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Health Service Executive

INSTITUTE OF OBSTETRICIANS & GYNAECOLOGISTS
ROYAL COLLEGE OF PHYSICIANS OF IRELAND

CLINICAL PRACTICE GUIDELINE

VENOUS THROMBOPROPHYLAXIS IN PREGNANCY

Institute of Obstetricians and Gynaecologists,
Royal College of Physicians of Ireland
and
HSE Clinical Care Programme in
Obstetrics and Gynaecology
and
Irish Haematology Society

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Key Recommendations

1. Women at risk of venous thromboembolism should ideally have a preconceptual assessment to outline the management plan for their pregnancy.

2. All women should have a risk assessment for venous thromboembolism documented at the booking antenatal visit.

3. Venous thromboembolism risks should be re-assessed at every episode of hospitalisation.

4. Low Molecular Weight Heparins (LMWHs) are the agents of choice for venous thromboembolism prophylaxis in pregnancy.

5. Peripartum management of women requiring thromboprophylaxis should be individualised and a delivery plan documented in the antenatal notes.

6. All women should be assessed after delivery for the need for thromboprophylaxis.

7. Women who are at particularly high risk of thrombosis must be managed in a combined haematology and obstetric service with experience in managing these groups of patients.

8. In general, testing for inherited thrombophilia is not indicated for placenta-mediated pregnancy complications. Such testing may be considered if there is a history of early onset preeclampsia resulting in delivery before 34 weeks gestation; low molecular weight heparin plus aspirin in subsequent pregnancies may improve outcome.

9. If testing for inherited thrombophilia is indicated, testing should be undertaken after explaining to the woman:
   (i) The uncertainty of the clinical significance
   (ii) The significance for family members
   (iii) The clear referral pathway to haematology is already in place

1. Purpose and Scope

The purpose of this guideline is to be a practical and user-friendly aid in improving the management of women with a moderate to high risk of venous thromboembolism in pregnancy and the puerperium. These guidelines are intended for maternity care health professionals, including those in training, who are working in HSE-funded obstetric and gynaecological services. They are designed to guide clinical judgement but not replace it. In individual cases a healthcare professional may, after careful consideration, decide not to follow a guideline if it is deemed to be in the best interests of the woman and her baby.

This guideline is based on consensus and is not designed to replace evidence based guidelines such as those published by the American College of Chest Physicians and the British Society for Haematology.

2. Background and Introduction

Venous thromboembolism (VTE) remains a leading cause of maternal mortality and morbidity. Maternal death caused by VTE was at a plateau until the most recent triennium when it has fallen. The absolute risk of VTE, however, is low (<1 per 1000 deliveries). Therefore, there are very few randomised trials to guide management choices. Clinical guidelines rely significantly on expert opinion. Evidence is frequently based on data from the non-pregnant population which has been extrapolated to pregnant women.

Low molecular weight heparins (LMWH) are the anticoagulant of choice for thromboprophylaxis in pregnancy and there is now a considerable experience of their use in pregnancy. LMWH appears to have an excellent safety profile in pregnancy (Greer, Nelson-Piercey 2005).

Inherited thrombophilias have been the focus of intense study over the past decade. Associations have been described between inherited thrombophilias and VTE (Robertson, 2006), and between inherited thrombophilias and the common pathologies in pregnancy (PET, IUGR, placental abruption, stillbirth) (Said 2010). The strength of these associations is weak. There is a growing consensus that in women at risk of both VTE and/or pregnancy complications there has been excessive testing for inherited thrombophilias (Rodgers, 2011).

Obese pregnant women who are hospitalised are at particular risk of VTE (Morgan 2012). There is poor data about optimal drug dosage in this group.

3. Methodology

Medline and the Cochrane Database of Systematic Reviews were searched using terms relating to thromboprophylaxis in pregnancy. Searches were confined to

the titles of English language articles published between Jan 2000 and July 2012. Relevant meta-analyses, systematic reviews, intervention and observational studies were sought. Guidelines reviewed included the Clinical Practice Guideline Royal College of Obstetricians and Gynaecologists (RCOG) Guideline No. 37a (2009); British Committee for Standards in Haematology (BCSH) Clinical Guideline for Testing Heritable Thrombophilia (2010) and Guidelines on the Investigation and Management of Antiphospholipid Syndrome (2012); American College of Chest Physician (ACCP) VTE, Thrombophilia, Antithrombotic Therapy and Pregnancy, 9th ED: ACCP Guideline (2012); American College of Obstetricians and Gynaecologists (ACOG) Practice Bulletin No. 123 (2011) and Practice Bulletin No. 124 (2011);Scottish Intercollegiate Guideline Network (SIGN) Guideline No. 122 (2010);European Society of Regional Anaesthesia (ESRA) Guidelines on Anticoagulation and Regional Anaesthesia (2007); Association of Anaesthetists of Great Britain and Ireland (AAGBI) Regional Anaesthesia in Patients with Abnormalities in Coagulation (2011). There are contrasting views in international guidelines on initiation, dosing and duration of thromboprophylaxis in pregnancy and postpartum. There is lack of randomised controlled trials to guide the management, thus, practice is guided not only by published guidelines but also by the large observational studies and clinical reviews.

The principal guideline developers were Professor John R Higgins, Dr. Siti K Ismail from the Anu Research Centre, Department of Obstetrics & Gynaecology, University College Cork and Dr. Susan O'Shea and Dr. Caroline Noone from the Comprehensive Coagulation Centre, Cork University Hospital. Further consultation took place with Consultant Haematologists nationally with experience in Obstetric Haematology. This guideline was presented for open discussions at the Joint Obstetrics and Haematology Study Day in Cork on 30th March 2012 and at the 2nd National Meeting on Medical Disorders in Pregnancy in Mullingar on 18th May 2012. This guideline was widely disseminated for consultation by the National Obstetrics and Gynaecology Clinical Care Programme and reviewed by the Association for the Improvement of the Maternity Services (AIMS) and the Clinical Advisory Group of the Institute of Obstetricians and Gynaecologists. This guideline is endorsed by the Irish Haematology Society (IHS).

4. Clinical Guidelines

4.1 Preconceptual Assessment

Recommendation:

- **Women at risk of venous thromboembolism (VTE) should ideally have a preconceptual assessment to outline the management plan for their pregnancy.**

VTE remains a leading cause of maternal mortality death in the UK (11% of all maternal deaths). In the CMACE 2011 report which covers 2006-2008 a maternal mortality rate of 0.79 per 100,000 maternities or 18 deaths was attributed to VTE and also a further four late deaths due to pulmonary embolism. This represents a sharp and statistically significant fall from 41 deaths in 2003–2005. The period from 2006-2008 represents the first full triennium since the publication of the first 2004 RCOG guidelines *"Thromboprophylaxis during pregnancy, labour and after normal vaginal delivery"*. It can be extrapolated that this reduction in mortality is due to better recognition of the risk factors for thromboembolism and increased use of thromboprophylaxis.

The highest risk for VTE is in the postpartum period but it must be remembered that VTE related deaths occur in all three trimesters of pregnancy. Indeed a three-decade observational study demonstrated that thrombotic events in pregnancy occur from early first trimester right through to the postpartum period (Heit 2005). Coagulation studies demonstrate activation of the haemostatic system from early pregnancy (McLean 2012, Dargaud 2010). Thromboprophylaxis should be instituted from the earliest possible stages of an at-risk pregnancy. Therefore women known to be at risk should be seen and counselled preconceptually.

4.2 Venous Thromboembolism Risk Assessment

Recommendations:

- **All pregnant women should have a documented risk assessment for VTE at their booking visit.**

- **VTE risk should be reassessed at each and every episode of hospitalisation, after delivery and on discharge.**
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- **Women with a past history of VTE (except those with a single episode of VTE provoked by a transient risk factor not related to oestrogen or pregnancy- see discussion below) should receive antenatal VTE prophylaxis and postpartum VTE prophylaxis for six weeks.**

The RCOG Green-top Guideline (No. 37a, 2009) has popularised a complex stratified risk assessment scoring scheme. It is widely referenced. The approach is based on the premise that multiple risk factors increase the risk of VTE. However, thromboprophylaxis is a preventative intervention designed to prevent a rare, albeit serious, complication. There is almost a complete absence of randomised controlled trials. Thus, a complex clinical algorithm is not justified by the weak evidence base. A modified approach is shown in *Appendix A*.

In the first stage of this approach, women with past personal history of VTE are identified. These women should be offered both antenatal and postnatal LMWH thromboprophylaxis. The only exception would be in women with a previous personal history of VTE with a clearly identifiable major transient risk factor that is no longer present and who have no other risk factors. Such women can be offered surveillance antenatally followed by postpartum LMWH thromboprophylaxis.

The second stage of this approach identifies women who have at least three risk factors; and on this basis should be considered for LMWH thromboprophylaxis.

A personal history of a previous VTE is the most potent risk factor for VTE in pregnancy. Reported recurrence rates of VTE in pregnant women varies between 1.4-11.1% and a relative risk of 3.5 (95% confidence interval, 1.6-7.8). At least a quarter of all cases of pregnancy–related VTE are recurrent (Pabinger 2002). Using the limited data available, attempts have been made to risk-stratify women with a previous history of a single VTE based on whether the VTE was unprovoked (Brill-Edwards 2000), oestrogen-provoked (Pabinger 2002, De Stefano 2006), thrombophilia-associated (De Stefano 2006) or associated with a transient risk factor (Brill-Edwards 2000, De Stefano 2006). It is now broadly accepted that if the previous VTE was provoked by a major transient risk factor then the risk of recurrence antenatally is low compared with the other subgroups. Thus with this exception, all women with a previous VTE should receive antenatal and postpartum thromboprophylaxis.

Women with a common inherited thrombophilia (eg. Factor V Leiden, Prothrombin gene polymorphisms) and a history of VTE will usually be managed based on the clinical history. However, women who have antithrombin deficiency, or multiple thrombophilia should be reviewed by a specialist in obstetric haematology for individualised management.

The list of risk factors for VTE is by necessity extensive. However, age, parity and obesity are worthy of particular focus, not because of the strength of the association but because of the prevalence of these risk factors. Obesity in particular has been highlighted in recent confidential enquiries (CEMACH 2007, CMACE 2011) and elsewhere as being a particularly important risk factor. This is discussed below in more detail and is itself the subject of a specific national guideline (RCPI National Clinical Practice Guideline: Obesity and Pregnancy, 2011).

4.3 Use of Anticoagulants

Recommendations:

- **Low Molecular Weight Heparin (LMWH) is the anticoagulant of choice for VTE prophylaxis in pregnancy.**
- **Oral direct thrombin inhibitors (dabigatran), or anti-Xa inhibitors (rivaroxaban, apixiban) are not recommended.**
- **Fondaparinux and Intravenous direct thrombin inhibitors should be limited to women with severe allergic reactions to heparin and should only be prescribed by specialists in obstetric haematology.**

Compared with unfractionated heparin, LMWHs show a more predictive dose response curve, do not require regular monitoring and have a significantly better side effect profile in terms of heparin induced thrombocytopenia or osteoporosis. In the obstetric field, LMWHs are mainly indicated for treatment of venous thrombosis, arterial and VTE thromboprophylaxis and prevention of fetal loss in placental dysfunction in thrombophilic women (Patel 2008). There is good data demonstrating the safety of LMWH in pregnancy (Greer, Nelson- Piercey, 2005). New oral anticoagulants, with as yet unknown safety profile in pregnancy, are not recommended.

4.4 Low Molecular Weight Heparin Prophylaxis in Pregnancy

Recommendations:

- **Women receiving antenatal thromboprophylaxis should commence their treatment as soon as the diagnosis of pregnancy has been confirmed.**
- **Women receiving antenatal thromboprophylaxis should have an early pregnancy scan performed as soon as possible**

Observational studies have demonstrated that VTE events occur over the whole gestation (Blanco-Mollina 2010). There is mechanistic evidence suggesting that activation of the coagulation system starts early in pregnancy and thrombin generation is increased within the first trimester compared with pre-pregnancy (McClean 2012, Dargaud 2010). Hence, women who are advised to take antenatal LMWH thromboprophylaxis should commence as soon as pregnancy has been confirmed. The rationale for an early pregnancy scan in women receiving LMWH thromboprophylaxis is to ensure the presence of an intrauterine pregnancy.

4.4.1 Dosage and monitoring

Recommendations:

- **When prescribing LMWH at a prophylactic dose, once a day dosing is reasonable; there is no need for routine anti-Xa monitoring and if an initial platelet count and renal function are normal, there is no need for on-going monitoring.**
- **A weight-adjusted regimen should be used (see table 1).**
- **Anti-Xa monitoring is not recommended for the vast majority of patients. For selected patients with extreme body weight, renal impairment or severe pre-eclampsia, additional advice should be sought from haematology.**

LMWH binds less to plasma proteins, rendering a more predictable dose-response relationship and clinically making it unnecessary to monitor its anticoagulant effect (Hirsh 2001 &2004). Most LMWH preparations have a longer plasma half-life due to lower incidence of binding to macrophages and endothelial cells; this longer bioavailability makes it possible for once daily treatment (Weitz 1997).

Anti-Xa activity is not increased when a weight adjusted dose LMWHs was administered to non-pregnant obese patients; and increased bleeding complications were not observed (Hainer 2002, Sanderink 2002, Smith 2003, Rondina 2010). Hence, it is recommended to use weight-adjusted LMWH dosing with anti-Xa monitoring in women with extreme body weight. Anti-Xa monitoring may be considered in this situation. Since LMWH is cleared via the renal route and drug clearance may be affected in renal disease or severe pre-eclampsia, anti-Xa monitoring is reasonable in such situation.

The fixed dose of LMWH e.g tinzaparin 4500iu/kg/day or enoxaparin 40 mg/day covers most of the obstetric population. Weight-adjusted dosing should be considered in obese women (*table 1*).

4.4.2 Thromboprophylaxis in Third Trimester

Recommendations:

- **Timing for LMWH administration should be confirmed with the woman. Early morning injection is recommended.**
- **All women should be provided with education on the symptoms of labour and instructed not to take their injection if labour commences.**
- **All women should be reminded of the importance of postpartum thromboprophylaxis**

The above recommendations should be discussed and documented with the woman during a clinic visit in the third trimester

4.5 Peripartum Thromboprophylaxis

Recommendations:

- **Management of labour and delivery should be in accordance with usual obstetric indications. There is no contraindication to spontaneous labour.**
- **If a woman on thromboprophylaxis is suitable for induction, and it is acceptable to her, then induction can be used to optimise the timing in relation to thromboprophylaxis**

4.5.1 Regional Anaesthesia

Recommendations:

- **Women receiving a prophylactic dose of LMWH should not have an epidural or regional anaesthesia administered or an epidural catheter removed until 12 hours after the previous dose, assuming normal renal function.**
- **Prophylatic dose of LMWH may be commenced, not less than 6 hours post removal of the epidural catheter or administration of spinal anaesthesia.**

The Association of Anaesthetists of Great Britain and Ireland (AAGBI) suggests that LMWH may be commenced 4 hours after removal of epidural catheter while the European Society of Regional Anaesthetists (ESRA) recommends LMWH administration after 6-8 hours after epidural catheter removal. Thus, this guideline recommends that LMWH may be commenced after 6 hours. Occasionally patients will have an epidural catheter left *in-situ* and in such cases, it is recommended that removal of an epidural catheter is deferred until 12 hours after last LMWH prophylactic dose.

4.5.2 Caesarean Delivery

Recommendations:

- **All women who have had an emergency caesarean section should receive thromboprophylaxis until discharge or longer if additional risk factors for VTE are present.**

- **It is reasonable for all women who have undergone an elective caesarean section to be considered for thromboprophylaxis while in hospital as the benefits of LMWH may outweigh the risk.**

Thromboprophylaxis is commonly prescribed after an elective after an elective caesarean section. A retrospective study looking at a Canadian registry spanning 14 years showed that the odds ratio for developing venous thromboembolism is OR 2.2 (CI 1.5-3.2) after a low risk planned caesarean section compared to planned vaginal delivery (Liu 2007). There is no randomized control trial addressing this issue. While the ACCP Guidelines (Bates et al 2012) recommend against use of thromboprophylaxis other than early mobilisation for women undergoing elective caesarean section with no additional risk factors, recent decision analysis study suggested that the benefit outweighs the risk in low risk women (Blandon 2010). Therefore, it is reasonable to consider commencing LMWH in women post elective caesarean section even in a low risk setting.

4.5.3 Postpartum Thromboprophylaxis

Recommendations:

- **Every woman should have a repeat VTE risk assessment after delivery.**
- **All women who received antenatal LMWH thromboprophylaxis should continue on treatment for at least six weeks postpartum.**
- **Women with a documented thrombophilia, no previous personal history of VTE but a positive family history of VTE, should be considered for postpartum thromboprophylaxis for at least six weeks.**
- **If LMWH thromboprophylaxis is indicated postpartum, it should be given until the woman is fully ambulant. This will usually coincide with discharge from hospital.**
- **There is no evidence to guide the optimum length of postpartum thromboprophylaxis. It is not clear what the additional benefit in extending thromboprophylaxis up to 7 days post delivery.**
- **Thromboprophylaxis beyond discharge from hospital need only be offered to women at high risk of VTE**.

The optimum length for thromboprophylaxis postpartum is not defined. It would seem reasonable given the current data to offer prophylaxis until women are ambulant which usually coincides with them leaving hospital. The risk of VTE postpartum continues beyond this period; however there is little evidence to allow an estimation of the additional benefit which would accrue from

widespread use of thromboprophylaxis up to seven days postpartum (Heit 2005). There appears to be different views in international guidelines on this specific issue with the RCOG Green Top Guideline suggesting that patients with intermediate risk would require seven days treatment, i.e. continued LMWH after discharge; this contrasts with the ACCP (2012) which does not offer the same specific recommendation.

4.5.4 Breastfeeding and Anticoagulation

Recommendation:

- **LMWH and Warfarin are suitable anticoagulants for use during breastfeeding.**

For women who require postpartum thromboprophylaxis, LMWH is the agent of choice (Greer, 2005). It has the added advantage over warfarin of not requiring monitoring. Warfarin is also safe to use with breastfeeding, however it has the added disadvantages of increased risk of postpartum haemorrhage and perineal haematoma (RCOG 2009).

4.6 Special Groups of Women

4.6.1 Women on life-long anticoagulation

Recommendations:

- **Women on life-long anticoagulation need highly specialised management with haematology and obstetric input.**
- **These women should have pre-conception counselling**
- **These women may be switched to LMWH for the preconceptual period or changed from warfarin to LMWH after the diagnosis of pregnancy (within 6 weeks of conception).**

Women who are on life-long anticoagulation require therapeutic anticoagulation during pregnancy. These women must be managed by specialists in obstetric haematology and high risk pregnancy. For most of these women anticoagulation can be achieved with therapeutic LMWH dosing. This may be converted to a prophylactic LMWH dose at term so that the risk of delivering while therapeutically anticoagulated is diminished. In women with high risk of thrombosis, consideration may need to be given to a planned induction of labour to minimise the time the patient is not therapeutically anticoagulated.

Prophylactic LMWH should be given at 6 hours post delivery and increased to therapeutic anticoagulation at 24 hours post delivery, assuming there is no excessive bleeding.

Women who are on life-long anticoagulation should be repeatedly counselled of the importance of attending for early onset obstetric care. The teratogenic potential of warfarin is gestation dependant. The risks are significantly diminished if warfarin is stopped before six weeks gestation (McLintock 2011).

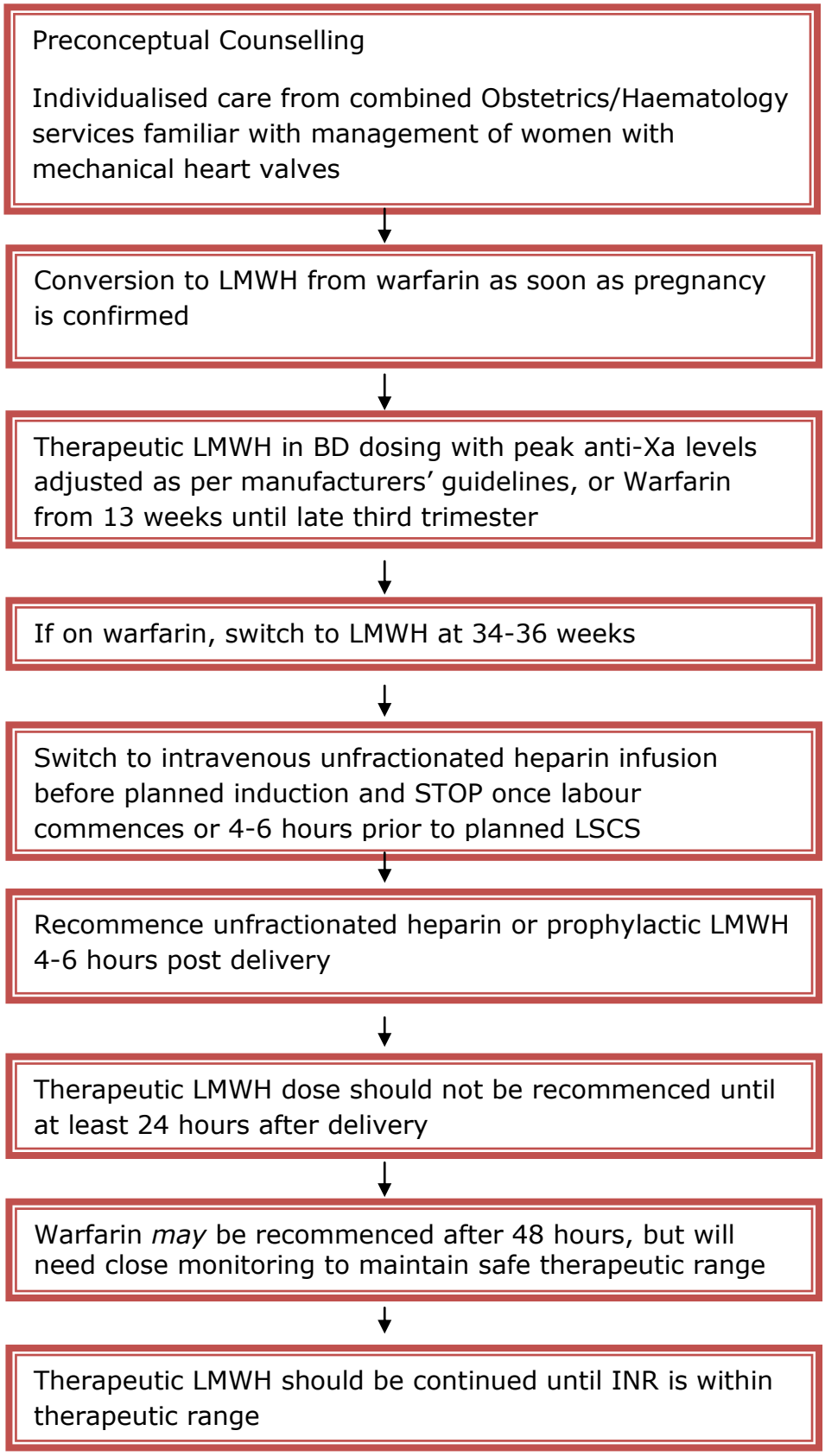
4.6.2 Women with Mechanical Heart Valves

Recommendations:

- **Women on life-long anticoagulation need highly specialist management with haematology and obstetric input.**
- **These women should have pre-conception counselling.**
- **An individualised management plan, devised by the specialist Obstetric and Haematology service, should be in place for pregnant women with mechanical heart valves. The following algorithm (figure 1) gives an overview of an approach for thromboprophylaxis in these women.**

The risk of valve thrombosis during pregnancy depends on the type and location of the valve replacement. These women must be managed by specialists in obstetric haematology and high risk pregnancy. Women with first generation, mitral valves are at highest risk (McLintock 2011). The risk of valve thrombosis poses a real and significant risk of severe maternal morbidity and mortality. Women with mechanical valves who decide to proceed with pregnancy should be well informed of these risks and the therapeutic options. Evidence suggests that the use of warfarin throughout pregnancy is likely to be the most successful method of preventing valve thrombosis but is associated with higher risk of fetal loss and abnormalities (McLintock BJOG 2009). The woman needs to be involved in the discussion on management. Recently there has been a growing experience with the use of therapeutic LMWH in pregnancy for this group of women. LMWH should be given in a twice daily dose with anti-Xa monitoring (Oran 2004, James 2006, Yinon 2009). The scheme outlined in Figure 1 is a reasonable approach and involves administering intravenous infusion of unfractionated heparin before and after delivery. These very high risk patients must be managed in regional centres with specialist obstetrics-haematology services. They require the closest co-operation and liaison between obstetrics, haematology and cardiology. All key clinical decisions should only be made by senior clinicians experienced in this area.

Figure 1. Thromboprophylaxis Regimen in Pregnancy for Women with Mechanical Heart Valves.



4.6.3 Women with Class-III Obesity

Recommendations:

- **It is reasonable to start thromboprophylaxis in women with Class-III obesity (BMI >40kg/m^2) during hospital admission.**
- **It is reasonable to use weight-adjusted LMWH dosing in all women with obesity.**

There is lack of high-level evidence regarding VTE prophylaxis in pregnancy and even less evidence in the obese parturient (Morgan 2012). Clinical studies have shown fixed-dose LMWH is associated with a higher rate of VTE in non obstetric obese population and weight-adjusted prophylaxis dosing results in acceptable anti-Xa levels (Freeman 2010). In the non-pregnant patient, studies using anti-Xa as a marker of activity have shown that individualised weight based therapy generates anti-Xa levels in the required therapeutic range and the data did not support capping doses (Clark 2008). Therefore, it is reasonable to use weight-adjusted LMWH dosing in women with obesity. The pharmacokinetic changes from pregnancy and obesity may result in lower peak concentration of LMWH and shorter elimination half-life (Morgan 2012). Hence anti-Xa monitoring in this group of women may be of value (SIGN Guideline 122; 2010).

4.6.4 Women with Recurrent Miscarriage

Recommendations:

- **Women with recurrent miscarriages who have proven antiphospholipid antibodies should be given prophylactic LMWH and low dose aspirin.**
- **In women with recurrent miscarriage without antiphospholipid antibodies there is insufficient evidence to recommend LMWH.**

Meta analysis of data from randomised trials testing the efficacy of unfractionated heparin (UFH) and aspirin vs aspirin alone, in patients with antiphospholipid antibodies and recurrent miscarriages, showed that the frequency of live births was significantly higher in the aspirin and heparin group compared with women randomised to receiving aspirin alone (Mak 2010).In contrast to UFH, the combination of LMWH and aspirin does not seem to reduce the rate of pregnancy loss compared with aspirin alone (Laskin 2009). There are few data comparing LMWH and UFH. Although there is limited evidence in efficacy, LMWH has largely replaced UFH in clinical practice for treatment of recurrent miscarriages in women with antiphospholipid syndrome. Pilot studies have shown that combination of LMWH and aspirin is equivalent to UFH and aspirin in preventing recurrent miscarriages (Stephenson 2004, Noble 2005).

Well-designed trials reported lack of efficacy of LMWH in the prevention of recurrent miscarriages in women without antiphospholipid antibodies or known thrombophilia (Clark 2010, Kandoorp 2010). Therefore, in women without thrombophilia, LMWH is not indicated in the management of recurrent miscarriage (Branch 2010). Currently available evidence is inconclusive with regards to the significance of inherited thrombophilia and recurrent miscarriage. Results of a completed treatment trial (Low Molecular Weight Heparin and/or Aspirin in Prevention of Habitual Abortion; ClinicalTrials.gov number, NCT009596211) that included women with recurrent miscarriage and inherited thrombophilias are awaited.

4.6.5 Women with History of Placenta-Mediated Pregnancy Complications

Recommendations:

- **Women with a history of early hypertensive disorders and/or fetal growth restriction should be considered for inherited thrombophilia testing and LMWH, if testing is positive. These women should also receive aspirin.**

One of the few randomised trials in this area has recently reported (De Vries 2012) that LMWH with aspirin reduced recurrence of hypertensive disorders, onset less than 34 weeks, in women with inherited thrombophilia and prior delivery for hypertensive disorders or small for gestation age less than 34 weeks.

- **For all other women with a history of pregnancy complications, there is insufficient evidence to recommend thrombophilia screening or thromboprophylaxis at the present time.**
- **In women with inherited thrombophilia and a history of placenta mediated obstetric complications, it is reasonable at the current time to consider medical surveillance without LMWH.**

The initial studies on the relationship between the inherited thrombophilias and pregnancy complications were mostly based on retrospective cohort studies. As more prospective cohort studies have become available, the reported strength of these statistical associations has diminished (Said JM 2010). The use of LMWH in the prevention of pregnancy complications in women with a past history of complications who are thrombophilia positive is not recommended as there is

insufficient clinical evidence to support the efficacy of this approach (Kaandorp 2009). If patients are to be offered thromboprophylaxis with LMWH for the prevention of pregnancy complications, it should be done in the context of randomised clinical trials. It is widely accepted that many clinicians have been using LMWH because of the published associations between the inherited thrombophilias and pregnancy complications and also because of the excellent safety profile for LMWHs in pregnancy. This recommendation is consistent with international guidelines from the RCOG, the ACOG and the ACCP.

4.7 Thrombophilia Testing

4.7.1 Indications for Thrombophilia Testing

Recommendations:

- **Thrombophilia Testing may be indicated in for asymptomatic women with a family history of VTE (first degree relative) if the event:**
  - **was unprovoked,**
  - **pregnancy or OCP related,**
  - **or associated with a known familial thrombophilia**
  - **women with a history of provoked VTE, if the provoking risk factor was mild or the effect of the risk factor is unknown,**

- **Thrombophilia Testing should *only* be performed when:**
  - **The risks, benefits and results of the testing can be clearly explained to the women, including the implications for relatives**
  - **An appropriate referral pathway to haematology is available**
  - **Management or treatment decisions are likely to be influenced by the test results**

Whilst these recommendations are in accordance with the most recent BCSH Guideline on thrombophilia testing (2010) it recognised that occasionally it may not be clear whether testing is indicated or not. In addition, patients may request testing when it is not clearly indicated. Testing may be performed if results will influence the decision to use antithrombotic therapy. The risks and unclear benefits of testing should be discussed with the woman and clearly documented in the medical charts.

- **Thrombophilia Testing is NOT indicated in the following:**
  - **women for whom the clinical risk assessment alone already recommends thromboprophylaxis (e.g. Previous unprovoked, oestrogen related VTE, history of recurrent VTE)**

- **women with a history of VTE due to a major provoking risk factor which is no longer present**
- **women who have asymptomatic relatives with Factor V Leiden or prothrombin gene polymorphisms**
- **asymptomatic women before assisted conception or with ovarian hyperstimulation**
- **at the time of acute thrombosis or while on anticoagulant therapy**

4.7.2 Thrombophilia Testing in Women with Recurrent Miscarriages

Recommendations:

- **Women with a history of recurrent miscarriages should be tested for antiphospholipid antibodies; this should be done before pregnancy if possible and repeat testing, if any initial test is positive, should be performed three months later.**

- **There is no clear indication for testing for inherited thrombophilia in women with recurrent miscarriages.**

Until the results of ongoing randomised controlled trial investigating the benefits of antithrombotic therapy is known, in women with recurrent miscarriages, there is no clear indication for inheritable thrombophilia testing in such women (Baglin 2010), Low Molecular Weight Heparin and/or Aspirin in Prevention of Habitual Abortion; ClinicalTrials.gov number, NCT009596211).

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6 Implementation Strategy

- Distribution of guideline to all members of the Institute and to all maternity units.
- Implementation through HSE Obstetrics and Gynaecology programme local implementation boards.
- Distribution to other interested parties and professional bodies.

7 Key Performance Indicators

- Proportion of pregnant women who have their VTE risk assessment performed accurately in early pregnancy, admission and postpartum
- Women receiving antenatal LMWH who have a discussion re:labour documented in their case notes
- Women with a history of VTE who receive six weeks LMWH for six weeks postpartum

8 Qualifying Statement

These guidelines have been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. Clinical material offered in this guideline does not replace or remove clinical judgement or the professional care and duty necessary for each pregnant woman. Clinical care carried out in accordance with this guideline should be provided within the context of locally available resources and expertise.

This Guideline does not address all elements of standard practice and assumes that individual clinicians are responsible for:

- Discussing care with women in an environment that is appropriate and which enables respectful confidential discussion.
- Advising women of their choices and ensuring informed consent is obtained.
- Meeting all legislative requirements and maintaining standards of professional conduct.
- Applying standard precautions and additional precautions, as necessary, when delivering care.
- Documenting all care in accordance with local and mandatory requirements.

Table 1: Suggested thromboprophylatic doses for antenatal and postnatal LMWH (adapted from RCOG 2009)

Weight (kg)	Enoxaparin	Dalteparin	Tinzaparin (75u/kg/day)
<50	20 mg daily	2500 units daily	3500 units daily
50-90	40 mg daily	5000 units daily	4500 units daily
91-130	60 mg daily*	7500 units daily	7000 units daily*
131-170	80 mg daily*	10 000 units daily*	9000 units daily*
>170	0.6 mg/kg/day*	75 units/kg/day*	75 u/kg/day*
High prophylactic (intermediate) dose for women weighing 50-90 kg	40 mg 12-hourly	5000 units 12-hourly	4500 units 12-hourly
Treatment dose	1 mg/kg/12 hourly antenatal 1.5mg/kg/daily postnatal	100 units/kg/ 12 hourly or 200 units/kg/daily postnatal	175 u/kg/daily (antenatal and post-natal)

*may be given in two divided doses

Appendix A – Rapid Risk Assessment Tool for VTE in Pregnancy

Women with personal history of VTE → **Antenatal and Postnatal LMWH Prophylaxis And Referral to Combined Obstetrics/Haematology Care**

Pre-existing Risk Factors	Please Tick
Family history	☐
BMI > 30	☐
Maternal age > 35 and parity > 3	☐
Smoking	☐
*Medical co-morbidities (refer to list below)	

*Medical Co-morbidities eg.	Please Tick
Varicose veins	☐
Paralegia	☐
Haematological condition – sickle cell disease , polycythaemia, essential thrombacthaemia or other myeloproliferative disorder	☐
Nephrotic syndrome	☐
Intravenous drug user	☐
Inflammatory Bowel Disease	☐
Other relevant risk factor	☐

Transient Risk Factors	Please Tick
Hospital admission or postpartum	☐
Surgery in pregnancy or puerperium	☐
Hyperemesis	☐
Dehydration	☐
Ovarian Hyperstimulation Syndrome	☐
Systemic Infection	☐
Immobility (>4 days bedrest)	☐
Pre-eclampsia	☐
Excessive blood loss (>1L or blood transfusion)	☐
Multiple pregnancy	☐
Assisted Reproduction	☐
Postpartum wound infection	☐

Women with THREE or more of the above risk factors → **Consider LMWH Thromborophylaxis**