|  |
| --- |
| **Clinical Guideline**Anticoagulation STRATEGIES for Metal 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**Raising awareness of Increased risk of valve thrombosis during pregnancyImportance of pre-pregnancy counselling The options for anticoagulation and risks and benefits associated with each option* Importance of stringent monitoring to ensure optimum anticoagulation
* Need for individualised care plans and multidisciplinary care.

According to current evidence, warfarin is the most effective anticoagulant in prevention of valve thrombosis, and therefore is the safest anticoagulant choice for the mother. However, warfarin crosses the placenta and increases the risk of fetal loss, especially with doses of more than 5mg.[1](#_ENREF_1) An alternative option is low molecular weight heparin (LMWH). LMWH does not cross the placenta, but is associated with a higher incidence of valve thrombosis. The risk of thrombosis is dependent upon the type, size and position of the valve(s), any prior valve complications and most importantly, likely compliance with anticoagulant therapy.**Pre-pregnancy counselling is recommended in every woman of child-bearing age with a mechanical prosthetic valve**Pre-pregnancy counselling 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 (see Table 1).
* Detailed discussion regarding risks associated with pregnancy and advantages and disadvantages associated with different anticoagulation options. Compliance with prior anticoagulant therapy should be considered. The overall maternal mortality rate for women with metal valves in pregnancy is 2.9%.[2](#_ENREF_2)
* 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.

Table 1 Risk factors for valve thrombosisHigher risk of valve thrombosis is associated with the following:* Valve type: certain types are associated with higher thrombogenicity (see table 3)
* Valve sites: Mitral> tricuspid> aortic
* Previous thrombosis
* Ventricular dysfunction
* Valvular dysfunction
* Atrial fibrillation
* Poor compliance

 **Table 2 Anticoagulant options during pregnancy**

|  |  |  |  |
| --- | --- | --- | --- |
| Regimen | Details of Regimen | Benefits | Risks |
| 1. Warfarin
 | Warfarin until 36 weeks, when replaced by dose-adjusted LMWH until delivery | Most effective anticoagulant for mother | * Valve thrombosis 3.9%[2](#_ENREF_2)
* Fetal embryopathy (0.6–10%)[3](#_ENREF_3)
* Increased risk of fetal loss (25-70%)[4](#_ENREF_4)
* Fetal haemorrhage
* Bleeding
 |
| 1. LMWHa: Low molecular weight heparin and low dose aspirin (75mgs)[5](#_ENREF_5)
 | Commence LMWH 1mg/kg twice daily as soon as pregnant(See below for monitoring and dose adjustment) | Does not cross the placenta: hence does not affect the fetus | Not as effective an anticoagulant especially in high risk cases (Table 1) * Valve thrombosis (estimated at 9%).[3](#_ENREF_3) This risk may be lower in low-risk valves with meticulous dose adjustment of anti-Xa.[6](#_ENREF_6) Consequences of valve thrombosis include
	+ Deterioration of cardiac function
	+ Stroke
	+ Maternal death
 |
| 1. Combination
 | LMWHa as soon as pregnancy confirmed to 13 completed weeks of gestation, followed by warfarin for the remainder of pregnancy until 36 weeks gestation, when LMWH re-substituted. Monitoring as described in the next section for LMWH as well as warfarin | Potentially* Prevents embryopathy
* Effective anticoagulation for majority of pregnancy whilst on warfarin
 | * All the risks above (associated with warfarin as well as LMWH)
* Risk of complications if suboptimal or excessive anticoagulation particularly when changing regimens and requires very close monitoring
 |

**Monitoring and Management**There is a marked increase in dose requirement secondary to increased plasma volume and increased renal clearance during pregnancy. The effectiveness of the anticoagulation regimen should be monitored weekly and clinical follow-up including echocardiography should be performed at least monthly. Any changes to the anticoagulation regimen during pregnancy should be planned and decided by the multidisciplinary team hospital. There is no single accepted treatment option for managing pregnant women with mechanical prosthetic valves. Given the limited and sometimes conflicting data, the following options should be considered .[7](#_ENREF_7)**Warfarin regimen:*** Valve-specific INR targets should be achieved and maintained whilst on warfarin (Table 3).
* All women taking warfarin in pregnancy (warfarin and 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 ‘Delivery’ section).

**Table 3 Target international normalized ratio (INR) for mechanical prostheses**[**7**](#_ENREF_7)

|  |  |  |
| --- | --- | --- |
| **Prostheses thrombogenicitya** | **No risk factorsb** | **Risk factors ≥ 1b** |
| Low | 2.5 | 3.0 |
| Medium | 3.0 | 3.5 |
| High | 3.5 | 4.0 |

**a** Prostheses thrombogenicity: Low- Carbomedics, Medtronic Hall, St Jude; Medium- other bileaflet valves; High- Star-Edwards, Bjork-Shiley and other tilting disc valves.**b** See Table 1: Risk factors for valve thrombosis other than valve type**Low moleculer weight heparin and low dose aspirin regimen (LMWHa) regimen:** * LMWH should not be used without weekly anti-Xa measurements. If this is impossible due to location or compliance, then warfarin should be recommended.[8](#_ENREF_8)
* Commence LMWH (Enoxaparin dose of 1mg/kg of body weight twice daily) on confirmation of pregnancy and stop warfarin. Aspirin 75mg od should be added.[5](#_ENREF_5)
* 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. The American College of Chest Physicians (ACCP) suggest achieving the manufacturer’s peak anti-Xa levels (approximately 1.0 IU/ml)[5](#_ENREF_5), whilst American College of Cardiology/American Heart Association (ACC/AHA) suggests 0.7-1.2 IU/ml[9](#_ENREF_9) and the European Society of Cardiology (ESC) recommends 0.8–1.2 U/ml.[3](#_ENREF_3) In view of our local experience of high incidence of valve thrombosis,[10](#_ENREF_10) we recommend peak anti-Xa levels are maintained between 1 and 1.2 IU/ml.[11](#_ENREF_11)
* The peak anti-Xa should be measured within 48 hours after every change of dose, adjusting dose to achieve the therapeutic range 1-1.2IU/ml.
* The peak anti-Xa level should be assessed weekly once optimal therapeutic levels (see above) are achieved.
* Trough (pre-dose) anti-Xa levels: There is sparse evidence regarding the optimal trough anti-Xa levels. Target levels of 0.4–0.7 IU/ml[6](#_ENREF_6) have been suggested. If trough levels are sub-therapeutic with therapeutic peak levels, consider 3 times daily dosing.[4](#_ENREF_4) 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.
* Therapeutic LMWH should be discontinued 24 hours before delivery. (See section on ‘Delivery’ for further advice).

**Combination regimen:*** Commence LMWH and aspirin and stop warfarin as above on confirmation of pregnancy.
* Recommence warfarin after 13 completed weeks of gestation. LMWH should be continued until the valve specific INR target is reached. Aspirin should be discontinued on commencing warfarin.
* 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.

**Valve thrombosis*** Echocardiography is indicated in women with mechanical valves presenting with dyspnoea and/or an embolic event, followed by trans-oesophageal echocardiography or fluoroscopy if necessary.
* Immediate management of the effects of valve thrombosis i.e. pulmonary oedema, is necessary. The adult congenital heart disease consultant (UHB) or consultant cardiologist on call should be contacted. Emergency surgery may be required.
* Management of valve thrombosis is comparable with management in non-pregnant patients.
* Consider transfer to tertiary unit if stable.
* Delivery should be considered depending on gestational age, maternal condition and need for intervention.

**Delivery** * Mode of delivery will be influenced by underlying cardiac pathology, current cardiac condition and obstetric indications.
* Planned vaginal delivery is usually the preferred management option. Induction of labour frequently follows an unreliable timescale and therefore an individualised plan will need to be made, taking into account the risks of valve thrombosis, likely timely success of induction and need for epidural anaesthesia. In some cases it may be necessary to consider temporary anticoagulation with intravenous unfractionated heparin. Advice from the Consultant Haematologist should be obtained.
* 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 (see below).
* Active management of the third stage is strongly advised (although it may be preferable to avoid ergometrine in many cardiac conditions).

**Peri-partum Anticoagulation****Anticoagulated on warfarin:*** Convert to therapeutic enoxaparin (Enoxaparin) at 36 weeks to allow fetus to clear warfarin before delivery
	+ 1mg/kg bd
	+ Monitor anti-Xa, 4 hours (post enoxaparin dose) after 48 hours following commencement of therapeutic enoxaparin; aim for anti-Xa to be 1-1.2 I/ml.
	+ Anti-Xa should be monitored every week unless dose changes are made, and then should be monitored 48hrs after dose change.

 * If preterm labour and 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 advise 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).

**Anticoagulated on enoxaparin (Enoxaparin)*** If preterm labour and on therapeutic enoxaparin
	+ Vaginal delivery most appropriate (unless other obstetric indications for caesarean).
	+ Discuss with haematologist as above.
	+ Protamine sulphate, 50mg can be given, but not reliably effective.
	+ Inform anaesthetist of admission.
* If awaiting spontaneous labour
	+ Tell woman to omit enoxaparin as soon as she thinks she is in labour or SRM and to attend delivery suite for review.
	+ If not in labour enoxaparin can be given, but regional anaesthesia is relatively contraindicated for 24 hours post therapeutic enoxaparin.
	+ If in doubt, latent phase or pre-labour rupture of membranes, prophylactic enoxaparin can be given and woman reviewed within 12 hours.
* If IOL planned
	+ It is reasonable to give prophylactic enoxaparin dose at the time of administering long acting prostaglandin such as Propess and then no further enoxaparin. However if prolonged IOL or likely to be quick IOL, discuss with consultant obstetrician regarding enoxaparin.
	+ After delivery restart therapeutic enoxaparin 6 hours post-delivery, assuming clinically stable (If there are concerns about haemostasis a prophylactic dose (40mg) could be given with full therapeutic dose (1mg/kg bd) starting 12 hours after this dose).
	+ Do not restart aspirin post delivery
	+ Restart warfarin 5-7 days post-delivery. If the patient is being discharged, liaise with her GP/anticoagulation service to arrange re-warfarinisation and INR monitoring.
	+ It is best to restart on previous dose rather than rapidly reload. It will take at least 3-5 days to achieve a therapeutic INR.
	+ Continue therapeutic enoxaparin until 2 consecutive INRs in therapeutic range for the valve (see valve specific INR in patient care plan) are obtained.
* For elective caesarean section (C/S)
	+ Last therapeutic dose of enoxaparin should be 24 hours previously.
	+ Aspirin should be stopped 10 days before the planned date of C/S.
	+ Post C/S, give thromboprophylactic dose of enoxaparin 6 hours after C/S if clinically stable and at least 4 hours after removal of epidural catheter.
	+ Restart therapeutic enoxaparin bd day 1 post C/S if surgically safe.
	+ Do not restart aspirin post-delivery.
	+ Restart warfarin 5-7 days post-delivery. If the patient is being discharged, liaise with her GP/anticoagulation service to arrange re-warfarinisation and INR monitoring.
	+ Continue enoxaparin until 2 INRs in therapeutic range for valve are obtained (see valve specific INR in patients care plan).
* Regional anaesthesia/analgesia
	+ 12 hours after prophylactic dose enoxaparin
	+ 24 hours after therapeutic dose enoxaparin
* Some patients may require individualised unfractionated heparin infusions. This is to be agreed by consultant Obstetrician, Cardiologist and Haematologist.

**Post-partum**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.

**Version 1****Authors of version 1**Sneha Basude Subspeciality trainee in Maternal and Fetal MedicineJohanna Trinder, Consultant in Maternal Medicine and ObstetricsReviewed by:Dr Stephanie Curtis Consultant in Adult Congenital Heart disease Dr Amanda Clark, Consultant HaematologistDr Issie Gardner, Consultant AnaesthetistReview led byConsultation processRatified by**Produced** **Review date**  |
| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
| **RELATEDDOCUMENTS** | http://nww.avon.nhs.uk/dms/download.aspx?did=2926 |
| **SAFETY** | This is a high risk situation |
| **QUERIES** | Contact Jo Trinder, Consultant 0117 3425250 |

## **References**

1. Vitale N, De Feo M, De Santo LS, Pollice A, Tedesco N, Cotrufo M. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. *Journal of the American College of Cardiology* 1999;33(6):1637-41.

2. Chan WS, Anand S, Ginsberg JS. Anticoagulation of Pregnant Women With Mechanical Heart Valves: A Systematic Review of the Literature. *Arch Intern Med* 2000;160(2):191-96.

3. Regitz-Zagrosek V, Lundqvist CB, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy. *European Heart Journal* 2011(10.1093/eurheartj/ehr218).

4. Pieper P, Balci A, Van Dijk A. Pregnancy in women with prosthetic heart valves. *Netherlands Heart Journal* 2008;16(12):406-11.

5. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy. *Chest* 2012;141(2 suppl):e691S-e736S.

6. McLintock C, McCowan L, North RA. Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin. *BJOG: An International Journal of Obstetrics & Gynaecology* 2009;116(12):1585-92.

7. Vahanian A, et al. . Guidelines on the management of valvular heart disease (version 2012) The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal* 2012;33:2451–96.

8. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, et al. Guidelines on the management of valvular heart disease: the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *European Heart Journal* 2007;28:230-68.

9. Bonow RO, Carabello BA, Chatterjee K, de Leon Jr AC, Faxon DP, Freed MD, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2008;118(15):e523- e661.

10. Basude S, Hein C, Curtis S, Clark A, Trinder J. Low‐molecular‐weight heparin or warfarin for anticoagulation in pregnant women with mechanical heart valves: what are the risks? A retrospective observational study. *BJOG: An International Journal of Obstetrics & Gynaecology* 2012;119(8):1008-13.

11. Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of Antithrombotic Agents During Pregnancy The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *CHEST Journal* 2004;126(3\_suppl):627S-44S.