-year-old woman with a BMI of 32 kg/m$^2$ undergoing CD in labour – a woman who would qualify for LMWH based on the current RCOG guideline.[49] Her risk during the first week would be approximately 0.3/1000 or 30/100 000. Assuming 70% protection with LMWH, 4300 similar women would need to be treated to prevent one VTE.

## Harm from LMWH

Few studies evaluate harm caused by LMWH in postpartum patients. Case series of postpartum women who received LMWH are of limited help because they often lack a comparison group who did not receive LMWH. An exception is a Swedish study that compared women with a personal history of previous VTE who received antepartum and postpartum LMWH prophylaxis with control women who did not.[4] A significant absolute risk increase (ARI) in haemorrhage >1000 ml was found (ARI = 4.4%; $P < 0.001$), which would likely be lower for women only receiving LMWH postpartum. Other observational studies estimate the risk of significant haemorrhage to be 0.3–1.1%.[5,50,51]

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**Table 1.** Postpartum VTE incidence and NNT for clinical risk factors

| Risk factor | VTE per 100 000 person-years | Incidence risk ratio | Risk during postpartum period (per 1000) | Risk during first postpartum week (per 1000) | NNT for 1 week of LMWH |
|---|---|---|---|---|---|
| None* | 300 | 1.0 | 0.69 | 0.17 | 8400 |
| Stillbirth | 2444 | 6.24 | 5.62 | 1.35 | 1060 |
| Preterm birth | 854 | 2.69 | 1.96 | 0.47 | 3000 |
| Obstetric haemorrhage | 963 | 2.89 | 2.21 | 0.53 | 2700 |
| Caesarean section | 637 | 1.99 | 1.48 | 0.35 | 4000 |
| BMI > 30 kg/m$^2$ | 926 | 3.75 | 2.13 | 0.51 | 2800 |
| Para 3+ | 904 | 2.07 | 2.08 | 0.50 | 2900 |
| Gestational diabetes | 1013 | 1.97 | 2.33 | 0.56 | 2600 |

Data from Sultan et al.[42] (Blood 2015).
*No risk factors = nulliparous; age 25–34 years; spontaneous delivery; normal BMI.

Meta-analyses of randomised trials of LMWH prophylaxis versus placebo in surgical patients demonstrate absolute risk increases for haemorrhage between 1.5% and 8.6%, depending on the severity of haemorrhage reported.[48,52] In a large meta-analysis of general surgical patients referenced in the ACCP guideline, LMWH caused more major haemorrhages (ARI = 1.5%; NNH = 67); wound haematomas (ARI = 4.9%; NNH = 20); and blood transfusions (ARI = 3.8%; NNH = 26) than placebo.[48] LMWH lowered the incidence of clinical VTE from 0.9% to 0.22% (ARR = 0.68%; NNT = 150). For each VTE avoided, there were two additional major haemorrhages, seven wound hematomas, and six transfusions. Awareness that the NNT exceeded the NNH underpins the ACCP recommendation that the incidence of post-surgical VTE should be at least 3% to justify LMWH prophylaxis.

For LMWH to be clinically useful, the NNT to prevent one episode of VTE should be lower than the NNH for major haemorrhage. The incidence of VTE and absolute benefit from LMWH is lower after CD than after major abdominal surgery (NNT of 4000 versus 150); therefore, the acceptable degree of haemorrhage is also lower. If conservatively, LMWH increases the absolute risk of major haemorrhage after CD by 0.5%, the corresponding NNH would be 200, which is 20-fold lower than the NNT. For every VTE prevented, 20 average women would experience a major haemorrhage.

LMWH also appears to increase the incidence of wound complications. In the Swedish study above, LMWH was associated with an absolute increase in haematomas of 2.1% ($P < 0.001$).[4] A non-randomised comparison of 1600 high-risk women who did or did not receive LMWH after CD showed an increase in overall wound complications with LMWH (ARI = 3.8%; NNH = 26; $P = 0.002$) and associated re-hospitalisation (ARI = 1.3%; NNH = 77; $P = 0.017$).[53] A small ARR in VTE (0.17%) was not significant in this cohort, and the authors estimated that an RCT would need 31 000 subjects to have enough statistical power to determine if this small a benefit is real. If real, the NNT in this high-risk population would have been 600, i.e. 10-fold greater than the NNH for wound complications.

Heparin-induced thrombocytopenia occurs primarily during prolonged unfractionated heparin use. Large studies of obstetric and non-obstetric patients receiving prophylactic LMWH have demonstrated minimal risk.[4,17,50,52]

## Death from pulmonary embolism

Approximately one-third of obstetric VTE episodes are pulmonary emboli, of which 2% are fatal. Of all VTE episodes, fewer than 1% are fatal.[27,31,54,55] For an average woman after CD, the risk of death from PE in the first week postpartum is approximately 0.4/100 000. Assuming 70% protection with LMWH, the NNT to prevent one PE death is approximately 360 000. If LMWH increases the risk of major haemorrhage by 1/200, then for every PE death avoided with LMWH, more than 1000 women experience major haemorrhage. Although an apparent drop in PE deaths in the UK from 2003 to 2008 has been attributed to increased VTE prophylaxis, newer data show no sustained decrease.[21,56,57] The incidence of fatal PE during 3-year time periods ending in 2002, 2005, 2008 and 2011 were 1.5, 1.94, 0.79 and 1.26 per 100 000 births.[58] Although not a randomised trial, implementation of universal mechanical prophylaxis with pneumatic compression devices after CD in a large US hospital system was associated with a reduction in fatal PE (7 of 458 097 CD versus 1 of 465 880 CD). If the association was causal, the NNT was approximately 80 000.[59] Data on nonfatal PE and DVT were not reported.


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## Prospective data on VTE risk after caesarean

Few prospective studies report the incidence of clinical VTE after CD. Although not designed to evaluate VTE, the vaginal birth after caesarean section study by Landon et al. collected prospective data from 20,560 women after CD. The incidence of VTE after elective CD was 0.63/1000; after emergency CD was 0.84/1000; and after successful vaginal birth after caesarean section was 0.23/1000.[60] It is unclear what proportion occurred during the first postpartum week. Many women had typical risk factors and heparin was not commonly given. The term breech trial also collected data on 1389 women after CD, of which 847 were in labour. There were no VTE.[61]

In the largest screening study to detect asymptomatic postpartum DVT, ultrasound was performed in 194 women 3 days after CD and again 2 weeks after CD.[34] Women had a mean BMI of 32 kg/m$^2$ and 80% were eligible for LMWH by the 2009 UK guidelines. None wore compression stockings or received heparin. The only DVT detected was symptomatic in a woman with sepsis requiring intensive care and a right femoral venous catheter.

Similar to the studies by Sultan et al., these findings refute the estimates found in the ninth ACCP VTE guideline.[40–42] During the first week after typical CD, the incidence of VTE is <1/1000 – a magnitude of risk 30 times lower than the 3% minimum felt to counterbalance the harm of LMWH prophylaxis in general surgical patients.[12]

## Lessons of evidence-based medicine

Why is the postpartum incidence of even asymptomatic DVT lower than expected? Pregnancy is a hypercoagulable state, but also one of enhanced thrombolysis.[36,62] A physiological balance exists between clot formation and dissolution and it is difficult to identify which women will develop VTE. Fewer than half of postpartum VTE occur within the first 2 weeks and 50% of these women have one or no risk factors.[27,42,44]

With the eighth edition of the ACCP VTE guideline, enthusiasm for LMWH reached a peak. Chemoprophylaxis was recommended for most hospitalised patients.[7] The ACCP identified intellectual and financial conflicts of interest for the eighth edition authors, and their involvement in the ninth edition was restricted.[9,63] Scientific rigour has improved. Asymptomatic VTE are acknowledged to be clinically unimportant; and screening studies have been removed from most of the ninth edition. However, the obstetric portion is still based on screening studies that inflate the incidence of VTE and the purported benefit of LMWH. The ACCP and most national obstetric organisations recommend liberal LMWH postpartum prophylaxis in women with common risk factors. The American Congress of Obstetricians and Gynecologists has not adopted this stance despite a recent push to follow suit.[64–66]

Enthusiasm for new cures is an essential stimulus for innovation in medical practice and has driven VTE guidelines. However, many new therapies adopted before adequate evaluation have later been found to lack benefit or to harm patients. Almost 40 years ago, Archie Cochrane challenged the medical profession to be more critical of new treatments and advised that they be carefully evaluated before widespread adoption.[67] Our response to that challenge was evidence-based medicine. According to its tenets, it remains unknown whether a women with common risk factors benefits from postpartum LMWH prophylaxis; however, observational evidence suggests that harm may outweigh benefit.

Investigators have called for RCTs to evaluate postpartum LMWH prophylaxis.[1,2,44,68] Although RCTs have drawbacks when applied to complex phenomena, they are ideally suited to evaluate drug therapy.[29,69] Since the magnitudes of potential benefit and harm are very small, the numbers required to achieve adequate power are daunting; however, large trials of medical and surgical patients have been conducted successfully. Using inclusion criteria from the current RCOG guideline, more than 80% of women undergoing CD would qualify.[2] With CD rates exceeding 30% in some jurisdictions, this equates to more than a thousand women annually in many large maternity hospitals. Along with careful randomisation, blinding, placebo control, and 12 weeks of follow up, it will be critical to accept equipoise about whether the benefit of LMWH outweighs harm. For most postpartum women, this will make it ethically justifiable, if not advisable, to only offer LMWH in the context of an RCT. In the current climate of liberal LMWH prophylaxis, this should overcome previous barriers to recruitment.[70]

Dr Cochrane's challenge has a practical and an ethical basis. The drug cost for 7 days of enoxaparin is approximately £22 in the UK and $100 in the USA, yielding a drug cost to prevent one VTE between £80,000 and $400,000, not including the costs of administration and treating complications. Ethically, the probability of net harm from LMWH for most postpartum women makes it difficult to justify offering it outside a research trial. Dr Cochrane asserted that net benefit of new therapies be proven in adequately powered RCTs before dissemination and Cochrane reviewers have concluded: 'There is insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the early postnatal period... Large scale, high-quality randomised trials of currently used interventions are warranted.'[1] Instead, guidelines recommend a costly, unproven, potentially harmful therapy in large numbers of birthing women. Without a power calculation, ethics approval, systematic measurement of benefit

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and harm, or truly informed patient consent, the specialty has embarked on an enormous uncontrolled experiment.

Rarely, a new therapy provides such obvious benefit that dissemination before thorough evaluation is justified. For the few women with previous VTE, potent thrombophilia, or prolonged immobilisation, observational evidence strongly suggests LMWH prophylaxis is warranted during pregnancy and for 6 weeks postpartum. However, for women with more common risk factors, the net clinical benefit of LMWH is unclear. Misled by odds ratios, asymptomatic VTE, and incidences unadjusted for time, we have neglected basic requirements of evidence-based medicine. Estimation of the ARR, NNT, ARI and NNH reveals that for most women, LMWH may do more harm than good. Only adequately powered placebo-controlled randomised trials can accurately measure the true magnitudes of benefit and harm. Until and unless such trials show net benefit, women with common risk factors should be offered LMWH prophylaxis only as part of a randomised trial. Obstetric VTE guidelines from the ACCP, Australia, New Zealand, Canada, Sweden and the UK should be re-examined.

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