Received: 2 January 2023 | Accepted: 17 March 2023

DOI: 10.1111/bjh.18781

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

GUIDELINE

British Society for Haematology guideline for anticoagulant management of pregnant individuals with mechanical heart valves

Will Lester[1] | Niki Walker[2] | Kailash Bhatia[3] | Etienne Ciantar[4] | Anita Banerjee[5] | Joanna Trinder[6] | Julia Anderson[7] | Kenneth Hodson[8] | Lorna Swan[2] | Charlotte Bradbury[9,10] | Juliette Webster[11] | Clare Tower[12]

[1]Centre for Clinical Haematology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

[2]Department of Cardiology, Golden Jubilee National Hospital West of Scotland Regional Heart and Lung Centre, Clydebank, UK

[3]Department of Anaesthetics, Manchester University NHS Foundation Trust, Manchester, UK

[4]Department of Obstetrics & Gynaecology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

[5]Guy's and Saint Thomas' NHS Foundation Trust, Women's Services, London, UK

[6]Department of Obstetrics, University Hospitals Bristol NHS Foundation Trust, Bristol, UK

[7]Department of Haematology, NHS Lothian, Edinburgh, UK

[8]Department of Maternity, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK

[9]Cellular and Molecular Medicine, University of Bristol, Bristol, UK

[10]Bristol Haematology and Oncology Centre, Bristol, UK

[11]Department of Maternity, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK

[12]Department of Obstetric and Maternal and Fetal Medicine, Manchester University NHS Foundation Trust, Manchester, UK

Correspondence
Will Lester, Centre for Clinical Haematology, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham B152TH, UK.
Email: will.lester@uhb.nhs.uk

Keywords: anticoagulation, embryopathy, mechanical heart valve, pregnancy

INTRODUCTION

Evidence is limited regarding the prevalence and optimal management of pregnancy in individuals with mechanical heart valves (MHVs). Studies are scarce, often with small numbers of patients included. Mechanical valve thrombosis (MVT) occurs more frequently in pregnancy and there is a high risk of postpartum haemorrhage (PPH). There are a number of options for anticoagulation with differing risks to the pregnant individual and foetus. In the absence of high-quality data, this guideline aims to give recommendations using observational data, evidence from outside of pregnancy and expert opinion to address the key risks at different stages during pregnancy, at delivery and postpartum. Although no single strategy for anticoagulation can be recommended, key risks are identified with recommendations to optimise current management options.

RECOMMENDATIONS

- Individuals with a MHV of childbearing age should be offered pre-pregnancy counselling as soon as appropriate (Grade 1D).
- Prior to cardiac surgery, all individuals of childbearing age should be counselled about the impact of valve replacement choice on future pregnancy risk (Grade 1D).
- Individuals with MHV who are pregnant should be managed in a designated specialist centre with an experienced multidisciplinary team (MDT) including obstetrics, cardiology, cardiac surgery, anaesthetics, neonatology and haematology (Grade 2C).
- Anticoagulation options, including risks and benefits to the mother and the foetus, should be discussed, and a written management plan incorporating patient preference should be agreed (Grade 1D).

- As low adherence with the chosen anticoagulant strategy is a common cause of morbidity and mortality in individuals with MHV in pregnancy, this should be a key component of pre-pregnancy counselling along with measures to facilitate adherence during pregnancy and postpartum (Grade 1D).
- Vitamin K antagonists (VKAs) are superior to low molecular weight heparin (LMWH) for preventing MVT in pregnancy and are recommended as optimal therapy for improving maternal outcomes (Grade 1C).
- There is insufficient evidence to recommend that lower doses of warfarin (e.g. less than 5 mg) are safe in terms of adverse foetal outcome (Grade 2C).
- When using VKAs in pregnancy, non-pregnancy international normalised ratio (INR) targets can be used. The INR should be checked at least weekly if unstable and if stable, at least fortnightly with the option of self-testing when appropriate (Grade 2C).
- When switching from VKA to LMWH in pregnancy, we recommend that the starting dose of LMWH should be higher than the standard therapeutic dose as there appears to be a high rate of MVT in the first trimester during transition (e.g. total 2.5 mg/kg/day for enoxaparin, 250 IU/kg/day for dalteparin and 250 IU/kg/day for tinzaparin in divided doses) (Grade 2C).
- Regular monitoring of LMWH using an anti-Xa assay is recommended; there is currently insufficient evidence to recommend the routine use of specific trough levels or the use of LMWH injections more frequently than twice daily. A peak anti-Xa target of 1.0–1.4 IU/mL taken 3–4 h following a BD (twice daily) LMWH dose is suggested as a reasonable compromise (Grade 2C).
- We recommend the addition of low-dose aspirin (LDA) 75 mg to anticoagulation with LMWH in individuals with MHV during pregnancy in the absence of a contraindication (Grade 2C).
- An increase in the dose of aspirin to 150 mg at 12-week gestation can be considered if indicated for prevention of pre-eclampsia (Grade 2D).
- Surgical management is recommended for miscarriage and termination of pregnancy in the first trimester (Grade 2C).
- MVT requires MDT management in a specialist centre with the use of thrombolysis where appropriate (Grade 2C).
- There is insufficient evidence to recommend a specific mode of delivery in pregnant individuals with MHV. An individualised plan for timing and mode of delivery should be agreed in advance, with input from the MDT, and involvement and agreement of the pregnant individual (Grade 2C).
- Documented delivery and emergency plans should be easily available, and a copy carried by the pregnant individual, in case of unplanned attendances at any maternity unit (Grade 2C).
- VKAs should be switched to heparin at least 2 weeks prior to anticipated delivery and by 36 weeks at the latest (Grade 1C).
- If presenting in labour and on VKA within 2 weeks of scheduled delivery, a caesarean birth should be considered to decrease foetal bleeding complications from labour (Grade 2C).
- Therapeutic LMWH should be paused for at least 24 h prior to surgical delivery to facilitate neuraxial analgesia/anaesthesia (Grade 1B).
- Prolonged pre-delivery interruption of anticoagulation should be avoided, for example, during induction of labour. Consideration should be given to the use of a prophylactic or an intermediate dose LMWH or intravenous (IV) unfractionated heparin (UFH) during induction of labour after MDT discussion with haematology and anaesthetic teams (Grade 2C).
- In view of the high risk of PPH, consider stopping aspirin for at least 3 days prior to scheduled delivery (Grade 2C).
- Prophylactic or intermediate doses of LMWH for the first 24–48 h postpartum are recommended. Restarting a VKA around days 5–7 should be considered to balance the risk of thrombosis against major bleeding (Grade 2C).
- If using UFH postpartum, a gradual increase in anticoagulant intensity is recommended for the first few days (Grade 2C).
- Postpartum, individuals should not leave hospital without a plan for contraception. Insertion of an intrauterine contraceptive device or implant may be suitable for some individuals at the time of delivery or on the postnatal ward (Grade 2C).
- Postnatal follow-up is recommended where the pregnancy can be reviewed and plans made for any future pregnancies (Grade 2C).

PRE-PREGNANCY

Prior to cardiac surgery, all individuals of childbearing age should be counselled about the impact of valve replacement choice on future pregnancy risk by an appropriately trained Cardiologist, recognising individual clinical situations. Discussion should include the risks of re-do surgery and involve a cardiac surgeon. Guidelines recommend consideration of bio-prosthetic valves or, where appropriate, a Ross operation in individuals of childbearing age in view of the high risk of complications during pregnancy in individuals with MHV.[1,2]

Pre-pregnancy counselling is recommended for every individual of reproductive age with a MHV and should be performed by a MDT, including an obstetrician/obstetric physician, cardiologist and a haematologist as appropriate, referred to in this guideline as the specialist team. Suggested roles and responsibilities of the specialist team are given in Appendix S2. Counselling should include the following:

- Evaluation of current condition: assessment of symptoms, echocardiographic evaluation of ventricular function and prosthetic valve function.

TABLE 1 Risk factors for thrombosis with MHV – adapted from Vahanian et al.[2]

Prosthesis thrombogenicity	Other factors that increase thrombosis risk
Lower	Mitral, tricuspid or pulmonary replacement
Carbomedics, Medtronic Hall, St Jude Medical, On-X	Previous thromboembolism Valve dysfunction/mismatch Left ventricular dysfunction Atrial fibrillation Poor adherence with medication
Medium	
Other bi-leaflet valves	
Higher	
Lillehei-Kaster, Omniscience, Starr-Edwards, Bjork-Shiley, other tilting-disc valves	

- Clarifying the valve type, number of MHVs, indication and age of the valve.
- Adherence with prior anticoagulant therapy.
- Risk stratification for thrombotic events (including MVT) based on prosthesis and patient factors to aid choice of anticoagulant regimen (Table 1).
- Detailed discussion regarding risks associated with pregnancy and advantages and disadvantages associated with different anticoagulation options (Table 2).
- Ensuring that the individual considering pregnancy is aware of the early effects of VKAs/warfarin on foetal development (from 6 weeks of gestation). It is important that they perform a pregnancy test early if they think they may be pregnant. Contact details for the specialist team should be provided for the individual to be reviewed at an early stage.
- The anticoagulation regimen that is chosen should be planned in detail. The individual should be made aware of the importance of adherence during pregnancy and the need for frequent hospital appointments, and that travel to the tertiary specialist centre with the relevant expertise will be required and that this may have financial and employment implications.
- Discussing the risks of unplanned pregnancy and the need for effective contraception when not planning pregnancy should be emphasised. Individuals should be signposted to family planning clinics/general practitioner (GP) practices to facilitate contraception provision.
- General aspects of preconception counselling should be addressed, including the need for folic acid, vitamin D, healthy lifestyle and the need to maintain a healthy weight. Other risks in pregnancy due to other specific patient-related factors should also be discussed.
- Patients with congenital heart disease should be informed of the increased risk of congenital heart disease in their newborn.
- All medication should be reviewed and optimised for pregnancy. The UK Teratology Information Service (www.uktis.org) is a helpful resource for information regarding medication use in pregnancy.
- Patients and their GP should be provided with a written summary of the discussion, including risks, benefits and plans for pregnancy. The method of making early contact as soon as pregnancy is confirmed with the specialist team must be included.

ASSISTED CONCEPTION

Assisted conception should not proceed without prior involvement of the specialist team who can recommend on the suitability, preparatory investigations and management of assisted conception. Assisted reproductive techniques (ART) involving ovarian stimulation are an additional risk factor for thrombosis. For invasive procedures associated with bleeding, for example, egg collection in an individual anticoagulated with a VKA should be bridged with twice-daily therapeutic LMWH for the minimum period of time before restarting the VKA. There is insufficient evidence to support admission for UFH.[3] The last dose of therapeutic LMWH should be ≥24 h before the scheduled procedure and immediate therapeutic anticoagulation should be avoided post-procedure as per bridging practices used in international studies.[4] The bleeding and thrombotic risks of egg collection in individuals anticoagulated for MHV are unknown and likely to be significant. Any individual with an MHV considering ART should have a consultation with the specialist team and their anticoagulation titrated accordingly.

ANTENATAL REFERRAL AND RISK ASSESSMENT

All individuals with MHV and confirmed pregnancy should be referred to the specialist team as a matter of urgency (as soon as a pregnancy test is positive) and ideally reviewed by the MDT before 6 weeks of gestation. Individuals should have been informed how to self-refer but any healthcare professional made aware of the pregnancy can refer as a matter of urgency. The first encounter may be with the anticoagulant clinic whose staff should escalate to the specialist team immediately. In very early pregnancy, complex decisions are required regarding optimal anticoagulation regimens and balancing competing risks. If not already completed pre-pregnancy, a written care plan should be agreed and widely circulated with a copy to the individual. Risks associated with pregnancy in this population overall are outlined in Table 2. Pregnancy in individuals with MHV is considered very high risk. Data from the United Kingdom Obstetric Surveillance System (UKOSS)[5] showed that maternal mortality was 9% and the risk of severe morbidity was 41%, with 16% of individuals suffering valve thrombosis and 9% having a cerebrovascular accident. Foetal risks are also high, with an increased risk of miscarriage, stillbirth, foetal haemorrhage, and warfarin-induced teratogenicity. Only 16 (28%) pregnant individuals had a good maternal and foetal

TABLE 2 Maternal and foetal benefits and risks of different anticoagulant regimens in pregnant individuals with MHV.[5,6,8–13]

Anticoagulation regimen	Maternal benefits/risks	Foetal benefits/risks
Warfarin from a positive pregnancy test until 36 weeks:	Lowest composite maternal risk (death, mechanical valve failure or thromboembolism) at 5%[8]	Highest overall foetal loss (32.54%).[10]
• Strongly consider when high risk of maternal MVT • Continue warfarin till 36 weeks • Introduce LMWH from 36 weeks to delivery to minimise the risk of foetal and maternal haemorrhage	Lowest maternal mortality rate 0.9% (0.4–1.4)[9]	Highest overall composite foetal risk (miscarriage, termination, foetal abnormality) 39%.[8]
	Lowest thromboembolic complications rate 2.7% (1.4%–4%)[9]	Live births 83.6% (75.8–91.4) with warfarin <5 mg/day and 43.9% (32.8–55) with warfarin >5 mg/day.[9]
	However, there is an increased risk of bleeding in some studies (both antepartum and postpartum)[5,11,12]	Foetal embryopathy/fetopathy 2.3% (0.7–4) with warfarin <5 mg/day and 12.4% (3.3–21.6) with warfarin >5 mg/day.[9]
		Foetal intracranial haemorrhage thought to be a risk with vaginal delivery if recent (<1 week) warfarin dosing
LMWH throughout pregnancy	Use of LMWH throughout has a higher composite maternal risk of 15.5%[8]	Lowest composite foetal risk at 13%[8]
	Higher mortality rate 2.9% (0.2–5.7)[9]	Overall foetal loss rate (mostly miscarriage) 12.2%[10] to 13.9%[8]
	Higher thromboembolic complications 8.7% (3.9–13.4),[9] but reported up to 53%[13]	Highest livebirth rate 92% (86.1–98)[9]
	Optimal dosing with the use of anti-Xa levels is not yet fully established so close monitoring is required	No placental transfer to foetus during pregnancy
Combination (sequential LMWH/warfarin/LMWH) • LMWH from positive pregnancy test to week 13 • Warfarin weeks 13–36	Combination/sequential LMWH/warfarin has a similar composite maternal risk to LMWH alone, of 15.9%[8]	Composite foetal risk 23%[8]
		Overall foetal loss rate 22.65%[10]
	Mortality rate 2% (0.8–3.1)[9] which is lower than LMWH throughout, but higher than with warfarin alone	Fetopathy (foetal haemorrhage) 1.4% (0.3–2.5)[9]
• LMWH week 36 until delivery (as above)	MVT risk higher than warfarin	Live birth 79.9% (74.3–85.6)[9]
	50% of MVT in pregnancy occur during first trimester LMWH[6]	Better livebirth rate than with >5 mg/day warfarin
	Thromboembolic complications, 5.8% (3.8–7.7)[9]	No placental transfer to foetus during first trimester
	Requires very close monitoring during transitions to limit sub-therapeutic anticoagulation	
	Requires high maternal compliance with treatment/monitoring regimes	
Unfractionated heparin only	Very rarely recommended due to MVT > 10% (11.2% [2.8–19.6])[9] and risk of maternal osteoporosis and thrombocytopaenia	Low rate of live births however number of pregnancies analysed small
Combination (UFH/warfarin)	Composite maternal risk of 33.6%[8] Slightly higher than LMWH/warfarin regimen	Composite foetal risk of 34%[8]
	More complex drug delivery/monitoring	
	Osteoporosis/thrombocytopenia	
Other anticoagulants	Have not been shown to be as effective as warfarin in patients with MHVs, and cross the placenta so are not recommended	Limited evidence, currently contraindicated
For example, dabigatran, rivaroxaban, apixaban, fondaparinux	Not recommended in individuals that are breast feeding	

Abbreviations: LMWH, low molecular weight heparin; MHV, mechanical heart valve; MVT, mechanical valve thrombosis.

outcome compared to the Registry of Pregnancy and Cardiac (ROPAC) disease European registry,[6] where individuals with a MHV had a 58% chance of experiencing an uncomplicated pregnancy with a live birth.

Caring for pregnant individuals with MHV is logistically challenging involving multiple specialist teams including maternal/foetal medicine, cardiology, haematology and anaesthesia. The UKOSS study estimated the incidence of MHV in pregnancy to be 3.7 (95% CI: 2.7–4.7) per 100 000 maternities, so familiarity in management of pregnant patients outside of specialist centres will be limited. In view of the high risks involved and requirement

for input by an experienced multidisciplinary specialist team, we support guidance by other specialist societies and recommend that all pregnant individuals with MHV are managed in a tertiary specialist centre with the relevant expertise.[1,2,7]

CHOICE OF ANTICOAGULANT REGIMEN

All anticoagulation regimens are associated with risks for the mother and foetus and management will be planned on an individual basis through discussion between the pregnant individual and the MDT ideally in a pre-pregnancy setting. Table 2 summarises the maternal and foetal benefits and risks of different anticoagulant regimens in pregnant individuals with MHV. Warfarin is the superior anticoagulant in terms of prevention of MVT but is associated with a higher risk to the foetus. The use of LMWH anticoagulation regimens avert the foetal risks observed with VKAs as they do not traverse the placenta, but their use is associated with poorer maternal outcomes.

FOETAL COMPLICATIONS OF VKAS

The most commonly used VKA in the UK is warfarin and most of the published data are for this coumarin; however, the same principles apply to other VKAs.

Warfarin is an established teratogen. Foetal warfarin syndrome (FWS) comprises of nasal bone hypoplasia and skeletal abnormalities and occurs following warfarin exposure between 6 and 12weeks of gestation. The risk of FWS varies, but recent studies would suggest that it affects between 6% and 12% of foetuses exposed. Some studies suggest a dose–response relationship with lower levels of FWS at warfarin dosages ≤5 mg/day[9,10,14]; however, the data are far from conclusive.[15] Running the INR target below the recommended range to keep the warfarin dose <5mg is not recommended due to the increased risk of MVT with this approach and the limitations of the studies on which the evidence regarding <5mg warfarin is based.

Warfarin readily crosses the placenta and the foetus is more anticoagulated than the mother, attributed to the immature foetal liver enzymes with low levels of vitamin K-dependent clotting factors and relative absence of foetal vitamin K. Beyond the first trimester of pregnancy, VKA use is associated with foetal, placental and neonatal haemorrhage.[16–18] Data on risk are summarised in Table 2. It should be noted that published rates of adverse events are susceptible to reporting bias. When restricted to prospective studies only, Xu et al.[10] found similar foetal loss rates for VKA, LMWH/VKA and LMWH regimens (18.44% vs. 18.36% and 16.98%). However, the prospective, observational ROPAC registry[6] showed that the use of VKA during pregnancy resulted in fewer live births, with a higher rate of miscarriage (28.6% vs. 9.2% in individuals receiving heparin; $p < 0.001$) and late foetal death (7.1% vs. 0.7%; $p = 0.016$). In this study, the reported rate of miscarriage and foetal loss were not significantly different in high- versus low-dose VKA (≤5 mg/day warfarin or ≤2 mg/day acenocoumarol or ≤3mg/day phenprocoumon).

It is currently considered likely that the neurodevelopmental effects of VKA are secondary to bleeding complications such as intracerebral haemorrhage. In a study of 274 school-age children with in utero exposure to coumarins,[19] the vast majority showed no clinically significant difference in growth and development compared with controls; however, 18 children (7%) of the coumarin-exposed cohort and 2 children (<1%) in the control cohort had two or more adverse outcome-measures, although the authors acknowledge potential confounding by indication, because the mothers of the exposed children had a medical indication for anticoagulation.

VKA MONITORING IN PREGNANCY

Cohort studies indicate that the use of a VKA throughout pregnancy is the best option for preventing MVT in pregnancy, although some international guidelines nuance the advice for the first trimester based on the individual's usual daily warfarin dose.[7] The choice of regimen ultimately requires careful counselling and an individual's preference and likely compliance will be a key factor. However, it is reasonable to weight recommendations from the specialist team towards warfarin for pregnant individuals at higher risk of MVT (Table 1) and any decision can be reviewed if circumstances change during the pregnancy.

The European Society of Cardiology (ESC) guidance[7] recommends using the same INR range as outside of pregnancy with INR monitoring weekly or every 2 weeks with self-monitoring of INR in suitable patients. It is particularly important to try and avoid high INRs in view of the enhanced anticoagulation in the foetus.

MONITORING OF LMWH DOSE

In the prospective multicentre study by van Hagen et al.,[6] half of the MVT occurred in pregnant individuals who were undergoing transition from a VKA to a LMWH in the first trimester with three events in second trimester and two in the third trimester and none described with onset postpartum. In a review of maternal and foetal complications in 92 individuals from 5 prospective cohort studies treated with dose-adjusted LMWH throughout pregnancy,[20] nine episodes of valve thrombosis were reported and were attributed to poor compliance or suboptimal LMWH doses in the majority of the cases. The majority of events occurred antenatally rather than postpartum. In a prior case series by the same author,[21] five cases of MVT were associated with enoxaparin therapy; three occurred in the first or second trimester and were all associated with inadequate anticoagulation and compliance issues and both cases of postpartum thrombosis were associated with subtherapeutic anticoagulation in late pregnancy (both received UFH peridelivery). The UKOSS survey did not give detail on the timing of onset of MVT in all cases but two of the five deaths occurred

in the first half of pregnancy.[5] Transition from VKA to heparin in the first trimester therefore requires particular attention as this represents a period of very high risk for MVT. As soon as a positive pregnancy test is confirmed, the individual should stop VKA and commence twice-daily LMWH injections. The INR need not be in the normal range when commencing LMWH. Many guidelines focus on the peripartum management of anticoagulation; however, evidence suggests that the risk of MVT is predominantly antenatal and poor adherence with anticoagulation is a key theme.

Although there is no firm evidence that monitoring LMWH with anti-Xa levels in pregnancy improves maternal outcomes,[22] there is evidence that standard fixed doses of LMWH are associated with a higher risk of MVT in pregnancy.[23,24] Fatal thrombotic events in two pregnant individuals in the HiP-CAT study occurred with low peak anti-Xa levels.[15]

In a small study of 11 pregnant patients[25] with a starting dose of 1 mg/kg BD enoxaparin and subsequent monitoring of LMWH to achieve a peak enoxaparin anti-Xa level of 1.0–1.2 IU/mL, a mean increase in LMWH dose of 54% was required. In another retrospective study,[26] an enoxaparin dose of 1.3 mg/kg BD was required to achieve a peak enoxaparin anti-Xa level of 1.0–1.2 IU/mL.

Based on data from the UKOSS study, the authors suggest starting doses of LMWH of 2.5 mg/kg/day for enoxaparin, 250 IU/kg/day for dalteparin and 250 IU/kg/day for tinzaparin to ensure minimal delay in reaching a reasonable level of anticoagulation.[5] It was also noted that most pregnant individuals required dose escalation between 10 and 20 weeks of gestation. Although LMWH products differ in terms of ratio of anti-Xa to antithrombin activity due to variation in processing and average molecular weight,[27] there is currently insufficient data to recommend a specific product for use in pregnant individuals with MHV.

Trough LMWH testing has been recommended by some groups.[28,29] A meta-analysis of six studies of mainly prophylactic LMWH dosing suggested a benefit to trough monitoring versus no monitoring but not for peak monitoring[30]; however, this was dominated by a study checking anti-Xa levels 12 h post a standard prophylactic dose of dalteparin in high-risk trauma patients.[31] Goland et al. defined subtherapeutic anticoagulation with LMWH in individuals with MHV in pregnancy as a trough level of <0.6 IU/mL; however, this definition was accepted as arbitrary.[32] They found that even with peak anti-Xa levels >1.2 IU/mL on a BD dosing regimen, 31% trough levels were <0.6 IU/mL. Peak and trough levels showed some correlation but with variability. In the UKOSS study,[5] the incidence of maternal complications was similar in individuals with post-dose only LMWH monitoring versus pre- and post-dose.

The American College of Cardiology and American Heart Association(ACC/AHA) guidelinesrecommendtarget LMWH levels by anti-Xa assay of 0.8–1.2 IU/mL at 4–6 h after dose.[1] They also state that measurement of trough levels to maintain a trough level>0.6 IU/mL may help pregnant individuals to maintain therapeutic anticoagulation while on LMWH. The ESC and European Association for Cardio-Thoracic Surgery guidelines recommend switching to LMWH during the first trimester with strict monitoring (peak therapeutic range: 0.8–1.2 IU/mL for aortic valve prosthesis; and 1.0–1.2 IU/mL for mitral and right-sided valve prosthesis).[2]

In summary, there are sufficient data to suggest that standard therapeutic doses of LMWH are inadequate and that monitoring is prudent. However, there are insufficient data on trough versus peak monitoring to make firm recommendations. We consider that a trough target of 0.6 IU/mL is arbitrary. An additional consideration is that it is more time-consuming and inconvenient for pregnant individuals to have both trough and peak levels monitored and the use of more frequent LMWH dosing than BD is highly invasive and not adequately studied in terms of risk/benefit. Moreover, one of the most important causes of MVT is poor adherence with anticoagulation and the physical burden and injection site toxicity of such a regimen could easily be counterproductive. In the absence of further supportive data, we consider a peak target of 1.0–1.4 IU/mL at 3–4 h post-BD dosing to be a reasonable target in the absence of bleeding complications and gives a better opportunity for a reasonable trough with a BD dosing regimen. Peak testing was preferred by the majority of haematology/thrombosis specialists in an ISTH SSC survey, although this survey did not have many cardiology respondents due to questionnaire distribution.[33] Routine use of trough LMWH levels cannot be recommended currently. Trough levels should not currently replace peak level monitoring. We consider that trough monitoring to achieve >0.6 IU/mL LMWH levels along with more than twice-daily LMWH dosing regimens should be evaluated as a matter of urgency to assess whether they offer superior protection against MVT to pregnant individuals without excessive bleeding.

Monitoring requires regular access to outpatient setting with timed blood sampling and excellent communication of results and impact on dose with plans for next levels. There is no clear evidence to guide the frequency of LMWH monitoring. However, in view of the risks of valve thrombosis in the initial transition to LMWH, we recommend at least weekly monitoring until the target level is achieved or when there is a below target at any stage and then regular monitoring thereafter (e.g. every 2–4 weeks depending on stability).

ASPIRIN

Historical studies outside of pregnancy show that the addition of LDA to VKAs in patients with MHV reduces the risk of MVT but at a cost of a higher risk of major bleeding.[34] Aspirin 75–100 mg in addition to anticoagulation has been recommended routinely in individuals with MHV in pregnancy.[14,35,36]

In the ROPAC registry, no pregnant patients on aspirin developed MVT but more haemorrhagic events were described; however, only 6.1% of patients were given aspirin so no conclusions can be drawn.[6]

The ACC/AHA guidelines[1] state that LDA is regarded as safe during pregnancy and can be used in individuals with

MHV if needed for other indications, for example, prevention of pre-eclampsia toxaemia (PET) rather than for thromboprophylaxis per se.

Although there is an absence of high-quality data on the role of aspirin in pregnant individuals with MHV, in view of the increased risk of valve thrombosis in pregnancy, it is reasonable to add LDA (75 mg daily) from early pregnancy onwards if there are no contraindications or bleeding concerns, especially in pregnant individuals with a higher risk MHV (Table 1) and this should be continued for the duration of pregnancy. In pregnant individuals with risk factors for placental failure/PET who are eligible for LDA at 12 weeks of gestation, there is indirect evidence that aspirin at a dose greater than 75 mg may be associated with the highest reduction in preterm pre-eclampsia.[37] In the absence of clear evidence of increased bleeding when increasing the aspirin dose from 75 to 150 mg daily in combination with therapeutic anticoagulation, we consider that an increase in the dose of aspirin from 75 to 150 mg at 12-week gestation can be considered if indicated for prevention of pre-eclampsia in individuals with MHV.

MANAGEMENT OF MISCARRIAGE AND TERMINATION OF PREGNANCY

Non-surgical management of first trimester miscarriage, that is expectant management (waiting for spontaneous miscarriage) or medical management with prostaglandin has become increasingly popular in comparison to surgical management. For anticoagulated pregnant individuals, the reduced success rates in achieving complete miscarriage, higher need for unplanned surgical evacuation and increased bleeding with these management options make them less suitable in this context.[38] Likewise, for termination of pregnancy, the benefits of surgical management in minimising blood loss and unplanned surgical intervention make it the recommended option. The gestation up to which this can be carried out will depend on the expertise within a unit. For later gestations, medical management will be required.

For both miscarriage treatment and termination of pregnancy, the duration of interrupted anticoagulation should be minimised whilst avoiding an excessive risk of bleeding which could prolong that interruption. A risk assessment by the specialist team is required and discussion regarding management of anticoagulation should be carried out. Contraception should be discussed and administered if appropriate (in the case of an intrauterine contraceptive device or progesterone implant).

DIAGNOSIS AND MANAGEMENT OF MVT

Diagnosis

This requires a low index of suspicion in view of the heightened risk in pregnancy. Signs and symptoms of potential valve thrombosis include no longer hearing the clicks from the valve closure, obstructive symptoms such as increased breathlessness, heart failure, syncope or pre-syncope, cardiogenic shock ± non-obstructive symptoms such as an embolic event, for example, stroke, renal or splenic infarct (manifesting as new onset abdominal pain). Right-sided mechanical valve replacement thrombosis obstructive symptoms may be more insidious with loss of appetite, lower limb oedema and/or ascites ± non-obstructive symptoms such as pulmonary emboli as embolic events.

Examination may reveal increased heart rate, low blood pressure, quiet or absent mechanical valve sounds, a new murmur, increased respiratory rate and inspiratory crepitations. A high index of suspicion for the potential of MVT with embolism is required with urgent senior cardiology review, urgent echo and further imaging (e.g. f luoroscopy, transoesophageal echo, +/or CT) as deemed appropriate.

Management of MVT presenting with stroke

In cases where MVT presents with a stroke, emergency stroke team review and assessment is essential. Senior MDT discussions including obstetrics, cardiology, anaesthetics, cardiac surgery and neurology/stroke medicine are recommended and location of care needs to balance the competing needs of the pregnant individual, considering MVT management, stroke and ongoing pregnancy needs and should be individualised.

Management of MVT with obstruction

Initial assessment is based on clinical stability of patient. If haemodynamically unstable, then this is a clinical emergency requiring MDT input from senior clinicians including obstetrician, cardiologist with interest in obstetrics, anaesthetist and cardiothoracic surgeon to consider management options. Ensure correct location for care and clear escalation plan, usually critical care unit/cardiac intensive care unit with obstetric input.[7]

Opinion generally supports a trial of thromboly- sis, especially for right-sided lesions but there are no comparative data of strategies.[7] Obstetric management will be based on the foetal condition and gestation in conjunction with the maternal condition. A molecular weight > 1000 Da prevents most thrombolytic agents from easily crossing the placenta. Alteplase (a recombinant tissue plasminogen activator) has the highest molecular weight and does not cross the placenta. Successful thrombolysis is defined as achieving at least two out of three of the following[39]:

1. Resolution of elevated Doppler gradient
2. Reduction in thrombus size (area or length) of >50%
3. Improvement in symptoms

If unsuccessful fibrinolysis by these criteria, consider repeating thrombolysis if haemodynamically stable.

Escalation of anticoagulant management should be considered in pregnant individuals with MVT, for example switch from LMWH to IV UFH and then to a VKA with aspirin 75 mg daily when no further immediate interventions required.

If the MDT opinion is that cardiac surgery is required either as the primary treatment modality or because of ongoing haemodynamic instability despite medical treatment, then an experienced MDT team should consider the optimal foetal management. If gestation supports emergent delivery at the start of the cardiac surgical procedure, then this should be performed with exquisite attention to haemostasis at the obstetric site. A meta-analysis in 2018 of cardiac surgery during pregnancy for all indications, that is not only MVT, suggested a maternal mortality rate of 11.2%, maternal complication rate of 8.1%, pregnancy loss rate of 33.1% and neonatal complications in 10.8%.[40] There are considerations in the cardiac surgical bypass procedure that may reduce the risks to the foetus including minimising hypothermia, maintaining mean arterial pressure > 70 mmHg, avoiding maternal hypoglycaemia, maintaining maternal haematocrit and maintaining a left lateral tilted position to minimise compression of the great vessels.

Peripartum care

Birth represents a particularly high-risk time to pregnant individuals with MHV, due to the need to balance the risk of haemorrhage with the risk of MVT because of a prolonged period of reduced anticoagulation. The MDT should document a delivery plan that should include the anticoagulation regimen, analgesic options during labour, anaesthetic options for an operative intervention (e.g. caesarean birth), haemodynamic monitoring, the uterotonic agents to be utilised and the recommended postpartum anticoagulation regimen following childbirth.

A high proportion of pregnant individuals will deliver by caesarean section (CS), but vaginal birth has advantages for selected individuals as it avoids the risk of surgical bleeding, in particular wound haematoma and is recommended by ESC guidelines.[7] The UKOSS surveillance data[5] reported a 53% rate of CS, only one of which was an emergency procedure and a 45% rate of vaginal birth. In one retrospective case series comparison between two large centres in the UK and the Netherlands,[41] the relative increased incidence of primary/secondary PPH and wound haematoma in one centre appeared to correlate with a higher rate of CS (Table 3). Scheduled delivery has been recommended for individuals on therapeutic LMWH in the context of venous thromboembolic (VTE) disease[42]; citations include a single-centre retrospective observational study of pregnant individuals receiving therapeutic-dose LMWH for the management of VTE; individuals with spontaneous onset of labour had a 1.9-fold (95% CI: 0.6–5.8) increase in the risk of PPH (≥500 mL) compared with planned induction of labour.[43]

Optimal anticoagulation prior to delivery

There is an absence of data to inform the best options for anticoagulation around the time of birth. Any data available are derived from registries/observational retrospective data. For individuals receiving VKAs, a transition to therapeutic LMWH or UFH is recommended by 36 weeks (or 2 weeks before the planned birth). If presenting in labour on VKA, the INR should be measured and corrected to decrease maternal haemorrhage risk with a four-factor prothrombin complex concentrate (PCC) at a dose of 25–50u/kg in addition to vitamin K 10 mg IV. This is preferable to administering 15 mL/kg of fresh frozen plasma, which is only partially effective at improving the INR, time-consuming and requires higher fluid volume.[44] A CS should be considered in view of the foetal bleeding risks.

For individuals with MHV, the risk of prolonged interruption of LMWH during the labour induction process is a potential risk for MVT. It is possible that this risk is reduced by bridging with UFH. It should be recognised that there are no studies examining the competing risks of bleeding versus valve thrombosis to inform recommendations on the mode of delivery in individuals with MHV.

It is recommended that, in individuals receiving therapeutic LMWH, the last dose should be ≥24 h prior to the planned induction. Consideration can be given to further doses, including prophylactic and intermediate doses, and this should be discussed by the MDT as it may impact choices for labour analgesia. However, there are no data on which to make clear recommendations. Alternatively, a switch to therapeutic IV UFH at least 36 h prior to scheduled induction can be considered, especially in individuals where induction may be prolonged. The UFH infusion needs to be discontinued 4–6 h prior to delivery, which may be difficult to predict. Practically, the infusion is stopped when the patient is in early labour. A meta-analysis in non-pregnant patients did not show superiority of UFH over LMWH for bridging patients with MHV and familiarity of doctors with UFH is poor and the risks of over and under anticoagulation are significant so LMWH may in practice offer less overall risk.[3] Many guidelines recommend a specific activated partial thromboplastin time ratio (APTTR) target range for pregnant individuals with MHV; however, the therapeutic APTTR range for UFH should be determined by the local laboratory as the appropriate therapeutic target depends on the reagents used. In addition, monitoring UFH by APTTR is problematic as the heparin dose to achieve the equivalent APTTR in pregnancy may differ from outside of pregnancy, usually requiring higher doses to achieve the same target APTTR with a risk of overdose and bleeding. UFH can be monitored using an appropriately calibrated anti-Xa assay[45] and we recommended this in preference to sole reliance on the APTTR; however, we acknowledge that this may not be available in a timely fashion in all laboratories.

TABLE 3 Observational cohort data on the risk of peripartum and postpartum haemorrhage in individuals with MHVs.

Reference		N (MHV)	Results	Comments
Vause 2017[5]	UKOSS Prospective	58	Primary PPH 2 (2%) Secondary PPH 6 (10%) Wound haematoma 6 (10%) Intraabdominal bleed 4 (7%) Vaginal haematoma 1 (2%)	17 (29%) patients needed return to theatre. (10 had delivered by CS and 7 delivered vaginally) Anticoagulation around delivery likely variable and not reported
Van Hagan 2015 (ROPAC)[6]	International registry, prospective	212	49 (23%) haemorrhagic complication. (15.1% major haemorrhagic event, 10.4% PPH)	Postpartum anticoagulation regimen not specified
Khader 2016[55]	Prospective, Egypt	40	5 (12.5%) PPH	UFH commenced 4–6 h after delivery
Abildgaard 2009[56]	Retrospective, Norway	*N* = 12	2 (16.6%) Primary PPH after CS	LMWH commenced within 24 h
Quinn 2009[25]	Retrospective UK	*N* = 12	3 (25%) PPH Wound haematoma 1 (8.3%) needing re-exploration	LMWH commenced within 24 h following delivery
Irani 2018[57]	Single unit, retrospective USA	14 pregnancies	6 (42%) deliveries – PPH Primary PPH 3 (21%), secondary PPH 3 (21%). Wound haematoma 2 (14%) intra-abdominal bleed and 2 (14%) wound haematomas	Anticoagulation re-started median 6 h, predominantly UFH IV. 2 intra-abdominal bleeds and one wound haematoma in those who restarted <6 h, no intra-abdominal bleeds in the <6 h group and 1 wound haematoma
Kariv 2018[58]	Single-centre prospective cohort, South Africa	29 pregnancies	5 (17%) returns to theatre (including 2 wound haematoma) 6 (21%) major haemorrhage. 1 (3.4%) Primary, 5 (17.2%) Secondary PPH	UFH initiated at 6 h if stable, warfarin on day after delivery
McLintock 2009[21]	Retrospective audit, New Zealand	47 pregnancies	15 (32%) PPH 6 (12.8%) primary PPH (3 abruptions) 9 (19%) secondary PPH	Restart UFH at 6 h post-VD 6–12 CS, warfarin on day 1 (VD) or day 2–3 (CS)
Cousin 2018[59]	Retrospective, single centre, France	18 cases	2 (11%) – Primary PPH 5 (30%) – Secondary PPH needing re-operation	Median time to restart anticoagulation 7 h post-delivery
Dos Santos 2021[41]	Retrospective Two centres, the UK and the Netherlands	44 pregnancies	17% Primary PPH 4 (31%) Secondary PPH 4 (31%) Wound haematoma 2 (10%) Intra-abdominal	All with PPH/haematoma received prophylactic dose of LMWH 4–6 h after delivery

Abbreviations: CS, caesarean section; LMWH, low molecular weight heparin; MHVs, mechanical heart valves; PPH, postpartum haemorrhage; UFH, unfractionated heparin; VD, vaginal delivery.

Protamine is a reversal agent for UFH and has been used occasionally in pregnant individuals with MHVs on IV UFH who present with life-threatening haemorrhage. Its role in reversing LMWH however is limited and is not recommended routinely. Potential risks of protamine include anaphylaxis, pulmonary oedema, bronchoconstriction, bradycardia and increased bleeding and thrombosis risk.

In pregnant individuals, who are at least partially anticoagulated at the time of delivery (<24 h), we recommend a low threshold for use of tranexamic acid 1 g IV post-delivery. Otherwise, it can be used as for normal PPH criteria. Evidence is lacking regarding any increased risk of MVT with the use of tranexamic acid[46] but a single dose is unlikely to be associated with a significant risk when considering the known very high risk of bleeding (Table 3) which could lead to prolonged period of pausing anticoagulation. However, the use of repeated doses of tranexamic beyond the two doses used in the WOMAN trial[47] is probably best avoided.

If using aspirin, it is not mandated to stop however, in view of the high risk of PPH in this group of individuals, we recommend consideration of stopping for at least 3 days prior to scheduled delivery with anticipated correction of any associated bleeding risk.[48,49]

Postpartum anticoagulation

There are no high-quality studies assessing the bleeding risk versus the benefits of early therapeutic anticoagulation post-delivery in individuals with MHV; however, there are extensive data on these risks in the postoperative setting. Therapeutic anticoagulation with heparins has been associated with a fivefold increase bleeding without reducing the thrombosis risk.[50]

Specifically, in patients with MHV, Passaglia et al.[51] concluded that 'Early bridging therapy with LMWH appears to be associated with consistently high bleeding rates across multiple analyses'.

In the PERIOP2 study[52] including patients with mechanical valve replacement ± AF, all received pre-procedure therapeutic LMWH bridging but were randomised to post-procedure escalation to therapeutic LMWH after 48 h versus no post-op therapeutic LMWH. There was no difference in bleeding; however, patients considered at higher risk of bleeding only received prophylactic LMWH post-procedure. No significant benefit was found for postoperative dalteparin bridging to prevent thromboembolism. Although pregnancy is associated with a pro-thrombotic state and significant risk of valve thrombosis, the risk of thrombosis after pausing anticoagulation over a brief period is likely to be low; however, the risk of bleeding is high in the peripartum period and is likely to be exacerbated using very early postpar- tum therapeutic anticoagulation.

The ESC guidance[7] recommends restarting UFH 4–6 h after delivery if there are no bleeding complications and NICE guidance NG121[53] recommends restarting therapeu- tic LMWH or UFH 4–6 h after birth. The Association of Anaesthetists (AOA) guidelines[54] provide recommendations on time intervals for commencing anticoagulation postpartum but also recommend delaying introducing therapeutic anticoagulation with LMWH for 24 h if a neuraxial block was utilised during birth and was traumatic. There is no supporting evidence for these recommendations in terms of risk/benefit. The UKOSS study[5] confirmed the high risk of haemorrhage for pregnant individuals with MHV who are anticoagulated. Postpartum bleeding complications necessitating return to theatre or transfusion occurred in 29%, and in 40% of pregnant individuals delivered by CS. Most bleed- ing complications occurred after 24 h in this observational study. The reasons for this cannot be established from observational data alone but the use of aggressive peripartum anticoagulation due to concerns over valve thrombosis may be a factor.

We recommend timely recognition and management of wound and intra-abdominal haematoma in this cohort as their occurrence can lead to interruptions in therapeutic anticoagulation. An MDT approach with low threshold for imaging (e.g. CT scan) and intervention (re-exploration) to rule out surgical bleeding is recommended and any unexpected fall in haemoglobin should be investigated quickly in view of the intensity of anticoagulation postpartum.

Table 3 summarises observational cohort data on the risk of peripartum and PPH in pregnant individuals with MHVs. Although there is no standardised definition of bleeding, making any comparisons difficult, the risk of bleeding appears to be high.

Haemorrhagic complications associated with delivery in pregnant individuals with MHV may result in a paradoxical increase in thrombosis risk as anticoagulants have to be reversed/paused after major bleeding, including returns to theatre for haematoma along with the attendant risk of wound infection and prolonged hospital stay. We therefore recommend a more cautious re-introduction of anticoagulation including a step-wise increase in the level of anticoagulation to try and reduce these risks. We recommend prophylactic or intermediate doses of LMWH for the first 24–48 h following delivery. The risk of MVT exists across the whole of pregnancy and postpartum period rather than being confined to peripartum period. However, the risk of major haemorrhage is concentrated in the relatively short period of time around delivery. We also recommend that individuals with MHV should start VKAs from 5 to 7 days following delivery, overlapping with LMWH until therapeutic INR achieved. Anecdotal experience suggests a higher bleeding risk with earlier reintroduction of VKAs. Registries collecting data on pregnancy outcomes of individuals with MHV should ideally have a standardised definition of bleeding.

ANAESTHETIC CONSIDER ATIONS

Labour analgesia

Patients with MHVs should be reviewed by an obstetric anaesthetist before 28 weeks (as preterm delivery rates are high) in a dedicated anaesthetic clinic.[60] This allows a detailed discussion on the options of the analgesic and the anaesthetic components of peripartum care.

For labour, non-neuraxial pharmacological analgesics that can be considered include simple oral analgesia (e.g. paracetamol, dihydrocodeine), a 50:50 mixture of nitrous oxide and oxygen, and parenteral opioids such as diamorphine or IV patient-controlled analgesia (PCA) using fentanyl or remifentanil. The advantage of non-neuraxial analgesic regimens in this cohort is that they are not dependent on cessation of anticoagulation. These are commonly utilised when a patient with MHV on therapeutic anticoagulation with LMWH presents in spontaneous labour.

The neuraxial labour analgesia regimens include the following: epidural, spinal, combined spinal–epidural or a dural puncture epidural. These provide superior analgesia compared to non-neuraxial techniques. Interventions using an epidural catheter have the advantage of extending the analgesia to anaesthesia in case of an emergent caesarean birth. Their disadvantage includes the need to cease anticoagulation at specific time intervals before they can be utilised. Also, specific time intervals need to elapse before anticoagulation can be recommenced.

The AOA have published guidelines on acceptable time intervals for neuraxial blockade in patients taking anticoagulants.[54] For individuals receiving VKAs, an INR ≤1.4 is necessary, whilst those receiving therapeutic LMWH, a 24-h interval between the last dose of LMWH and neuraxial blockade is recommended. If a prophylactic dose of LMWH has been administered to the patient after interrupting therapeutic anticoagulation for 24 h, then the recommended time interval for placement of neuraxial labour analgesia is 12 h. For patients receiving UFH, a minimum of 4 h should elapse without UFH, ideally confirmed with a normal APTTR and platelet count before a neuraxial blockade is attempted.

The guidance and the recommended time intervals for administering a prophylactic dose of LMWH following an epidural catheter insertion for labour analgesia varies internationally (AOA[54] 4–6 h and American Society of Regional Anesthesia[61] 12 h). The MDT needs to evaluate the risks and benefits of administration of any anticoagulant whilst an epidural is in situ very carefully and discuss the same with the patient. If a prophylactic dose of LMWH is administered with an epidural catheter in situ, the epidural catheter should be removed 12 h after the last prophylactic dose of LMWH following delivery in line with AOA guidance. Alternatively, non-neuraxial labour analgesia techniques could be considered in patients needing anticoagulants whilst in labour.

Anaesthesia for caesarean birth (or any operative intervention)

The above-mentioned time intervals need to be adhered to for patients having a caesarean birth under a neuraxial anaesthetic technique. When above recommended intervals have not been met, a general anaesthetic (GA) is usually administered. The reported GA rates in patients with MHV having a caesarean birth vary from 36%,[5] 52%,[41] 55%[57] to 100%.[59] Sedation or a GA can be considered in a pregnant patient having a surgical termination if neuraxial anaesthesia cannot be performed.

Postoperative analgesia

Multi-modal analgesia using paracetamol, opioids and a short course of non-steroidal anti-inflammatory agents (NSAIDS) may be utilised following the operative intervention. Outside of pregnancy, an increased bleeding risk has been shown in individuals on therapeutic anticoagulation for VTE when taking NSAIDS and appropriate alternatives (oral or IV opioids) may be necessary.[62] Opioid PCA is often necessary following a GA for a caesarean birth.[63]

Uterotonic agents

Oxytocin is commonly utilised to improve and maintain uterine tone in this cohort. Sublingual or rectal misoprostol, prostaglandin F2α (in the absence of asthma, right heart dysfunction or pulmonary hypertension) or ergotamine (in the absence of vasculitis or hypertensive disorders of pregnancy, concurrent aortopathy, known coronary disease or ventricular dysfunction) are the alternative agents that can be used in this cohort.

Neonatal considerations

If presenting in labour and on VKA within previous 2 weeks, a caesarean birth should be considered to decrease foetal complications from labour. Instrumentation and invasive foetal monitoring should be avoided. However, in very advanced labour, if indicated, an outlet forceps delivery may be less traumatic to the foetus than a second stage CS. Ventouse should not be used. Close liaison with the neonatology team is required and a coagulation screen should be performed on the newborn. An INR above the age-appropriate reference range should be managed with IV vitamin K (30 μg/kg by slow IV infusion) rather than the standard neonatal prophylactic dose and FFP or 20–30 IU/kg PCC should be considered.[64,65]

Breast feeding

Breast feeding can be safely undertaken on UFH, LMWH or VKAs.

Postpartum cardiology Care of Individuals with MHV

The maternal physiology changes rapidly during the postpartum period, and the cardiac output peaking between 24 and 48 h following birth, making this a time when heart failure symptoms may manifest if there is left ventricular systolic dysfunction. Women with MHV need a tailored plan for postnatal care and monitoring, including plan for postnatal echocardiography as required (e.g. if there is concern about valve function or cardiac function). The expected duration of inpatient monitoring should be discussed in the antenatal period acknowledging the need to re-establish anticoagulation. Pre-discharge arrangements for INR testing should be put in place together with a plan for postnatal follow-up for clinical review, discussion about pregnancy-related concerns or events and future pregnancy plans.

Contraception

All postpartum individuals must leave hospital with a plan for contraception, agreed with the individual and the MDT. This should include consideration of the risks of future pregnancy, need for reversibility, drug interactions, compliance and cardiovascular risk from insertion.

In some individuals, insertion of an intrauterine contraceptive device or implant may be appropriate at the time of delivery or on the postnatal ward. The faculty of Sexual Health and Reproductive Healthcare has provided guidance for the contraceptive choices for individuals with cardiac disease.[66] This includes UK Medical Eligibility Criteria for Contraceptive use. There is no specific advice on contraceptive choice in individuals with MHV but it recommends against oestrogen containing contraception in individuals with complex valvular and congenital heart disease and the guidance also states that the presence of a MHV increases the risk of thrombus formation. We consider long-acting reversible contraceptives to be preferable in the postpartum period.

REVIEW PROCESS

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every 3 years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made, an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk/guidelines).

DISCLAIMER

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the publishers accept any legal responsibility for the content of this guidance.

AUTHOR CONTRIBUTIONS

All authors contributed to writing, editing and reviewing the manuscript.

ACKNOWLEDGEMENTS

WL chaired the writing group. All authors contributed to writing, editing and reviewing the manuscript. Additional members of the BSH Haemostasis and Thrombosis Task Force at the time of writing this guideline were as follows: Keith Gomez, Raza Alikhan, Deepa Arachchillage, Julia Anderson, Tina Biss, Elaine Grey, Stella Williams, Khalid Saja, Renu Riat, Karen Breen, Peter Baker, Sean Platton and Ian Jennings.

CONFLICT OF INTEREST STATEMENT

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a full declaration of interests to the BSH and Task Force Chairs which may be viewed on request. WL has received speaker fees from Sanofi Aventis and Leo Pharma and speaker fees and attendance of advisory boards for Pfizer. CB has received speaker fees and financial support to attend scientific meetings from Sanofi Aventis and speaker fees and attendance of advisory boards for Pfizer.

METHODOLOGY

This guideline was compiled according to the BSH process at [https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org. In the manuscript, the term 'should' indicates a strong recommendation and the term 'recommends' suggests a recommendation that is conditional. A literature search was performed using the terms given in Appendix S1 until April 2022.

REVIEW OF MANUSCRIPT

Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Haemostasis and Thrombosis Task Force, BSH Guidelines Executive Committee and by the Haemostasis and Thrombosis sounding board of the BSH. It has also been sent to the following organisations for review: UK Maternal Cardiology Society, MacDonald Obstetric Medicine Society, Obstetric Anaesthesia Association and the UK teratology information service. These organisations do not necessarily approve or endorse the contents.

ORCID

Will Lester https://orcid.org/0000-0001-8790-7112

REFERENCES

1. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021;143:e35–71.
2. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur J Cardiothorac Surg. 2021;60:727–800.
3. Caldeira D, David C, Santos AT, Costa J, Pinto FJ, Ferreira JJ. Efficacy and safety of low molecular weight heparin in patients with mechanical heart valves: systematic review and meta-analysis. J Thromb Haemost. 2014;12:650–9.
4. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med. 2015;373:823–33.
5. Vause S, Clarke B, Tower CL, Hay C, Knight M. Pregnancy outcomes in women with mechanical prosthetic heart valves: a prospective descriptive population based study using the United Kingdom obstetric surveillance system (UKOSS) data collection system. BJOG. 2017;124:1411–9.
6. van Hagen IM, Roos-Hesselink JW, Ruys TP, Merz WM, Goland S, Gabriel H, et al. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). Circulation. 2015;132:132–42.
7. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cífková R, De Bonis M, et al. 2018 ESC guidelines for

the management of cardiovascular diseases during pregnancy. Eur Heart J. 2018;39:3165–241.
8. Steinberg ZL, Dominguez-Islas CP, Otto CM, Stout KK, Krieger EV. Maternal and fetal outcomes of anticoagulation in pregnant women with mechanical heart valves. J Am Coll Cardiol. 2017;69:2681–91.
9. D'Souza R, Ostro J, Shah PS, Silversides CK, Malinowski A, Murphy KE, et al. Anticoagulation for pregnant women with mechanical heart valves: a systematic review and meta-analysis. Eur Heart J. 2017;38:1509–16.
10. Xu Z, Fan J, Luo X, Zhang WB, Ma J, Lin YB, et al. Anticoagulation regimens during pregnancy in patients with mechanical heart valves: a systematic review and meta-analysis. Can J Cardiol. 2016;32:1248.e1–9.
11. Batra J, Itagaki S, Egorova NN, Chikwe J. Outcomes and long-term effects of pregnancy in women with biologic and mechanical valve prostheses. Am J Cardiol. 2018;122:1738–44.
12. Lameijer H, van Slooten YJ, Jongbloed MRM, Oudijk MA, Kampman MAM, van Dijk AP, et al. Biological versus mechanical heart valve prosthesis during pregnancy in women with congenital heart disease. Int J Cardiol. 2018;268:106–12.
13. Güner A, Kalçık M, Gürsoy MO, Gündüz S, Astarcıoğlu MA, Bayam E, et al. Comparison of different anticoagulation regimens regarding maternal and fetal outcomes in pregnant patients with mechanical prosthetic heart valves (from the multicenter ANATOLIA-PREG registry). Am J Cardiol. 2020;127:113–9.
14. Ayad SW, Hassanein MM, Mohamed EA, Gohar AM. Maternal and fetal outcomes in pregnant women with a prosthetic mechanical heart valve. Clin Med Insights Cardiol. 2016;10:11–7.
15. McLintock C. The obstetric haematology manual. 2nd ed. Cambridge, UK: Cambridge University Press; 2018.
16. Ikonen E, Merikallio E, Osterlund K, Seppälä M. Mitral-valve prosthesis, warfarin anticoagulation, and pregnancy. Lancet. 1970;2:1252.
17. Pauli RM, Hall JG, Wilson KM. Risks of anticoagulation during pregnancy. Am Heart J. 1980;100:761–2.
18. van Driel D, Wesseling J, Sauer PJ, Touwen BC, van der Veer E, Heymans HS. Teratogen update: fetal effects after in utero exposure to coumarins overview of cases, follow-up findings, and pathogene- sis. Teratology. 2002;66:127–40.
19. Wesseling J, Van Driel D, Heymans HS, Rosendaal FR, Geven-Boere LM, Smrkovsky M, et al. Coumarins during pregnancy: long-term effects on growth and development of school-age children. Thromb Haemost. 2001;85:609–13.
20. McLintock C. Anticoagulant therapy in pregnant women with mechanical prosthetic heart valves: no easy option. Thromb Res. 2011;127(Suppl 3):S56–60.
21. McLintock C, McCowan LM, North RA. Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin. BJOG. 2009;116:1585–92.
22. Kjaergaard AB, Fuglsang J, Hvas A-M. Anti-Xa monitoring of low-molecular-weight heparin during pregnancy: a systematic review. Semin Thromb Hemost. 2021;47:824–42.
23. Oran B, Lee-Parritz A, Ansell J. Low molecular weight heparin for the prophylaxis of thromboembolism in women with prosthetic mechanical heart valves during pregnancy. Thromb Haemost. 2004;92:747–51.
24. James AH, Brancazio LR, Gehrig TR, Wang A, Ortel TL. Low-molecular-weight heparin for thromboprophylaxis in pregnant women with mechanical heart valves. J Matern Fetal Neonatal Med. 2006;19:543–9.
25. Quinn J, Von Klemperer K, Brooks R, Peebles D, Walker F, Cohen H. Use of high intensity adjusted dose low molecular weight heparin in women with mechanical heart valves during pregnancy: a single-center experience. Haematologica. 2009;94:1608–12.
26. Berresheim M, Wilkie J, Nerenberg KA, Ibrahim Q, Bungard TJ. A case series of LMWH use in pregnancy: should trough anti-Xa levels guide dosing? Thromb Res. 2014;134:1234–40.
27. Gray E, Mulloy B, Barrowcliffe TW. Heparin and low-molecular-weight heparin. Thromb Haemost. 2008;99:807–18.
28. McLintock C. Thromboembolism in pregnancy: challenges and controversies in the prevention of pregnancy-associated venous thromboembolism and management of anticoagulation in women with mechanical prosthetic heart valves. Best Pract Res Clin Obstet Gynaecol. 2014;28:519–36.
29. Elkayam U, Goland S. The search for a safe and effective anticoagulation regimen in pregnant women with mechanical prosthetic heart valves. J Am Coll Cardiol. 2012;59:1116–8.
30. Wu T, Xia X, Chen W, Fu J, Zhang J. The effect of anti-Xa monitoring on the safety and efficacy of low-molecular-weight heparin anticoagulation therapy: a systematic review and meta-analysis. J Clin Pharm Ther. 2020;45:602–8.
31. Droege ME, Mueller EW, Besl KM, Lemmink JA, Kramer EA, Athota KP, et al. Effect of a dalteparin prophylaxis protocol using anti-factor Xa concentrations on venous thromboembolism in high-risk trauma patients. J Trauma Acute Care Surg. 2014;76:450–6.
32. Goland S, Schwartzenberg S, Fan J, Kozak N, Khatri N, Elkayam U. Monitoring of anti-Xa in pregnant patients with mechanical prosthetic valves receiving low-molecular-weight heparin: peak or trough levels? J Cardiovasc Pharmacol Ther. 2014;19:451–6.
33. Malhamé I, Othman M, Casais P, D'Souza R, Wald RM, Silversides CK, et al. Communication from the ISTH SSC subcommittee on Women's health issues in thrombosis and Haemostasis: a survey on anticoagulation for mechanical heart valves in pregnancy. J Thromb Haemost. 2021;19:859–64.
34. Massel DR, Little SH. Antiplatelet and anticoagulation for patients with prosthetic heart valves. Cochrane Database Syst Rev. 2013;2013:Cd003464.
35. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the Management of Patients with Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:2440–92.
36. Elkayam U. Anticoagulation therapy for pregnant women with mechanical prosthetic heart valves: how to improve safety? J Am Coll Cardiol. 2017;69:2692–5.
37. Van Doorn R, Mukhtarova N, Flyke IP, Lasarev M, Kim K, Hennekens CH, et al. Dose of aspirin to prevent preterm preeclampsia in women with moderate or high-risk factors: a systematic review and meta-analysis. PloS One. 2021;16:e0247782.
38. Chu J, Hardy P, Beeson L, Coomarasamy A. What is the best method for managing early miscarriage? BMJ. 2020;368:l6438.
39. Özkan M, Çakal B, Karakoyun S, Gürsoy OM, Çevik C, Kalçık M, et al. Thrombolytic therapy for the treatment of prosthetic heart valve thrombosis in pregnancy with low-dose, slow infusion of tissue-type plasminogen activator. Circulation. 2013;128:532–40.
40. Jha N, Jha AK, Chand Chauhan R, Chauhan NS. Maternal and fetal outcome after cardiac operations during pregnancy: a meta-analysis. Ann Thorac Surg. 2018;106:618–26.
41. Dos Santos F, Baris L, Varley A, Cornette J, Allam J, Steer P, et al. Mechanical heart valves and pregnancy: issues surrounding anticoagulation. Experience from two obstetric cardiac centres. Obstet Med. 2021;14:95–101.
42. Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv. 2018;2:3317–59.
43. Knol HM, Schultinge L, Veeger NJ, Kluin-Nelemans HC, Erwich JJ, Meijer K. The risk of postpartum hemorrhage in women using high dose of low-molecular-weight heparins during pregnancy. Thromb Res. 2012;130:334–8.
44. Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, et al. Guidelines on oral anticoagulation with warfarin—fourth edition. Br J Haematol. 2011;154:311–24.
45. Vandiver JW, Vondracek TG. Antifactor Xa levels versus activated partial thromboplastin time for monitoring unfractionated heparin. Pharmacotherapy. 2012;32:546–58.
46. Taeuber I, Weibel S, Herrmann E, Neef V, Schlesinger T, Kranke P, et al. Association of intravenous tranexamic acid with thromboembolic events and mortality: a systematic review, meta-analysis, and meta-regression. JAMA Surg. 2021;156:e210884.

47. Effect of early tranexamic acid administration on mortality, Hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;389:2105–16.
48. Li C, Hirsh J, Xie C, Johnston MA, Eikelboom JW. Reversal of the anti-platelet effects of aspirin and clopidogrel. J Thromb Haemost. 2012;10:521–8.
49. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, et al. Aspirin in patients undergoing noncardiac surgery. N Engl J Med. 2014;370:1494–503.
50. Siegal D, Yudin J, Kaatz S, Douketis JD, Lim W, Spyropoulos AC. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. Circulation. 2012;126:1630–9.
51. Passaglia LG, de Barros GM, de Sousa MR. Early postoperative bridging anticoagulation after mechanical heart valve replacement: a systematic review and meta-analysis. J Thromb Haemost. 2015;13:1557–67.
52. Kovacs MJ, Wells PS, Anderson DR, Lazo-Langner A, Kearon C, Bates SM, et al. Postoperative low molecular weight heparin bridging treatment for patients at high risk of arterial thromboembolism (PERIOP2): double blind randomised controlled trial. BMJ (Clinical Research Ed). 2021;373:n1205.
53. Intrapartum care for women with existing medical conditions or obstetric complications and their babies. NICE guideline 121. Published 6 March 2019. www.nice.org.uk/guidance/ng121-complications-and-their-babies-pdf-66141653845957 [Accessed 30 December 22].
54. Regional anaesthesia and patients with abnormalities of coagulation: The Association of Anaesthetists of Great Britain & Ireland the Obstetric Anaesthetists' Association regional Anaesthesia UK. Anaesthesia. 2013;68:966–72.
55. Khader KA, Saad AS, Abdelshafy M. Pregnancy outcome in women with mechanical prosthetic heart valves treated with unfractionated heparin (UFH) or enoxaparin. J Obstet Gynaecol India. 2016;66:321–6.
56. Abildgaard U, Sandset PM, Hammerstrøm J, Gjestvang FT, Tveit A. Management of pregnant women with mechanical heart valve prosthesis: thromboprophylaxis with low molecular weight heparin. Thromb Res. 2009;124:262–7.
57. Irani RA, Santa-Ines A, Elder RW, Lipkind HS, Paidas MJ, Campbell KH. Postpartum anticoagulation in women with mechanical heart valves. Int J Womens Health. 2018;10:663–70.
58. Kariv S, Azibani F, Baard J, Osman A, Soma-Pillay P, Anthony J, et al. Haemorrhage and other complications in pregnant women on anticoagulation for mechanical heart valves: a prospective observational cohort study. Cardiovasc J Afr. 2018;29:289–95.
59. Cousin B, Guglielminotti J, Iung B, Montravers P. Retrospective study of anaesthetic management of pregnancy patients with mechanical heart valve prosthesis and anticoagulants. Anaesth Crit Care Pain Med. 2018;37:225–31.
60. Bhatia K, Shehata N, D'Souza R. Anaesthetic considerations and anticoagulation in pregnant patients with mechanical heart valves. BJA Educ. 2022;22:273–81.
61. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (fourth edition). Reg Anesth Pain Med. 2018;43:263–309.
62. Davidson BL, Verheijen S, Lensing AW, Gebel M, Brighton TA, Lyons RM, et al. Bleeding risk of patients with acute venous thromboembolism taking nonsteroidal anti-inflammatory drugs or aspirin. JAMA Intern Med. 2014;174:947–53.
63. Caesarean Birth NICE Guideline NG 192. Published: 31 March 2021. www.nice.org.uk/guidance/ng192 [Accessed 30 December 22].
64. Noga T, Bruce AA, Blain H, Nahirniak S. Four-factor prothrombin complex concentrates in paediatric patients—a retrospective case series. Vox Sang. 2016;110:253–7.
65. Mitsiakos G, Karametou M, Gkampeta A, Karali C, Papathanasiou AE, Papacharalambous E, et al. Effectiveness and safety of 4-factor prothrombin complex concentrate (4PCC) in neonates with intracta- ble bleeding or severe coagulation disturbances: a retrospective study of 37 cases. J Pediatr Hematol Oncol. 2019;41:e135–40.
66. FSRH. Clinical guideline: contraceptive choices for women with cardiac disease. 2014 https://www.fsrh.org/documents/ceu-guidance-contraceptive-choices-for-women-with-cardiac/ [Accessed 20 March 22].

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lester W, Walker N, Bhatia K, Ciantar E, Banerjee A, Trinder J, et al. British Society for Haematology guideline for anticoagulant management of pregnant individuals with mechanical heart valves. Br J Haematol. 2023;00:1–14. https://doi.org/10.1111/bjh.18781