Low-dose aspirin versus placebo in postpartum venous thromboembolism: a multi-national, pilot, randomised, placebo-controlled trial

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Summary

Background Despite the morbidity and mortality of venous thromboembolism, there is little evidence to guide postpartum thromboprophylaxis in patients at moderate risk. We aimed to assess the feasibility of conducting a double-blind, randomised trial of aspirin versus placebo in postpartum individuals with two or more venous thromboembolism risk factors, mild-to-moderate thrombophilia, or both.

Methods The pilot PARTUM trial, a multi-national, randomised, double-blind, placebo-controlled trial, was conducted in seven centres across Canada, France, Ireland, and the Netherlands. Postpartum individuals aged 18 years or older with venous thromboembolism risk factors, including mild-moderate inherited thrombophilia, antepartum immobilisation, pre-pregnancy BMI of 30 kg/m^2 or higher, pre-pregnancy smoking, previous superficial vein thrombosis, and other pregnancy-related conditions, were eligible. Participants were randomly assigned (1:1) within 48 h of delivery to aspirin 81 mg (80 mg in Europe) orally daily (low-dose aspirin group) or placebo orally once daily (placebo group) for 42 days. Follow-up visits occurred at 6 weeks and 90 days postpartum. The primary outcome was the mean recruitment rate (participants per site per month). Additional feasibility metrics were reported, and clinical outcomes were analysed by intention to treat. This study is registered with ClinicalTrials.gov, NCT04153760, and EudraCT, 2020-000619-58, and is completed.

Findings Between Nov 2, 2020, and June 19, 2023, 10 040 patients were assessed for eligibility and 808 met all eligibility criteria, of whom 257 (32%) provided consent and were enrolled. 127 were randomly assigned to the low-dose aspirin group and 130 to the placebo group. The median follow-up was 91 days (IQR 89–96). The median age was 34·0 years (IQR 30·0–37·0), and 161 (63%) of participants were White. The mean recruitment rate was 6·3 (95% CI 5·5 to 7·2) patients per site per month. No venous thromboembolism events occurred in the low-dose aspirin group, and one participant had distal deep vein thrombosis in the placebo group (–0·82 [95% CI –2·42 to 0·78]). No major bleeds occurred. Three (2%) participants in the low-dose aspirin group versus one (1%) in the placebo group had clinically relevant non-major bleeds (absolute risk difference 1·66 [95% CI –1·54 to 4·86]). Ten serious adverse events occurred in nine (4%) of 257 participants, and 11 serious adverse events occurred in ten (4%) of 271 infants of participants. No treatment-related death occurred.

Interpretation A global postpartum thromboprophylaxis trial evaluating low-dose aspirin is possible and needed to provide high-quality data.

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Introduction

Pulmonary embolism is a leading cause of maternal death during pregnancy and up to 6 weeks postpartum in high-income countries.[1–3] Serious morbidity from venous thromboembolism (deep vein thrombosis and pulmonary embolism) includes post-thrombotic syndrome after deep vein thrombosis and reduced physical function after pulmonary embolism.[4,5] Compared with the antepartum period, the shorter 6-week postpartum period has a greater daily venous thromboembolism risk,[6,7] and compared with the non-pregnant state,[8] the 6-week postpartum period is associated with increased risk of venous thromboembolism.[6,7,9]

Patients with venous thromboembolism experience psychological sequelae and have impaired quality of life. Given that maternal mental health can be an important predictor of neonatal outcomes, including breastfeeding duration and infant development,[10–14] individuals at risk of postpartum venous thromboembolism deserve an evidence-based prevention strategy. However, high-quality data to guide postpartum thromboprophylaxis

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Research in context

Evidence before this study

We conducted a systematic literature search on MEDLINE (1946 to Oct 1, 2024), Embase (1947 to Oct 1, 2024), Cochrane Central Register of Controlled Trials (from database inception to Oct 1, 2024) using the OVID interface, for randomised trials and meta-analyses of randomised trials that evaluated pharmacological thromboprophylaxis (low-molecular-weight heparin or aspirin group) versus a control group (placebo or no treatment group) to prevent venous thromboembolism in the postpartum period. We used the search terms "postpartum period" or "puerperium" or "cesarean delivery" AND "venous thromboembolism" or "venous thrombosis" or "thrombophlebitis" or "pulmonary embolism" AND "prophylaxis" or "thromboprophylaxis" AND "anticoagulants" or "oral anticoagulants" or "aspirin". A 2021 Cochrane meta-analysis reported the evidence about the benefits and harms of venous thromboembolism thromboprophylaxis in the early postpartum period for individuals at increased risk of venous thromboembolism as very uncertain. In our review, we identified five published randomised trials and one abstract. The largest published trial included 141 postpartum participants and evaluated enoxaparin 40 mg versus a placebo group, with the duration of thromboprophylaxis determined by the treating physician (>90% of participants received <8 days of treatment). In the second week after delivery, one participant had a pulmonary embolism in the enoxaparin group and no venous thromboembolism was reported in the placebo group. No published trials have evaluated aspirin as an intervention.

Added value of this study

Our trial included 257 participants, which is the largest trial of a postpartum thromboprophylaxis intervention that included a control group. This is the first trial to evaluate aspirin thromboprophylaxis in the postpartum period to prevent venous thromboembolism for individuals at risk. Although there are not enough clinical data to change practice, we identified that it is feasible to conduct a larger-scale global pragmatic postpartum trial evaluating an aspirin-based thromboprophylaxis intervention.

Implications of all the available evidence

There is a general scarcity of data to guide postpartum thromboprophylaxis, but trials are possible and are urgently needed to improve the care of postpartum individuals at risk of venous thromboembolism. Aspirin is a low-cost and accessible intervention that requires additional study to prevent venous thromboembolism in the postpartum period.

use for patients with moderate risk (eg, combinations of other venous thromboembolism risk factors or mild-to-moderate inherited thrombophilia) are scarce, which has led to differing guideline recommendations and clinical practice variation.[15–18] Small randomised controlled trials (RCTs) have investigated postpartum low-molecular-weight heparin (LMWH) thromboprophylaxis versus a control group.[19–25] The PROSPER pilot trial evaluated the feasibility of dalteparin 5000 IU subcutaneously daily after delivery for 21 days versus placebo in patients with two or more venous thromboembolism risk factors or mild-to-moderate inherited thrombophilia in six centres in Canada and the USA.[21] This pilot trial had low recruitment (mean 0·7 participants per centre per month).[21] On the basis of patient survey feedback that 27% were uncomfortable with the need for LMWH injections, a second 6-month pilot trial run was conducted with an open-label design and only 10 days of LMWH.[21,22] Low recruitment persisted (mean 0·9 participants per centre per month), leading to the conclusion that a similarly designed larger thromboprophylaxis trial was not feasible.[22]

See Online for appendix

An oral medication would probably improve patient acceptance of a trial intervention, and low-dose aspirin has been found to be non-inferior to LMWH and rivaroxaban in prevention of venous thromboembolism in patients at high risk after hip and knee arthroplasty (after a short lead-in of anticoagulation)[26] and fractures.[27] The ongoing EPCATIII non-inferiority RCT (NCT04075240) compares aspirin 81 mg daily starting the day after hip or knee surgery versus rivaroxaban for 5 days, followed by daily aspirin. Unlike direct oral anticoagulants, low-dose aspirin is compatible with breastfeeding and has a favorable safety profile with respect to bleeding.[28,29]

Given the previous challenges of conducting postpartum thromboprophylaxis trials, assessing feasibility in a pilot trial design is needed before embarking on a large, definitive RCT evaluating postpartum thromboprophylaxis with low-dose aspirin. In this study, we aimed to assess the feasibility of conducting a multi-national, randomised, double-blind, placebo-controlled trial of low-dose aspirin in postpartum individuals with two or more venous thromboembolism risk factors, mild-to-moderate inherited thrombophilia, or both.

Methods

Study design and participants

The pilot PARTUM trial, a multi-national, randomised, double-blind, placebo-controlled trial, was conducted in Canada (one centre each in Calgary [AB], Ottawa [ON], Toronto [ON], and Vancouver [BC]), France (one centre in Saint-Étienne), Ireland (one centre in Dublin), and the Netherlands (one centre in Amsterdam; appendix p 8). Because the study aim was feasibility, each centre was open to participant recruitment for 6 months and had an additional 3 months for follow-up visits.

Postpartum individuals with venous thromboembolism risk factors were eligible for inclusion if they met at least one first-order criterion or at least two second-order criteria (appendix p 1). First-order criteria were

mild-to-moderate inherited thrombophilia, including heterozygous factor V Leiden mutation, heterozygous prothrombin gene mutation, protein C deficiency, protein S deficiency, or antepartum immobilisation (defined as 90% of waking hours spent in bed at any time during the antepartum period) for at least 7 days. Second-order criteria were a pre-pregnancy BMI of 30 kg/m² or higher, smoking five or more cigarettes per day pre-pregnancy, history of superficial vein thrombosis (outside pregnancy, previous pregnancy, or current pregnancy), pre-eclampsia, current pregnancy ending in stillbirth, unplanned caesarean delivery, small-for-gestational-age infant at time of delivery (below the third percentile adjusted for sex and gestational age), postpartum infection, or postpartum haemorrhage of more than 1000 mL, regardless of delivery mode (see appendix p 2 for definitions). Participants could be enrolled with more than the minimum inclusion criteria, including a combination of first-order and second-order criteria, at the discretion of the treating physician or local investigator.

Exclusion criteria were age younger than 18 years; longer than 48 h since delivery of the placenta; more than two doses of LMWH received since delivery; the need for postpartum LMWH prophylaxis or systemic anti-coagulation for reasons that could include but were not limited to previous venous thromboembolism, mechanical heart valve, antiphospholipid syndrome, or high-risk thrombophilia (antithrombin deficiency, homozygous factor V Leiden, homozygous prothrombin gene mutation, or more than one thrombophilia defect); the need for postpartum aspirin for reasons that could include but were not limited to previous myocardial infarction, ischaemic stroke, or transient ischaemic attack; contraindication to aspirin, including history of aspirin allergy, documented history of gastrointestinal ulcer, known platelet count of less than 50×10^9 cells per L at any time during the current pregnancy or postpartum, most recent known haemoglobin of 70 g/L or less documented during the current pregnancy or postpartum, known severe hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >120 mm Hg) during the current pregnancy or postpartum, and active bleeding at any site, excluding normal vaginal bleeding, at the time of randomisation; and unable or unwilling to provide informed consent (appendix pp 2–3). No laboratory tests were required for trial eligibility. Exclusion criteria were added by European sites after undergoing country-specific authority reviews (appendix p 1).

This trial is registered with ClinicalTrials.gov, NCT04153760, and EudraCT, 2020-000619-58, and was approved by the University of Calgary Conjoint Health Research Ethics Board (REB19-1237), and the research ethics boards or ethics committees of all participating sites. The protocol is in the appendix (pp 11–56). Written informed consent was obtained from all patients before randomisation.

Randomisation and masking

Eligible and consenting participants were randomly assigned (1:1) using permuted block randomisation with variable block sizes of two, four, six, and eight to the low-dose aspirin group or the placebo group. A randomisation list was generated by an independent biostatistician, stratified by site to control for potential differences in clinical practice or geographical influences. Randomisation was centralised, secure, and concealed using the University of Calgary Clinical Research Unit's web-based Study Manager software. After trial eligibility was confirmed by a local investigator, a trained research team member completed the randomisation procedure.

All participants and the research team, including investigators, clinical staff, the data management group, the data safety monitoring board (DSMB), and the sponsor, were masked to the randomisation codes and study group. Blinding was assessed in a subset of participants at the 6-week visit by asking participants and their research coordinators to guess the treatment assignment (aspirin, placebo, or unsure).

Procedures

Individuals who were at risk of venous thromboembolism were identified during pregnancy, labour, and delivery, and including up to 48 h postpartum. All sites identified and approached patients after delivery, but two sites also approached patients during pregnancy (see appendix p 8 for recruitment strategies). No laboratory monitoring or imaging was required in trial follow-up. After confirmation of eligibility and randomisation, the first dose of blinded study medication (aspirin 81 mg [or 80 mg in Europe], or placebo orally) was given between 6 h and 48 h after delivery of the placenta and continued daily for 42 days. Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) and pneumatic compression devices was allowed and recorded. After a baseline visit, data collection was completed in hospital, and follow-up occurred at 6 weeks (42 days [±6 days]) post-randomisation by an in-person visit, telephone, or video call, and 90 days (±10 days) post-randomisation by telephone call. Most postpartum venous thromboembolism events occur in the first 6 weeks, leading to the rationale for a treatment duration of 42 days. However, because the heightened venous thromboembolism risk extends to 12 weeks postpartum,[9] a 90-day follow-up was adopted to capture all events.

Participants were asked to record study medication adherence and NSAID use in a participant booklet, and study bottles were collected from participants after 6 weeks. Breastfeeding data were recorded at the 6-week visit. Having an active COVID-19 infection did not preclude enrolment (decision left to the treating physician or local investigator). COVID-19 infection status (positive, negative, or not done) within 14 days of delivery was recorded for all participants.

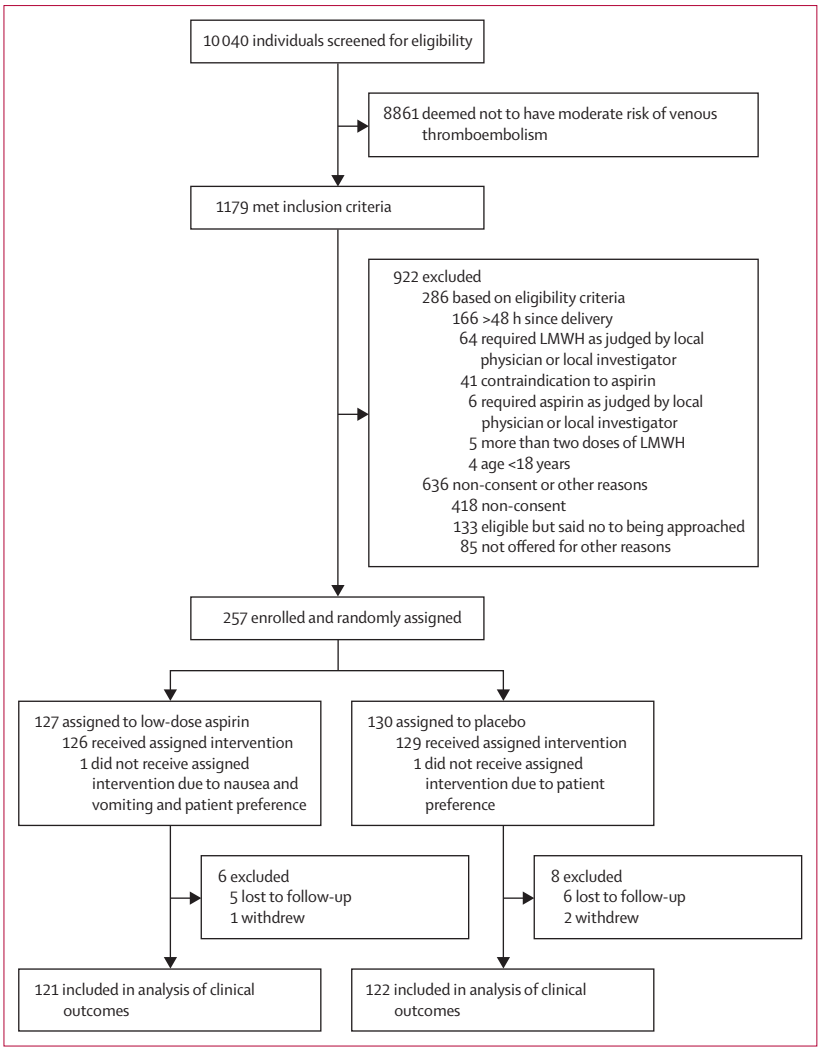

Figure: **Trial profile**
LMWH=low-molecular-weight heparin.

Adverse events were monitored throughout the trial duration and were screened for at the 6-week visit (participants and their infants) and 90-day visit (participants).

Suspected clinical outcomes were adjudicated through a central adjudication on the Canadian Venous Thromboembolism Research Network (CanVECTOR)-affiliated web-based platform, VERDICT. Adjudication members underwent trial-specific training and were masked to the treatment assignment.

Outcomes

The primary pilot trial outcome was mean participant recruitment rate per site per month (patients per site per month), excluding those recruited in the first 14 days after opening a trial site (termed a 14-day site lead-in period). The 14-day site lead-in period was determined a priori not to be included in the recruitment rate calculation because it can take 2 weeks to fully implement trial procedures after opening a site. Participants recruited in the first 14 days at a site were included in other feasibility and clinical data analyses.

Secondary pilot trial outcomes included consent rate for eligible and approached individuals, rate of study withdrawal or loss to follow-up, time required to obtain ethics approvals and legal contract agreements at each centre, adherence rate with the study medication (defined as the percentage of individuals with more than 80% of study medication taken), and estimates of clinical event rates.

In addition to feasibility data, clinical outcome data was collected in the pilot trial, including symptomatic venous thromboembolism (major venous thromboembolism, defined as proximal deep vein thrombosis or pulmonary embolism involving segmental or higher arteries) in the first 6 weeks postpartum, late symptomatic venous thromboembolism from 6 weeks to 90 days, superficial vein thrombosis, distal deep vein thrombosis, subsegmental pulmonary embolism, unusual site thrombosis, major bleeding and clinically relevant non-major bleeding (CRNMB) according to International Society on Thrombosis and Haemostasis definitions,[30] symptomatic arterial thromboembolism (ischaemic stroke, transient ischaemic attack, myocardial infarction, or peripheral arterial embolism), new postpartum pre-eclampsia, and all-cause mortality (see appendix pp 4–7 for definitions). Bleeding events were captured up to 90 days and further described as occurring within the first 6 weeks or between 6 weeks and 90 days. It was determined a priori that wound haematomas would undergo bleeding outcome adjudication if the wound haematoma required intervention (drainage or packing) or the haematoma was larger than 100 cm^2. Because all bleeding events were adjudicated, minor bleeding was also reported even though it was not an a priori outcome. Minor bleeding was defined as bleeding not meeting the criteria for major bleeding or CRNMB and excluded normal vaginal bleeding.

Wound infections were not a predefined outcome and were not independently adjudicated. However, given their importance in clinical practice, especially for those on anticoagulants or antiplatelets, wound infections were reported based on the 6-week visit question "Has the [participant] been diagnosed with a postpartum wound infection requiring antibiotics?", and were cross-referenced with adverse events to ensure all wound infections were captured.

Statistical analysis

A priori feasibility targets were set for each feasibility outcome and included mean recruitment rate of 4 patients per site per month, more than 30% of eligible participants who consent, less than 15% loss to follow-up or withdrawals, less than 25% of sites with longer than 18 months to research ethics board and legal contract

approvals, and more than 70% of participants who had a study medication adherence of more than 80%. The mean recruitment rate of 4 participants per site per month was determined on the basis of the lower limit of the 95% CI (3·8 participants per site per month) that would be required for 53 sites to complete the full trial in 5 years. At the time of planning the pilot PARTUM trial, the full sample size was estimated at 12 051 patients based on a baseline venous thromboembolism risk of 2%, 30% relative risk reduction, 80% power, an alpha value of 0·05, and lost to follow-up rate of 5%.

The primary analysis was an estimate of the mean monthly recruitment rate per site with the 95% CI of the mean, and the a priori recruitment target was four patients per site per month.

Secondary feasibility outcomes were descriptively reported, including categories of non-consent from eligible patients who declined participation. Study medication adherence was estimated using bottle pill counts. Mean medication adherence based on bottle pill count was reported descriptively overall and by study group. Study medication adherence was also captured based on returned participant booklets.

Descriptive statistics were used to report baseline characteristics by group. Continuous data were summarised using descriptive statistics including mean with SD and median with IQR. Categorical variables were summarised using frequency counts and percentages. Categories of race and ethnicity were adapted from the US National Institutes of Health, and included the option to identify as multiple categories or not answer.

Clinical outcomes per group were analysed in the intention-to-treat population, which was defined as all participants grouped by randomly assigned treatment, regardless of treatment received but excluding participants with no follow-up data. For the primary and secondary clinical outcomes, proportions were compared between trial groups by a Fisher's exact test, with risk differences and 95% CIs reported. Serious adverse events were reported per group according to Medical Dictionary for Regulatory Activities categories. All analyses were conducted using R (version 4.2.2). We did not impute missing data, and we only analysed observed data.

An independent DSMB completed quarterly reviews of enrolment and safety data. A predefined interim analysis was conducted after the first 100 participants (ie, 50 participants per group) were enrolled, which included a predefined safety review of participants with more than two venous thromboembolism risk factors.

Study data were captured and managed using REDCap Cloud software (nPhase, Encinitas, CA, USA).

Role of the funding source

The funders of this investigator-initiated trial had no role in the study design, data collection, data analysis, interpretation, or writing of the report.

	Low-dose aspirin group (n=127)	Placebo group (n=130)
General characteristics		
Age, years	34·0 (30·0–37·0)	34·5 (31·0–37·0)
Race or ethnicity		
White	75 (59%)	86 (66%)
Asian or southeast Asian	27 (21%)	23 (18%)
Black or African Heritage	11 (9%)	10 (8%)
Hispanic or Latino	7 (6%)	5 (4%)
Indigenous	2 (2%)	0
Pacific Islander	0	1 (1%)
Multiple ethnicities	5 (4%)	3 (2%)
Unknown	0	2 (2%)
Geographical region		
Canada	106 (83%)	108 (83%)
France	7 (6%)	8 (6%)
Ireland	12 (9%)	11 (8%)
Netherlands	2 (2%)	3 (2%)
Pre-pregnancy weight, kg	78·9 (59·3–93·0)	80·6 (64·5–97·5)
Pre-pregnancy BMI, kg/m²	29·4 (22·8–33·3)	30·8 (24·5–34·9)
Current weight, kg*	90·5 (71·4–105·0)	92·9 (77·3–110·0)
Primipara	87 (69%)	82 (63%)
Para (including current pregnancy)	1·0 (1·0–2·0)	1·0 (1·0–2·0)
Multiples (twins)	7 (6%)	7 (5%)
Eligibility venous thromboembolism risk factors		
Inherited thrombophilia	2 (2%)	2 (2%)
Heterozygous factor V Leiden mutation	2 (2%)	1 (1%)
Heterozygous prothrombin gene mutation	0	1 (1%)
Antepartum immobilisation† for ≥7 days	7 (6%)	2 (2%)
Pre-pregnancy BMI ≥30 kg/m²	60 (47%)	71 (55%)
Smoking at least five cigarettes per day pre-pregnancy	17 (13%)	17 (13%)
Previous clinical history of superficial vein thrombosis	0	0
Pre-eclampsia	25 (20%)	28 (22%)
Current pregnancy ending in stillbirth	0	0
Unplanned caesarean delivery	102 (80%)	104 (80%)
Infant was small for gestational age at time of delivery	14 (11%)	17 (13%)
Postpartum infection	8 (6%)	15 (12%)
Postpartum haemorrhage	41 (32%)	43 (33%)
Delivery details		
Gestational age at birth, weeks^{+days}	38^{+5} (36^{+1}–40^{+0})	38^{+5} (37^{+1}–40^{+0})
Type of labour		
Induction of labour	68 (54%)	73 (56%)
Spontaneous labour	42 (33%)	39 (30%)
No labour	17 (13%)	18 (14%)
Mode of delivery		
Caesarean delivery	107 (84%)	110 (85%)
Planned	5/107 (5%)	7/110 (6%)
Unplanned	102/107 (95%)	103/110 (94%)
Vaginal delivery	20 (16%)	20 (15%)
Unassisted	17/20 (85%)	17/20 (85%)
Assisted	3/20 (15%)	3/20 (15%)

(Table 1 continues on next page)

	Low-dose aspirin group (n=127)	Placebo group (n=130)
(Continued from previous page)		
Clinical characteristics		
Previous medical conditions		
Asthma	13 (10%)	9 (7%)
Hypertension (before pregnancy)	7 (6%)	3 (2%)
Type 2 diabetes (before pregnancy)	3 (2%)	2 (2%)
Type 1 diabetes (before pregnancy)	0	1 (1%)
Known cardiac disease	5 (4%)	4 (3%)
Known kidney disease	3 (2%)	0
Inflammatory bowel disease	2 (2%)	0
Systemic lupus erythematosus	1 (1%)	0
Sickle cell disease	0	0
Other inflammatory or autoimmune disorder†	17 (13%)	10 (8%)
Family history of venous thromboembolism		
First-degree relative	10 (8%)	13 (10%)
Second-degree relative	11 (9%)	8 (6%)
Aspirin and thromboprophylaxis data		
Aspirin use during pregnancy	56 (44%)	40 (31%)
Low-molecular-weight heparin use after delivery but before randomisation		
None	76 (60%)	72 (55%)
One dose	27 (21%)	38 (29%)
Two doses	24 (19%)	20 (15%)
Compression device use	40 (31%)	43 (33%)
Pneumatic compression devices	28/40 (70%)	30/43 (70%)
Graduated compression stockings	7/40 (18%)	7/43 (16%)
TED stockings	5/40 (13%)	6/43 (14%)
Duration of compression device use, h	20·44 (10·75)	21·19 (9·30)
Time from delivery to first mobilisation, h‡	9·6 (6·5–15·5)	9·8 (5·7–15·8)
Concomitant non-steroidal anti-inflammatory use	117 (92%)	118 (91%)

Data are median (IQR) or n (%). Gestational age at birth is shown as the number of weeks+days. TED=thromboembolic deterrent. *Data missing for five patients in the aspirin group and six in the placebo group. †Other inflammatory or autoimmune disorders included thyroid disorders (six in the low-dose aspirin group and four in the placebo group), polycystic ovarian syndrome (five in the low-dose aspirin group and two in the placebo group), Crohn's disease and ankylosing spondylitis (one in the low-dose aspirin group), rheumatoid arthritis (one in the low-dose aspirin group), hidradenitis suppurativa (one in the placebo group), autoimmune arthritis of hips (one in the placebo group), autoimmune disorder unspecified (one in the low-dose aspirin group), HIV (one in the placebo group), eczema (one in the placebo group), previous gastritis (one in the low-dose aspirin group), cerebral palsy (one in the low-dose aspirin group), and surgery for cervical intraepitheial neoplasia (CIN 2; one in the low-dose aspirin group). ‡Data were missing for one patient in the low-dose aspirin group and six patients in the placebo group.

Table 1: **Baseline characteristics**

Results

Between Nov 2, 2020, and June 19, 2023, among 10 040 patients assessed for eligibility, 808 met all eligibility criteria, of whom 257 (32%) provided consent and were enrolled (figure). The most frequent reasons for the subcategory of exclusion due to aspirin contraindication included haemoglobin values of 70 g/L or less (18 [44%] of 41 patients), a known platelet count of less than 50×10^9 cells per L (five [12%]), and history of known aspirin allergy (three [7%]). Four patients were excluded due to additional safety criteria for contraindication to aspirin (one with known severe liver disease and three with a known bleeding disorder).

Baseline characteristics are reported in table 1. Median age was 34·0 years (IQR 30·0–37·0), median pre-pregnancy BMI was 30·2 kg/m² (24·0–34·4), and the 161 (63%) of 257 participants were White.

Four (2%) of 257 participants had inherited thrombophilia, and nine (4%) had 7 days or longer of strict antepartum immobilisation. The most common venous thromboembolism risk factors were unplanned caesarean delivery (206 [80%] participants), pre-pregnancy BMI of 30 kg/m² or higher (131 [51%]), and postpartum haemorrhage (84 [33%]; table 1). The number of venous thromboembolism risk factors ranged from one to five, and 61 (24%) of 252 participants (25 [20%] of 127 in the low-dose aspirin group and 36 [29%] of 125 in the placebo group) had three or more venous thromboembolism risk factors. Two (1%) participants had COVID-19 diagnosed within 14 days of delivery (9 days and 1 day before delivery, respectively), both of whom were in the low-dose aspirin group. 51 (20%) participants had a negative COVID-19 test within 14 days of delivery, and 204 (79%) with no testing available within 14 days of delivery. All patients had livebirths.

The mean recruitment rate per site was 6·3 (95% CI 5·5–7·2) patients per site per month, or 240 participants over 38 months (excluding 17 patients recruited in the 14-day site lead-in), which was above the a priori recruitment target of 4 patients per site per month. 27 (range 9–65) patients per site per month met inclusion criteria. Excluding patients recruited in the 14-day lead in, Canadian sites had a mean recruitment rate of 8·5 (95% CI 7·4–9·8) patients per site per month, and non-Canadian sites had a mean recruitment rate of 2·6 (1·8–3·6) patients per site per month, driven by two lower recruiting sites (see appendix p 8 for site-specific details, including recruitment strategies). Additional feasibility outcome results are listed in table 2. The reasons for non-consent among otherwise eligible patients were not wishing to take additional medication (133 [32%] of 418), not interested in the study or research (118 [28%]), being overwhelmed or too busy postpartum (109 [26%]), language barrier (27 [6%]), and other reasons (30 [7%]); the reason was unknown for one (<1%) patient. Other reasons (30 [7%]) given were delivery within 48 h but not enough time for all trial procedures (eight [27%] of 30), perceived high risk of venous thromboembolism without LMWH or not following standard of care (11 [37%]), perceived low risk of venous thromboembolism where no additional thromboprophylaxis was needed (four [13%]), participation in competing trials (three [10%]), medication side-effects (two [3%]), unable to follow up (one [3%]), and no indication for aspirin but patient preference to take aspirin thromboprophylaxis outside a clinical trial (one [3%]).

167 (69%) of 243 participants returned study medication bottles. Of the 167 participants who returned bottles, 124 (74%) had taken more than 80% of pills. The mean number of pills taken were 33·96 (SD 12·92; 81%) of 42 tablets overall, with 32·04 (14·15; 76%) in the low-dose

aspirin group and 35·89 (11·31; 85%) in the placebo group. The number of pills taken as recorded by the participant study booklet was similar to by pill count. Of the 161 participants who returned booklets, 124 (77%) had stated that they took more than 80% of pills.

Due to the COVID-19 pandemic, most follow-up visits were conducted virtually. The median follow-up time was 91 days (IQR 89 to 96). Clinical outcomes were reported for 243 (95%) of 257 participants, as 14 (5%) participants were lost to follow-up (n=11) or withdrew (n=3) from the trial (figure). No proximal deep vein thrombosis or pulmonary embolism events were recorded. No participants had venous thromboembolism events recorded in the low-dose aspirin group versus one (1%) of 122 participants who had distal deep vein thrombosis in the placebo group (absolute risk difference –0·82 [95% CI –2·42 to 0·78]; table 3). This event occurred 5 days postpartum in an individual with venous thromboembolism risk factors that included pre-pregnancy BMI higher than 40 kg/m², pre-eclampsia, and an infant who was small for gestational age, below the third percentile, and they were treated with 3 months of rivaroxaban.

No major bleeding events occurred in either group. Three (2%) of 121 participants had CRNMB in the low-dose aspirin group versus one (1%) of 122 in the placebo group (absolute risk difference 1·66 [95% CI –1·54 to 4·86]; table 3). All four CRNMB events consisted of vaginal bleeding requiring medical attention, three (75%) of which occurred within the first 6 weeks postpartum (two in the low-dose aspirin group and one in the placebo group). Three (2%) participants in the low-dose aspirin group and six (5%) in the placebo group had minor bleeds (absolute risk difference –2·44 [95% CI –7·17 to 2·29]; table 3). Among the nine minor bleeds, two (22%) occurred within the first 6 weeks postpartum (one in the low-dose aspirin group and one in the placebo group), and seven (78%) occurred after 6 weeks postpartum (two in the low-dose aspirin group and five in the placebo group). No participants had wound haematomas that required intervention (drainage or packing) or had a haematoma size larger than 100 cm². There were no arterial events, new pre-eclampsia, or participant mortality.

A postpartum wound infection requiring antibiotics was diagnosed in 12 (10%) of 121 participants in the low-dose aspirin group and 15 (12%) of 122 participants in the placebo group. Five postpartum wound infections required a procedure (four [3%] in the low-dose aspirin group and one [1%] in the placebo group). The median duration of lochia in days was 30 days (IQR 21 to 35) in the low-dose aspirin group and 28 days (21 to 35) in the placebo group. Nine (8%) of 118 participants in the low-dose aspirin group and 16 (14%) of 118 participants in the placebo group had ongoing lochia at the 6-week visit (absolute risk difference –5·68 [95% CI –13·28 to 1·92).

A subset of participants (196 [76%] of 257) and their research coordinators were asked to guess their treatment assignment (aspirin, placebo, or unsure) relating to blinding. About equal numbers of patients in the low-dose aspirin group guessed that they were on aspirin (19 [20%] of 97) or placebo (20 [21%]), which was similar to their research coordinators' answers (15 [15%] of 97 *vs* 16 [16%]). Equal numbers of participants in the placebo group guessed they were on aspirin (15 [15%] of 99) or placebo (15 [15%]), which was similar to their research coordinators' answers (18 [18%] of 99 *vs* 17 [17%]). The majority of participants (127 [65%] of 196) and coordinators (130 [66%] of 196) stated they were unsure. We concluded that blinding was well maintained.

Ten serious adverse events occurred in nine (4%) of 257 participants, and 11 serious adverse events occurred in ten (4%) of 271 infants of participants (table 4). Three (1%) participants stopped their study medication for reasons deemed to be related (dry mouth) or possibly related (localised allergic reaction and worsening chemotherapy-induced cardiomyopathy). 93 infants received breastmilk during the treatment period from participants in the low-dose aspirin group (71 [76%] of 93 infants received breastmilk ≥50% of the time during the treatment period). There was one neonatal death relating to a known cardiac and brain malformation condition that was determined to be unrelated to the study medication; the participant was assigned to the low-dose aspirin group, but the infant did not receive breastmilk.

	Feasibility targets	Pilot trial outcomes
Mean recruitment rate excluding a 14-day site lead in (primary outcome)	4 patients per site per month	6·3 (95% CI 5·5–7·2) patients per site per month
Eligible patients who consent	>30%	257/808 (32%)
Study withdrawal or loss to follow-up	<15%	14/257 (5%)
Sites with >18 months to ethics board or contract approvals	<25%	4/6 (67%)*
Study medication adherence >80% by pill count for participants who have completed follow-up	>70%	167/243 (69%) bottles returned; 124/167 (74%) had taken >80% of pills

Data are n/N (%) unless otherwise stated. *Documents were distributed to sites on Jan 28, 2020, and COVID-19 was declared a pandemic on March 11, 2020; the ethics and legal contract submissions were on hold at all sites during the early COVID-19 pandemic.

Table 2: **Feasibility outcomes**

	Low-dose aspirin group (n=121)	Placebo group (n=122)	Risk difference (95% CI)	p value
Major venous thromboembolism*	0	0	..	..
Venous thromboembolism	0	1 (1%)†	–0·82 (–2·42 to 0·78)	1·00
Major bleeding	0	0	..	..
Clinically relevant non-major bleeding	3 (2%)	1 (1%)	1·66 (–1·54 to 4·86)	0·37
Minor bleeding	3 (2%)	6 (5%)	–2·44 (–7·17 to 2·29)	0·50
Wound haematoma requiring intervention or >100 cm²	0	0	..	..

Data are n (%) unless otherwise stated. *Defined as proximal deep vein thrombosis or pulmonary embolism involving segmental or higher arteries. †Distal deep vein thrombosis.

Table 3: **Clinical outcomes and safety data**

	Events	Treatment group
Participants		
Endometritis	2 (1 participant)	Placebo
Pre-eclampsia*	2	1 placebo; 1 aspirin
Abscess†	2	Aspirin
Cardiomyopathy	1	Aspirin
Hypertension	1	Placebo
Thyroidectomy	1	Placebo
Wound infection‡	1	Aspirin
Infants		
Jaundice	3	Placebo
Hypoxia	2 (1 infant)	Placebo
Aortic valve repair	1	Placebo
Cyanosis (from cardiac valve)	1	Aspirin (breastfeeding)
Death (from cardiac and brain malformation)	1	Aspirin (no breastfeeding)
Respiratory infection	1	Placebo
Respiratory failure	1	Placebo
Staphylococcus spp infection	1	Placebo

*Previously known to have pre-eclampsia. †One ischiorectal abscess and one abscess at the caesarean incision site. ‡Wound infections requiring antibiotics are further described in the main text and might not have met the criteria for being a serious adverse event.

Table 4: **Serious adverse events**

Among the 93 infants who received any breastmilk from participants in the low-dose aspirin group, there was one (1%) reported infant serious adverse event unrelated to the study medication (cyanosis related to a cardiac valve disorder; table 4).

Discussion

The pilot PARTUM trial has shown the acceptability of randomly assigning patients to low-dose aspirin in the postpartum period, and the feasibility of conducting a large international postpartum RCT that includes a low-dose aspirin intervention. The primary aim of the pilot PARTUM trial was feasibility, and the mean recruitment rate was 6·3 patients per site per month, which was higher than our a priori target and about six times higher than that reported in previous postpartum thromboprophylaxis randomised trials of LMWH.[21,22] We also report clinical outcomes, and although our sample size is too small to draw any conclusions there were no concerning safety signals. So far, the pilot PARTUM trial is the largest trial published to evaluate a placebo-controlled thromboprophylaxis intervention in the postpartum period.

Despite the pilot PARTUM trial being during the COVID-19 pandemic, our a priori feasibility targets were largely met. Most participant follow-up visits were conducted virtually, so there are now feasibility data for conducting virtual follow-up for a future large RCT. Limitations relating to the COVID-19 pandemic include only collecting adherence data by pill count and participant self-report booklets, because both methods required the participant to send back the bottles and booklets. A higher venous thromboembolism incidence is seen in non-pregnant individuals with COVID-19 than in those without COVID-19.[31,32] It is possible that an active SARS-CoV-2 infection would further increase the venous thromboembolism risk in the postpartum period. Two participants in the low-dose aspirin group had COVID-19 within 14 days of delivery, and they did not have venous thromboembolism complications. The majority of patients had either a negative COVID-19 test or no COVID-19 testing; hence, the study population probably reflects the non-COVID-19 postpartum population.

The pilot PARTUM trial was conducted in seven sites across four countries and screened more than 10 000 patients, reflecting the feasibility of a large global trial. The ratio of screened patients to enrolled patients was high (about 12% met inclusion criteria and 8% were enrolled). However, the initial screened patient population represents almost all patients admitted to labour and delivery and not only the subset at moderate risk of venous thromboembolism.

Compared with the PROSPER pilot trials of LMWH versus placebo or no LMWH in a similar study population,[21,22] the feasibility metrics were improved with an aspirin intervention in the pilot PARTUM trial. The PROSPER pilot trials included follow-up doppler ultrasound scans of the legs at the time of an in-person follow-up visit, and the first postpartum visit was at 10 days or 21 days postpartum.[21,22] By contrast, the pilot PARTUM trial required no additional blood work or imaging tests, and the first follow-up visit was at 42 days postpartum and could be by telephone. We speculate that the improved feasibility relates to both the more simple and pragmatic design, as well as an oral medication that is well known, inexpensive, and well tolerated. Guideline panels now prioritise the outcome of symptomatic venous thromboembolism in decision making instead of asymptomatic venous thrombo-embolism identified by screening tests.[33–35] Among eligible patients who did not consent to participate in the PROSPER pilot trial, 27% were uncomfortable with the need for LMWH injections.[21] However, this might be site specific, as a recent pilot trial of postpartum enoxaparin injections daily for 10 days versus no treatment in postpartum patients with venous thromboembolism risk factors was conducted at a single site in Switzerland and confirmed local recruitment feasibility of a larger postpartum LMWH trial that includes a non-LMWH group.[23]

Among all pilot PARTUM trial participants, four participants had CRNMB and five had postpartum wound infections requiring a procedure; however, further data are still needed for definitive safety statements. A USA-based study that evaluated outcomes in about

24 000 postpartum individuals before and after implementation of an institutional LMWH order set reported an increase in wound haematomas (adjusted OR 2·3 [95% CI 1·5–3·6]) and transfusions (1·3 [1·1–1·6]) after implementation.[36] After a more restricted protocol was introduced at the same institution, the percentage of wound haematomas reduced post-intervention.[37]

Postpartum venous thromboembolism event rates are low, even for those individuals with venous thromboembolism risk factors, which makes it a difficult area to complete RCTs because very large sample sizes are required to detect or exclude clinically important differences. Only one venous thromboembolism event occurred in the pilot PARTUM trial despite our sample size, which supports the feasibility and importance of conducting a future trial.

Although our feasibility metrics were met overall, there were additional challenges identified relating to the placebo group. Two sites recruited below the a priori target mean recruitment rate, and recruitment rates were variable across sites (appendix p 8). We identified site recruitment barriers at all sites because of competing local, national, and international LMWH prophylaxis guidelines (despite no available RCT evidence; ie, guidelines based on poor or scarce evidence). For example, at the Netherlands site (mean 2·5 patients recruited per month), the pilot PARTUM trial opened concurrently with the launch of new Dutch postpartum thromboprophylaxis guidelines that recommended 6 weeks of LMWH for the majority of patients who met trial inclusion criteria. Given the scientific equipoise in this area, participating obstetricians temporarily adapted the local LMWH protocol and successfully recruited to the pilot PARTUM trial (no patients were recruited before change in guidelines *vs* five enrolled participants per month after the change). However, competing with, modifying, or removing guidelines for a whole country is not practical, regardless of the underlying scarcity or poor quality of evidence to support these guidelines. In addition to competing clinical practice guidelines, one pilot site in Europe had restrictions placed by their ethical committee not to recruit patients with more than the minimum number of venous thromboembolism risk factors, and another site in Europe restricted recruitment within their site to only a subset of venous thromboembolism risk factors, based on the discretion and comfort of local researchers. Clinical practice guidelines should be interpreted along with the grade of evidence, and there should be flexibility in enrolling participants into research trials where existing evidence is weak and recommendations are conditional—as is the case in thromboprophylaxis for postpartum venous thromboembolism. Often providers, regulatory organisations, and ethics committees do not layer in the quality of evidence in guidelines, ignoring the fact that interventions are at clinical equipoise. Continued guideline implementation might in fact add unnecessary burden and risk without a proven benefit, and affect the conduct of subsequent trials that seek to improve the quality of evidence and ultimately high-value care.

Based on the recruitment and practical experiences of the pilot PARTUM trial at all sites, we have changed the future full PARTUM trial to a non-inferiority design that compares low-dose aspirin versus a usual care of a LMWH regimen (NCT06494878). Given the usual-care LMWH regimen comparator group, if low-dose aspirin is non-inferior at preventing venous thromboembolism, then the trial results will lead to greater global uptake and acceptability of aspirin by patients, health-care providers, hospitals, and guideline committees, and thus have a greater impact. Although we met our feasibility target, the loss-to-follow-up and withdrawal rate was 5%. Other pragmatic changes to the full trial design to improve recruitment and retention include consenting during pregnancy to allow patients time and space to consider participation, a 1-week post-randomisation text or email reminder to improve adherence to study medication and procedures, and postpartum follow-up using an electronic patient questionnaire.

Limitations to our pilot trial include the COVID-19 pandemic-related issues, including bottle return and tracking adherence as discussed previously, varying eligibility dictated by local LMWH prophylaxis protocols, and a small sample size in the setting of a low venous thromboembolism event rate, which precludes clinical recommendations but does yield important feasibility information. The majority of patients recruited were from the second-order criteria of venous thromboembolism risk factors, which is a group more commonly seen in clinical practice. Most participants recruited were White. Race and ethnicity categories might differ by country, and participants might better identify with other categories than what we collected. Further research on how best to collect and report race and ethnicity for a future global trial is needed.

Although challenges remain when conducting postpartum thromboprophylaxis trials, the pilot PARTUM trial has shown that recruitment is feasible. We provide feasibility data and offer options for pragmatic trial interventions to help pave the way for global postpartum thromboprophylaxis trials.

Contributors

LS co-designed the research study, performed research, collected data, analysed and interpreted data, and wrote the first draft of the manuscript. AKM, DE, W-SC, JD, CC, WG, SW, CM, AB, HW, PSG, FNÁ, AG, and JB contributed to the design of the study, performed research, collected data, interpreted data, and reviewed the manuscript. SD, SM, LD, and SMB contributed to the design of the study, interpreted the data, and reviewed the manuscript. BCL performed the statistical analysis and reviewed the manuscript. MAR co-designed the research study, interpreted data, and reviewed the first and subsequent drafts of the manuscript. LS and BCL directly accessed and verified the reported data. All authors approved the final draft of the manuscript, including all data, and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Aggregated participant data will be made available upon email request to the corresponding author.

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