

SPECIAL ARTICLE

Anticoagulation therapy during pregnancy and puerperium

Sultana Habib*, Amin M Khuwaja**, Najma Amjad***

*Assistant Professor of Cardiology

**Assistant Professor of Cardiac Anesthesia

*** Professor of Cardiac Anesthesia

National Institute of Cardiovascular Diseases (NICVD), Karachi (Pakistan)

Correspondence: Dr. Amin M Khuwaja, Assistant Professor, National Institute of Cardiovascular Diseases (NICVD), Rafiqi Shaheed Road, Karachi-75510, (Pakistan); Telephone: (021) 99201271-5; E-mail: aminkhuwaja@yahoo.com

ABSTRACT

Thrombotic complications are three to five times higher than non-pregnant women and even in pregnant women anticoagulant therapy is indicated for the prevention and treatment of a number of cardiac and non-cardiac conditions. This therapy may have some serious concerns for the safety of the new life in the womb of the mother or to the mother if she has to undergo some type of operative delivery. Whether, anti-coagulation is achieved with oral or injectable drugs, we must be fully aware of the pharmacology, and the means to control the undesirable side effects.

Key words: Anticoagulant drugs; Venous thromboembolism; Platelet aggregation inhibitors; Heparin; Warfarin

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INTRODUCTION

Normal pregnancy is accompanied by changes in hemostasis which leads to a hypercoagulable state and this may not return to normal ranges for at least 8 weeks after delivery.¹ It is a period of increased risk for thrombotic complications. Thrombotic complications are three to five times higher than non-pregnant women.¹ During pregnancy, anticoagulant therapy is indicated for the prevention and treatment of number of cardiac and non-cardiac conditions. The use of anticoagulant therapy during pregnancy is challenging, firstly because of its potential risk for maternal and fetal complications^(2,3) and secondly there is paucity of data on the efficacy and safety and side effects on anticoagulation drugs in pregnancy.^(4,5) Therapeutic regimens are well defined for non-pregnant than pregnant women. When indicated, careful anticoagulation can proceed with minimal risk to the mother and fetus by following the current guideline.⁶

Following are the indications where anticoagulation needs to be continued or need to be started during pregnancy^{3,6} (Box 1).

Box 1: Reasons for Anticoagulation during Pregnancy:

1. Mechanical heart valves, with AF or LV clot
2. Acute venous thromboembolism (VTE/PE) and DVT
3. To prevent thromboembolism in women with;
 - a. Previous history of thromboembolism (15-25%)
 - b. Hereditary or acquired thrombophilia
 - c. Other risk factors for thromboembolism

ANTICOAGULATION DRUGS

There are two types of anticoagulation drugs, oral and parenteral^(1,3,4,6-8) Oral anticoagulation drugs available are warfarin and new oral anticoagulants. Currently new oral anticoagulants are not

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recommended to be used during pregnancy. As parenteral anticoagulation we have unfractionated heparin (UFH), low molecular weight heparin (LMWH), and other heparinoids. Newer heparinoids are safe in pregnancy but they should only be used if there is a contraindication to the use of UFH and LMWH.

It is very important to have baseline laboratory tests, e.g. PT and INR, anti-Xa levels, urea, serum creatinine, electrolytes, and LFT, for any evidence of renal and hepatic failure. Caution is required for the use of anticoagulation in the presence of these conditions.

Hazards of Anticoagulation Drugs:⁶

It is important to be aware of their hazards during pregnancy. Warfarin (Coumadin) is the most widely used drug because it has a predictable onset and duration of action and excellent bio-availability. Coumarins freely cross the placenta and thus pose a risk of 'warfarin embryopathy' which is about 25-30% between 6-12 weeks. Embryopathy can be avoided if it has been withdrawn within 6 weeks of last menstrual period and replaced by parenteral anticoagulation drugs between 6-12 weeks and again should be withdrawn at 36 wks of gestation to avoid complications at the time of delivery. If anticoagulant therapy is indicated during pregnancy, the risks should be explained before conception. Given their potential for deleterious effects on the fetus, vitamin K antagonists should only be used during pregnancy when potential maternal benefits justify potential fetal risks / patient risks (Box 2).

UFH has been used for both prevention and treatment of thromboembolism for decades and does not cause teratogenesis. Its main limitations in pregnancy are its inconvenient dosing and its potential maternal adverse effects (mainly osteoporosis and heparin-induced thrombocytopenia). For avoiding side effects it is recommended to use it in a dosage not greater than 20,000 iu in 24 hours and not to exceed a duration of 6 months (Box 2, 3).

LMWH: Over the last 10 years LMWHs have become the preferred anticoagulants for treating and preventing thromboembolism in all patients. LMWH during pregnancy offers a number of advantages over unfractionated heparin; e.g. equivalent efficacy, once or twice daily dosing, lower risk of heparin-induced thrombocytopenia and osteoporosis, and requirement of less intensive monitoring. The physiologic changes of pregnancy alter the metabolism of LMWH, resulting in lower

peak levels and a higher rate of clearance, so a pregnant woman may need higher doses or more frequent dosing. Currently LMWH is the drug of choice as anticoagulation drug during pregnancy except in patients with mechanical prosthetic valves and with renal failure (Box 3).

Antiplatelet Drugs:⁶ Aspirin is an antiplatelet agent rather than an anticoagulant. Low doses have been shown to be safe throughout pregnancy.

Box 2: Hazards of warfarin

- Crosses the placental barriers
- Risk of embryopathy. (10 – 25%)
- CNS and adverse pregnancy outcomes
- Warfarin effect in fetus
- Major bleeding in mother

Box 3: Intravenous agents

A. Unfractionated Heparin(UFH)

1. UFH do not cross placenta
2. Thrombocytopenia
3. Osteoporosis
4. Maternal hemorrhage

B. Low Molecular Weight Heparin (LMWH)

C. Other Heparinoids

MANAGEMENT APPROACH^{1,3-5,8}

All women coming to antenatal clinic should be identified for presence of any risk for thromboembolism. Risk stratifies them early. All women at risk should be seen by consultant obstetrician, plan of their care and planned delivery should be documented in the antenatal record. Close communication between the obstetrician and the hematologist is the key to the success of anticoagulation therapy during pregnancy. There should be individual care plan for each woman based on her risk category. Both woman and her partner should be counseled about the risks of anticoagulation therapy to both mother and the fetus and the logistics of treatment so that they can also become part of their treatment plan. If pregnancy is still desired, two options can reduce the risk of warfarin embryopathy:

(1) Performance of frequent pregnancy tests and substitution of adjusted-dose UFH or LMWH for warfarin when pregnancy is achieved; or

(2) Replacement of vitamin K antagonists with UFH or LMWH before conception is attempted.

RISK CATEGORIES: The associated risks have been

stratified into low, intermediate, and high risks. Depending upon their risk the anticoagulation therapy can either be continued throughout antenatal period, during delivery and puerperium or only during peripartum period.

Management of Anticoagulation Therapy in Different risk Categories During Pregnancy:^{1,5,7,8}

Patients with high, intermediate, and low risk factors for thromboembolism, patients with prosthetic heart valves, and patients with acute venous thromboembolism (VTE). If oral anticoagulants are used, the INR can be kept between 2.0 and 2.5, thus minimizing the risk to the fetus. In pregnant women with high-risk mechanical valves (e.g., older generation prosthetic mitral valves or a history of thromboembolism), we suggest the use of oral anticoagulants over heparin.⁸ For pregnant women with prosthetic valves at high risk of thromboembolism, we recommend the addition of low-dose aspirin 75 to 100 mg/day.

MANAGEMENT OF ANTICOAGULATION^(1-5,8)

Ongoing anticoagulation is essential postpartum, as the puerperium is the period of highest day-to-day risk of thromboembolic events. Almost one-third of pregnancy associated events occur during these 6 to 12 weeks. Heparin should be resumed 6 to 12 hours after delivery, once hemostasis is confirmed.

It is suggested that a thrombosis risk assessment be performed in all women undergoing cesarean section to determine the need for thromboprophylaxis. In high risk patients anticoagulation therapy should be continued for at least six months or can be continued upto at least six months in case of persisting risk factors for thromboembolism. In low risk early mobilization/or stocking after C-section. Continue oral anticoagulation for at least 6 weeks post delivery. In case of prosthetic valves, restart warfarin 2 days after delivery under cover of UFH and keep INR 2.5 to 3.5.

Epidural Anesthesia:^{2,8}

In case of expected caesarian section it is safe to use UFH 24 hours of expected delivery and discontinued it 6-hours before delivery, in order to avoid spinal hemorrhage/hematoma. LMWH is not safe due to its long acting effect or it should be discontinued completely 24 hours before expected delivery.

Breast Feeding:

It is safe to use all recommended anticoagulation drugs during breast feeding

CONCLUSION

During pregnancy, anticoagulant therapy is indicated for the prevention and treatment of number of cardiac and non-cardiac conditions. The

A. Anticoagulation In High Risk Patients

ANTEPARTUM:

1. Change from warfarin to UFH heparin infusion
2. Switch to adjusted intermediate dose of S/C LMWH or UFH continue throughout antenatal, peripartum and puerperium
3. Monitoring of APTT and Anti-Xa to achieve therapeutic levels of UFH/LMWH respectively at least every 4 weeks throughout pregnancy

DELIVERY/LABOUR:

1. Stop S/C UFH 12 and LMWH 24 hour before delivery
2. Restart S/C immediately provided that there is no postpartum haemorrhage
3. Start Warfarin on day 2 overlap heparin until therapeutic INR (2-3)

B. Anticoagulation in Low risk Patients

1. Clinical surveillance during antepartum in case of intermediate risk Aspirin 100mg can be used
2. Prophylactic intermediate-dose /low dose LMWH or UFH in peripartum period
3. Delivery: Same as high risk.
4. Postpartum: Early mobilization/or stocking after C-section. Continue oral anticoagulation for at least 6 weeks post delivery.

C. Anticoagulation in Women with Medium Risk Factors

1. **Previous thromboembolism in pregnancy:** Start prophylactic anticoagulation with heparin 4-6 weeks prior to gestation of previous event .Continue with heprin / warfarin until 3 /12 postpartum.
2. **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
3. **Sickle cell disease:** Start Heparin 5000 IU sc bd from 36 weeks to 6 weeks postpartum. At this dose monitoring is not required.
4. **Protein C or S (no previous thromboembolic events):** Individual assessment of risk required give prophylactic Heparin usually mid to late pregnancy. Continue with Heparin/ Warfarin until 6 weeks postpartum.

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D. Anticoagulation in Prosthetic Cardiac Valve

1. Stop warfarin ASAP and give UFH infusion and change to adjusted full dose SC of UFH/LMWH bid till 12 wks gestation. From 12-36 weeks introduce warfarin again.
2. **Follow up:** Monitor PT and INR, APTT, anti-Xa and clinical follow-up weekly. Adjust dose of UFH/LMWH throughout pregnancy to keep the mid-interval aPTT at least twice control or attain an anti-Xa heparin level of 0.35 to 0.70 U/ml. Echo should be performed monthly.
3. **From 36 weeks:** Stop warfarin and restart UFH infusion.
4. Change to S/C bid after dose adjustment. Restart heparin infusion 24 hours before delivery in dose 10,000 IU /24h hours.
5. **Delivery:** Discontinue UFH 6 hours before delivery. Restart with full dose immediate postpartum.

E. Anticoagulation in Acute Thromboembolism

1. Investigate for pulmonary embolism.
2. Start heparin infusion immediately for 7 days.
3. Start LMWH or UFH S/C continued throughout pregnancy.
4. **Thrombolysis:** Safe in pregnancy. Only be used in patient with shock and unstable.
5. **Delivery:** Discontinue heparin at least 12-24 hrs prior to labor. Restarted 6 h after a vaginal and 12 hours after a cesarean delivery.

F. Labor and delivery in women on warfarin

1. Check INR.
2. If INR is < 2.5 caesarian section is safe.
3. If INR is >2.5 give FFP amount will depend upon INR post FFP.
4. If INR is >4.5 a small dose (0.5 – 2.0) of oral vitamin K may be considered.
5. Check INR of baby immediately post delivery. Give vitamin K IV only in to the cord. If neonatal bleeding, give 10 ml/kg FFP and monitor INR.

use of anticoagulant therapy during pregnancy is challenging because the potential for fetal, as well as maternal, complications must be considered. LMWH, UFH and the heparinoid, danaparoid, are safe for the fetus. The key to optimal management is close liaison between the obstetricians and hematologists. When indicated, careful

anticoagulation can proceed with minimal risk to the mother and fetus. Treatment with anticoagulants during pregnancy must therefore be carefully considered, with judicious selection of the agent, and with reflection on the physiologic changes of pregnancy to ensure appropriate dosing.

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