South African National Essential Medicines List
Adult Hospital Level Medication Review Process
Component: Obstetrics

MEDICINE REVIEW:

EXECUTIVE SUMMARY

Date: 27 January 2020 update post NEMLC 5 December
Medicine (INN): Heparin (unfractionated or low molecular weight)
Indication: anticoagulation
Patient population: pregnant women with mechanical prosthetic heart valves (MPHV)
Prevalence of the condition: rare (3.7 per 100 000 pregnancies)
Level of Care: Tertiary
Prescriber level: Specialist
Current Standard of Care: heparin (1st trimester), warfarin (13 to 36 weeks), heparin (from 36 weeks)
Outcome: maternal mortality, maternal morbidity due to thromboembolism and/or haemmorhage, fetal mortality, fetal morbidity
Findings: We searched for published clinical guidelines on clinical guideline databases, including GIN, WHO, NICE, and SIGN. We also conducted a systematic search for systematic reviews and primary studies in PubMed, Scopus and the Cochrane Database of Systematic Reviews. We did single screening of the titles and abstracts of all records retrieved through the literature search, with full text articles only sought of systematic reviews.
Six relevant clinical guidelines of moderate to good quality were identified. The majority of the recommendations in the reviewed guidelines were based on consensus opinion of experts along with consideration of the non-randomised studies. Due to the lack of high quality evidence to guide the optimal management of this patient population, there was no single medical management strategy, and several options were proposed. Most guidelines agreed that these patients require specialist management in a tertiary facility. In addition, there was a strong emphasis on the role of patient preference in the decision, after informed consideration of the risks and benefits of the treatment options to themselves and the foetus. Two guidelines recommended that low molecular weight heparin (LMWH) only be administered to this population if anti-factor Xa concentrations can be monitored weekly and doses adjusted accordingly.
Six systematic reviews were considered to be of sufficient quality to inform further deliberation using the AMSTAR II tool. Overall there was very low certainty evidence to inform whether the choice of regimen has an impact on the clinical outcomes for the mother or fetus. All studies were observational in design and most studies had very small participant numbers. The largest meta-analysis (Xu et al 2016) included 2113 pregnancies, and reported methodological limitations, serious heterogeneity and serious imprecision of included studies. Xu et al 2016 reported the following when reviewing treatment with heparin followed by warfarin followed by heparin compared with treatment with LMWH throughout pregnancy, all results were very low certainty:

- *Maternal mortality:* 9 fewer deaths per 1000 women (ranging from 16 fewer to 33 more)
- *Major thrombo-embolic events:* 30 more events per 1000 women (ranging from 15 fewer to 145 more)
- *Major antenatal haemorrhage events:* 35 fewer events per 1000 women (ranging from 8 fewer to 40 fewer)
- *Fetal mortality:* 104 more deaths per 1000 women (ranging from 6 more to 276 more)

The committee recommended against use of heparins throughout pregnancy, but rather to use the approach of heparin for first trimester, warfarin until 36 weeks, followed by heparin until post-delivery. The was due to uncertain benefit for use of heparins throughout and added costs of medicines and related laboratory tests. The choice of heparin will depend on the access to medicines and laboratory tests at the tertiary centre.
Additional comments from the committee included that an important consideration in this population is counselling of women with MPHVs to avoid pregnancy, and to provide reliable contraception. Should a woman with MPHV become pregnant, she should be informed of the risks to herself and fetus and be included in shared-decision making regarding her specialised treatment.

Reviewer name(s): Ebrahim Bera, Tamara Kredo, Maryke Wilkinson, Jenna Patterson
PTC affiliation: Rahima Moosa Hospital PTC – Ebrahim Bera

Disclosures: submitted, none declared
Funding support: South African Medical Research Council, Evidence Response Initiative

REVIEWERS: Ebrahim Bera, Tamara Kredo, Maryke Wilson, Jenna Patterson

AFFILIATION AND OCNFLICT OF INTEREST:

- Ebrahim Bera: Department of Obstetrics & Gynaecology, University of the Witwatersrand, Adult Hospital Level Committee (2017-2020); no conflicts of interests to declare.
- Tamara Kredo: Cochrane South Africa, South African Medical Research Council; no relevant financial or academic interests to declare.
- Maryke Wilson: Cochrane South Africa, South African Medical Research Council; no relevant financial or academic interests to declare.
- Jenna Patterson: Cochrane South Africa, South African Medical Research Council; no relevant financial or academic interests to declare.

INTRODUCTION/BACKGROUND

The management of pregnant women with mechanical prosthetic heart valves (MPHV) is complex and challenging at best. It is a rare condition, occurring in approximately 1 in 27 000 pregnancies.[1] Hence no single centre will amass sufficient patients to conduct the gold standard clinical trial, however, several cohorts, registries and case series have been reported to inform guidance on the optimal course of management.

Anticoagulation poses specific challenges to the pregnant woman with MPHV as well as her foetus. Warfarin is easy to use, and International Normalized Ratio (INR) monitoring is easy, relatively accessible and inexpensive, but warfarin crosses the placenta and is a known teratogen in the first trimester. Beyond the first trimester warfarin continues to anticoagulate the foetus, and the risks of miscarriage, foetal and neonatal death remain elevated.[2,3]

Heparin doesn't cross the placenta but it has to be administered parenterally. Subcutaneous (SC) low molecular weight heparin (LMWH) requires regular monitoring of anti-Xa levels. It is unclear how frequently anti-Xa monitoring should be performed, nor is it entirely clear whether peak, trough, or both peak and trough levels best predict suboptimal anticoagulation. LMWH may be associated with better foetal/neonatal outcomes, but its use may increase the risks of maternal valve thrombosis and dysfunction, thrombo-embolic events, and obstetric haemorrhage.[4]

The costs of the medicines and tests reviewed is listed in table 1 and table 2. An average dosing schedule for warfarin, unfractionated heparin (UFH) and enoxaparin is included in the evidence to decision table for consideration. Costs of testing required for each of the options should also be considered.

Table 1. Prices of available medicines for anticoagulation in pregnancy

Generic name	Formulation	Strength	Unit cost	Source
Warfarin	Tablet (100 tablet container)	5mg	R65,96	DoH pharmaceutical tender price*
Enoxaparin	SC injection (0.4mL pre-filled syringe)	40mg/0.4mL	R31,30	DoH pharmaceutical tender price**
Enoxaparin	SC injection (0.6mL pre-filled syringe)	60mg/0.6mL	R47,68	DoH pharmaceutical tender price**
Enoxaparin	SC injection (0.8mL pre-filled syringe)	80mg/0.8mL	R53,66	DoH pharmaceutical tender price**
Unfractionated Heparin	IV (5ml vial)	1000 IU/mL	R19,21	DoH pharmaceutical tender price**
Unfractionated Heparin	IV (5ml vial)	5000 IU/mL	R35,57	DoH pharmaceutical tender price**

*Contract circular RT289-2019

** Contract circular RT297-2019

Table 2. Prices of anticoagulation testing

Description	Class code	BHF code	Cost per test	Source
Warfarin dosing (INR)	2446	3806	R45,05	NHLS state price list (2018)
Antifactor Xa	2324	3728	R506, 43	NHLS state price list (2018)
Partial Thromboplastin Time	2460	3837	R52,40	NHLS state price list (2018)

The purpose of this review is to re-examine the existing (and more recent) literature on the safety of heparin and warfarin for pregnant women with MPHVs. It is worth noting that no published randomised controlled trials (RCTs) addressing this issue have been conducted, but rather observational data is available to inform the decision alongside consideration of high quality, up-to-date guidelines that may be adopted or adapted.

MEDICINE REVIEW OBJECTIVE

To evaluate the effectiveness and safety regimen of heparin throughout pregnancy compared to the standard of care, heparin/ warfarin/ heparin, for the management of pregnant women with MPHVs.

Population: pregnant women with MPHVs
Intervention: heparin throughout pregnancy
Comparison: heparin in first trimester / warfarin (13 – 36 weeks) / heparin from 36 weeks
Outcomes:

- *Maternal:* death, valve thrombosis, thrombo-embolic events, major obstetric haemorrhage
- *Foetal:* miscarriage, in-utero foetal death (IUFD), preterm birth, neonatal death, neonatal morbidity, birth defects

METHODS AND FINDINGS

Part 1: Guidelines

Full guidelines report (**appendix 1**).

Summary of methods used to find and appraise the guidelines

Electronic searches for guidelines was completed in September 2019. Simple search terms used included: warfarin, heparin, anticoagulant*, pregnancy, mechanical heart valve, valvular heart disease, antithrombotics in the following databases:

Table 3. Database search description

Name	Website	Searched (x)
WHO – World Health Organization	www.who.int/publications/guidelines/en/	x
GIN – Guidelines International Network	www.g-i-n.net	x
NICE – National Institute for Health Care Excellence (England and Wales)	www.nice.org.uk/guidance	x
SIGN – Scottish Intercollegiate Guidelines Network (Scotland)	www.sign.ac.uk	x
National Guideline Clearinghouse (USA)	www.guideline.gov	
Clinical Practice Guidelines Portal (Australia)	www.clinicalguidelines.gov.au/portal	x
Electronic search (e.g. google)		x

Six guidelines were identified and appraised, all with moderate to good quality of reporting using the AGREE II tool:

Table 4. Guideline appraisal results

Name of guideline	AGREE II overall score
VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy (2012)[5]	**Good**
Clinical practice guideline venous thromboprophylaxis in pregnancy (2013)[6]	**Moderate**
Antithrombotics: indications and management (2012)[7]	**Good**
Canadian stroke best practice consensus statement: Secondary stroke prevention during pregnancy (2017)[8]	**Good**
Guidelines on the Management of Cardiovascular Diseases during Pregnancy (2018)[9]	**Moderate to good**
2014 AHA/ACC Guideline 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 (2014)[10]	**Good**

Summary of guidelines and their recommendations

The reviewed guidelines stated limitations in the quality of the evidence available to address this review question and as a result, the majority of the recommendations were based on consensus opinion of experts along with consideration of the non-randomised studies. Due to the lack of certain evidence to guide the optimal management of this patient population, there was no general agreement on a medical management strategy, and several options were proposed.

Most of the guidelines suggested that pregnant patients with mechanical heart valves require specialist management in a tertiary facility. This is due to the highly specialized and individualized decision that needs to be made on the patient's treatment approach, as well as the related monitoring requirements throughout pregnancy. In addition, there was a strong emphasis on the role of patient preference in the decision, after informed consideration of the risks and benefits of the treatment options to themselves and the foetus (risk of thrombosis vs risk of fetal abnormalities).[11]

Vitamin K Antagonists (VKAs), like warfarin, can cause embryopathy. Particularly during the 6-13 weeks period or foetal development. Withdrawal of the VKA prior to six weeks gestation is therefore likely to minimize that risk. VKAs are the most effective antithrombotics for prevention of thrombosis of mechanical heart valves.[7] Both the AHA/ACC Valvular Heart Disease Guideline and the ESC Guidelines on the Management of Cardiovascular Diseases during Pregnancy favoured the use of VKAs in the second and third trimesters, while the other guidelines (VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy, Antithrombotics: Indications and Management, Clinical Practice Guideline: Venous Thromboprophylaxis in Pregnancy, and the Canadian Stroke Best Practice Consensus Statement: Secondary Stroke Prevention during Pregnancy) did not indicate a strong preference for one of the treatment options presented.

The AHA/ACC Valvular Heart Disease Guideline and the ESC Guidelines on the Management of Cardiovascular Diseases during Pregnancy both included a recommendation aimed at reducing harm, stating that LMWH should not be administered to this population unless anti-Xa levels can be monitored weekly and doses adjusted accordingly.

Both the AHA/ACC Valvular Heart Disease Guideline and ESC Guidelines on the Management of Cardiovascular Diseases during Pregnancy proposed treatment algorithms based on patient's VKA dose.

Part 2: Systematic reviews:
Table of published relevant systematic reviews (**appendix 2**).

Summary of methods used to find and appraise the systematic reviews

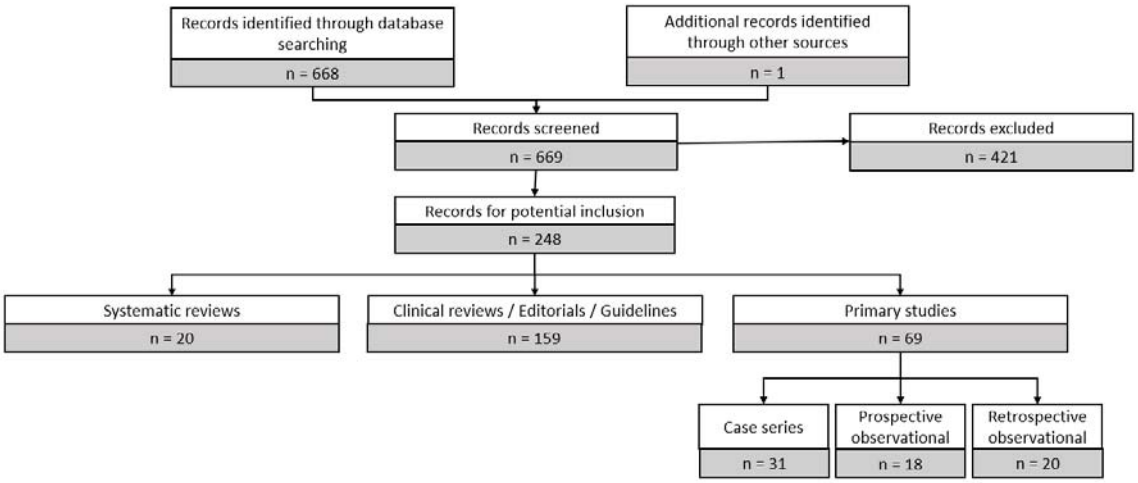
Electronic searches for systematic reviews and primary studies were done on 27 June 2019 in PubMed, Scopus and the Cochrane Database of Systematic reviews. Search strategy for PubMed shown in table 5. We did single screening

of all records to review the title and abstract. Only full texts of systematic reviews were sought for further appraisal and reporting below. The Prisma flow diagram for the search output is shown below (figure 1).

Table 5. Search strategy for PubMed

Search	Query	Items found
#4	Search (#1 AND #2 AND #3)	343
#3	Search (heparin[mh] OR heparin*[tiab])	102117
#2	Search (heart valve prosthesis [mh] OR heart valve prostheses[tiab] OR heart valve prosthesis[tiab] OR cardiac valve prosthesis[tiab] OR cardiac valve prostheses[tiab] OR mechanical heart valve*[tiab] OR prosthetic heart valve*[tiab] OR prosthetic cardiac valve*[tiab])	35288
#1	Search (pregnancy[mh] OR pregnan*[tiab])	973204

Figure 1. Prisma flow diagram of search results



Six systematic reviews were considered to be of sufficient quality to summarise to inform further deliberation using the AMSTAR II tool. Details of the included reviews are available in appendix 2.

The most recent and applicable evidence review was from NICE. The evidence review was conducted by the Royal College of Obstetricians and Gynaecologists (published in March 2019)[12] to inform *NICE Guideline 121 (NG121): Intrapartum care for women with existing medical conditions or obstetric complications and their babies.* Although evidence review was for intrapartum care, it included the relevant patient population throughout pregnancy. Thus this review was selected as the most up-to-date review which GRADED the certainty of evidence and is relevant for this topic to inform the panel's decision. The evidence within the NICE systematic review includes the reviews from Vause 2107[1], and Xu 2016[2].

Summary of findings from the NICE evidence review[12]:

Maternal outcomes (see table 5): heparin/ warfarin/ heparin compared to LMHW

1. Death was reported in the Xu 2016 review, included observational studies with methodological limitations, serious heterogeneity and very serious imprecision. There was a RR 0.49 (95% CI 0.08 to 2.88), that is 9 fewer deaths per 1000, ranging from 16 fewer deaths to 33 more). Overall very low certainty evidence whether the choice of regimen impacts on number of deaths.

2. Major thrombo-embolic events reported in Xu 2016 including observational with methodological limitations, very serious unexplained heterogeneity and very serious imprecision reported a RR 1.68 (95% CI 0.66 to 4.28), that is 30 more events per 1000 women, ranging from 15 fewer to 145 more events. Overall very low certainty evidence whether the choice of regimen impacts thromboembolic events.
3. Major obstetric haemorrhage events were reported in Xu 2016 including observational with methodological limitations and heterogeneity and serious imprecision reported a RR 0.15 (95% CI 0.03 to 0.8) that there were 35 fewer events per 1000 women, ranging from 8 to 40 fewer events. Although there were consistently fewer thromboembolic events, overall there is very low certainty evidence whether the choice of regimen impacts major obstetric haemorrhage.

Foetal outcomes captured as death or 'poor foetal outcomes' (see table 6): heparin/ warfarin /heparin compared to LMHW

Poor foetal outcome is a composite of the following: any pregnancy loss (miscarriage or termination of pregnancy), stillbirth, neonatal death, foetal abnormality, Apgar score of <7 at 5 minutes or admission to the neonatal unit.

1. Deaths were reported in the Xu 2016 review which included observational studies with methodological limitations, very serious heterogeneity and serious imprecision. There was a RR 1.85 (1.05 to 3.25), that is 104 more deaths per 1000 women, ranging from 6 more deaths to 276 more). Overall there is very low certainty evidence whether the choice of regimen impacts on number of deaths.
2. Poor foetal outcomes were reported in Vause 2017 including observational with methodological limitations and very serious imprecision reported a RR 0.68 (0.26 to 1.81) that there were 156 fewer per 1000 (from 361 fewer to 395 more). Overall there is very low certainty evidence whether the choice of regimen impacts major obstetric haemorrhage.

Table 5. Maternal outcomes evidence profiles: heparin/warfarin/heparin versus LMHW

Quality assessment						No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Heparin / warfarin / heparin**	**LMWH**	**Relative (95% CI)**	**Absolute**		
Mortality (all causes)											
1 (Xu 2016)	Observational studies	Serious[1]	Serious[2]	No serious indirectness	Very serious[3]	3/348 (0.86%)	2/113 (1.8%)	RR 0.49 (0.08 to 2.88)	9 fewer per 1000 (from 16 fewer to 33 more)	⨁⨀⨀⨀ VERY LOW	CRITICAL
Major morbidity: major thromboembolic event											
1 (Xu 2016)	Observational studies	Serious[1]	Very serious[2]	No serious indirectness	Very serious[3]	25/337 (7.4%)	5/113 (4.4%)	RR 1.68 (0.66 to 4.28)	30 more per 1000 (from 15 fewer to 145 more)	⨁⨀⨀⨀ VERY LOW	CRITICAL
Major morbidity: major antenatal haemorrhagic event											
1 (Xu 2016)	Observational studies	Serious[1]	Very serious[2]	No serious indirectness	Serious[4]	2/329 (0.61%)	4/98 (4.1%)	RR 0.15 (0.03 to 0.8)	35 fewer per 1000 (from 8 fewer to 40 fewer)	⨁⨀⨀⨀ VERY LOW	CRITICAL
Poor maternal outcome[a]											
1 (Vause 2017)	Observational studies	Serious[5]	Not applicable	Serious[6]	Very serious[3]	3/9 (33.3%)	23/41 (56.1%)	RR 0.59 (0.23 to 1.56)	230 fewer per 1000 (from 432 fewer to 314 more)	⨁⨀⨀⨀ VERY LOW	CRITICAL / IMPORTANCE *

CI: confidence interval; RR: risk ratio; LMWH: low-molecular weight heparin; MID: minimal important difference

[a] Poor maternal outcome: maternal death or serious morbidity – admission to intensive care for >1day, valve thrombosis, valve dysfunction resulting in heart failure, cerebrovascular accident or bleeding requiring transfusion or return to theatre (primary postpartum haemorrhage, secondary postpartum haemorrhage, intraabdominal bleeding, vaginal haematoma, wound haematoma)

[1] Xu 2016 – systematic review of cohort and case series; unclear prior study design; unclear conflict of interest

[2] This is a systematic review of observational studies

[3] The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds

[4] The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold

[5] Vause 2017 – prospective cohort; unclear comparability

[6] The composite outcome included the outcomes outside of this review's interest and thus, downgraded by one level

* This composite outcome consisted of critical and important outcomes for the woman

Source: NICE Evidence reviews for heart disease (2019) [12]

Table 6. Foetal outcomes evidence profiles: heparin/warfarin/heparin versus LMHW

Quality assessment						No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Heparin / warfarin / heparin**	**LMWH**	**Relative (95% CI)**	**Absolute**		
Mortality											
1 (Xu 2016)	Observational studies	Serious[1]	Very serious[2]	Serious[3]	Serious[4]	77/340 (22.6%)	12/98 (12.2%)	RR 1.85 (1.05 to 3.25)	104 more per 1000 (from 6 more to 276 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Poor foetal outcome[a]											
1 (Vause 2017)	Observational studies	Serious[5]	Not applicable	Serious[6]	Very serious[7]	3/9 (33.3%)	20/41 (48.8%)	RR 0.68 (0.26 to 1.81)	156 fewer per 1000 (from 361 fewer to 395 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL / IMPORTANCE*

CI: confidence interval; RR: risk ratio; LMWH: low-molecular weight heparin; MID: minimal important difference

[a] Poor foetal outcome: any pregnancy loss (miscarriage or termination of pregnancy), stillbirth, neonatal death, foetal abnormality, Apgar scroe of <7 at 5 minutes or admission to the neonatal unit

[1] Xu 2016 – systematic review of cohort and case series; unclear prior study design; unclear conflict of interest

[2] This is a systematic review of observational studies

[3] This outcome comprised of abortion and downgraded by one level

[4] The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold

[5] Vause 2017 – prospective cohort; unclear comparability

[6] The composite outcome included the outcomes outside of this review's interest and thus, downgraded one level

[7] The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds

* This composite outcome consisted of critical and important outcomes for the woman

Source: NICE Evidence reviews for heart disease (2019) [12]

Part 3: Costing analysis

Information regarding the costs of preventative anticoagulation treatments and their related monitoring tests for week 6 to week 36 gestation are estimated in table 7.

Table 7. Pharmaceutical and test costs associated with week 6-36 of the pregnancy

Description of treatment sequence	Number of weeks	Pharmaceutical costs	Test costs	Combined costs
Enoxaparin 60mg bd (week 6-12) Warfarin 5mg (week 13-36)	6 24	R4 005,12 R110,81	R3 038,58 R833,43	R7 987,94
Enoxaparin 80mg bd (week 6-12) Warfarin 5mg (week 13-36)	6 24	R4 507,44 R110,81	R3 038,58 R833,43	R8 490,26
UFH 10 000 IU bd (week 6-12) Warfarin 5mg (week 13-36)	6 24	R1 195,15 R110,81	R314,40 R833,43	R2 453,79
UFH 15 000 IU bd (week 6-12) Warfarin 5 mg (week 13-36)	6 24	R1 792,73 R110,81	R314,40 R833,43	R3 051,37
Enoxaparin 60mg bd (week 6-36)	30	R20 025,60	R15 192,90	R35 218,50
Enoxaparin 80mg bd (week 6-36)	30	R22 537,20	R15 192,90	R37 730,10
UFH 10 000 bd (week 6-36)	30	R5 975,76	R1 572,00	R7 547,76
UFH 15 000 bd (week 6-36)	30	R8 963,64	R1 572,00	R10 535,64

Costing analysis assumptions:

1. Warfarin dose of 5mg once a day was used in calculations. Due to the low cost of Warfarin, even a doubling in the dose will have a minimal effect on the final cost of treatment.
2. Scenarios were presented for twice daily doses of Enoxaparin 60mg/0,6mL and Enoxaparin 80mg/0,8mL (initiation dose will be based on the weight of the woman), and UFH 10 000 IU and 15 000 IU.
3. Costs for Warfarin dosing test (INR) was calculated for a frequency of one test a day for the first week, and then one test every two weeks thereafter.
4. The cost of anticoagulation testing for patients on Enoxaparin was calculated as a once weekly anti-Xa test
5. The cost of anticoagulation testing for patients on UFH was calculated as a once weekly Partial Thromboplastin Time (aPPT) test

Part 4: Summary of Findings

After consideration of relevant recent, up-to-date guidelines and systematic reviews, we summarised the recommendations from these sources for the management of pregnant women with mechanical heart valves as follows:

Convert the pregnant patient on warfarin therapy to one of these treatment options soon as pregnancy is confirmed within the first trimester:

- Adjusted-dose LMWH administered subcutaneously every 12 h throughout pregnancy with monitoring factor Xa.

  OR
- Adjusted-dose UFH* administered subcutaneously every 12 h throughout pregnancy with monitoring aPTT.

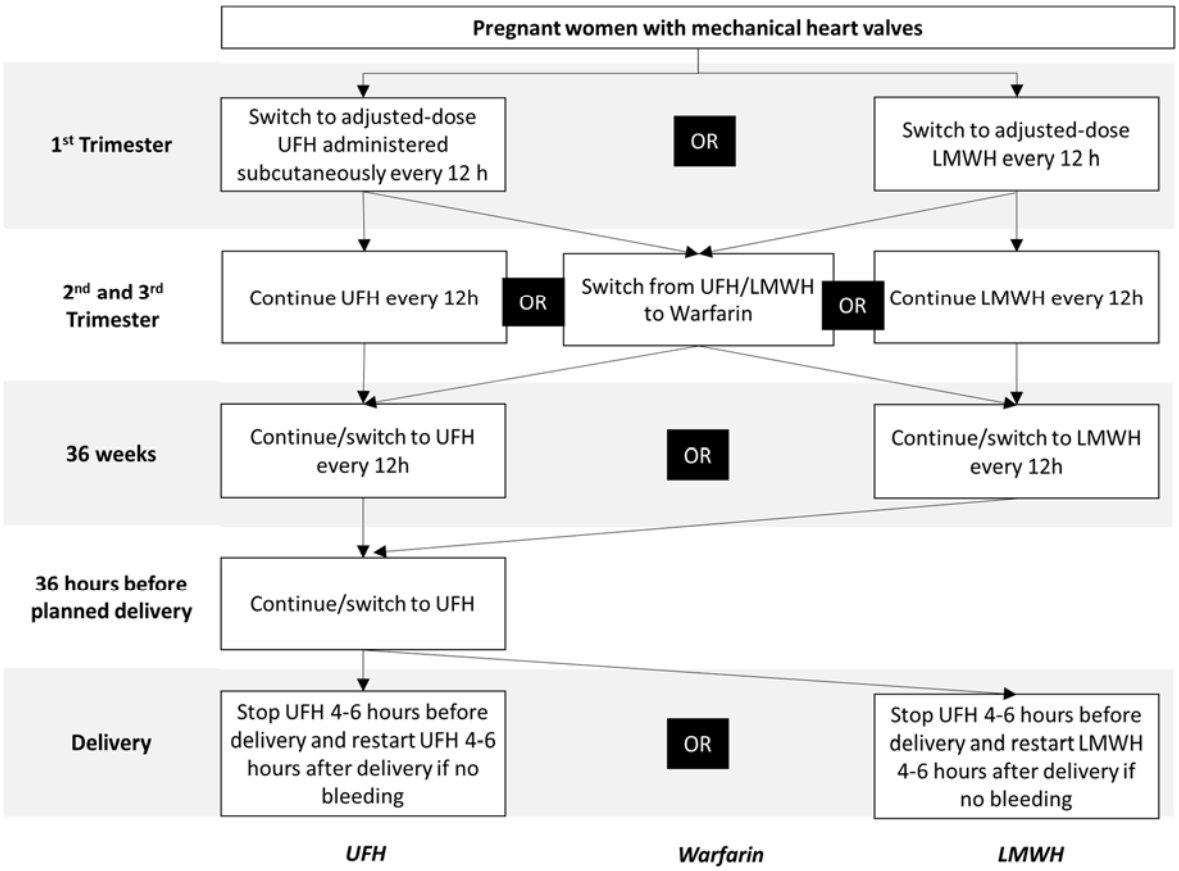
  OR
- UFH* or LMWH administered subcutaneously every 12 h until the 13th week, with substitution with warfarin until week 36 when UFH or LMWH is resumed.

Strong consideration should be given to giving warfarin throughout pregnancy in very high-risk patients in whom concerns exist about the efficacy and safety of UFH or LMWH (e.g. older generation prosthesis in the mitral position or history of thromboembolism) with replacement by UFH or LMWH close to delivery. Woman's values and preferences should inform the decision and they should be involved in the decision to balance the risk to the foetus and themselves.

* Note: UFH preparation that can be administered SC is not currently available in South Africa

Figure 2 provides a visual representation of this summary of the findings.

Figure 2. Summary of guidelines: anticoagulant treatment algorithm for pregnant women with mechanical heart valves



Note: Concentrated UFH preparation that can be administered subcutaneously is not currently available in South Africa. For practical management, the more dilute formulation may be administered subcutaneously, 8 hourly.

DISCUSSION

All studies were observational in design and most studies had limited participant numbers (table 5 and table 6). The largest meta-analysis included 2113 pregnancies.

Maternal death was relatively common in almost all studies, ranging from 0.9% in the Xu meta-analysis to 8.6% in the UKOSS study.[1,2] For comparison, in the ROPAC study, maternal death was 1.4% among women with mechanical valves vs 0.2% among women with structural heart disease without prosthetic valves vs 0.007-0.043% within the general obstetric population.[4]

Warfarin throughout pregnancy was associated with lowest rates of maternal death, followed by sequential treatment and LMWH, respectively. UFH was associated with the highest maternal mortality in the D'Souza analysis.[13]

Thrombo-embolic events, including valve thrombosis, occurred more often with the use of UFH than with any other regimen, whereas warfarin use was associated with lowest risk of thrombo-embolism.[14] In the studies which reported on the timing of valve thrombosis, it occurred more frequently in the first trimester, and occurred more often with heparin use.

Foetal and neonatal outcomes were not reported in a standardised manner. The definition of miscarriage and foetal death varied between studies. The distinction between termination of

pregnancy (TOP) for warfarin embryopathy, or other reasons, was unclear. Congenital abnormalities other than those related to warfarin use, could not readily be extracted out. Only a few studies reported on preterm delivery and neonatal morbidity.

In general, live birth rates were higher with heparin use compared with warfarin. Embryopathy and foetal intraventricular haemorrhage occurred more often with warfarin. Miscarriages occurred more frequently with warfarin compared with heparin (28.6% vs 9.2% in the ROPAC analysis).[4] Foetal death also occurred more often with warfarin use compared with LMWH (4.1% vs 3.6%) in the Steinberg meta-analysis.[14] Yet in another meta-analysis, both maternal and fetal complications were highest when UFH was used throughout pregnancy.[13] The route of administration of UFH – subcutaneous or intravenous – was however, not specified.

Alternative agents

Given the disappointing pregnancy outcomes with current treatment, a new molecule is urgently needed to address safety of anticoagulation for these women. The new oral anticoagulants, e.g. rivaroxaban, were shown to be non-inferior to enoxaparin/warfarin for the treatment of venous thrombo-embolism (VTE) and are associated with significantly lower risks of recurrent VTE.[19] Safety data in pregnancy are however, lacking. Rivaroxaban crosses the placenta. Animal studies have shown reproductive toxicity (post-implantation loss, retarded ossification, other congenital malformations) at clinically relevant plasma concentrations.[20] There are no human studies of rivaroxaban in pregnancy, since pregnant women are generally excluded from experimental studies.

It will be several years before we can either confirm the safety or refute the teratogenicity of rivaroxaban in pregnancy, since this can only be established confidently through a prospective pregnancy registry.

Other considerations

The most important consideration is counselling of women with MPHVs to avoid pregnancy, and to provide them with reliable and effective contraception. Pregnancy should be avoided lifelong, or until safer treatment options become available. Should a woman with MPHV become pregnant, she should be informed of the risks to herself and foetus and be included in shared-decision making regarding her specialised treatment.

RECOMMENDATION: EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [ ] Not confident [ ] Uncertain [X]	The evidence is from observational studies with low numbers of women included and often very few events of interest. There is therefore very low certainty evidence to suggest which regimen may be better under which circumstances
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [ ] Harms outweigh benefits [ ] Benefits = harms or Uncertain [X]	The balance of benefits and harms of the options are uncertain based on the available evidence.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives (comparators) available: Yes [ ] No [X] List the members of the group. List specific exclusion from the group:	A review was not done to consider therapeutic alternatives. To date, data on use of oral direct thrombin (e.g., dabigatran) and anti-Xa (e.g., rivaroxaban, apixaban) inhibitors are scarce in pregnancy. We did note a recommendation from ACCP guidelines 2012 as follows: 3.0.4. For pregnant women, recommend avoiding the use of oral direct thrombin (e.g., dabigatran) and anti-Xa (e.g., rivaroxaban, apixaban) inhibitors (Grade 1C)
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [X]	Data was not sought about the value that women in South Africa, or elsewhere, place on the treatment options and the reported outcomes. Data was not sought about the preferences of the specialists treating women.

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [X] Less intensive [ ] Uncertain [ ]</td><td>Heparin throughout pregnancy is likely to have a greater budget impact than the heparin / warfarin / heparin regimen based on the costs of medicines and testing required (especially a LMWH regimen) throughout pregnancy.

Details provided in appendix C.

Cost of medicines / month:
<table>
<tr><th>Generic name and dose</th><th>Cost per month</th></tr>
<tr><td>Warfarin 5mg daily</td><td>R20,06</td></tr>
<tr><td>Enoxaparin 60mg SC 12 hourly</td><td>R2 900,53</td></tr>
<tr><td>Enoxaparin 80mg SC 12 hourly</td><td>R3 264,32</td></tr>
<tr><td>UFH 10 000 IU 12 hourly</td><td>R865,54</td></tr>
<tr><td>UFH 15 000 IU 12 hourly</td><td>R1 298,31</td></tr>
</table>
Additional resources: Anticoagulation tests
<table>
<tr><th>Description</th><th>Cost per month</th></tr>
<tr><td>Warfarin dosing</td><td>R90,10</td></tr>
<tr><td>Antifactor Xa</td><td>R2025,72</td></tr>
<tr><td>Partial Thromboplastin Time</td><td>R209,60</td></tr>
</table></td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes [ ] No [ ] Uncertain [X]</td><td>There may be no change in equity. Mainly, this is a tertiary specialist managed clinical condition; there are inherent impacts on equity in terms of where women with mechanical valves should live to be in proximity of care.
However, ensuring women have an opportunity for informed choice regarding their treatment and to choose whether the treatment that favours their health or that of the foetus will increase equity and autonomy.</td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes [ ] No [ ] Uncertain [X]</td><td>The intervention should be feasible, based on access to medicines and testing required for the choice of regimen.</td></tr>
</table>

Type of recommendation	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☒	☐	☐	☐

Recommendation
Based on this evidence review, the Adult Hospital Level Committee suggested that for women with mechanical heart valves who conceive, should be offered the approach of heparin for the first trimester, warfarin until 36 weeks, and heparin from 36 weeks until post delivery.
The decision was based on the very low certainty evidence of any difference with use of any choice of medicines, and the substantial increase in resources when heparin is used throughout pregnancy.

Should a woman with MPHV become pregnant, she should be informed of the risks to herself and foetus and be included in shared-decision making regarding her specialised treatment.

Additional comments include that women with mechanical heart valves who conceive, termination of pregnancy (TOP) should be offered routinely. This should be done as early in pregnancy as possible. Women who decline TOP must receive the care of a specialist team that should include an obstetrician and cardiologist. Access to echocardiography and laboratory services are essential. Care should be centralised, where possible.

This medicine review and proposed treatment algorithm will be able to inform management of pregnant women with mechanical heart valves, at Tertiary and Quaternary level of care – to be referred to the Tertiary and Quaternary Expert Review Committee.

Rationale: Available evidence shows an unacceptably high maternal mortality rate and considerable maternal morbidity associated with valvular heart disease (requiring prosthetic valves) and its treatment.
Level of Evidence: III Systematic review of observational studies, Guidelines

Review indicator: Tertiary and Quaternary level review

M & E considerations: Audits of current treatment practices and adverse events in this patient cohort. Acceptability of stakeholder surveys

Research priorities: More local data and epidemiological research

REFERENCES

1. Vause S, Clarke B, Tower CL, Hay CRM, Knight M (on behalf of UKOSS). 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: 1411-1419.
2. Xu Z, Fan J, Luo X, et al. Anticoagulation regimens during pregnancy in patients with mechanical heart valves: a systematic review and meta-analysis. *Can J Cardiol* 2016; 1248.e1-1248.e9. https://www.ncbi.nlm.nih.gov/pubmed/26927861
3. Soma-Pillay P, Nene Z, Mathivha TM, MacDonald AP. The effect of warfarin dosage on maternal and fetal outcomes in pregnant women with prosthetic heart valves. *Obstetric Medicine* 2011; 4: 24-27.
4. van Hagen IM, Roos-Hesslink JW, Ruys TPE, 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.
5. Bates, Shannon M., Ian A. Greer et al. VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy. *Chest* 2012; 141 (2): e691S-e736S. https://doi.org/10.1378/chest.11-2300
6. Institute of Obstetricians and Gynaecologists (Royal College of Physicians of Ireland), HSE Clinical Care Programme in, and Obstetrics and Gynaecology Irish Haematology Society. Clinical Practice Guideline Venous

Thromboprophylaxis in Pregnancy. 2013. https://rcpi-live-cdn.s3.amazonaws.com/wp-content/uploads/2016/05/15.-Venous-Thromboprophylaxis-in-Pregnancy.pdf
7. Scottish Intercollegiate Guidelines Network. Antithrombotics: Indications and Management (SIGN CPG 129). 2012. https://www.sign.ac.uk/assets/sign129.pdf
8. Swartz, Richard H, Noor Niyar, N Ladhani, et al. 2018. Canadian Stroke Best Practice Consensus Statement: Secondary Stroke Prevention during Pregnancy. *Canada International Journal of Stroke* 2018; 13 (4): 406–19. https://doi.org/10.1177/1747493017743801
9. Baumgartner, Helmut, Volkmar Falk et al. 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. *European Heart Journal* 2017; 38 (36): 2739–91. https://doi.org/10.1093/eurheartj/ehx391
10. Nishimura, Rick A et al. 2014 AHA/ACC Guideline 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. *JAC* 2014; 63: e57–185. https://doi.org/10.1016/j.jacc.2014.02.536
11. Regitz-Zagrosek, Vera, Jolien W Roos-Hesselink, Johann Bauersachs et al. ESC Guidelines for the Management of Cardiovascular Diseases during Pregnancy. *European Heart Journal* 2018; 39 (34): 3165–3241. https://doi.org/10.1093/eurheartj/ehy340
12. Royal College of Obstetricians and Gynaecologists (National Guideline Alliance). Intrapartum care for women with existing medical conditions or obstetric complications and their babies - Evidence reviews for heart disease. 2019. https://www.nice.org.uk/guidance/ng121/evidence/march-2019-evidence-reviews-6716840077?tab=evidence
13. D'Souza RD, Ostro J, Shah PS, et al. Anticoagulation for pregnant women with mechanical heart valves: a systematic review and meta-analysis. *Eur Heart J* 2017; 38: 1509-1516. https://www.ncbi.nlm.nih.gov/pubmed/28329059
14. Steinberg ZL, Dominguez-Islas CP, Otto CK, Stout KK, Krieger EV. Maternal and fetal outcomes of anticoagulation in pregnant women with mechanical valves. *JACC* 2017; 69:2681-91. https://www.ncbi.nlm.nih.gov/pubmed/28571631