South Australian Perinatal Practice Guidelines

Thrombophilia in pregnancy

Note:

This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach.

Information in this statewide guideline is current at the time of publication.

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This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for:

- Discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes the use of interpreter services where necessary,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

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Thrombophilia in pregnancy

Introduction

- Pregnancy induces a state of hypercoagulability with decreasing anticoagulation and increasing coagulation (Gibson et al. 2003)
- Pregnancy may reveal a thrombophilia after a venous thromboembolism or an adverse obstetric outcome

Thrombophilia

- Thrombophilias are inherited or acquired conditions that have been strongly associated with venous thromboembolism (VTE) such as deep vein thrombosis and pulmonary embolism

Inherited thrombophilias:

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

Deficiencies of endogenous proteins in the coagulation cascade

- Protein C
- Protein S
- Antithrombin

Acquired thrombophilias:

- The presence of antiphospholipid antibodies lupus anticoagulant (LAC) and / or anticardiolipin antibodies (ACA) (Gibson et al. 2003)

Mixed inherited and acquired

- Hyperhomocysteinemia (elevated plasma homocysteine)

Literature review

- Taken together, the inherited thrombophilias are common, affecting around 15 % of Western populations (Greer 2003)
- VTE complicates around 1 in 1,000 pregnancies. Inherited and acquired thrombophilias cause more than half of all maternal VTE (Greer 2003; Lockwood and Silver 2004)
- Thrombophilias have been implicated in adverse obstetrical outcomes, such as:
  - Severe early-onset Intrauterine growth restriction (IUGR) requiring birth < 34 weeks' gestation
  - Stillbirth

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- Severe early onset preeclampsia requiring birth < 34 weeks' gestation
- Placental abruption
  (Walker et al. 2004)

- In the absence of data from large randomised controlled trials, there is a lack of consensus among experts about the role of anticoagulation in pregnant women with inherited thrombophilias
- International randomised trials are in progress (e.g. Thrombophilia in pregnancy prophylaxis [TIPPS]). Contact Dr Bill Hague for enrolment (WCH)
- Heparin (low molecular weight heparin) administration in pregnancy may reduce the risk of the above adverse obstetrical outcomes
- Low dose aspirin with or without low molecular weight heparin is the mainstay of treatment for acquired thrombophilias (e.g. antiphospholipid syndrome) in pregnancy (Khare and Nelson-Piercy 2003)

Diagnosis

- 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
  - Venous thrombosis in pregnancy thrombosis
  - Stillbirth
  - Early-onset preeclampsia (< 34 weeks gestation)
  - IUGR (delivery < 34 weeks gestation)

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

An inherited predisposition can be identified in 60 to 70 % of women presenting with deep venous thrombosis (Buchanan et al. 2003)

Management

- Women with known risk factors for thrombophilia should be referred early on to an obstetric medicine clinician (physician or obstetrician with expertise in high-risk obstetrics)
- When a thrombophilia disorder is diagnosed, arrange ongoing maternity care in a Level II or III hospital
- In the absence of evidence, management (increased feto-placental surveillance, aspirin, aspirin + low-molecular weight heparin) is primarily based on the woman's

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obstetrical and individual risk profile and often empiric. Management of individual women can be discussed with South Australian colleagues with specific interest and expertise in this area (Dr Bill Hague, Dr Mark Morton [WCH], Prof Gus Dekker [LMHS], Dr Cathy Miller [FMC])

Management Factor V Leiden (FVL) mutation

Factor V Leiden

- Factor V Leiden occurs as a result of a single point mutation in the factor V gene at the cleavage site (position 506) where protein C acts. FVL is the most common cause of activated protein C resistance (APCR) (Lockwood 2001). The most cost efficient way of screening for FVL is to check for the abnormal phenotype (aPC resistance)
- Heterozygosity for the FVL mutation is present in 20 to 40 % of nonpregnant individuals with venous thromboembolism (VTE) (Lockwood and Silver 2004)
- Homozygosity for the FVL mutation carries an 80 fold risk of VTE (Buchanan et al. 2003)

Incidence

- Occurs in 5 to 15 % of ethnic European populations
- Rarely found in Asian or African populations

Associated risks

- Given the low prevalence of VTE in pregnancy, the risk of VTE in asymptomatic FVL carriers is only 0.2 % (Gerhardt et al. 2000)

Other associated risks

- Second and third trimester fetal loss
- Severe intrauterine growth restriction (IUGR)
- Abruption
- Severe early onset preeclampsia
- Preterm delivery
- When compared with non-carriers, FVL carriers demonstrate an increased proportion of pathological Doppler measurements, including bilateral uterine artery notches

Management Prothrombin Gene mutation

Prothrombin gene mutation

- A mutation at nucleotide 20210 in the gene encoding prothrombin resulting in higher circulating levels of prothrombin, the precursor of thrombin (Said and Dekker 2003)
- Only small studies have been completed to date (Said and Dekker 2003)

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Thrombophilia in pregnancy

Incidence

- Prevalence of the gene in the general population is 2 to 5 % (Buchanan et al. 2003)
- More prevalent in Caucasian women

Associated risks

- Threefold increased risk of venous thrombosis
- Controversy remains about whether prothrombin gene mutation is associated with pre-eclampsia
- Intrauterine growth restriction
- Placental abruption

Laboratory investigations

- Evaluation for the prothrombin gene mutation is best performed through direct genetic analysis to identify the G20210A transition (Buchanan et al. 2003)

Management Protein C, Protein S and Antithrombin deficiency

Protein C (PC)

- Generally autosomal dominant
- Can result from protean mutations producing two primary phenotypes:
  - Type I: both immunoreactive protein levels and protein C activity are reduced
  - Type II: immunoreactive levels are normal but activity is reduced (Lockwood 2001)
- Robust functional assay, no major physiological drop during normal pregnancy. Protein C is highly senstive to consumption, as may be caused by systemic thrombosis or surgery. Protein C levels are reduced in women with disseminated intravascular coagulation (DIC), liver disease, and women that use vitamin K antagonists

Protein S (PS)

- Three subtypes:
  - Type I: characterized by reduced total and free immunoreactive protein levels and activity
  - Type II: characterized by normal total and free immunoreactive protein S levels but reduced activity
  - Type III: normal total immunoreactive levels but reduced free immunoreactive levels and activity because of increased binding to the C4b-BP carrier protein (Lockwood 2001)
- Although, the currently used free protein S assay is more robust than its predecessors, it still is a vulnerable test. To diagnose a woman with protein S deficiency, 2 separate measurements outside pregnancy (at least 8 weeks post-partum) are required. Free protein S shows a marked physiological decrease during pregnancy. This decrease is one of the main drives behind the physiological aPC resistance. Protein S should not be measured during pregnancy

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Antithrombin

- Can result from a myriad of possible mutations
- Rarest and most thrombogenic of the inherited thrombophilias
- Two primary types:
  - Type I: characterized by reductions in both circulating immunoreactive protein levels and activity
  - Type II: characterized by normal immunoreactive protein levels but decreased activity (Lockwood and Silver 2004)
- In uncomplicated pregnancy antithrombin (AT) activity levels show no change or a marginal decrease. Decreased antithrombin activity levels have been demonstrated in women with preeclampsia and DIC

Incidence

- The prevalence of PC deficiency is 0.3 %
- The prevalence of PS deficiency is 0.1 %
- The prevalence of antithrombin deficiency is low (1: 1,000 to 1: 5,000)

Associated risks

Protein C and Protein S

- Venous thromboembolism (< 5 % of cases)
- Increased risk of stillbirth
- Fetal loss (recurrent for PS)
- Increased rates of pre-eclampsia, abruption, and IUGR

Antithrombin deficiency

- Early fetal loss
- Rarely stillbirth, severe pre-eclampsia, IUGR or abruption
- Women with antithrombin deficiency are at a particularly high risk of thrombo-embolic complication. AT deficiency is the only thrombophilia that 'always' will require thromboprohylaxis during pregnancy and post-partum

Management: Antiphospholipid antibodies

Antiphospholipid syndrome

- Antiphospholipid syndrome (APS) is an autoimmune disorder defined by the association of vascular thrombosis and / or pregnancy morbidity with specified levels of the antiphospholipid antibodies (APLAs), either lupus anticoagulant (LAC) and/or anticardiolipin antibody (ACA) (Lockwood and Silver 2004)
- APS is the most common acquired thrombophilia in pregnancy and predominantly affects young women (Khare and Nelson-Piercy 2003)
- Not all individuals with APS will have both LAC and ACA; therefore testing for both antiphospholipid antibodies is recommended

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- Consider screening women with the following history for antinuclear factor (ANF) and ACA:
  - Early onset (less than 32 weeks) pre-eclampsia and / or IUGR (especially if there is evidence of placental infarction, or more than 2 recurrent early fetal deaths)
  - Fetal death
  - Placental abruption
- The presence of anti-phospholipid antibodies, and especially in conjunction with a history of thromboembolism (arterial or venous), carries an increased risk of placental thrombosis and infarction, IUGR and fetal death

Lupus anticoagulant

- LAC is present in many individuals without Systemic Lupus Erythematosus and is associated with thrombosis, not anticoagulation
- Diagnosis of APS requires detection of antiphospholipid antibodies in the blood on two or more occasions at least six weeks apart

Anticardiolipin antibodies

- Reported as low, medium or high positive
- Diagnosis of APS requires anticardiolipin IgG or IgM antibodies present at moderate or high levels in the blood on two or more occasions at least six weeks apart
- The clinical significance of anticardiolipin IgM antibodies in isolation is uncertain

Incidence

The prevalence of aPL (LAC and ACA) in pregnant women is approximately 2 %

Associated risks

- Recurrent early pregnancy loss (less than 10 weeks gestation)
- Preeclampsia
- Thrombosis
- Abruption
- Intrauterine growth restriction (IUGR)
- Preterm birth

Management

Preconception counselling

- Women with APS should be informed of the potential maternal and obstetric complications
- Confirm significant levels of ACA / LAC
- Assess for evidence of anaemia, thrombocytopenia, underlying renal disease, or associated SLE
- Educate the woman about starting low-dose aspirin (100 mg daily)
- Pregnant women with positive ACA and / or LAC should be offered treatment with low dose aspirin (100 mg / day), from 12 weeks gestation in cases of previous late fetal

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death or IUGR, or from early pregnancy / pre-pregnancy in cases of recurrent early loss
- Advise women with APS who have a history of thrombosis and are on long term warfarin that they will need to change to therapeutic dose low molecular weight heparin preferably before conception and at least within two weeks of a missed period. Warfarin is teratogenic between the sixth and twelfth weeks of pregnancy (Khare and Nelson-Piercy 2003)
- Check rubella status and commence on pre-conceptual folic acid

Antenatal

- Early dating scan in the first trimester
- Close surveillance with regular blood pressure checks and urinalysis to detect early-onset preeclampsia
- Uterine artery waveforms at 20 and 24 weeks of gestation
  - Growth scan every 2 - 3 weeks for pregnancies with evidence of early diastolic notch (high risk of PE and IUGR)
  - Consider vitamin C and E if previous PE or bilateral notches
- Ultrasound every 4 weeks to assess growth and amniotic fluid volume (if no uterine artery notch)
- Uterine artery Doppler studies as indicated to allow timely intervention for fetal reasons
- Develop (in discussion with the woman) a management plan for intrapartum and postpartum care and document in the case notes

Drug treatment

- Aspirin 100 mg daily as ordered
- Consider Heparin if:
  - LAC is detectable
  - Strongly positive cardiolipin antibody titres
  - In women with a previous fetal death or evidence of placental infarction and growth restriction. Consult with obstetric physicians or haematologists.
- The use of corticosteroids in women with APS is limited to maternal thrombocytopenia or coexisting systemic lupus erythematosus. Ensure regular blood glucose monitoring for women on long-term steroids.

Intrapartum

- Aspirin can be continued until birth
- Low-dose aspirin does not affect the use of regional anaesthesia during labour
- Send the placenta for histopathology if there is preeclampsia, IUGR, previous stillbirth or miscarriage/s

Postpartum

Drug treatment

- Women with a history of previous thrombosis should receive LMWH or warfarin for 6 weeks postpartum.

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- Women without previous history of thrombosis who have other risk factors for venous thrombosis should receive postpartum LMWH for 5 days.
- For women recommencing warfarin:
  - Recommence warfarin treatment on day 2 - 3 as ordered for women on long term warfarin treatment
  - Discontinue LMWH when the international normalized ratio (INR) is > 2.0

Breastfeeding

- Encourage breastfeeding
- There is minimal excretion of warfarin into breast milk

Follow up

- Counsel women about the possible risks of developing non-obstetric disorders associated with APS
- Counsel women about the implications for future pregnancies

Management: Hyperhomocysteinemia

Homocysteine

- In normal pregnancy, homocysteine levels fall
- Homocysteine is generated from the metabolism of the amino acid methionine and in healthy women during their reproductive years normally circulates in the plasma at concentrations of 4 - 7 µmol / L (Lockwood 2001)
- Dietary (vitamin B12 and folic acid, vitamin B6, GI disease resulting in vitamin malabsorption), metabolic (renal and thyroid deficiency) and environmental (smoking, coffee) factors affect the venous concentrations of homocysteine (Hague 2003)
- There are genetic polymorphisms of other enzymes involved in the metabolism of homocysteine e.g. methylene tetrahydrofolate reductase (MTHFR), the enzyme required for the synthesis of 5-methyl tetrahydrofolate, the methyl donor required for the conversion of homocysteine to methionine (Hague 2003)

Hyperhomocysteinemia

- Hyperhomocysteinemia (elevated plasma homocysteine) can be inherited or acquired (Walker et al 2004)
- Defects in either the transsulphuration pathway or remethylation pathway will lead to increased blood concentrations of homocysteine known as hyperhomocysteinemia
- The thermolabile C677T variant of the gene for MTHFR has been associated with a tendency to mild to moderate hyperhomocysteinemia, especially in the presence of folic acid deficiency (Hague 2003)
- It is the phenotype of hyperhomocysteinemia that is associated with a high frequency of early-onset preeclampsia rather than any associated genotype e.g. MTHFR (Hague 2003)
- The severe form results from extremely rare homozygous deficiencies in either cystathionine ß-synthase (CBS) or methylene tetrahydrofolate reductase (MTHFR) enzymes.

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Thrombophilia in pregnancy

Investigations

- Blood for homocysteine levels
  - Severe: > 100 µmol / L
  - Moderate: 25 - 100 µmol / L
  - Mild: 16 - 24 µmol / L
- For women of reproductive age in South Australia, 10 mmol / L represents the 97.5 centile level. These levels would be considered to be in the upper range of normal in the general population; however, in a young woman, these levels represent marked hyperhomocysteinemia

Incidence

Homozygosity for the 667C-T MTHFR thermolabile mutant is present in up to 11 % of ethnic European populations and is the leading cause of mild and moderate hyperhomocysteinemia

Associated risks

- Early onset preeclampsia, placental abruption (Hague 2003; Walker et al 2004)
- Fetal neural tube defects (mild and moderate hyperhomocysteinemia)
- Stillbirth
- Intrauterine growth restriction (IUGR)
- Vascular disease e.g. coronary artery disease
- Recurrent VTE (severe hyperhomocysteinemia)
- There is no consistent association between hyperhomocysteinemia and recurrent spontaneous abortions in general, but a clear association between hyperhomocysteinaemia and fetal loss

Management

Preconception counselling

- Women with hyperhomocysteinemia should be informed of the potential for maternal and obstetric complications
- Advise the woman to reduce or avoid lifestyle variants known to increase homocysteine levels e.g. smoking, coffee and alcohol consumption
- Assess for evidence of underlying renal impairment or thyroid deficiency
- Encourage well balanced diet. Hyperhomocysteinemia is exacerbated by deficiencies in vitamin B6, B12 and folic acid
- Commence on pre-conceptual folic acid. The risk - benefit ratio between high (5 mg) versus low (0.5 mg) folate is currently undetermined. The same holds true for additional vitamin B12 and B6. In vitro data suggest that feto-placental hyperhomocysteinemia would require high dose folate and vitamin B12, but human randomised controlled trials are lacking. Because of these uncertainties, women with a history of preeclampsia and hyperhomocysteinemia are currently asked to participate in the South Australian HOPE trial - contact Dr Bill Hague at Women's and Children's Hospital

Antenatal care

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- Early dating scan in the first trimester, plus early (11-13 weeks) transvaginal screening for neural tube defect
- Close surveillance with regular blood pressure checks and urinalysis to detect early-onset preeclampsia
- Regular ultrasound and Doppler to assess growth, feto-placental circulation and amniotic fluid volume
- In the absence of evidence, management (increased feto-placental surveillance, type and dose of vitamin supplementation) is primarily based on the woman's obstetrical and individual risk profile and often empiric. Management of individual women can be discussed with South Australian colleagues with specific interest and expertise in this area (Dr Bill Hague, Dr Mark Morton [WCH], Prof Gus Dekker [LMHS], Dr Cathy Miller [FMC])

Intrapartum care

- Send the placenta for histopathology

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