Review article:

Thrombophilia in Pregnancy and Puerperium

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Introduction

Thrombophilia is an abnormality of blood coagulation that increases the risk of thrombosis (blood clots in blood vessels). Pregnancy is associated with major physiological changes that affect coagulation and the fibrinolytic system.[1,2,3] An imbalance in this system leads to a hypercoagulable state and pregnant women are therefore at an increased risk of VTE, especially if they are affected by an associated thrombophilia.[2,3,4]

Two factors that may exaggerate this risk:

- High-risk nature of the thrombophilia
- History of a previous unprovoked VTE.[5,6]

High-risk hereditary thrombophilia includes

- Antithrombin deficiency
- Prothrombin gene mutation (PGM)
- factor V Leiden (FVL)
- Presence of lupus anticoagulant or anti-cardiolipin antibodies are considered as acquired risk factors.[7,8]
- Homozygosity or presence of a combination of thrombophilia factors will aggravate the VTE risk by certain fold.[7,8,9]

Hence, pregnancy induces a state of hypercoagulability with decreasing anticoagulation and increasing coagulation.[10]

Incidence

The thrombotic potential of pregnancy is high, complicating **1 in 1600 births** and is the leading cause of maternal morbidity in the United States.

- Pulmonary embolism (PE) remains a leading direct cause of maternal death in the UK
- NICE estimates that low-molecular-weight heparin (LMWH) reduces VTE risk in medical and surgical patients by 60% and 70% respectively.[11]
- A Scandinavian study[11] found a relative risk reduction of VTE of 88% in obstetric patients with one previous VTE given LMWH.
- Caesarean section is a significant risk factor[12,13,14,15] but women having vaginal deliveries are also at risk.[16]

Etiology of thrombophilia

Thrombophilias are inherited or acquired conditions that have been strongly associated with VTE such as deep vein thrombosis and pulmonary embolism.

A. Inherited thrombophilias:

i. Abnormalities of pro-coagulant factors.

- Factor V Leiden mutation causing activated protein C resistance (APCR)
- Prothrombin gene mutation (prothrombin G20210A)
- Plasminogen activator inhibitor - 1 (PAI - 1) gene mutation

ii. Deficiencies of endogenous proteins in the coagulation cascade.

- Protein C
- Protein S
- Antithrombin

B. Acquired thrombophilias:

i. The presence of antiphospholipid antibodies lupus anticoagulant (LAC) and/or
ii. Anticardiolipin antibodies (ACA)[10]
iii. Mixed inherited and acquired

Hyperhomocysteinemia (elevated plasma homocysteine)

Complications

- Venous Thromboembolism (VTE)
- Increased risk of early miscarriages
- intrauterine growth restriction (IUGR)
- pregnancy loss.[17,18]

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Risk Factors for VTE in pregnancy and puerperium

- Pre-existing risk factors
- Obstetric risk factors
- New onset

Risk factors

Pre-existing: Risk factors:

- Previous VTE
- Thrombophilia
- Heritable
  - Antithrombin deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Factor V Leiden
- Prothrombin gene mutation
- Acquired
  - Antiphospholipid antibodies
  - Persistent lumps anticoagulant and/ or persistent moderate/ high titre anticardiolipin antibodies
- And/or $ß_2$-glycoprotein 1 antibodies
- Medical comorbidities
  - Cancer;
  - Heart failure;
  - Active SLE,
  - Inflammatory polyarthropathy or IBD;
  - Nephrotic syndrome;
  - Type I diabetes mellitus with Nephropathy;
  - Sickle cell disease;[49]
  - Current intravenous drug user

Obstetric Risk factors:

- **Age>35 years**
- **Obesity (BMI ≥ 30 KG/m^2) either prepregnancy or in early pregnancy**
- **Parity ≥ (a women becomes para 3 after her third delivery**
- **Smoking**
- **Gross varicose veins (symptomatic or above knee or with associated phlebitis, oedema/skin changes)**
- **Paraplegia**

New onset/transient risk factors:

- **Any surgical procedure in pregnancy and puerperium**

Risk Factors for VTE / Score

Pre-existing risk factors	Score
Previous VTE (except a single event related to major Surgery)	4
Previous VTE provoked by major surgery	3
Known high-risk thrombophilia	3
Medical comorbidities e.g. cancer, heart failure; active systemic lupus erythematosus, inflammatory polyarthropathy or inflammatory bowel disease; nephrotic syndrome; type I diabetes mellitus with nephropathy; sickle cell disease; current intravenous drug user	3
Family history of unprovoked or estrogen-related VTE in first degree relative	1
Known low-risk thrombophilia (no VTE) Age (> 35 years)	1a
Obesity	1 or 2b
Parity ≥ 3	1
Smoker	1
Gross varicose veins	1

Obstetric risk factors	Score
Pre-eclampsiaincurrent pregnancy	1
ART/IVF(antenatalonly)	1
Multiple pregnancy	1
Currentsystemicinfection	1
Caesareansection in labour	2
Electivecaesarean section	1
Mid-cavity orrotationaloperativedelivery	1
Prolongedlabour(>24hours)	1
PPH(>1 litreortransfusion)	1
Pretermbirth <37+0 weeksin current pregnancy	1
Stillbirthincurrent pregnancy	1

Transient risk factors	Score
Anysurgicalprocedurein pregnancyorpuerperiumexcept immediaterepairofthe perineum,e.g.appendicectomy, postpartumsterilisation	3
Hyperemesis	3
OHSS(firsttrimesteronly)	4
Currentsystemicinfection	1
Immobility,dehydration	1

Scoring of Thrombophilia[19]

Score	Routine thromboprophylaxis with LMWH
01	No
02	Postnatally only-consider for at least 10 days post- partum
03	Consider from 28 weeks antenatal and 6 weeks postnatal
04	Throughout antenatal period and 6 weeks postnatal

Risk assessment for venous thromboembolism (VTE)

Antenatally

- Iftotalscore≥4,considerthromboprophylaxis from the first trimester.
- If total score 3, consider thromboprophylaxis from 28 weeks.

Postnatally

- Iftotalscore≥2,considerthromboprophylaxis for at least 10 days.

If admitted to hospital

- Antenatally……consider thromboprophylaxis.
- Prolonged admission…. (≥ 3 days) / readmission to hospital within the puerperium……. consider thromboprophylaxis.

Diagnosis of Thrombophilia in pregnancy

- **History**

Pregnant women with the following history may be investigated for inherited or acquired thrombophilias:

- Strong family history of venous thrombo-embolic disease in 1st and 2nd degree relatives - check only for inherited thrombophilias.
- Recurrent miscarriages (three or more first trimester miscarriage)
- Second trimester fetal loss 12 - 20 weeks
- Any previous history of venous thrombosis in pregnancy
- Stillbirth
- Early-onset preeclampsia (< 34 weeks gestation)
- IUGR (delivery < 34 weeks gestation)[19,20]
- **Previous VTE**

This should be confirmed, where possible, by looking at the woman's record.

- ***If confirmed, it is recommended that the woman should have antenatal and 6 weeks post-natal LMWH at a prophylactic dose.***
- If a previous VTE occurred in context of major surgery and there are no other risk factors decision about thromboprophylaxis should be taken in obstetric/haematology clinic.
- Thromboprophylaxis with LMWH should be started as soon as possible after pregnancy has been confirmed, ideally, this can be done prior to the first antenatal clinic visit.

Investigations

Investigations may include venous blood for:

- Lupus anticoagulant
- Protein C and S
- Activated protein C resistance (APCR)
- Factor V Leiden
- Prothrombin gene
- MTHFR
- Homocysteine
- Anticardiolipin antibody.[20]

Timing of the VTE risk assessment

- At booking by midwife.
- At 28 weeks the assessment should be **repeated**.

Should be done by the community midwife, unless the woman has a hospital visit scheduled for this time.

Women who score 3 or more at 28 weeks should be offered antenatal thromboprophylaxis for the remainder of their pregnancy.

- On admission to **hospital** and **reassessed** every **five days.**
- Women who remain in the community but have other problems,
- Hyperemesis
- Ovarian hyperstimulation,
- Factors leading to immobility,
- Concurrent illness, Should be reassessed and given LMWH if they score three or more.

- At **delivery** or immediately **post-partum**.[19]

Delivery

Some women will be at a particularly high thrombotic risk and will have an individualised plan for LMWH. These women will have been seen in the obstetric/ haematology clinic and the plan will be written in their part 1 and on Medway.[19]

- Spontaneous labour
- Induction of labour
- Caesarean section

Spontaneous Labour

- Women should be advised to **omit** the LMWH at the onset of labour.
- Such women should be assessed on delivery suite to confirm the onset of labour. If labour is not confirmed, they should continue to take their LMWH.
- Women who have **vaginal bleeding** should **omit** their LMWH until they have been assessed by medical staff.
- Women who labour successfully within the **twelve hours** window can be reassured that their risk of major haemorrhage is similar to women who do not take LMWH, most of the haemostasis after delivery is down to uterine tone. However, third stage should be managed actively.[19]

Induction of Labour

- Take the **last dose** of LMWH the day before**, at least 12 hours** before the start of the planned induction.
- **Restart** the same dose of prophylactic LMWH on the **same day** as delivery, taking into account the timing of regional analgesia.

Caesarean Section

- Take the **last dose** of LMWH the day before; this should be at least **12 hours** before the time planned for caesarean.
- All emergency caesarean sections require **ten days postnatal prophylaxis**. This will be extended to six weeks if there are additional risk factors (these will have been highlighted in the antenatal period).
- Women who have undergone an elective caesarean section, and are suitable for the enhanced recovery pathway, do not require.
- LMWH once mobile if they do not score for any other risk factor (i.e. their antenatal score was 0, the caesarean section is their only risk factor).
- Women who require thromboprophylaxis should receive LMWH for ten days.

Caution during using of Regional Analgesia

- Regional anaesthetics are **avoided** for the **first twelve hours** following a prophylactic dose of LMWH.
- This period is **longer** for women who have had therapeutic LMWH, such cases should be discussed with the obstetric anaesthetist (it is usually 24 hours).
- LMWH should **not be given for 4 hours** after the use of a spinal. anaesthetic, or after the epidural catheter has been removed.
- The **epidural catheter** should not be removed within twelve hours of the most recent injection.[19]

Post-Partum

- The prothrombotic changes associated with pregnancy **do not revert** to normal until several weeks after delivery.
- The puerperium is a particularly high risk period for VTE.
- In the six weeks following delivery the risk is equal to that in the whole of the precedingpregnancy.[19]
- The relative risk postpartum is five-fold higher compared to antepartum[21] and a systematic review of risk of postpartum VTE found that the risk varied from 21- to 84-fold from the baseline nonpregnant, nonpostpartum state in studies that included an internal reference group.[22]
- The absolute risk peaked in the first 3 weeks postpartum (421 per 100 000 person-years; 22-fold increase in risk).[22]
- All women should have the VTE Risk Assessment (Appendix 1) completed
- If required, their LMWH/LMWH + Graduated elastic compression stockings (GECS) prescribed before transfer from Delivery Suite.
- The postnatal assessment score is added to the booking visit score.

Postpartum Thromboprophylaxis

Many women will **not** require pharmacological thromboprophylaxis but vigilance is necessary at this time to detect the onset of new risk factors,

- immobility secondary to excessive blood loss or postpartum infection, which may alter the risk profile.
- If the woman encounters new risk factors during this time a further risk assessment must be performed and management adapted accordingly.

- Women at **high risk** of VTE should have **6 weeks postnatal thromboprophylaxis**.
- Women at **intermediate risk**, a recommendation of a minimum **10 days** is given.
- Women with **no** risk factors following vaginal delivery should be encouraged to mobilise early and avoid dehydration.
- Women who have additional persistent (lasting more than 10 days postpartum) risk factors, such as prolonged admission, wound infection or surgery in the puerperium, thromboprophylaxis should be extended for up to **6 weeks** or until the additional risk factor/s is/are no longer present.
- Women who remain as in-patients after 10 days but are well and mobile are likely to be at no greater risk than they would have been at home and can stop their thromboprophylaxis.

Suggested thromboprophylactic doses for antenatal and postnatal LMWH

Weight	Enoxaparin	Dalteparin	Tinzaparin (75 u/kg/ day)
< 50 kg	**20 mg daily**	**2500 units daily**	**3500 units daily**
50-90 kg	**40 mg daily**	**5000 units daily**	**45000 units daily**
91-130 kg	**60 mg daily***	**7500 units daily**	**7000 units daily***
131-170kg	**80 mg daily***	**10 000 units daily**	**9000 units daily***
>170kg	**0.6 mg/kg day***	**75 u/kg/day**	**75 u/kg/day***
High prophylactic dose for women weighing 50-90kg	**40 mg 12 hourly**	**5000 units 12 hourly**	**45000 units 12 hourly**

*may be given in 2 divided doses

The 28 week and delivery assessment should be scored using the woman's weight at that time

RCOGrecommendations

- *Prepregnancy and antenatal risk assessment*
- Previous VTE
- Stratification of women with previous VTE
- Testing for thrombophilia in women with prior VTE
- *Timing of initiation of thromboprophylaxis*
- Thrombophilia in women at high risk of harmorrhage
- Asymptomatic thrombophilia
- Caesarean section
- Which agents should be used for thromboprophylaxis?
- *Contraindications to LMWH*
- *Risk scoring methodologies*

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