1. Introduction and who the guideline applies to:

This guideline covers the anticoagulation treatment of any pregnant woman with mechanical heart valves and applies to any member of staff involved in their care.

Background:

The management of women on mechanical valves during pregnancy can be difficult due to the conflict between the optimal management for the mother to avoid valve thrombosis, versus the risk of anticoagulation to the embryo or foetus. In non-pregnant women with metallic valves, the incidence of valve thrombosis on warfarin is approximately 1% per year (2). This risk is greater for tricuspid or mitral valves compared to the aortic position. Other risk factors include a history of previous thrombosis, atrial fibrillation and the presence of multiple prosthetic valves. The risk of thrombosis during pregnancy would be expected to be higher due to pregnancy related haemostatic changes that cause hypercoagulability. There is also difficulty in INR control, which is known to be a major risk factor for valve thrombosis (3). The physiological changes in cardiac output may also impact a woman's outcome.

It is clear that all women with metallic valves require therapeutic anticoagulation throughout pregnancy, but there is a lack of reliable data on the safety and efficacy of anticoagulation which means that the optimal regime is uncertain. Conflict also exists in international guidelines. The American and European Cardiology societies favour continuing warfarin during the second and third trimesters (4, 5), whilst the American college of Chest physicians offers several alternative options (1). The presence of therapeutic anticoagulation is associated with a risk of pregnancy-specific bleeding, with an increased risk of antepartum haemorrhage (6, 7).

2. General Recommendations

1. Pre-pregnancy counselling should be clearly documented regarding the risks associated with anticoagulation, including warfarin embryopathy and maternal and fetal bleeding risks, as well as risk of valve thrombosis
2. Women should be managed in a cross-speciality team, with joint care involving Haematology, Obstetrics, Cardiology and Obstetric Anaesthetists
3. An antenatal care plan should be discussed and agreed and should follow one of the recommended treatment regimens below
4. Regular cardiac monitoring is required, to include review by Cardiologist in each trimester and an echocardiogram in (at least) 1st and 3rd trimester
5. Regular anticoagulant monitoring is required dependent on treatment regimen (see below) and women seen with the results in Haematology/Obstetric Clinic
6. A definitive intra-partum care plan should be discussed and agreed with all members of the joint team and distributed to relevant clinical areas/staff
7. The delivery should be flagged for the attention of the Paediatric Team for Neonatal assessment

Preconception evaluation and counselling

- All women with prosthetic heart valves should receive preconception assessment including cardiological assessment with specific expertise in managing patients with valvular heart disease during pregnancy.
- For discussion of anticoagulation, women should be referred to the Obstetric Haematology Clinic to counsel them on the maternal and fetal risks of continuing therapeutic anticoagulation. Patients should be aware of the life threatening risk of thromboembolic events regardless of the anticoagulation regime chosen.
- Women with regular periods who are attempting to conceive should be advised to continue warfarin until a positive pregnancy test. The risk of warfarin embryopathy is low in the first six weeks of gestation and it is following this time that women should be switched to an alternative anticoagulation.

Anticoagulation during pregnancy

Three options are primarily available for anticoagulation throughout pregnancy. Option 1 is favoured in UHL in view of difficulty in INR stabilisation in pregnancy, along with the risks of teratogenicity and fetal complications with warfarin. Each woman should be counselled on all options and a care plan documented pre-conception (or in early antenatal period if this is not possible). Recommended regimes include:

1. Adjusted-dose twice daily low molecular weight heparin(LMWH)throughout pregnancy to achieve manufacturer's peak anti-Xa(Dalteparin level taken 3 hours post dose, target range*1.0-1.2iu/ml)*

2. Oral anticoagulation substituted with low molecular weight heparin between 6-14 weeks with adjusted dose BD LMWH to achieve peak anti-Xa target as above. Maintain oral anticoagulation with warfarin between 14 and 36 weeks and substitute with adjusted dose BD LMWH from 36 weeks to delivery.

3. Continual warfarin throughout pregnancy

In high risk patients, the addition of Aspirin 75mg OD can be considered to reduce thromboembolic complication rates.
Direct oral anticoagulants (Dabigatran, Rivaroxaban, Apixaban, Edoxaban) are contraindicated in both pregnancy and in use for prosthetic valves and **should not** be considered

Therapeutic anticoagulation with frequent monitoring is essential. Decisions are primarily based on prospective and retrospective cohort studies.

Warfarin:

- This is the safest anticoagulation for the mother as it is the most effective agent to prevent valve thrombosis. Pooled data of all reported pregnancies (N=1169) reported a 3.8% incidence of thromboembolic complications. There was a live birth rate of 66.6%, but an overall incidence of warfarin embropathy of 4.2% (2).
- Warfarin freely crosses the placenta andis thought to inhibit vitamin K dependent osteocalcins that play a role in calcification which occurs during embryogenesis (8). Features of warfarin embropathy include characteristic nasal hypoplasia and skeletal abnormalities (foetal warfarin syndrome).The critical time of exposure is weeks 6-9 of gestation.
- The risk of warfarin embryopathy may be higher in women with warfarin doses >5mg per day, which has led some international guidelines to differentiate management based on the woman's warfarin dose(4,5). This is not widely practised in UHL.
- Warfarin exposure after the first trimester increases the risk of fetal bleeding with an increased rate of foetal loss and stillbirth. This is influenced by the foetal INR running at a higher level than that of the mother due to hepatic immaturity.

Heparin:

- Unfractionated heparin (UFH) does not cross the placenta and has no known harmful effects on the foetus. Thromboembolic complication rates are higher in women treated with SC UFH throughout pregnancy compared to warfarin (25-33%) (9). Prolonged use causes bone density loss. It is therefore not recommended for prolonged use.
- LMWH is preferred to UFH due to apparent lower rate of valve thrombosis (rate 10.6% in pooled data of 104 pregnancies)(2) . Fewest events are reported in those centres where therapeutic doses are used and regular anti-Xa monitoring is carried out. Active treatment failure in women taking LMWH with therapeutic anti-Xa levels is reported as 4.8% (2). Therapeutic dose should be based on booking weight and given in split daily doses (see table below)

Booking weight	Dalteparin dose
<50kg	5000iu twice daily
50-69kg	5000iu morning, 7500iu evening
70-89kg	7500iu twice daily
90-109kg	10000iu twice daily
110-125kg	12500iu twice daily
>125kg	As determined by haematology

- The timing of anti-Xa levels is dependent on the LMWH used. Dalteparin is primarily used in UHL, with peak levels taken at 3 hours post dose. Data suggests that a peak target range of 1.0-1.2iu/ml should be used and some centres also advocate measuring trough levels in addition, although this is not advised routinely. Levels should be taken on a regular basis and we advocate levels monthly. Women should be seen with the results in the Haematology Obstetric Clinic to adjust treatment where necessary.

Role of aspirin:

- The rate of thromboembolic complications with single agent aspirin in women with metallic heart valves is reported to be as high as 25% (9). It cannot therefore be used as single agent therapy but may be added to therapeutic anticoagulation in those high risk patients.

Treatment regimens throughout pregnancy – Based on reference 1

Plan for delivery

- Obstetric Haematology Team should be informed of admission at earliest opportunity
- Mode of birth should be determined by maternal and obstetric indications
- Women should be advised to omit fragmin when labour starts or on the day of a planned caesarean section/induction of labour if this is required
- Regional anaesthesia or analgesia techniques should not be undertaken until at least 24 hours after the last therapeutic dose of LMWH
- LMWH should not be given for 4 hours after the use of spinal anaesthesia or after the epidural catheter has been removed.
- The epidural catheter should not be removed within 12 hours of the most recent injection
- Maternal IM injections should be avoided
- Prophylactic antibiotics should be given in line with national guidance

- Women should maintain hydration and mobilisation where possible
- IV unfractionated heparin 5000iu may be required if labour is prolonged and this should be discussed with the on call Haematology SpR or Haemostasis Consultant on call
- If urgent or emergency delivery is required, the management of anticoagulation reversal will depend on the regime chosen throughout pregnancy. Full reversal of anticoagulation is not required for vaginal or caesarean delivery, but in the event of life threatening bleeding or to protect the fetus, reversal may be required. Such cases should be urgently discussed with the Haematology SpR or Haemostasis Consultant on call.

Plan for 3rd stage of labour

- Active management of the 3rd stage with IV syntocinon infusion

Postpartum Care

- Restart fragmin at prophylactic dose 4 hours post-partum, and give therapeutic dose at 12 hours with BD dosing with reduced first dose at 50%
- If no excessive bleeding, this should be increased to twice daily dosing on the following day (dose as per pre-delivery). *If a caesarean is required, delay in full treatment dose may be required and this should be discussed with the Haematology Obstetric Team*
- Anti-Xa level should be checked post 4th/5th dose (1 citrate sample taken 3 hours post dose and hand delivered to Special Haematology Lab, Level 2 Sandringham building). Please contact lab on 6619 when sample taken.
- Observe for excessive bleeding and consider norethisterone is necessary
- Restart warfarin 2-3 days after delivery if there is a low risk of bleeding. Higher doses of Warfarin are frequently required in the early puerperium.
- Continue BD LMWH until INR within desired therapeutic range on 2 consecutive tests
- Advise breast feeding safe on both warfarin and LMWH

Neonatal Management

- Paediatric team should be informed of delivery and complete full assessment in view of bleeding risk and potential teratogen exposure
- Warfarin use in mother close to delivery (<4 weeks) will lead to risk of bleeding in baby and assessment for bleeding should be carried out. Neonatal Vitamin K should be given but the route should be discussed with Neonatologist (po/im). Repeat doses may be indicated.

Management of valve thrombosis

- This is associated with major morbidity or death and any women with suspected valve thrombosis require an urgent cardiology review and echocardiogram to assess the valve. Treatment is controversial, with approaches including intravenous UFH with strict APTT monitoring, thrombolysis or urgent cardiac surgery. Early involvement with the on call Haematologist regarding anticoagulation in this setting is advised.

3. Education and Training:
None

4. Monitoring compliance:
None

5. Supporting References:

1. Bates et al. VTE, thrombophilia, antithrombotic therapy and pregnancy: Antithrombotic Therapy and prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based clinical Practice Guidelines *Chest* 2012;141:e691S
2. Unpublished data, Haematology and Obstetric Manual.....
3. Piper C et al. Prosthetic valve thrombosis: predisposition and diagnosis *European Health Journal Supplements* 2001:3:16-21
4. Nishimura et al 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report ofthe American College of Cardiology/American Heart Association Task force on Practice Guidelines. *J Am CollCardiol*2014;63:e57
5. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC). European Association for Cardio-Thoracic Surgery (EACTS), Vahanian et al. Guidelines on the management of valvular heart disease (version 2012) *Eur Heart J* 2012;33:2451

6. McLintock C et al. Maternal complications and pregnancy outcomes in women with mechanical prosthetic heart valves treated with enoxaparin. *BJOG* 2009;116:1585

7. Quinn et al. Use of high intensity adjusted low molecular weight heparin in women with mechanical heart valves during pregnancy: a single centre experience. *Haematologica* 2009;94:1608

8. Howe et al. Severe cervical dysplasia and nasal cartilage calcification following prenatal warfarin exposure *Am J Med Genet* 1997;71(4):391-6

9. Chan et al. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature *Arch Int Med* 2000;160(2):191-6

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT		
Author / Lead Officer:	A Webster	**Job Title:** Obstetric Consultant and Sub Speciality Trainee
Reviewed by:	B Myers and A Bolger	
Approved by:	Guidelines Group Maternity Service Governance Group	**Date Approved:** 19.07.17

REVIEW RECORD			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**
July 2017	V2	As above	
August 2020	V3	As above	Regional anaesthesia should not be taken until at least 24 hours after. Epidural catheter not to be removed within 12 hours. Fragmin not to be given for at least 4 hours following a spinal.

DISTRIBUTION RECORD:			
Date	**Name**	**Dept**	**Received**
July 2017	All Obstetricians, Obstetric Haematologists and Midwives	Maternity	
August 2020	All obstetricians, All midwives, Obstetric Haematologists.	Maternity	