Guidelines for Anticoagulation Therapy in Pregnancy

Pages with reference to book, From 133 To 136

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Normal pregnancy is associated with an increased frequency of venous thromboembolism, a risk which is further aggravated when the woman has additional thrombotic risk factors or when there is a previous history of thromboembolism. The incidence of thromboembolic episodes during pregnancy is approximately 1 per 1000 women and increases to 2 per 1000 during the postnatal period. There is, at present, no real consensus as to the optimal management of anticoagulation in pregnant women at risk of thromboembolism. Both Heparin and Warfarin have disadvantages (see below) and the duration and intensity of anticoagulation remains uncertain. At Central Middlesex Hospital, London, the patients are managed according to local guidelines, devised by haematologists and obstetricians; these guidelines are based on the recent recommendations from the British Society of Haematology[1]. The investigation of maternal thromboembolic disease is not discussed in this article; the reader is advised to refer to the above guidelines.

Guidelines for anticoagulation Therapy in pregnancy

Anticoagulant drugs (Heparin and Warfarin) during pregnancy may be given for the following reasons:

1. As part of life long treatment in patients with heart valve repacement or other cardiovascular disorders.
2. To treat venous thromboembolism [deep vein thrombosis (DVT) and/or pulmonary embolism (PE)].
3. To prevent venous thromboembolism in women with (a) a previous history of thromboembolism; (b) hereditary or acquired thrombophilia and (c) other risk factors for thromboembolism (see below).

Anticoagulation drugs Heparin must be given by the parenteral route (iv or Sc) and is monitored by plasma KPTT or anti-factor Xa levels. In pregnancy, ani.i-factorXa levels (whenavailable) are probably a more accurate reflection of Heparin levels. Heparin does not cross the placenta and, therefore, does not anticoagulate the fetus. Long term treatment with high doses of Heparin (>20,000 IU daily for >5 months) has been associated with development of osteoporosis in some women[2]. Heparin requirements increase throughout pregnancy and regular monitoring is required. Heparin may be associated with thrombocytopenia which, in some circumstances, may be severe and associated with thrombosis. All patients receiving Heparin should have their platelet counts monitored at regular intervals (see below). Heparin monitoring should be performed 4 hours post iv infusion and 4-6 hours post sc injection. Warfann is given orally and requires regular monitoring by the International Normalised Ratio (INR) for each patient. Drug interactions are particularly important in affecting the level of anticoagulation in patients. Warfarin is associated with embiyopathy particularly in the first trimester[3]. In most cases subcutaneous Heparin must be substituted as soon as possible and before the critical period of 6-12 weeks gestation. Warfarin crosses the placenta and the fetus becomes as and perhaps more anticoagulated than the mother. This increases the risk of haemorrhage, especially cerebral haemorrhage at the time of delivery and all mothers should have their Warfarin changed to Heparin at the end of pregnancy (usually from 36 weeks).

The doctor must ensure that no contraindications exist before prescribing Heparin or Warfarin. Heparin and Warfarin are not secreted in breast milk and mothers taking these drugs can safely breast feed.

Approach to management

The key to optimal management is close liaisonbetween the obstetricians and haematologists.

1. Identify women at risk in the antenatal booking clinic by taking careful and detailed history (patients on Warfarin as soon as pregnancy confirmed). Many of these will have already been counseled at a

clinic.
2. All women considered to be at risk should be seen by the consultant obstetrician incharge when seen for the first time at the Antenatal Booking Clinic (ABC). If seen initially by other medical staff, the patient should be referred to the consultant for an opinion.
3. For all women close communication between the obstetricians and haematologists is essential and the patient should be seenpromptly at the anticoagulant clinic. Sister incharge of the ABC should keep a record of all patients referred to the Haemostasis/ Anticoagulant clinic.
4. Each woman requires an individual care plan based on assessed degree of thrombotic risks and previous history of thromboembolism. Planned delivery may be required. This care plan must be fully documented in the antenatal notes.
5. Because of the risks to both mother and foetus, women and their partners should be counselled of these risks and the logistics of treatment so that they can participate in the care plan.
6. Contraception options in the postnatal period should be addressed by the obstetrician and discussed with haematologist and the woman. The combined oral contraceptive pill should be avoided and alevonorgestrel only pill considered.

High risk women

Women on long term anticoagulation with Warfann for recurrent thrombosis. These will include: hereditary thrombophilia with previous thromboembolic events e.g., protein C and protein S deficiencies, women with a thrombotic history but no identifiable thrombophilic abnormality, arterial thromboembolism, antiphospholipid antibodies (lupus anticoagulants and/or anticardiolipin antibodies) with thromboembolic events, cardiac arrhythmias, all ATIII deficient patients. Women in these groups should be aware to present as soon as pregnancy is confirmed. They will require prophylactic anticoagulation throughout pregnancy and postpartum (Table I).

Table I. Anticoagulation in women with high risk factors for venous thromboembolism during pregnancy and postpartum.

1. Change from Warfarin to Heparin as soon as possible and before critical time of 6 weeks gestation.
2. Start 10000 iv Heparin sc bd (at 7 am and 7 pm). Adjust dose to maintain detectable anticoagulation with KPTT ratio not >1.5 (Anti-Xa levels <0.3 iv/ml). Patients will be taught to self administer. Hospital admission to teach injection technique will be arranged by the obstetrician.

Heparin requirements increase during pregnancy, therefore these women require monitoring atleast every 4 weeks throughout pregnancy in the haemostasis clinic. Because Heparin can cause thrombocytopenia, the full blood count (FBC) also needs regular monitoring. If platelet count falls <100x109/I stop Heparin and consult haematologist.

3. Delivery: Stop Heparin on day of delivery (tell women not to take injections if they go into spontaneous labour).
4. Epidurals (see text).
5. Restart Heparin immediately post-delivery 7500 IU sc bd and monitor to KPTT ratio < 2.0.
6. Start Warfarin on day 2 (i.e., as soon as 24 hours post- delivery). Overlap Heparin and Warfarin until therapeutic INR (2.0-3.0) on 2 consecutive days (normal overlap period usually totals ~5 days). Loading doses of 7 mg, 7 mg, 5 mg should be given orally once daily for the first 3 days respectively. Check with haematologist whether dose reduction is necessary.
7. Refer to next available Anticoagulant clinic and arrange interim INR if necessary.

ATIH deficiency: Prophylactic Heparin is needed throughout pregnancy even in asymptomatic patients. Higher anti-Xa levels may be needed. Cover delivery and immediate postpartum period with ATIII concentrates. Regime to be decided by haematologist. This may require planned induction. Continue anticoagulation with Heparin/Warfarin until 3/12 postpartum.

Antiphospholipid antibodies: These women may also need aspirin. The regime should be decided by haematologist.

Medium risk women

Women not on Warfarin but with established risk factors: proven or highly likely DVT/PE in previous pregnancy or outside of pregnancy; asymptomatic protein C or S deficiency, sickle cell disease will need prophylactic anticoagulation in later pregnancy and in postpartum period (Table II).

Table II. Anticoagulation in women with medium risk factors for venous thromboembolism during pregnancy and postpartum.

Previous thromboembolism in pregnancy: Start prophylactic anticoagulation with Heparin 4-6 weeks prior to gestation of previous event (doses as above). Continue with Heparin/Warfarin as outlined above until 3/12 postpartum.
Previous TE outside of pregnancy: Individual assessment of risk required; timing will depend on severity of previous event. Continue with Heparin/Warfarin until 3/12 postpartum. Anticoagulant dosage as above.
Sickle cell disease: Start Heparin 5000 IU sc bd from 36 weeks to 6 weeks postpartum. At this dose monitoring is not required.
Protein C or S (no previous thromboembolic events): Individual assessment of risk required: give prophylactic Heparin (doses as above) usually mid to late pregnancy. Continue with Heparin/Warfarin until 6 weeks postpartum.

Timing of initiation of anticoagulation and duration depends on individual assessment.

Prosthetic cardiac valves

These women require therapeutic anticoagulation throughout pregnancy and postpartum period. Details of management are given in Table III.

Table III. Management of anticoagulation in pregnant women with prosthetic cardiac valves. Please note that Heparin monitoring should be performed 4 hours post iv infusion and 4-6 hours post sc injection.

1. Stop Warfarin ASAP and Heparinise to 12 weeks. Start Heparin iv infusion 30000 IU/24 hrs. as inpatient. Adjust to keep KPTT ratio 1.5-2.0 (or anti-Xa levels 0.35-0.7 iu/ml). Change to bd sc regime (generally 15000-20000 IU/bd) when dose established. Frequent monitoring is required throughout as requirements may change with increasing gestation. Also monitor FBC regularly.
2. 12-36 weeks: introduce Warfarin. Take haematological advice regarding Warfarin dose regimes. Adjust dose to maintain INR to 2.5-3.0.
3. From 36 weeks: Stop Warfarin and restart Heparin iv 40000 IU/24 hrs. Maintain KPTT ratio (or anti-Xa levels) as above.
4. Delivery: Planned delivery required. Reduce Heparin on day of delivery to 10000 IU/24 hrs. Check KPTT ratio <1.5.
5. Postpartum: Restart full dose Heparin immediately post delivery at starting dose of 30000 IU/24 hrs. to maintain KPTT ratio (or anti-Xa levels) as above. Start Warfarin on day 2. Overlap Heparin and Warfarin until therapeutic INR (3.0-4.5) on atleast 2 consecutive days (normally total ~ 5 days) (see Table I).
6. Refer to next available Anticoagulant clinic arrange interim INR if necessary.

Other women at possible risk

The risks not well defmed and are associated with conditions of pregnancy. Risk factors often occur in conjunction and decision to anticoagulate will be based on clinical judgement. Risk factors include operative delivery, prolonged bed rest, obesity, age/parity, strong family history of thromboembolism. Short term anticoagulation is required in this case.

Operative delivery: TED stocking and Heparin 5000 IU scbd immediately postLSCS and postpartumuntilfully mobile. No monitoring required.

Immobilisation or other risk factors: TED stocking and in individual cases 5000 IU sc bd (discuss with obstetrician/haematologist). No monitoring required.

Epidural anaesthesia in women taking anticoagulant

Contraindicated in women on therapeutic anticaogulation. Other cases are controversial. If anticoagulation has been stopped or reduced and a full clotting screen (PT, KPTF, TI') and FBC are normal, it is probably safe to proceed[1,4] but discuss with anaesthetist/obstetric consultant/haematologist. The plan should be made before hand after discussion with consultants and documented in notes. NB: Epidurals should not be used in women receiving low molecular weight Heparin because clotting studies do not reflect degree of anticoagulation.

Suspected DVT/PE during pregnancy

Maintain a high index of suspicion if symptoms of calf or acute chest pain, swollen leg etc. It is important to confirm objectively by ultrasound and/or venography as the diagnosis will have implications for future management. Diagnostic procedures should be discussed with Radiologist/Obstetrician. If pulmonaiy embolism is suspected, do CXR, ECG, blood gas, V:Q scan and consult medical specialist regarding management. Details of therapeutic anticoagulation for acute venous thromboembolism are given in Table IV.

Table IV. Anticoagulation management of women with acute thromboembolism during pregnancy. Please note that Heparin monitoring should be performed 4 hours post iv infusion and 4-6 hours post sc injection

1. Check clotting screen, FBC, routine biochemistry.
2. Start Heparin immediately while awaiting results of investigations. Heparin starting dose 30000 IU <20 weeks, 40000 IU>20 weeks. Monitor by KPTT to ratio 1.5-2.0 or anti-Xa 0.35- 0.7 iu/ml (if available).
3. In antenatal women substitute bd sc Heparin after 7 days. Dose regime will be determined by monitoring but is usually 10000-15000 IU bd. Continue therapeutic anticoagulation for 3 months. Thereafter, continue prophylactic Heparin as for high risk woman (see above).
4. Delivery: STOP Heparin on day of delivery (tell women not to give injections if they go into spontaneous labour).
5. In postnatal woman start Warfarin from Day 3 and overlap Heparin and Warfarin until therapeutic INR (2.0-3.0) on atleast 2 consecutive days (normally total ~5 days).
6. Refer to next available anticoagulant clinic and arrange interim INR if necessary.
7. In all women the duration of postpartum anticoagulation to be decided by

Surgical intervention may be required for life threatening pulmonary embolism or massive ileofemoral thrombosis. Women with thromboembolic disease in pregnancy may be considered for further investigations for inherited thrombophilia, particularly if there is a significant past or family history. These tests are ideally performed in the non-pregnant state and should be performed after discussion with the haematologist.

Reversal of Warfarin

If a woman on Warfann goes into premature labour delivery by Caesarean section should be considered to protect the fetus. Emergency LSCS may require some reversal of anticoagulation. Discuss all cases with consultant obstetrician/haematologist and proceed along the guidelines outlined in Table V.

Table V. Management of labour and delivery in women taking Warfarin.

1. Check INR.
2. If INR is <2.5 (ideally <2.0), Caesarean section is probably safe but fresh frozen plasma (FFP) (available in approximately 30 minutes) may be required for maternal bleeding.
3. If INR >2.5, give FFP; amount to be determined by haematologist depending on INR. Check INR post FFP infusion.
4. It may be dangerous to fully reverse anticoagulation particularly in women with prosthetic valves. Large doses of vitamin K1 should not be given as it may render subsequent anticoagulation with Warfarin difficult. If INR >4.5, a small dose (0.5-2 mg) should be considered but only after consultation with a haematologist.
5. Check INR of baby immediately post-delivery. Give vitamin K1 iv (not im) into the cord in all cases. If neonatal bleeding, give 10 ml/kg FFP and monitor INR.
6. Post delivery start Heparin immediately. Regime to be determined by haematologist depending on thrombotic risk. Substitute Warfarin on Day 2 (>24 hrs. post-delivery) and overlap Heparin and Warfarin until therapeutic INR on atleast 2 consecutive days (normally total ~5 days) see (Table I).

Remember that epidural anaesthesia is contraindicated.

Reversal of Heparin

Heparin is rapidly cleared from the blood. It is usually sufficient to stop Heparin as most surgical procedures can be carried out without the risk of bleeding in the presence of low dose Heparin. If the patient is bleeding or emergency surgery is necessary, check full clotting screen and consult consultant obstetrician/haematologist if KPTT ratio is >1.5. Protamine sulphate neutralisation may be required for those women on iv Heparinorwithin 2 hours following bolus Heparin. Protaminc sulphate dose in mg is calculated as follows:

Dose given as bolus or amount given in last hour by infusion 100

Maximum dose of protarnine sulphate that should be prescribed is 50 mg.

References

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