

Low Molecular Weight hEparin vs. Aspirin Post-partum (LEAP)

Version 1: October 25, 2020

Version 2: July 27 2021 – changes as per minor protocol change on randomization system and data collection table, indicated on the pink highlights with comment.

Version 2.1: September 13, 2021- reference list added, indicated on the yellow highlights.

Version 2.2: October 29, 2021 - Screening time changed in the table, Randomization section updated as per suggestions

Version 2.3: November 11, 2021- Screening time changed in the table from day -14 to day -1 to week -8 to day -1, Randomization section updated in the latest version of Protocol from September 29

Version 2.4: December 13, 2021- In 'Trial Schematic Table' data will be collected for concurrent medication at 3 month follow up.

Version 2.5: December 29, 2021- In 'Trial Schematic Table' Bleeding Assessment Score has been added for 3 week follow up, 6 week follow up, early discontinuation form.

Version 2.6: January 14, 2022- In 'Trial Schematic Table' Data for Quality Of Life Assessment will not be collected on dosing day.

Version 3: October 11, 2022- Study title changed to Low Molecular Weight hEparin vs. Aspirin Post-partum (LEAP)

Low Molecular Weight hEparin vs. Aspirin Post-partum (LEAP) Title

Low Molecular Weight hEparin vs. Aspirin Post-partum (LEAP)

Aim and Overall Objective

The principal question to be addressed, in a large definitive trial, is whether a combination of low molecular weight heparin (LMWH) and low dose aspirin is non-inferior to standard of care of LMWH for venous thromboembolism prophylaxis (VTE) postpartum. This single-center randomized pilot feasibility study will address enrollment, adherence and feasibility for the definitive trial.

Introduction

Expert opinion from the American Society for Hematology (ASH), the Royal College of Obstetricians and Gynecologists, UK, as well as the 'Society of Obstetricians and Gynecologists' guidelines recommends a minimum of 6 weeks of prophylactic LMWH for patients with a history of VTE or high-risk thrombophilias. This recommended duration is based on expert consensus and observational data that do not clearly define the risk of VTE and the risk reduction with LMWH therapy. LMWH requires daily subcutaneous injections, is associated with an increased risk of bleeding and is expensive. There are no randomized controlled trials (RCTs) determining the optimal duration of anticoagulation postpartum. A 2014 Cochrane review concluded that there is *insufficient evidence on which to base thromboprophylaxis in the pregnancy setting, and high-quality randomized trials are warranted* (Bain *et al.*, 2014).

A recent RCT randomized patients following total hip and knee arthroplasty (surgery associated with a high risk of VTE) to limited duration of prophylactic anticoagulation followed by aspirin (ASA) compared to the standard practice of prophylactic anticoagulation treatment. Limited duration of anticoagulation followed by ASA was found to be non-inferior to LMWH (Anderson *et al.*, 2018). The combination of standard prophylactic anticoagulation for a reduced duration followed by ASA may also be non-inferior for postpartum prophylaxis. This proposal is the first step to determine whether postpartum prophylactic LMWH for women requiring prophylaxis with 3 weeks of LMWH followed by 3 weeks of low dose ASA is non-inferior to 6 weeks of prophylactic LMWH. The safety of ASA in the antepartum period (Rolnik *et al.*, 2017; CLASP study, 1994) and during breastfeeding (Datta *et al.*, 2017) has been well established.

Background

For women not already receiving extended duration therapeutic anticoagulant therapy who have a history of VTE that was unprovoked or associated with a hormonal risk factor, the ASH guidelines recommend postpartum anticoagulant prophylaxis for 6 weeks. VTE occurring within 6 weeks postpartum affects 6.5% of pregnancies in women with a history of VTE (95% CI, 4.3%-9.7%) (Rodger *et al.*, 2014), compared with a risk of approximately 0.6 of every 1000 deliveries for the general population (Tepper *et al.*, 2014; Kourlaba *et al.*, 2016; Parunov *et al.*, 2015; Kamel *et al.*, 2014). Overall, the incidence during the 1st week postpartum is 9 in 10,000 deliveries, reducing to 2.5 and 1.5 in 10,000 by the 2nd and 3rd week postpartum, respectively (Tepper *et al.*, 2014). In women with a history of VTE who were treated with postpartum prophylaxis (LMWH, UFH), the risk of postpartum VTE was substantially lower at 1.7% (95% CI, 1.2%-2.7%) (Roger *et al.*, 2014), representing a decrement in risk similar to that seen with extended LMWH prophylaxis after high-risk orthopedic procedures (Hull *et al.*, 2001). In the presence of a high-risk thrombophilia and LMWH prophylaxis postpartum, the pooled VTE incidence was 0.2% (95% CI, 0%-1.2%).

In contrast to LMWH, which is expensive and requires daily subcutaneous injections, ASA is an inexpensive, generic, and widely available oral antiplatelet drug. Furthermore, in the postpartum period LMWH is associated with a 0.3% (95% CI: 0%-1%) risk of major bleeding events, 1.8% risk of skin reactions and wound complications after cesarean delivery. ASA use compared to placebo in the antenatal period did not demonstrate increased bleeding complications in 798 patients, with no gastrointestinal (GI) bleeding noted (Rolnik *et al.*, 2017), and in the orthopedic setting with a two-week administration post total knee

replacement, the GI bleeding was 1.7 per 1000 patient-years in the ASA group compared to 31.9 per 1000 patient-years with LMWH (Nielen *et al.*, 2016). Clinical trials and meta-analyses have suggested that ASA is non-inferior for the prevention of VTE in patients post- operatively (Anderson *et al.*, 2018; PEP trial, 2000; Antiplatelet Trialists' Collaboration, 1994). Notably, orthopedic patients are at particularly high risk of DVT/ PE within 90 days following total hip and knee replacement (incidence 5% and 2%, respectively), despite treatment with either warfarin, LMWH or ASA (Matharu *et al.*, 2020). ASA administered daily post-operatively has been shown to be non-inferior to LMWH when used for VTE thromboprophylaxis following these procedures (RR 0.76; 95% CI, 0.37- 1.56), and has a similar safety profile (Matharu *et al.*, 2020). Furthermore, Anderson *et al.*, 2018, NEJM, demonstrated clinical safety and non-inferiority of a combination of 5 days of rivaroxaban followed by 81mg of ASA for 30 days after total hip arthroplasty and 9 days after total knee arthroplasty.

It has been suggested that overall, the highest risk period for VTE in all postpartum women is between 1-3 weeks, with a sharp decline documented following this time period (Abdul Sultan *et al.*, 2014). The weekly distribution incidence of all VTEs within a 6 week period is 61.1%, 16.3%, 9.9%, 6.3%, 4.0% and 2.4% respectively, with an incidence of 9.41/10,000 in the 1st week, 2.58/10,000 in the 2nd , 1.62/10,000 in the 3rd, 1.00/10,000 in the 4th and 0.67 and 0.40/10,000 in the 5th and 6th week respectively (Tepper *et al.*, 2014). The median time for readmission with VTE in a retrospective study of 6,269,641 patients between 2013 and 2014 using a Nationwide Readmissions Database in the USA was 14 and 11.7 days for deep vein thrombosis and pulmonary thromboembolism, respectively (Wen *et al.*, 2018). This data clearly emphasizes the sharp reduction in risk of VTE one week after delivery, followed by a significantly lower risk 3-6 weeks postpartum.

Further supporting the reduction in risk of VTE after the first few weeks postpartum are plasma levels of progesterone and estrogen. The association between increased serum estrogen and progesterone levels and VTE is clearly described in the literature of oral contraceptive (OC) use. With 'low dose' OC containing < 50 μ g of estradiol, the risk of VTE is increased three to six-fold (World Health Organization). Furthermore, progestogens such as levonorgestrel have an up to a three-fold increase in VTE (Kemmeren *et al.*, 2001), and OC in the presence of obesity increased the risk 10-fold. Mechanisms postulated are a documented acquired resistance to activated protein C (Rosing *et al.*, 1997), and a hormone-induced venous stasis which in pregnancy coupled with endothelial damage and a hypercoagulable state are thought to lead to the 7-10 fold increase in daily risk of VTE antepartum and 15-35 fold postpartum. Plasma levels of progesterone one week postpartum have been noted to be 1.46 ± 1.53 nmol/L, which is less than the 5.00 ± 10.39 (nmol/L) in non- pregnant matched controls (Abou-Saleh *et al.*, 1998). Estrogen one week postpartum has also returned to non-pregnancy levels (124.40 ± 60.23 pmol/L vs 128.72 ± 395.39 pmol/L). The normalization of estrogen and progesterone to non-pregnancy levels at 1 week postpartum suggests a reduction in VTE risk.

Based on (A) the demonstrated non-inferiority of ASA as compared to LMWH in the orthopedic cohort of patients whose VTE risk is known to be high and (B) taking into account that the median time for VTE readmission postpartum is between 11.7 and 14 days suggesting that this is the risk period for VTE, (C) that pregnancy hormones have returned to normal by 1 week after delivery, and (D) LMWH is associated with a higher risk of bleeding than ASA, **I propose a pilot study to determine whether the duration of LMWH postpartum can be reduced to 3 weeks followed by ASA for a 3-week period.** The purpose of pilot studies is to determine the acceptability and feasibility of the treatment strategies. It is imperative to determine feasibility prior to embarking on a definitive study to identify barriers to recruitment and address clinical uncertainty, if any.

Study Design

This is a single-center pilot feasibility RCT comparing 3 weeks of LMWH followed by 3 weeks of ASA compared to standard care of 6 weeks of LMWH prophylaxis.

Inclusion Criteria: The inclusion criteria are to include all patients who are deemed to require prophylaxis for 6 weeks postpartum.

- 1) Personal history of VTE prior to pregnancy and not prescribed indefinite therapeutic anticoagulation (ASH guidelines).
- 2) Family history of VTE and antithrombin deficiency, protein C or protein S deficiency (ASH guidelines).
- 3) Combined thrombophilia or homozygous for factor V Leiden mutation or prothrombin gene mutation, regardless of family history (ASH guidelines).
- 4) > 18 years old
- 5) English speaking and able to provide informed consent

Exclusion criteria:

1. Pre-existing indication for therapeutic LMWH
2. Contraindication to ASA:
 - a. Known ASA allergy
 - b. Documented history of gastrointestinal ulcer
 - c. Known platelet count < 50x10⁹/L at any time during the current pregnancy or postpartum
3. Contraindication to LMWH, e.g. known allergy
4. Active bleeding at any site, excluding physiological vaginal bleeding
5. Patients with bleeding disorders for example hemophilia or von Willebrand disease
6. Known severe hypertension (SBP >200mm/hg and/or DBP >120mm/hg) during the current pregnancy or postpartum
7. Unable to provide or declining informed consent for data collection

Intervention:

Patients allocated to the LMWH and ASA strategy will receive a prophylactic dose of LMWH according to weight (< 100kg: Dalteparin 5000 units daily, Enoxaparin 40 mg daily, Tinzaparin 4500 units daily; > 100kg: Dalteparin 10,000 units daily, Enoxaparin 80mg daily, Tinzaparin 9000 U) by subcutaneous injection for 3 weeks followed by ASA 81 mg orally daily for three weeks. A clinic nurse will teach participants how to self-administer the LMWH injections.

Patients randomized to the LMWH strategy will receive a prophylactic dose of LMWH according to weight, daily for 6 weeks.

All participants will receive the first injection within 12 hours of delivery.

Randomization

Patients will be identified in the Hematology Clinic of the Special Program at Mount Sinai Hospital, where consent will be obtained. Patients will be randomized immediately following consent. Randomization has been developed for RedCap to allocate the patient into one of the two strategies in a 1:1 ratio, with the assistance of a statistician from Princess Margaret Hospital. Following delivery, the research assistant will dispense the assigned medication to the participant. Blinding or masking of treatment allocation will not be used in the pilot but a placebo control for ASA is intended for the definitive trial.

Baseline Assessment

Baseline assessments will be undertaken at the time of randomization and include age, weight, parity, indication for VTE prophylaxis, gestational age at delivery, medications and delivery complications. Baseline laboratory tests at the time of delivery will include complete blood count, serum creatinine level, coagulation profile and alanine aminotransferase. This limited testing is intended to reflect a pragmatic approach to this trial.

Primary Outcomes:

1. Potential enrollment rate (patients eligible)
2. Consent rates (patients approached/consent obtained/rationale for non-consent)
3. Adherence to study protocol (incidence and reasons for nonadherence, withdrawal of consent, rates of contamination and utilization of co-interventions).
4. Missing data

Secondary Outcomes:

1. VTE event rate three months following delivery
2. Bleeding event rate three months following delivery
3. Quality of life (QoL) assessment using the modified Duke Anticoagulation Satisfaction Scale (Appendix) at delivery and three and six weeks postpartum

Confirmation of VTE

VTE must be confirmed either by Doppler ultrasound or V/Q scan or computer tomography (CT). Imaging will not be performed on all patients, only those with symptoms. For the definitive trial, imaging will be adjudicated.

Bleeding outcomes

Bleeding will be reported according to the International Society on Thrombosis and Hemostasis (ISTH) scoring system (<https://bleedingscore.certe.nl/>) (Schulman *et al.*, 2005; Schulman *et al.*, 2009). Bleeding will be assessed at 3 and 6 weeks postpartum using a telephone questionnaire.

Follow up duration

All patients will be followed until 3 months postpartum. Patients will be contacted by telephone at 3 weeks, 6 weeks and 12 weeks after delivery.

Participant trial discontinuation

Participants may discontinue the study at any time. The participant will immediately discontinue the study medication, and the patient will be treated according to the standard of care. The patient will have a discontinuation telephone follow-up visit.

Statistical analysis

The analysis of this trial is mainly descriptive, as this is a pilot study to ensure adequate enrollment and adherence. All demographics and baseline characteristics will be summarized using mean, median, standard deviation, minimum and maximum for continuous variables, and frequency and percentages for categorical variables. The feasibility outcomes (primary outcomes) will be summarized using frequency counts and percentages with associated 95% confidence intervals.

The definitive trial is designed to show the non-inferiority of a combination of LMWH and ASA over LMWH in decreasing the incidence of composite VTE. However, for the pilot study, the clinical endpoints will only be presented using descriptive statistics. In the definitive trial, VTE, bleeding, and

event-free outcomes will be compared between the two arms using a stratified log-rank test. A non-inferiority margin of 1.0 % will be used based on expert opinion. Statistical analysis will be carried out using SPSS statistical software.

The feasibility trial will be deemed a success and will proceed to a full trial under the current protocol if all the criteria below are met:

- Participant recruitment is > 60%
- Participant adherence to study drug > 80%
- Compliance with study procedures > 80%
- Proportion of participants lost to follow up <25%

Sample size calculation: I plan to recruit 50 patients, 25 patients treated according to each strategy. The outcomes from these patients will be included in the definitive trial.

Recruitment rate: Recruitment is anticipated to be completed in 18 months as we anticipate to enroll 1 patient/week.

Trial registration: The trial will be registered at www.clinicaltrials.gov.

Data Management: Appropriate training and security measures will be completed. The case report form will be developed electronically and piloted. All patient-related information, including case report forms, will be kept strictly confidential. All records will be kept in a secure, locked location, and only research staff will have access to the records. Patients will be identified only by means of a coded number specific to each patient. All computerized databases will identify patients by numeric codes only, and will be password protected and housed in a locked office.

Data Safety Monitoring Committee: A data safety monitoring board will be assembled, consisting of one hematologist and one obstetrician. Any VTE or bleeding event will be reviewed by this committee.

Ethics: The study will be submitted for research ethics board approval. Virtual consent during the current COVID-19 pandemic is currently feasible and is an option for this trial.

Safety: I will be responsible for ensuring that the patient or her substitute decision-maker understands the risks and benefits of participating in the study, answering any questions the patient or family member may have throughout the study and sharing any new information in a timely manner that may be relevant to the patient's willingness to continue her participation in the trial. All study participants will be informed of the objectives of the study and the potential risks. Consent forms will also discuss the benefits and risks of this pilot trial and the definitive study. All patients will be informed of the signs and symptoms of VTE that would necessitate emergency room visits as participants in both arms may develop a VTE.

Significance: This single center pilot feasibility study will address enrollment, adherence of two anticoagulant strategies postpartum in women who require prophylaxis with LMWH. The results of this study will be used to design a large definitive multicentered trial. All clinical outcomes from the pilot study will be used to inform the final trial design. Demonstrating the non-inferiority of ASA and LMWH to LMWH will lead to a shorter course of LMWH postpartum, potentially reducing bleeding risk, need for subcutaneous injections as well as cost while improving quality of life. If the definitive trial does not show inferiority, the results will provide evidence that six weeks of postnatal thromboprophylaxis is warranted.

Trial Schematic Timeline

Participant	Screening Week -8 to Day -1	Dosing Day 1	3-week phone call ± 5 days	6-week phone call (end of study) ± 5 days	3-month phone call ± 5 days	Early discontinuation visit
Informed Consent	X	---	---	---	---	---
Inclusion / Exclusion criteria and Eligibility	X	---	---	---	---	---
Baseline demographics	X	---	---	---	---	---
Concurrent medications	X	---	X	X	X	X
Weight/BMI	X	X	X	X	X	X
Delivery Data: Type of Delivery/ Complications	---	X	---	---	---	---
Laboratory Data: Complete blood count / Creatinine / INR / aPTT / ALT	---	X	---	---	---	---
Drug dispensation	---	X	---	---	---	---
Adherence assessment	---	---	X	X	---	X
Bleeding Assessment Score	---	---	X	X	---	X
Quality of life assessment	---	---	X	X	---	X

APPENDIX: MODIFIED DUKE ANTICOAGULATION SCALE

During the past 3 weeks...	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Fear of bleeding while taking blood thinners limited my participation in vigorous activities.					
Fear of bleeding while taking blood thinners limited my participation in activities of daily living					
I was concerned about the possibility of excessive bruising while taking blood thinners					
Taking blood thinners limited my diet (e.g. food or drink, including alcohol).					
Taking blood thinners added stress to my life					
Taking my blood thinner was difficult to carry out					
Taking my blood thinner required a great deal of time to carry out					
Taking my blood thinner caused me a great deal of worry					
Taking my blood thinner caused me a great deal of irritation					
Taking my blood thinner caused me a great deal of frustration.					

Taking my blood thinner was a burden to me					
Taking my blood thinner negatively impacted my quality of life					
I have confidence that my blood thinner will protect my health (prevent blood clots, stroke, heart attack)					
I am satisfied with my blood thinner					

References

- 1) Abdul Sultan A, Grainge MJ, West J, Fleming KM, Nelson-Piercy C, Tata LJ. Impact of risk factors on the timing of first postpartum venous thromboembolism: a population-based cohort study from England. *Blood*. 2014;124(18):2872-2880. doi:10.1182/blood-2014-05-572834.
- 2) Abou-Saleh MT, Ghubash R, Karim L, Krymski M, Bhai I. Hormonal aspects of postpartum depression. *Psychoneuroendocrinology*. 1998;23(5):465-475. doi:10.1016/s0306-4530(98)00022-5.
- 3) Andersen BS, Steffensen FH, Sorensen HT, Nielsen GL, Olsen J. The cumulative incidence of venous thromboembolism during pregnancy and puerperium—an 11-year Danish population-based study of 63,300 pregnancies. *Acta Obstet Gynecol Scand*. 1998;77:170-173.
- 4) Anderson DR, Dunbar M, Murnaghan J, et al.. Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty. *N Engl J Med*. 2018;378(8):699-707. doi:10.1056/NEJMoa1712746.
- 5) Bain E, Wilson A, Tooher R, Gates S, Davis L, Middleton P. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. *Cochrane Database of Systematic Reviews* 2014, Issue 2. Art. No.: CD001689. DOI: 10.1002/14651858.CD001689.pub3.
- 6) CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. *Lancet*. 1994;343(8898):619-629.
- 7) Collaborative overview of randomised trials of antiplatelet therapy--III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Antiplatelet Trialists' Collaboration. *BMJ*. 1994;308(6923):235-246.
- 8) Datta P, Rewers-Felkins K, Kallel RR, Baker T, Hale TW. Transfer of Low Dose Aspirin Into Human Milk. *J Hum Lact*. 2017;33(2):296-299. doi:10.1177/0890334417695207.
- 9) Folkerdinga N, Brouwer JL, Korteweg FJ, Veeger NJ, Erwich JJ, van der Meer J. High risk of pregnancy-related venous thromboembolism in women with multiple thrombophilic defects. *Br J Haematol*. 2007;138(1):110-116.
- 10) Friederich PW, Sanson BJ, Simioni P, et al.. Frequency of pregnancy-related venous thromboembolism in anticoagulant factor-deficient women: implications for prophylaxis. *Ann Intern Med*. 1996;125(12):955-960.
- 11) Hull RD, Pineo GF, Stein PD, et al.. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med*. 2001;135(10):858-869.
- 12) Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB, Elkind MS. Risk of a thrombotic event after the 6-week postpartum period. *N Engl J Med*. 2014;370(14):1307-1315.
- 13) Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. *BMJ*. 2001;323(7305):131-134. doi:10.1136/bmj.323.7305.131
- 14) Kourlaba G, Relakis J, Kontodimas S, Holm MV, Maniadakis N. A systematic review and meta-analysis of the epidemiology and burden of venous thromboembolism among pregnant women. *Int J Gynaecol Obstet*. 2016;132(1):4-10.
- 15) Liu S, Rouleau J, Joseph KS, et al.. Epidemiology of pregnancy associated venous thromboembolism: a population-based study in Canada. *J Obstet Gynaecol Can*. 2009;31:611-620.
- 16) Mahmoodi BK, Brouwer JL, Ten Kate MK, et al.. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening asymptomatic relatives of patients with hereditary deficiencies of protein S, protein C or antithrombin. *J Thromb Haemost*. 2010;8(6):1193-1200.

17) Matharu GS, Kunutsor SK, Judge A, Blom AW, Whitehouse MR. Clinical Effectiveness and Safety of Aspirin for Venous Thromboembolism Prophylaxis After Total Hip and Knee Replacement: A Systematic Review and Meta-analysis of Randomized Clinical Trials [published online ahead of print, 2020 Feb 3]. *JAMA Intern Med.* 2020;180(3):376-384. doi:10.1001/jamainternmed.2019.6108

18) Parunov LA, Soshitova NP, Ovanesov MV, Panteleev MA, Serebriyskiy II. Epidemiology of venous thromboembolism (VTE) associated with pregnancy. *Birth Defects Res C Embryo Today.* 2015;105(3):167-184.

19) Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJ. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. *J Thromb Haemost.* 2008;6:632-637.

20) Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet.* 2000;355(9212):1295-1302.

21) Rodger M. Pregnancy and venous thromboembolism: 'TIPPS' for risk stratification. *Hematology Am Soc Hematol Educ Program.* 2014;2014:387-392.

22) Rolnik DL, Wright D, Poon LCY, et al.. ASPRE trial: performance of screening for preterm pre-eclampsia [published correction appears in *Ultrasound Obstet Gynecol.* 2017].

23) Rosing J, Tans G, Nicolaes GA, et al.. Oral contraceptives and venous thrombosis: different sensitivities to activated protein C in women using second- and third-generation oral contraceptives. *Br J Haematol.* 1997;97(1):233-238. doi:10.1046/j.1365-2141.1997.192707. Dec;50(6):807]. *Ultrasound Obstet Gynecol.* 2017;50(4):492-495. doi:10.1002/uog.18816.

24) Saving Lives, Improving Mothers' Care. Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2014-16. MBRRACE-UK. <https://www.npeu.ox.ac.uk/downloads/files/mbrrace-uk/reports/MBRRACE-UK%20Maternal%20Report%202018%20-%20Web%20Version.pdf>

25) Tepper NK, Boulet SL, Whiteman MK, et al.. Postpartum venous thromboembolism: incidence and risk factors. *Obstet Gynecol.* 2014;123(5):987-996.

26) van Boven HH, Vandebroucke JP, Bri " et E, Rosendaal FR. Gene-gene and gene- environment interactions determine risk of thrombosis in families with inherited antithrombin deficiency. *Blood.* 1999;94(8):2590-2594.

27) World Health Organization. Medical Eligibility Criteria for Contraceptive Use. 4th ed Geneva, Switzerland: World Health Organization; 2009.

28) Schulman S and Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost.* 2005; 3(4): 692-694. Doi: <https://doi.org/10.1111/j.1538-7836.2005.01204.x>

29) Schulman S, Angerås U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost.* 2010;8(1):202-204. doi:10.1111/j.1538-7836.2009.03678.x

30) <https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37b.pdf>

29) <https://www.jogc.com/action/showPdf?pii=S1701-2163%2815%2930569-7>

30) <https://bleedingscore.certe.nl/>