A pilot study assessing the feasibility of a randomized controlled trial evaluating aspirin in postpartum women at risk of developing venous thromboembolism

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Ethical review	Approved WMO
Status	Completed
Health condition type	Postpartum and puerperal disorders
Study type	Interventional

Summary

ID

NL-OMON50986

Source
ToetsingOnline

Brief title
PARTUM

Condition

- Postpartum and puerperal disorders
- Embolism and thrombosis

Synonym
deep vein thrombosis, pulmonary emboslism

Research involving
Human

Sponsors and support

Primary sponsor: The University of Calgary
Source(s) of monetary or material Support: Universiteit van Calgary

Intervention

Keyword: Aspirin, postpartum, prevention, VTE

Outcome measures

Primary outcome

The primary full trial objective is to determine the efficacy of low-dose ASA

of preventing symptomatic VTE in the first 6 weeks postpartum, compared to

placebo.

Secondary outcome

Secondary objectives include:

1. Late symptomatic VTE from 6 weeks to 90 days

2. Superficial vein thrombosis

3. Distal deep vein thrombosis

4. Subsegmental pulmonary embolism

5. Unusual site thrombosis

6. Major bleeding

7. Clinically relevant non-major bleeding

8. Symptomatic ATE (ischemic stroke/TIA or myocardial infarction or peripheral

arterial embolism)

9. Postpartum pre-eclampsia

10. All-cause mortality

Study description

Background summary

Pulmonary embolism (PE) is the leading cause of maternal mortality in the developed world, and the morbidity associated with venous thromboembolism (VTE: PE or deep vein thrombosis) can be significant. Women are at risk of VTE during pregnancy and postpartum because of venous stasis, vascular damage and hypercoagulability. It is unknown whether postpartum thromboprophylaxis is effective at preventing VTE in patients with VTE risk factors.

Previous trials evaluating postpartum low-molecular-weight heparin (LMWH) prophylaxis use in patients with VTE risk factors have had low recruitment rates. One major barrier to recruitment is patients* lack of comfort with the need for daily LMWH injections. The use of an orally administered medication would almost certainly improve patient acceptance of thromboprophylaxis in the postpartum period. The direct oral anticoagulants have similar efficacy to LMWH in non-pregnant populations, but they are contraindicated while breastfeeding and may increase the risk of vaginal bleeding. Extended aspirin (ASA) prophylaxis after 5-10 days of anticoagulation was found to be non-inferior at preventing VTE after major orthopedic surgery, when compared to other anticoagulants such as LMWH or rivaroxaban (EPCAT, Ann Intern Med 2013; EPCATII, NEJM 2018)

Low-dose aspirin (ASA) is considered safe in breastfeeding women. In postpartum women who were taking ASA 81 mg daily (1-8 months postpartum), ASA was undetectable in breast milk and salicylate was detected at very low levels (relative infant dose: 0.4%, threshold considered safe: <10%)3. In a prospective cohort study that evaluated adverse medication effects in breast-fed infants, there were no adverse effects seen in 15 breast-fed infants of mothers taking ASA4. The American College of Chest Physician guidelines, Canadian Cardiovascular Guidelines and American Academy of Pediatrics support the use of regular low-dose aspirin in breast feeding women, but recommend against the use of higher ASA doses given the potential for adverse effects.

If ASA is efficacious in preventing postpartum VTE, use of this simple and cost-effective medication could change practice and save lives around the world.

Study objective

The purpose of this pilot trial is to determine whether it is feasible to conduct a full multicentre randomized controlled trial (RCT) to determine whether low-dose aspirin (ASA) is efficacious and safe at preventing postpartum venous thromboembolism (VTE) in women at increased risk of VTE, compared to

placebo.

Study design

Multicentre randomized controlled pilot trial

Intervention

Treatment with aspirin or placebo , 6 weeks postpartum

Study burden and risks

Risk: Adverse events of study treatment
Burden: Two times 15 minutes study visit by telephone

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

ONE (or more) First Order Criterion:
1. Known inherited thrombophilia prior to enrolment: Heterozygous factor V Leiden or
heterozygous prothrombin gene variant or protein C deficiency or protein S deficiency
2. Antepartum immobilization (strict bedrest) for >=7 days at any time during the pregnancy
OR TWO (or more) Second Order Criteria:
1. Pre-pregnancy BMI >=30 kg/m2
2. Smoking >=5 cigarettes/day pre-pregnancy
3. Previous clinical history of superficial vein thrombosis
4. Pre-eclampsia (SBP >=140 and/or DBP >=90 mmHg on at least one occasion and proteinuria of >=0.3 grams/24 hours or >=30 mg/mmol on a random urine sample)
5. Current pregnancy ending in stillbirth (fetal loss >20 weeks gestation)
6. Emergency cesarean birth (emergency = not planned)
7. Small-for-gestational-age infant at time of delivery (<3rd percentile adjusted for
gestational age and sex using the standardized international INTERGROWTH chart)
8. Postpartum infection (symptoms/signs and documented fever and laboratory evidence of infection)
9. Postpartum hemorrhage (>1000 mL regardless of delivery mode)

Exclusion criteria

1. More than 48 hours since delivery of the placenta at the time of randomization
2. Received more than 2 doses of LMWH since delivery of the placenta*
3. Need for postpartum LMWH prophylaxis or systemic anticoagulation as judged by their physician and/or local investigator. May include but is not limited to:
a. Documented history of provoked or unprovoked VTE
b. Mechanical heart valve(s)
c. Known antiphospholipid syndrome (APS) (according to the revised Sapporo/Sydney criteria)
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d. Known high-risk inherited thrombophilia
i. Antithrombin deficiency (two abnormal and no normal tests based on local laboratory cutoffs)
ii. Homozygous factor V Leiden (genotyping result required)
iii. Homozygous prothrombin gene mutation (genotyping result required)

iv. Compound heterozygosity factor V Leiden and prothrombin gene mutation (genotyping result required)
v. More than 1 thrombophilia: any combination of 2 or more: factor V Leiden, prothrombin gene mutation, protein C deficiency, protein S deficiency, as previously defined.
4. Need for postpartum ASA as judged by their physician and/or local investigator. May
include but is not limited to:
a. Documented history of myocardial infarction
b. Documented history of ischemic stroke or transient ischemic attack (TIA)
5. Contraindication to ASA including**:
a. History of known ASA allergy
b. Documented history of a gastrointestinal ulcer
c. Known platelet count <50 x 109/L at any time during the current pregnancy or postpartum
d. Active bleeding at any site, excluding normal vaginal bleeding, at the time of
randomization
e. Most recent known hemoglobin <=70 g/L during the current pregnancy or postpartum
f. Known severe hypertension (SBP >200 mmHg and/or DBP >120 mmHg) during the current pregnancy or postpartum
6. <18 years of age
7. Unable or refused consent
*Pneumatic compression devices or graduated compression stockings are not a contraindication to enrolment but will be recorded.
**Postpartum non-steroidal anti-inflammatories NSAID) use is not a contraindication to
enrolment but will be recorded.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	25-05-2023
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aspirine
Generic name:	Acetylsalicyclic acid
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	26-04-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-000619-58-NL
CCMO	NL75956.018.21