Chapter

Venous Thromboembolism in the Context of Reproduction: The Royal College of Obstetricians and Gynecologists Recommendations

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Abstract

Venous thromboembolism complicates 1–2 of every 1000 deliveries. It may manifest as deep vein thrombosis or pulmonary embolism. Pregnancy-associated venous thromboembolism is an important major cause of maternal morbidity and mortality. Prophylaxis and therapy in pregnancy are complicated by the need to take both fetal and maternal well-being into consideration. Risk factors for venous thromboembolism during pregnancy or the puerperium are multiple. They include, but are not limited to, thrombophilia, multiparity, orthopedic injuries, medical comorbidities, prior venous thromboembolism, smoking, gross varicose veins, age, if older than 35, obesity, multiple pregnancy, preeclampsia, cesarean section, prolonged labor, instrumental vaginal delivery, stillbirth, preterm birth, postpartum hemorrhage, hyperemesis gravidarum, ovarian hyperstimulation syndrome, immobility, long periods of hospitalization, and long haul travel. This chapter is a clinical guide that covers prophylaxis and therapy of pregnancy-associated venous thromboembolism, based on evidence-based research and consensus opinion.

Keywords: obstetrics, pregnancy, prophylaxis, deep vein thrombosis, pulmonary embolism, anticoagulants

1. Introduction

Worldwide, childbearing carries a major risk to the life of women [1]. The Millennium Development Goals (MDGs) were the eight international development goals, and the 192 United Nations states and 23 international organizations had agreed to achieve those goals. Reducing maternal mortality by three quarters over 15 years was a specific part of Goal 5 (Improving Maternal Health) of the eight MDGs [2].

The WHO defines maternal mortality as "the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes" [3].

The maternal mortality ratio (MMR) is a key performance indicator for efforts to improve the safety of mothers before, during, and after childbirth per country. It is the annual number of deaths per 100,000 live births from causes related to or aggravated by pregnancy or its management (not accidental or incidental). It is not to be confused by the maternal mortality rate, which is the number of deaths (direct

and indirect) in a given period per 100,000 women of reproductive age during the same time period [1–3].

The regional MMRs for the year 2015 ranged from 11 to 14 for developed regions to 511–652 for sub-Saharan Africa [4].

In a study that estimated the MMR (maternal deaths per 100,000 live births) among Jordanian women aged between 15 and 49 years, there were 76 maternal deaths out of 397,588 live births. The MMR being 19.1. Of these, 43 (56.6%) deaths were caused by hemorrhage, thrombosis, and sepsis [5].

In this same study, avoidable deaths were found in 53.9% of the dead women, 52.6% had substandard care, and 31.5% were poor hospital attenders, having had three or less antenatal visits [5].

Regarding family planning, less than one third of the 76 dead women had ever used any form of contraception [5].

2. Epidemiology

The incidence of venous thromboembolism (VTE) is 1–2 per 1000 pregnancies. In the antenatal period, there is a fivefold higher incidence than nonpregnant women of same age, with deep venous thrombosis (DVT) being more common. In the postnatal period, there is a 20-fold higher incidence, with pulmonary embolism (PE) being more common. Therefore, VTE is considered as one of the leading causes of pregnancy-related deaths [6–10].

3. Pathophysiology

The German physician, anthropologist, pathologist, prehistorian, and "father of modern pathology," Rudolf Virchow (1821–1902), postulated a triad to explain the pathophysiology of the increased incidence of VTE in pregnancy, as follows [11]:

1. Compression of Lt iliac vein by Rt iliac artery or ovarian artery, with 90% DVT on left (vs. 55% nonpregnant), and 70% in iliofemoral veins (vs. 9% nonpregnant)

2. Hypercoagulability

   - Increased clotting factors V, VII, VIII, X, VWf, and fibrinogen
   - Increased resistance to protein C
   - Decreased protein S activity
   - Increased levels of fibrinolytic inhibitors via decreased tissue plasminogen activators and increased plasminogen activator inhibitors
   - Acquired antithrombin III deficiency

3. Endothelial injury

   - Compression by the uterus (and edema)
   - Vascular damage during delivery

There are identifiable risk factors in numerous fatal and nonfatal cases of PE in relation to VTE in pregnancy and puerperium. Therefore, there is a need for risk stratification to determine pharmacological thromboprophylaxis [12].

The risk assessment may be conducted in early pregnancy or prepregnancy at antenatal clinics, at admission to hospital for any reason, intrapartum and immediately postpartum [13].

Hypercoagulability or prothrombotic states increase the risk of thrombosis. Pathologies of this kind are found in a large proportion of women who report one or more episodes of hypercoagulability, such as lower limb or pelvic vein thrombosis, especially when these occur without being provoked by other conditions. A significant number of women have a detectable thrombotic abnormality, where the majority would develop VTE that is related to one or more additional prothrombotic risk factors [13].

4. History

Following the description of the development of thrombosis in 1856 by Virchow, antithrombin deficiency was described in 1965 by Norwegian hematologist Egeberg [14]. Researchers from the Scripps Research Institute described protein C deficiency in 1981 [15]. Researchers at the University of Oklahoma described protein S deficiency in 1984 [16–18].

Graham Hughes, British rheumatologist, described antiphospholipid syndrome 1980s after the finding of antibodies that were associated with SLE and thrombosis [19].

In the 1990s, more studies described genetic thrombophilias and resistance to activated protein C. In 1994, researchers from Leiden, the Netherlands, described a mutation that affected factor V, which made it resistant to activated protein C. Being a genetic defect, it was named factor V Leiden mutation, after its place of discovery [20]. This was followed by the discovery of prothrombin gene mutation by the same group. This mutation results in an increase in prothrombin levels, which may result in some thrombotic episodes [21].

Studies of the human genome and minor gene changes are likely to reveal more genetic abnormalities in cases of hereditary thrombosis [16, 17].

5. Thrombophilia classification

Thrombophilia can be congenital or acquired. Congenital thrombophilia refers to hereditary conditions that increase the tendency to develop thrombosis, while acquired thrombophilia arise later in life [22–24]. The types of thrombophilia are:

Inherited thrombophilias

- Factor V Leiden mutation
- Prothrombin C 20210 mutation (PTM)
- Antithrombin III deficiency
- Protein S deficiency
- Protein C deficiency
- MTHFR mutation (homocysteine)

Acquired thrombophilias - Antiphospholipid syndrome

- Anticardiolipin antibodies
- Lupus anticoagulant antibodies
- Anti β2 glycoprotein 1 antibodies

Thrombophilia is divided into two groups according to risk types:
High risk

- Factor V Leiden mutation, homozygous
- Prothrombin C 20210 mutation, homozygous
- Antithrombin III deficiency
- Antiphospholipid syndrome

Low risk

- Factor V Leiden mutation, heterozygous
- Prothrombin C 20210 mutation, heterozygous
- Protein S deficiency
- Protein C deficiency

Most thrombophilias have no specific therapy, but when thrombosis is recurrent, long-term prophylactic anticoagulation is necessary [22–24].

In general, thrombophilia testing is required for women with history of idiopathic or recurrent episodes of VTE, in addition to women with history of thrombophilia in a first-degree relative [25–28].

6. Risk factors

The risk factors for VTE are:

- Thrombophilia
- Parity of three children or more
- Major orthopedic surgery
- Lower-extremity paralysis due to spinal cord injury
- Fracture of the pelvis, hip, or long bones
- Multiple trauma
- Paraplegia

- Medical comorbidities, for example, cancer, heart failure, SLE, nephrotic syndrome, type I diabetes mellitus with nephropathy, sickle cell disease, and drug addiction
- Prior VTE
- Smoking
- Gross varicose veins
- Age, if older than 35
- Obesity (BMI more than 30)
- Multiple pregnancy
- Preeclampsia
- Cesarean section
- Prolonged labor
- Mid-cavity-assisted vaginal delivery
- Stillbirth
- Preterm birth
- Postpartum hemorrhage
- Hyperemesis and dehydration
- Ovarian hyperstimulation syndrome (OHSS)
- Immobility, such as hospitalization and during long travel
- Oral contraceptives or estrogen treatment for menopause symptoms
- Family history of VTE, especially in a first-degree relative
- Physical inactivity

7. Thromboembolic risk profile

Women who are pregnant or have just had a baby are at greater risk of developing a blood clot. The risk is greater in the presence of other factors. A score is given to each risk factor as follows:

- 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 = 3
- Obesity BMI ≥ 30 = 1; BMI ≥ 40 = 2
- Cesarean section in labor = 2
- Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum + = 3
- Hyperemesis =3
- OHSS (first trimester only) = 4
- Any other = 1

8. Thromboprophylaxis

Prophylaxis is administered according to the risk assessment's total score as follows:

- ≥4 antenatal: prophylaxis from first trimester and puerperium
- 3 antenatal: prophylaxis from 28 weeks and puerperium
- ≥2 postnatal: prophylaxis for at least 10 days

There should be a lower postnatal threshold for prophylaxis than antenatally as risk per day is higher and duration of risk is shorter.

Women with antithrombin deficiency are often on long term oral anticoagulants, and extra advice is necessary as follows:

- Prophylaxis with a higher dose of low molecular weight heparin (LMWH) antenatally and 6 weeks postpartum or until return to oral therapy
- Anti-Xa monitoring (4-h peak levels 0.5–1.0 iu/ml)
- Possible antithrombin therapy at start of labor or prior to cesarean section (CS)

Women with previous recurrent VTE need extra advice as follows:

- Higher doses of LMWH
- If on long-term warfarin or other oral anticoagulants
    - Counsel about the risks to the fetus
    - Stop oral therapy, change to LMWH, within 2 weeks of the missed period and before the sixth week of pregnancy
- Not on oral anticoagulants: LMWH as soon as pregnancy test is +ve

There are other first trimester risk factors for VTE that include:

- Women with hyperemesis should be considered for prophylaxis with LMWH. Discontinue when it resolves
- Women with OHSS need prophylaxis with LMWH in the first trimester
- In vitro fertilization pregnancy and three other risk factors need prophylaxis, with LMWH starting in the first trimester

Thromboprophylaxis should be interrupted for delivery in the case of any vaginal bleeding or labor, no further LMWH is administered [13].

When regional anesthetic techniques are considered, the following should be implemented:

- Avoid for 12 h after the previous prophylactic dose of LMWH
- No LMWH for 4 h after spinal or after epidural catheter removal
- No catheter removal for 12 h of injection
- If on a therapeutic LMWH, it should be avoided for 24 h after the last dose

With regard to prophylaxis in labor and delivery:

- Women on antenatal LMWH having an elective CS should receive prophylactic LMWH on the day prior to CS
- The morning dose on CS day should be omitted, the operation should take place that morning
- The first prophylactic dose of LMWH should be given 4–6 h after vaginal delivery, 6–12 h after CS (if no postpartum hemorrhage or regional anesthesia)
- Women with previous VTE and postpartum thromboprophylaxis should receive LMWH or warfarin for at least 6 weeks regardless of mode of delivery
- Women that undergo emergency CS should receive cover with LMWH for 10 days. The same applies for elective CS in the presence of additional risk factors

With regard to LMWH:

- It is the agent of choice for antenatal and postnatal prophylaxis
- For prophylaxis, the doses based on booking or most recent weight
- Platelet count needs monitoring only if prior exposure to unfractionated heparin (UFH)
- No need for monitoring of anti-Xa levels if LMWH is for prophylaxis

- LMWH should be reduced in renal impairment
- LMWH is safe in breastfeeding

Unfractionated heparin should be considered in cases of very high risk of thrombosis, and an increased risk of hemorrhage, UFH may be used peripartum, especially if regional anesthetic may be required. If UFH is used, platelet count should be monitored every 2–3 days from days 4–14 or until UFH is stopped [13].

The molecular weight (MW) of natural heparin is 5000–40,000 Daltons. The MWH is less than 8000 Daltons. The half-life of UFH is 1–2 h, whereas LMWH is 4–8 h.

Danaparoid and fondaparinux are used only when heparins cannot be used due to heparin induced thrombocytopenia or a skin allergy and perhaps should be prescribed by a hematologist with expertise in hemostasis in pregnancy. Regional anesthesia is to be avoided because of 24-h half-life [13].

Low-dose aspirin is not recommended for thromboprophylaxis in obstetric patients [13].

Dextran should be avoided antenatally and intrapartum because it is less effective than LMWH, increases the risk of bleeding and anaphylaxis that has been associated with uterine hypertonus, fetal distress, fetal neurological abnormalities, and fetal death [13].

Oral thrombin and Xa inhibitors are non-vitamin K antagonist oral anticoagulants (NOACs) that should be avoided in pregnant women and are not currently recommended in breastfeeding [13].

Warfarin crosses placenta. If used between 6 and 12 weeks, there is a dose-dependent risk of embryopathy, as 5% of fetuses develop nasal bridge hypoplasia, heart defects, vetriculomegaly, agenesis of corpus callosum, and stippled epiphysis. In addition, it is associated with an increased incidence of spontaneous miscarriage, stillbirth, neurological problems, and fetal and maternal hemorrhage. Its use in pregnancy is restricted to women with mechanical heart valves. It is safe in breastfeeding, and may convert from LMWH to warfarin postpartum when risk of hemorrhage is low, 5–7 days after delivery [13].

The suggested daily thromboprophylactic doses for antenatal and postnatal LMWH are weight dependent. For the average weight of 50–90 kg, the doses of enoxaparin, dalteparin and tinzaparin are 20 mg, 2500 and 3500 iu, respectively.

Contraindications to LMWH are the following:

- Known bleeding disorder
- Previous or current allergic reactions
- Active antenatal or postpartum bleeding
- High risk of major hemorrhage
- Thrombocytopenia $<75 \times 10^9/l$
- Acute stroke in previous 4 weeks
- Severe renal or liver disease
- Uncontrolled hypertension

9. Acute management of VTE

Diagnosis of acute VTE requires high index of suspicion. Its symptoms and signs are:

- Leg pain and swelling, usually unilateral
- Lower abdominal pain
- PE: dyspnea, chest pain, hemoptysis and collapse
- Low-grade pyrexia and leukocytosis can occur

The symptoms or signs of VTE require objective testing and treatment with LMWH expeditiously. If DVT remains untreated, 20% will develop pulmonary embolism (PE), which, in pregnancy is fatal in 15%, and in 66% of these, death will result within 30 min of the embolic event [13], that is, there are three deaths per 100 DVTs.

The investigations for suspected DVT include compression duplex ultrasound, CBC, coagulation screen, kidney, and liver function tests. D-dimer and thrombophilia screen are not recommended prior to therapy [13].

The following is recommended in the initial anticoagulant treatment of VTE in pregnancy:

- Clinically suspected DVT or PE, LMWH immediately until the diagnosis is excluded by objective testing, unless strongly contraindicated
- LMWHs are not associated with an increased risk of severe PPH
- Lower risk of heparin-induced osteoporosis with LMWH versus UFHs
- LMWH titrated against booking or early pregnancy weight. Insufficient evidence for once daily or in two divided doses
- No routine peak anti-Xa activity of LMWH except in weight < 50 kg and > 90 kg or with renal impairment or recurrent VTE
- Routine platelet count monitoring should not be carried out
- Initial management of DVT, leg elevation, and a graduated elastic compression stocking. Mobilization with graduated elastic compression stockings
- Temporary IVC filter peripartum for patients with iliac vein VTE to reduce the risk of PE or recurrent PE despite adequate anticoagulation
- Therapeutic doses of subcutaneous LMWH for the remainder of pregnancy and for at least 6 weeks postnatally and for at least 3 months of treatment in total
- Because of their adverse effects on the fetus, warfarin should not be used for antenatal VTE treatment

With regard to anticoagulation during labor and delivery, the following should apply:

- VTE at term: consider IV UFH, more easily manipulated
- If on LMWH for maintenance and in early labor, no further heparin
- Planned elective CS or induction of labor, discontinue LMWH maintenance 24 h in advance
- No regional anesthesia or analgesia for 24 h after therapeutic LMWH dose
- No LMWH for 4 h after spinal anesthesia or after epidural catheter removal. No epidural catheter removal within 12 h of the most recent injection

The initial daily therapeutic doses of enoxaparin, dalteparin, and tinzaparin are weight dependent, their initial doses for the average women between 50 and 90 kg are 60 mg twice daily or 90 mg once daily, 6000 iu twice daily or 1200 iu once daily, 175 iu/kg once daily, respectively [13].

For anticoagulated patients undergoing CS, the following is recommended:

- If therapeutic doses of LMWH: wound drains (abdominal and rectus sheath) at CS. Skin closure with interrupted sutures for drainage of any hematoma
- Women at high risk of hemorrhage, in whom continued heparin is considered essential, manage with IV UFH until the risk factors for hemorrhage resolve

The regimen for the IV UFH is:

- Loading dose of 80 u/kg, followed by a continuous IV infusion of 18 u/kg/h
- In case of thrombolysis, omit loading dose and infusion starts at 18 u/kg/h
- Mandatory APTT 4–6 h after loading dose, 6 h after dose change, then daily when in therapeutic range. The target is 1.5–2.5 X control value
- The infusion rate should be adjusted according to the APTT

To monitor heparin therapy in pregnancy, routine measurement of peak anti-Xa activity of LMWH for acute VTE, if body weight is less than 50 and more than 90 kg, in renal impairment or recurrent VTE is required. Postoperative women receiving UFH should have platelet count every 2–3 days until heparin is stopped. Women are taught to self-inject LMWH and to safely dispose needles etc. [13].

In cases of acute PE, CXR, compression duplex ultrasound and ECG should be performed. ECG may show "S1Q3T3" pattern (large S wave in lead I, Q wave in lead III, and inverted T wave in lead III), Rt BBB, M wave V1 and broad S V6, due to acute right heart strain [13].

If DVT is present, no further investigations are required, and treatment should continue [13].

In suspected PE without symptoms and signs of DVT, CT pulmonary angiogram or V/Q lung scan should be performed. If CXR is abnormal with suspicion of PE, CTPA is better than V/Q scan. In cases of normal ventilation with multiple segmental perfusion deficits, the probability of PE is 80%. There is a slightly increased

risk of childhood Ca but lower risk of maternal breast Ca than CTPA. The absolute risk is very small in both [13].

Anticoagulation should be continued until PE is definitively excluded [13].

In acute PE, it is recommended that:

- Shocked women who are pregnant or in the puerperium are managed individually regarding IV UFH, thrombolytic therapy or thoracotomy and embolectomy
- Multidisciplinary involvement of senior physicians, obstetricians, surgeons, and radiologists
- IV UFH is preferred in massive PE with cardiovascular compromise
- Urgent portable ECG or CTPA within 1 h of presentation. Immediate thrombolysis should be considered
- Maternal resuscitation as per immediate life support. Cardiopulmonary resuscitation in a left lateral tilt. Perimortem CS by 5 min if resuscitation is unsuccessful and the pregnancy is more than 20 weeks

10. Key points

- LMWH is the agent of choice for antenatal prophylaxis
- Score ≥ 4 antenatal: prophylaxis in first trimester and 6 weeks postnatally
- Score = 3 antenatal: prophylaxis from 28 weeks and 6 weeks postnatally
- Score ≥ 2 postnatal: prophylaxis for a minimum of 10 days
- Women on antenatal prophylaxis are for postnatal prophylaxis for 6 weeks
- Women with symptoms or signs of VTE should have LMWH until the diagnosis is excluded by objective testing, unless strongly contraindicated
- All women should undergo a documented thromboembolic risk profile for VTE before conception and in early pregnancy
- The documented thromboembolic risk profile should be repeated if admission to hospital is required or if an intercurrent medical condition does occur
- A repetition of the thromboembolic risk profile is required intrapartum and in the immediate postpartum period

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