

Clinical Guideline

ANTICOAGULATION STRATEGIES FOR MECHANICAL HEART VALVES DURING PREGNANCY AND THE POSTPARTUM PERIOD

SETTING	University Hospitals Bristol
FOR STAFF	Obstetricians, Cardiologists, Anaesthetists and Midwives
PATIENTS	Women with mechanical heart valves during pregnancy and the postpartum period

GUIDANCE

Background

- Evidence is limited around the prevalence and optimal management of pregnancy in women with mechanical heart valves (MHV)
- MHV have been demonstrated to be a predictor of adverse outcome in pregnancy but studies are scarce and numbers are small
- Recent European registry data shows that only 42% of women with MHV experience serious events in pregnancy compared with only 22% of other cardiac patients¹
- Mechanical valve thrombosis (MVT) occurs more frequently in pregnancy and therefore the need to maintain adequate anticoagulation must be balanced against the risks of fetal and maternal haemorrhagic complications
- MVT risk is dependent on compliance with anticoagulant therapy in addition to the type, size and position of the valve(s) and history of prior valve complications
- The character and nature of maternal and fetal risks of anticoagulation are dependent on the regimen used and the quality of anticoagulation control

Pre-pregnancy

Pre-pregnancy counselling is recommended for every woman of reproductive age with MHV and should be performed by multidisciplinary team, including an obstetrician, cardiologist and possibly a haematologist.

Counselling should include:

- Evaluation of current condition: assessment of symptoms, echocardiographic evaluation of ventricular function, and prosthetic valve function.
- Compliance with prior anticoagulant therapy should be considered.
- Risk stratification for thrombotic events (including MVT) based on prosthesis and patient factors to aid choice of anticoagulant regimen (see table 1)
- Detailed discussion regarding risks associated with pregnancy and advantages and disadvantages associated with different anticoagulation options.
- Ensuring that the women are aware of the teratogenic effects of warfarin and therefore the importance of early diagnosis of pregnancy.
- The management of the regimen that is chosen should be planned in detail.
- Discussing the risks of unplanned pregnancy and need for effective contraception when not planning pregnancy should be stressed.

Prosthesis thrombogenicity	Patient-related risk factors
Lower Carbomedics, Medtronic Hall, St Jude Medical, ON-X	Mitral or tricuspid replacement Previous thromboembolism
Medium Other bileaflet valves	Valve dysfunction Ventricular dysfunction
High Lillehei-Kaster, Omniscience, Starr-Edwards, Bjork-Shiley, other tilting-disc valves	Atrial fibrillation

Table 1: Risk factors for thrombosis with MHV – adapted from Vahanian et al.²

Antenatal

Referral and risk assessment

- All women with MHV and confirmed pregnancy should be referred to the Joint Obstetric Cardiac Clinic as a matter of urgency and ideally reviewed in this setting before 6 weeks gestation. Risks associated with pregnancy in this population overall are outlined in Table 2. Historical data suggests a risk of MVT of up to 25% with no anticoagulation and 2 – 10% with anticoagulation.

	Maternal Risk ^{1,2,3,4}	Fetal Risks ³
All pregnancies with MHV	Mortality (1.4-1.8%) MVT 6.1% <ul style="list-style-type: none"> - Cardiac failure - Stroke - Mortality Miscarriage (15.6%) Haemorrhage (23.1%) Hospital admission (36.7%) Caesarean section (45%)	Stillbirth (15.6%)

Table 2: Risks associated with pregnancy in context of mechanical heart valve

Choice of antenatal anticoagulation regimen

- There is a lack of consensus regarding the optimal method of anticoagulation⁵⁻⁷ and no randomised trials have compared approaches.
- All options are associated with risks for the mother and fetus and management will be planned on an individual basis through discussion between the woman and the multi-disciplinary team ideally in a pre-pregnancy setting.
- Relative risks and benefits of different anticoagulation regimens are outlined in Table 3:

Anticoagulation regimen	Maternal benefits/risks	Fetal benefits/risks
Warfarin until 36 weeks: <ul style="list-style-type: none"> Strongly consider when high risk of thrombosis Continue to 36 weeks LMWH from 36 weeks to delivery to minimise risk of fetal and maternal haemorrhage 	Lowest MVT risk (2.4%) ⁵ <ul style="list-style-type: none"> 0% in 1st trim in one study¹ Risk of bleeding (antepartum and postpartum)	Reduction in live births (vs LMWH in 1 st trimester) ^{1,7} <ul style="list-style-type: none"> Miscarriage 28-33%^{1,7} Stillbirth 7.1- 16%^{1,7} Fetal embryopathy 0.6-10% ⁵ <ul style="list-style-type: none"> Ass with warfarin at 6-12 weeks Risk likely to be lower at <3% if <5mg/day^{6,7} CNS abnormalities 1% ¹ Fetal haemorrhage <ul style="list-style-type: none"> Intracranial haemorrhage associated with vaginal delivery if recent warfarin dosing
LMWH throughout pregnancy	MVT up to 10% ^{5,9} Optimal dosing with use of factor Xa levels not yet fully established so close monitoring required	No placental transfer to fetus during pregnancy
Combination (LMWH/warfarin) <ul style="list-style-type: none"> LMWH from positive pregnancy test to week 13 Warfarin week 13-36 LMWH week 36 until delivery (as above) 	MVT risk higher than warfarin ⁵ <ul style="list-style-type: none"> 3.6% overall 50% of MVT in pregnancy occur during 1st trim LMWH Requires very close monitoring during transitions to limit sub-therapeutic anticoagulation	No placental transfer to fetus during first trimester Better live birth rate (vs warfarin 1 st trimester) ¹ <ul style="list-style-type: none"> Miscarriage 9.2% Stillbirth 0.7% Fetal haemorrhage <ul style="list-style-type: none"> Intracranial haemorrhage associated with vaginal delivery if recent warfarin dosing
Unfractionated heparin only	Rarely recommended due to MVT > 10% and risk of maternal osteoporosis and thrombocytopenia ⁵	
Combination (UFH/warfarin) <ul style="list-style-type: none"> Rarely used at STMH 	Slightly higher rate MVT than LMWH/warfarin regimen ⁵ More complex drug delivery/monitoring. Osteoporosis/thrombocytopenia.	As per combination LMWH/warfarin
New anticoagulant drugs e.g. dabigatran, rivaroxaban, apixaban	Not recommended due to current lack of safety data or evidence in context of either mechanical valve replacement or pregnancy	

Table 3: Risks and benefits of anticoagulation regimens

Monitoring and dose adjustments

- Warfarin regimen

- Thrombosis risk is related to a combination of prosthesis and patient-related risk factors and should be used to guide INR targets as shown in Table 3.
- All women taking warfarin in pregnancy (combined regimen as well as women who continue to be on warfarin beyond 6 weeks for any reason) should be referred to the Fetal Medicine Unit for detailed assessment of fetal anatomy and follow up.
- If labour starts within one week of taking warfarin, caesarean delivery is indicated for fetal reasons (See 'Perinatal' section).

Prosthesis thromogenicity*	Patient-related risk factors	
	None	1 or more of: Mitral or tricuspid replacement Previous thromboembolism Mitral stenosis LVEF<35%
Lower risk	2.5	3.0
Medium risk	3.0	3.5
High risk	3.5	4.0

Table 4: Target INR based on risk stratification for thromboembolic event ²

*see table 2

- **Low molecular weight heparin regimen**

- There is a marked increase in dose requirement for LMWH in pregnancy in order to keep levels therapeutic. Dosing can also be challenging in the context of obesity or renal impairment.
- LMWH should NOT be used without weekly anti-Xa measurements. If this is impossible due to location or compliance, then warfarin should be recommended⁵.
- Commence LMWH (Enoxaparin dose of 1mg/kg of body weight twice daily) on confirmation of pregnancy (positive pregnancy test) and stop warfarin.
- Peak (post-dose) anti-Xa levels:
 - LMWH dose should be adjusted, based on **weekly** peak anti-Xa levels (4-6 hours post-dose). The data regarding the therapeutic range for prevention of valve thrombosis is variable. In view of our local experience of high incidence of valve thrombosis, we recommend peak anti-Xa levels are maintained between 1 and 1.2 IU/ml.¹⁰
 - The peak anti-Xa should be measured within 48 hours after every change of dose, adjusting dose to achieve the therapeutic range.
 - The peak anti-Xa level should be assessed weekly once optimal therapeutic levels (see above) are achieved.
- Trough (pre-dose) anti-Xa levels:
 - The importance of monitoring pre-dose anti-Xa and the need to maintain this level above 0.6IU/ml has not been studied sufficiently to allow firm recommendations⁵. If trough levels are sub-therapeutic with therapeutic peak levels, consider 3 times daily dosing. We recommend measuring anti-Xa trough levels weekly to help reduce the risk of thrombotic complications in high risk women with mechanical valves in pregnancy.
 - **Due to local experience we can only recommend LMWH as an anticoagulant option if the woman is prepared to attend for weekly trough and peak anti Xa levels**
- Therapeutic LMWH should be discontinued 24-36 hours before delivery. (See section on 'Perinatal' for further advice).

- **Addition of aspirin to LMWH regimen**

- The additive use of low dose aspirin in the prevention of thromboembolic events has been shown to be beneficial in patients with mechanical valves and vascular disease. The extrapolation of this data to the pregnant population and those without vascular disease remains unproven. In general, we would support the addition of aspirin to LMWH in this context where no contra-indications are present.
- Aspirin should be ceased 10 days prior to the planned delivery date where possible.

- **Combined regimen (LMWH/warfarin/LMWH)**

- All changes to anticoagulation regimen during pregnancy should be implemented in hospital⁵.
- Commence LMWH +/- aspirin and stop warfarin as above on confirmation of pregnancy with a positive pregnancy test, ideally prior to 6 weeks from LMP.
- LMWH dosing should be based on factor Xa (peak and trough) levels as detailed previously.
- Recommence warfarin after 13 completed weeks of gestation. LMWH should be continued until the patient specific INR target is reached.
- Change to LMWH at 36 weeks and monitor post-dose anti-Xa within 48 hours after every change of dose, adjusting dose to achieve the therapeutic range 1-1.2IU/ml, and then weekly.
- Therapeutic LMWH should be discontinued 24-36 hours before delivery. (See section on 'Perinatal' for further advice).

Presentation of valve thrombosis

- Valve thrombosis should be suspected in any high-risk patient presenting with dyspnoea, heart failure and/or an embolic event
- Immediate management of the effects of valve thrombosis is necessary e.g. acute pulmonary oedema
 - The adult congenital heart disease consultant or consultant cardiologist on call should be contacted
 - Emergency surgery may be indicated
 - Urgent transthoracic echocardiography is indicated¹ and may be followed by trans-oesophageal echocardiography or fluoroscopy in discussion with cardiology team
- Delivery may be considered as part of the multi-disciplinary team plan depending on gestational age, maternal and fetal conditions and need for intervention

Perinatal

- **All patients should have a clearly documented individualised perinatal anticoagulation plan which will reflect their risk of thrombosis, likely timely success of induction and need for epidural anaesthesia.**
- Mode of delivery will be influenced by underlying cardiac pathology, current cardiac condition and obstetric indications.
- Planned vaginal delivery via induction of labour is usually the preferred management option.
- If a woman who has taken warfarin in the past 7 days needs delivery, a caesarean section is recommended to reduce the risk of fetal haemorrhage.
- Patients taking warfarin at any stage of pregnancy should have converted to therapeutic enoxaparin at 36 weeks as outlined above
 - Therapeutic enoxaparin should ideally be ceased 24h prior to delivery
 - Where the risk of thrombosis is high, ACCP and ESC guidelines support the use of intravenous unfractionated heparin cover for the immediate peripartum period. This should continue from cessation of enoxaparin until 4-6h pre-delivery and restarted 4-6h post-delivery if no bleeding complications are encountered⁵.
 - Due to the unpredictable timing of induction of labour and delivery, an individualised anti-coagulation plan should be in place in consultation with a consultant Haematologist.
- Patients will be informed to withhold enoxaparin and seek medical attention in the context of suspected onset of labour or rupture of membranes.
- Epidural anaesthesia is contraindicated within 24h of therapeutic enoxaparin
- Active management of the third stage is strongly advised (although it may be preferable to avoid ergometrine in many cardiac conditions).

Preterm labour in patients on warfarin

- If possible deliver by emergency caesarean section (advised to prevent fetal haemorrhage). However this may not be possible and may be of greater maternal risk if the timescale is short.
- Send urgent INR, coagulation, FBC, group and cross match.
- Inform anaesthetist of admission.
- Contact haematologist on call (in hours bleep 2677, out of hours contact on call haematology registrar).
- Give Vitamin K 5mg IV. It takes up to 6 hours to be fully effective. If earlier delivery is required, then consider prothrombin complex concentrate e.g. Octaplex; a supply is available in the fridge on central delivery suite at St Michaels (discuss with haematologist for advice on dose). If prothrombin complex is used, check INR 15 minutes after administration.
- Ensure oral Vitamin K given to neonate (consider oral rather than IM to avoid the risk of intramuscular haematoma).

Preterm labour in patients on enoxaparin

- Vaginal delivery is usually most appropriate unless there are other obstetric indications for caesarean
- Send urgent INR, coagulation, FBC, group and cross match.
- Inform anaesthetist of admission and last dose of enoxaparin
- Contact haematologist on call (in hours bleep 2677, out of hours contact on call haematology registrar)
 - A detailed anticoagulation plan will need to be discussed due to the uncertain time course of preterm labour and delivery
- Protamine sulphate 50mg can be given for active bleeding but it is not reliably effective. It is of most use soon after enoxaparin administration
- Early consideration of the use of tranexamic acid if actively bleeding

Postnatal

- The haemodynamic changes immediately following delivery can worsen the cardiac condition.
 - Close cardiac and obstetric monitoring, in a HDU setting, by trained staff.
 - Postpartum echocardiogram and cardiology review prior to discharge, the timing of which will be determined by cardiac function, site and type of valve.
- Anticoagulation with therapeutic enoxaparin should be recommenced 6h post-delivery if there are no concerns regarding bleeding
 - Where concerns exist regarding the balance between bleeding and anticoagulation, consultant Haematology advice should be sought.
- Warfarin can be recommenced day 5-7 post-delivery irrespective of delivery mode unless there are concerns regarding ongoing bleeding risk.
 - This should usually be restarted at normal pre-pregnancy doses.
 - Therapeutic enoxaparin should be continued until 2 INRs are within the patient's individualised therapeutic range (see Table 4).
 - If the patient is being discharged, there must be clear direct communication with the GP or anticoagulation service to arrange close monitoring of INR and ensure appropriate continuation of therapeutic enoxaparin.
- No clear data exists regarding changes to enoxaparin dosing postpartum or the role of ongoing factor Xa level monitoring in the immediate postpartum period.
 - It may be prudent to monitor of peak factor Xa levels at 48h postpartum and 48h post dose changes to ensure adequate dosing in view of postnatal haemodynamic changes.

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RELATED DOCUMENTS None

SAFETY If there are unusual or unexpected safety concerns (to staff or patient), emphasize them here

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