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Anticoagulation during pregnancy in women with prosthetic valves: evidence, guidelines and unanswered questions

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ABSTRACT

The management of women with mechanical heart valves during pregnancy remains difficult and controversial. There is no ideal anticoagulation regimen for this unique population, as there are inherent risks and benefits of each approach for both mother and fetus. There has been limited data available to guide the clinician in the optimal treatment strategy for an individual patient. The AHA/ACC Guidelines for the Management of Patients with Valvular Heart Disease created class recommendations for this population based upon current evidence, which is summarized in this review.

INTRODUCTION

All women with mechanical prosthetic heart valves should receive long-term anticoagulation to prevent the disastrous consequences of valve thrombosis and systemic embolic events. This is particularly true during pregnancy when prothrombotic changes occur throughout pregnancy, labour and delivery. However, there is no ideal anticoagulant for this unique population, in which the outcome of the fetus must be considered as well as the safety of the mother.[1–8] Oral vitamin K antagonists (VKA) are the optimal anticoagulant in terms of prevention of valve thrombosis and embolic events but are associated with detrimental effects on the fetus, including warfarin embryopathy, ocular and neurological abnormalities, as well as late fetal loss and stillbirth.[9 10] Unfractionated heparin (UFH) does not cross the placental barrier and thus does not cause fetal embryopathy, but has shown to be a poor anticoagulant in terms of prevention of valve thrombosis. Low-molecular-weight heparin (LMWH) also does not cross the placental barrier, has good bioavailability and ease of use, but controversy still exists as to its efficacy in preventing valve thrombosis during pregnancy.[1 3 5 11 12]

Physicians need guidance regarding these difficult management challenges. In the case of anticoagulation for mechanical valves in pregnancy, there has been a lack of consensus due to limited data and evolving treatment strategies. Recent recommendations from both the American Heart Association (AHA)/American College of Cardiology (ACC) 2014 Guidelines for the Management of Patients with Valvular Heart Disease[13] as well as the European Society of Cardiology (ESC) 2011 Guideline on the Management of Cardiovascular Diseases during Pregnancy[14] have addressed these issues. This article will summarise the evidence used to make the class recommendations for the AHA/ACC guidelines, and their clinical implications.

BACKGROUND

VKA are an accepted and necessary treatment for all patients with mechanical valve prostheses for prevention of valve thrombosis and systemic embolic events. Hall *et al*[9] in 1980 established that mothers taking VKA during pregnancy had an increased incidence of the fetus developing a warfarin embryopathy during the 6th to 9th week of gestation characterised by nasal hypoplasia and stippled epiphyses, thought to be due to inhibition of vitamin K-dependent osteocalcins that play a role in calcification during embryogenesis. In addition to the first trimester embryopathy, there may be an associated 'fetopathy' of central neurological system abnormalities, with an increased risk of fetal loss, haemorrhage and stillbirth when VKA are administered during the second and third trimester of pregnancy.[10]

Although the use of VKA is associated with detrimental effects on the fetus, historical observational studies showed that one of four women with a mechanical prosthesis who were on no anticoagulation during pregnancy had a thromboembolic event, indicating that some form of anticoagulation is necessary to prevent valve thrombosis.[15] The use of UFH given subcutaneously throughout pregnancy was implemented to avoid the adverse fetal effects of VKA but resulted in a high incidence (up to 33%) of valve thrombosis.[15 16] Thus a common approach in the past was to use UFH in the first trimester to avoid the teratogenic effects of warfarin, switching back to VKA in the second and third trimester. Intravenous UFH would then be used at the end of the third trimester and stopped just prior to delivery to prevent fetal brain haemorrhage during the mechanical stress of a vaginal delivery. However, the use of UFH only in the first trimester followed by warfarin in the second and third trimester was still found to be associated with an incidence of valve thrombosis of 5–10%.[15 17]

LMWH was subsequently developed, used initially for patients with acute coronary syndromes and venous thrombosis. Targeting the inhibition of factor II and Xa, LMWH is a more powerful anticoagulant than UFH with more reliable absorption and bioavailability when given through a subcutaneous injection. This treatment was subsequently used in pregnant women with mechanical prostheses, with high expectations and enthusiasm. However, prospective studies were stopped prematurely due to several deaths from valve thrombosis

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in the LMWH arm,[18] leading to a US Food and Drug Administration black box warning against the use of LMWH in pregnancy. Subsequent studies suggested that the problem with LMWH was due to weight-based dosage rather than adjusting dosage according to factor Xa levels, but even with meticulous monitoring of peak factor Xa levels, valve thrombosis has still occurred.[12 19–27]

There remains limited data regarding the optimal anticoagulation regimen in pregnant women with mechanical valve prostheses, and controversy continues. Based upon the data outlined below, the AHA/ACC Guidelines for Valvular Heart Disease[13] produced a set of recommendations for clinicians, which were in accordance with the recommendations that had been arrived at independently by the ESC Pregnancy Task Force.[14]

SUPPORTING EVIDENCE

The writing process and methodology of the AHA/ACC 2014 Valve Guidelines was modified from prior valve guidelines. First, a discrete taxonomy was created to conform to the needs of the clinician for data storage, search, retrieval and regular updates. Thus for each valve lesion and valve problem, the sections were divided into the clinically relevant question including (1) diagnosis and follow-up, (2) medical therapy and (3) intervention. To create more evidence-based recommendations, exhaustive evidence tables were generated by the authors, describing the relevant available studies pertaining to the specific clinical question. After a critical review of the evidence tables, class recommendations were created only after discussion and final consensus by the entire committee.

Two tables were generated of published papers reporting the effects of the different anticoagulant regimens on the mother and fetus. The first table included studies before the use of LMWH and the second included studies examining the use of LMWH. Table 1 is an abbreviated version combining the key elements from these two tables, which also adds several references that were published following the guideline creation.

EVIDENCE LIMITATIONS

In contrast to the large numbers of patients in multiple randomised trials that provide guidelines for treatment of heart failure, coronary disease and hypertension, the available evidence for anticoagulation in pregnant women is limited. The current data available consist of retrospective studies of small numbers of patients with incomplete data. The type and location of the valve prosthesis may not have been specified in the studies, despite the knowledge that newer generation prostheses have a lower incidence of thrombosis, particularly in the aortic position. Data on the older generation prostheses may not be applicable to the newer generation prostheses. Details on the adequacy of the anticoagulation regimens are not always available, and patient compliance with the therapy have not been fully documented. The definitions of adverse outcomes, such as warfarin embryopathy, fetal wastage, maternal bleeding and thrombosis, have been highly variable throughout all studies. This has prompted the development of a large registry documenting outcomes in larger number of patients, which will hopefully provide further data in the future.[28]

SUMMARY OBSERVATIONS

Despite these multiple limitations of the current data, there were a number of observations that were gleaned from the studies and are listed in table 1:

1. Some form of anticoagulation is necessary to prevent thromboembolic events in all patients with mechanical prostheses during pregnancy.
2. UFH throughout pregnancy is a poor anticoagulant with a high incidence of thromboembolic events.
3. VKA throughout pregnancy appear to be the safest in terms of prevention of thromboembolic events for the mother but do have an increased incidence of fetal malformations and fetal wastage.
4. The complications of VKA for both mother and fetus are dose dependent, with fewer adverse effects when doses of less than or equal to 5 mg of warfarin are used.
5. There are no data on the use of the newer oral anticoagulants in the pregnant women with a mechanical prosthesis.
6. Weight-based LMWH should not be given to the pregnant patient with a mechanical prosthesis.
7. If LMWH is used, the dosage should be given based upon factor Xa levels. However, despite meticulous monitoring of Xa levels, valve thrombosis may still occur even in newer generation prostheses. The appropriate frequency of testing is unclear, but probably at least every two weeks is necessary.
8. It is unclear whether the addition of trough levels to peak levels of factor Xa facilitates optimum dosing of LMWH, with the aim of reducing maternal thromboembolic risk, but with the possible side effect of increased bleeding as the dose is increased.
9. All women should be converted to continuous infusion of UFH prior to planned delivery to allow sufficient time for VKA to be cleared from the fetus in anticipation of a planned delivery, while at the same time providing adequate anticoagulation for the mother. Interruption of all anticoagulation is necessary during delivery and intravenous UFH may be discontinued with complete and rapid cessation of anticoagulation just prior to delivery to allow epidural anaesthesia as well as minimise the risk of haemorrhage.

CURRENT AHA/ACC GUIDELINE RECOMMENDATIONS

Based upon the interpretation of the current evidence, the following Class Recommendations were generated:

Class I

1. Therapeutic anticoagulation with frequent monitoring is recommended for all pregnant patients with a mechanical prosthesis (*Level of Evidence: B*).
2. Warfarin is recommended in pregnant patients with a mechanical prosthesis to achieve a therapeutic international normalised ratio (INR) in the second and third trimesters (*Level of Evidence: B*).
3. Discontinuation of warfarin with initiation of intravenous UFH (with an activated partial thromboplastin time (aPTT) >2 times control) is recommended before planned vaginal delivery in pregnant patients with a mechanical prosthesis (*Level of Evidence: C*).

Class IIa

4. Continuation of warfarin during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin to achieve a therapeutic INR is 5 mg/day or less after full discussion with the patient about risks and benefits (*Level of Evidence: B*).
5. Dose-adjusted LMWH at least two times per day (with a target anti-Xa level of 0.8–1.2 U/mL, 4–6 h postdose) during the first trimester is reasonable for pregnant patients with a

Table 1 Studies of anticoagulation in pregnant women with mechanical valves

Author and year	Type of study	Number of pregnancies	Anticoagulation regimen	Maternal mortality	Thromboembolic risk	Fetal anomalies	Fetal wastage	Summary
Sbarouni 1994[16]	Questionnaire of European centres	214 pregnancies in 182 patients (133 with mechanical prosthesis)	Centre dependent	Maternal deaths—6 pts (3.3%) (4 valve thrombosis, 1 cerebral embolism, 1 pulmonary oedema)	Valve thrombosis—13 pts (6%) (10/13 on heparin, 12/13 MVR) Embolic events—8 pts (3.7%) (5/8 heparin)	No embryopathy in 36 women on warfarin	Fetal outcome similar for warfarin vs heparin—22% abortion and 10% stillbirths	Heparin is neither effective or safe for both fetus and mother with increased risk thromboembolism and bleeding
Salazar 1996[17]	Single-centre experience—prospective trial of UFH in first trimester	40 pregnancies in 37 patients	Subq UFH from 6–12 weeks and then last 2 weeks' gestation	One death—gastrointestinal bleed	Two cases massive thrombosis tilting disc MVR	No embryopathy	37% spontaneous abortion 2.5% neonatal death	Subq UFH is a poor anticoagulant and does not prevent massive thrombosis
Meschengieser 1999[29]	Single-centre experience—consecutive unselected	92 pregnancies in 59 women	1. VKA throughout 2. UFH 1st trimester, then VKA		1. 0.3/100 pt mos 2. 4.9/100 pt mos		Fetal wastage 1. 25% 2. 19%	Reduction of thromboembolic events for mother best with VKA throughout pregnancy
Vitale 1999[30]	Single-centre experience—consecutive unselected	58 pregnancies in 43 patients	1a. VKA <5 mg throughout pregnancy 1b. VKA >5 mg throughout pregnancy	None	Valve thrombosis—2 pts (3.4%)	1a. 28/32 healthy babies (none embryopathy) 1b. 3/25 healthy babies (2 embryopathy)	Fetal wastage 1a. 12% 1b. 76%	Fetal wastage and embryopathy dose dependent
Chan 2000[15]	Literature review	1234 pregnancies in 976 women	1. VKA throughout 2. UFH 1st trimester, then VKA 3. UFH throughout pregnancy 4. No A/C	Mortality 1. 1.8% 2. 4.2% 3. 15% 4. 4.7%	Thromboembolic events 1. 3.9% 2. 9.2% 3. 33% 4. 24%	Fetal anomalies 1. 6.4% 2. 3.4% 3. 0% 4. 3.3%	Fetal wastage 1. 33% 2. 26% 3. 43% 4. 20%	Reduction of thromboembolic events for mother best with VKA throughout pregnancy. Worse maternal outcome with UFH, especially throughout pregnancy
Sadler 2000[31]	Historical cohort from New Zealand	147 pregnancies in 79 patients	1. VKA throughout 2. VKA 6 weeks then UFH 3. VKA 28 weeks then UFH		Valve thrombosis/ emboli 1. 0%/0% 2. 20%/20% 3. 0%/25%		Live births 1. 30% 2. 78% 3. 67%	High rate of fetal loss on VKA but high rate of thromboembolism on heparin
Rowan 2001[22]	Single-centre experience	14 pregnancies in 11 patients	LMWH throughout pregnancy		Valve thrombosis—1 pt (9%)		Live births—9/14 (3 miscarriages and 2 terminations)	First use of LMWH with risk of valve thrombosis—fixed dose—no Xa levels monitored
Al Lawati 2002[32]	Single-centre experience in Oman—consecutive unselected pregnancies	63 pregnancies in 21 patients	1. VKA throughout 2. UFH 1st trimester, then VKA		Valve thrombosis 1. None 2. 2 pts	No embryopathy	Spontaneous abortion 1. 26% 2. 14% Live births – 74% – 71%	In countries with low socioeconomic status VKA recommended
Cotrufo 2002[33]	Single-centre experience—consecutive unselected	71 pregnancies in 52 patients	1a. VKA <5 mg throughout pregnancy 1b. VKA >5 mg throughout pregnancy	None	None	Warfarin embryopathy—4/71 (5.5%) 3 with dose >5 mg	Poor outcome 1a. 3 (10%) 1b. 27 (90%)	Warfarin is safe for mother with poor fetal outcome at dose >5 mg
Oran 2004[21]	Meta-analysis	81 pregnancies in 75 patients	1. LMWH throughout pregnancy 2. LMWH 1st trimester then VKA		Valve thrombosis—8.6% Thrombo-emboli—12%		Live births—87% (spontaneous abortion 7.4%, stillbirth 1.2%)	All thromboembolic events occurred in patients with MVR and LMWH throughout pregnancy without Xa levels
DeSanto 2005[34]	Single-centre experience	48 pregnancies in 37 patients	1a. VKA <5 mg throughout pregnancy 1b. VKA >5 mg throughout pregnancy 2. UFH throughout pregnancy		1a. 0% 1b. 0% 2. 100% (2/2)	Adverse fetal event 1a. 2/23 (8.6%) 1b. 17/21 (81%)		No maternal events if continue VKA throughout pregnancy. Adverse fetal outcome if dose >5 mg

Continued

Table 1 Continued

Author and year	Type of study	Number of pregnancies	Anticoagulation regimen	Maternal mortality	Thromboembolic risk	Fetal anomalies	Fetal wastage	Summary
James 2006[20]	Single-centre experience and medline search	76 pregnancies	LMWH throughout pregnancy	Mortality—4%	Valve thrombosis—22%	No anomalies	Spontaneous abortion —8	LMWH high risk thrombosis—no Xa levels monitored
Abildgaard 2009[26]	Historical cohort from Norway	12 pregnancies in 12 patients	LMWH throughout pregnancy		Valve thrombosis—1 pt (3.5%) Systemic embolism—1 (3.5%)		Live births—100%	Use Xa levels in 10/12 pregnancies—no thromboembolic risk if therapeutic
McLintock 2009[12]	Two-centre experience	47 pregnancies in 31 patients	1. VKA throughout pregnancy 2. LMWH 1st trimester then VKA 3. LMWH throughout pregnancy		Valve thrombosis—7 pt (15%) (5 with LMWH)		Live births 1. 75% 2/3. 96%	All valve thrombosis in patients with subtherapeutic Xa levels
Yinon 2009[25]	Single centre	23 pregnancies in 17 patients	LMWH throughout pregnancy	Mortality—4% due to valve thrombosis	Valve thrombosis—1 (4%) with therapeutic Xa level		Live births—19 (2 miscarriages and 2 intrauterine deaths)	Thrombosis may occur with therapeutic Xa levels and low-risk AVR
Quinn 2009[27]	Single centre	12 pregnancies in 11 patients	LMWH throughout pregnancy		Valve thrombosis—1 pt (8.3%)		Live births—11/12	Valve thrombosis in patient with subtherapeutic Xa levels
Saeed 2011[23]	Prospective	15 pregnancies in 15 patients	LMWH throughout pregnancy	None	None			No valve thrombosis with therapeutic Xa levels and 2nd generation prostheses
Sillesen 2011[24]	Historical cohort from Denmark	155 pregnancies in 79 patients	1. VKA throughout pregnancy 2. LMWH or UFH 1st trimester then VKA 3. LMWH or UFH throughout pregnancy	Mortality—3% (1 bleed and 1 CHF)	Thromboembolic event—4 pts (2.6%) (all on UFH)	Warfarin embryopathy 1. 2/25 (8%) 2. 0% 3. 0%	Miscarriage 34%, induced abortion 27%	Warfarin embryopathy only in patients on high dose (>10 mg). High thromboembolic rate 38% in heparin-treated patients
Suri 2011[35]	Single centre from India	70 pregnancies in 40 patients	1. VKA throughout pregnancy (45 pts) 2. Subq UFH 1st trimester then VKA (23 pts)	Mortality—2/70 (2.8%) due to valve thrombosis	Thrombotic complications 1. 3 (6.7%) 2. 1 (4.3%) Valve dysfunction 3. 4 (8.9%) 4. 3 (13%)	Warfarin embryopathy—none	Live births 1. 67% 2. 78%	Valve thrombosis occurred in two patients on VKA throughout Increased haemorrhagic complications in patients on heparin. No embryopathy noted
Bian 2011[36]	Single centre from China	58 pregnancies in 58 patients	VKA low-dose throughout pregnancy (INR 1.5–2.0)	None	Valve thrombosis 1/58 (1.7%)	No embryopathy —2/61—fetal malformation	Live births 56/58 (96%)—2 spontaneous abortion	Low-dose warfarin throughout (2.7 mg/day) safe and effective
Mazibuko 2012[37]	Single centre from South Africa	61 pregnancies in 61 patients	UFH during 1st trimester treatment of choice but 78% presented at 2nd trimester on VKA	Mortality—1/61 (1.6%) due to intracerebral bleed	Valve Thrombosis 4/61 (6.6%)—2 stopped VKA prior to pregnancy—all had dose >5 mg.	Warfarin embryopathy—4 (all with dose >5 mg)	Live births 41/61 (67%) (6 still births and 12 miscarriages)	High rate maternal complications if warfarin dose >5 mg. 0/29 pts on VKA <5 mg had no embryopathy—all four with embryopathy had dose >5 mg
Basude 2012[19]	Single centre	32 pregnancies in 15 patients	1. VKA throughout pregnancy (22) 2. LMWH 1st trimester then VKA (6) 3. LMWH throughout pregnancy (4)	Mortality 1. 0 2. 0 3. 1/4 (25%)—intracerebral haemorrhage	Valve thrombosis 1. 0 2. 1/6 (16%) 3. 2/4 (50%)		Live births 1. 5/22 (23%) 2. 3/6 (50%) 3. 3/4 (75%)	High rate of serious maternal adverse events in LMWH group, using Xa levels. High fetal loss on warfarin

AVR, aortic valve prosthesis; INR, international normalised ratio; LMWH, low-molecular-weight heparin; mos, months; MVR, mitral valve prosthesis; pts, patients; subq, subcutaneous; UFH, unfractionated heparin; VKA, vitamin K antagonists.

mechanical prosthesis if the dose of warfarin is >5 mg/day to achieve a therapeutic INR (*Level of Evidence: B*).

6. Dose-adjusted continuous intravenous UFH (with an aPTT at least two times control) during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is >5 mg/day to achieve a therapeutic INR (*Level of Evidence: B*).

Class IIb

7. Dose-adjusted LMWH at least two times per day (with a target anti-Xa level of 0.8–1.2 U/mL, 4–6 h postdose) during the first trimester may be reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is 5 mg/day or less to achieve a therapeutic INR (*Level of Evidence: B*).
8. Dose-adjusted continuous infusion of UFH (with aPTT at least two times control) during the first trimester may be reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is 5 mg/day or less to achieve a therapeutic INR (*Level of Evidence: B*).

Class III

9. LMWH should not be administered to pregnant patients with mechanical prostheses unless anti-Xa levels are monitored 4–6 h after administration (*Level of Evidence: B*).

CLINICAL IMPLICATIONS AND REMAINING QUESTIONS

It is clear that (1) there are limited data regarding anticoagulation during pregnancy and (2) there is no perfect anticoagulation regimen for the pregnant woman with a mechanical prosthesis. The optimal care for a young woman with valvular heart disease requires pre-pregnancy counselling. Decisions regarding the choice of valve prosthesis should be made before a valve operation is performed in women of childbearing age. Implantation of a tissue valve versus a mechanical valve will pose the lowest risk to both mother and fetus during and after pregnancy. Implicit in this decision, however, is the recognition that a valve re-replacement will be necessary in the future and thus the risks of a second operation at the available institution must be taken into consideration and discussed fully with the patient and partner. If possible, the ideal intervention for valve disease prior to pregnancy would be valve repair, which may necessitate referring a patient to valve centres of excellence.[13]

In the context of a mechanical prosthesis, the selection of an anticoagulation regimen must be individualised and requires long and detailed discussions with the patient and partner by someone with expertise in the management of pregnant patients with valve disease. Ultimately, this should be a shared decision-making process so that the final decision is based upon the patient's own desires and preferences after a comprehensive understanding of the pros and cons of each approach. The safety of the mother should be weighed against the desire for an optimal fetal outcome, which is an extremely difficult decision. This shared decision making requires the caregiver to have a complete understanding of the current data and its limitations.

The current guideline recommendations were written in terms of generalisation for all mechanical prostheses. However, it is well recognised that there are subgroups of patients with mechanical prostheses who are at highest risk of thrombosis, particularly the older generation tilting disc prostheses in the mitral position. The socioeconomic aspects of each approach must also be considered, particularly in developing countries and indigent populations where it may be difficult to accomplish meticulous follow-up.

Questions still remain regarding the ideal anticoagulation regimen for a woman with a mechanical prosthesis during pregnancy. The use of warfarin during the second and third trimester is not a universally accepted approach because of the increased risk of fetal haemorrhage and fetal loss when using warfarin, as well as the risk of under-anticoagulation and over-anticoagulation during the switchover period. Other questions include the methodology for giving and monitoring LMWH—for example, the optimal peak factor Xa level required for dose adjustment, the appropriate frequency of monitoring and dosing, and the utility of using trough as well as peak levels of factor Xa, since subtherapeutic pre-dose anti-Xa levels frequently coexist with therapeutic peak anti-Xa levels. The additive benefit of measuring other factors that LMWH impacts, such as factor II levels, has yet to be explored. The exact 'cut-off' dosage of VKA balancing the risk of maternal thrombosis versus fetal outcome needs to be further evaluated, and the addition of genomic information regarding metabolism of VKA may be of incremental benefit to dosing and complications. The additive use of low-dose (75–100 mg) aspirin appears to be helpful but unproven, recommended by the AHA/ACC guidelines but not the ESC guidelines.

The safest approach to restarting anticoagulation following delivery remains to be determined, which is when the mother is at highest risk of postpartum haemorrhage. Some have advocated delaying the introduction of VKA for at least 48 h postdelivery to avoid over-anticoagulation. However, the greatest risk of postpartum haemorrhage occurs from the administration of heparin, which is used as a bridge until there is a therapeutic INR.

There is a growing body of knowledge involving the care of these high-risk patients, with the formation of a large international registry and networks of specialised care centres. Hopefully, these will provide further information regarding the safest and most effective anticoagulation for these patients in the future. For optimal outcomes, these very high-risk patients should be managed in centres that provide a full multidisciplinary approach involving cardiologists with an expertise in management of pregnant patients, high-risk obstetricians, anaesthesiologists and cardiovascular surgeons.

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