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Anticoagulation Management for Pregnant Women with Mechanical Heart Valves

Obstetric Consensus Conference

Timothy Mitchell, MD
Zachary Steinberg, MD
Karen Stout, MD
Edith Cheng, MD, MS
Eric Krieger, MD
Thomas Easterling, MD

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TABLE OF CONTENTS

	<u>PAGE</u>
INTRODUCTION	1
PRECONCEPTION	2
MANAGEMENT DURING PREGNANCY	4
POSTPARTUM	7
ANTICOAGULATION RESOURCES	7
REFERENCES	8

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INTRODUCTION

Pregnancy is a hypercoagulable state and associated with an increase in venous and arterial thromboembolism. As a result, pregnant women with mechanical heart valves are at high risk for thromboembolic complications (1, 2). Vitamin K antagonists (VKAs), the anticoagulant of choice for the prevention of mechanical valve dysfunction and thromboembolism, is associated with fetal teratogenicity. Therefore, women with mechanical heart valves are an especially vulnerable population with imperfect choices for anticoagulation, which require balancing maternal and fetal risks.

Warfarin continued throughout pregnancy offers the best thromboembolic protection to the mother, but carries a higher risk of fetal loss with well recognized teratogenic effects during early gestation (1). Due to these fetal risks some advocate treating women with low molecular weight heparin (LMWH) during pregnancy (3). Women treated with LMWH experience a reduced risk of warfarin embryopathy and fetal loss, but an increased risk of thromboembolic complications compared to the use of warfarin, even when anti-Xa levels are used to guide dosing (4).

Current American College of Cardiology/American Heart Association (ACC/AHA) valvular heart disease guidelines support the use of warfarin at doses ≤ 5 mg/day throughout pregnancy. It is thought that at these lower doses, the risk of fetal toxicity is decreased as compared to higher warfarin doses (5). When the dose to achieve the target INR exceeds 5 mg, substitution with LMWH or continuous unfractionated heparin (UFH) during the first trimester, the critical phase of organogenesis, is recommended. These guidelines advocate treatment with VKA after the 1st trimester for reduction in maternal risk but recognize treatment with LMWH as a second option based on fetal considerations.

The 2012 Ninth American College of Chest Physicians (ACCP) guidelines vary slightly from the ACC/AHA, in that they offer every 12-hour adjusted-dose LMWH or UFH therapy throughout pregnancy as an option in addition to the recommendations found in the ACC/AHA guidelines (2). The Chest guidelines emphasize consideration of additional thromboembolic risk factors (valve type, position, history of thromboembolism) and patient choice in anticoagulation management during pregnancy.

Elkayam (3) has reported considerable experience with use of LMWH. He emphasizes that thromboembolic events are often associated with “sub therapeutic anticoagulation secondary to inappropriate dosing, poor monitoring, or poor patient compliance.” He reports that the use of a dosing protocol based on peak effect will frequently result in sub therapeutic trough effect and the appearance of “adequate dosing” when in fact trough effect is sub therapeutic.

Steinberg et al (6) have reported a meta-analysis of outcomes of anti-coagulation in pregnant women with mechanical heart valves. To provide clinical relevance, reports with ball-in-cage valves and fixed doses of UFH or LMWH were not included. The lowest thrombotic maternal risk profile was associated with VKA though out pregnancy (5%) compared to LMWH, (16%), and LMWH and VKA (16%). The lowest fetal risk was associated with LMWH (13%) compared to VKA (39%) and LMWH and VKA (23%).

Direct-acting oral anticoagulants, (DOACs), have not been shown effective in patients with mechanical valves and are not to be used.

All major guidelines are based on varying levels of evidence in the literature. Current evidence is limited by inherent biases of single-center case series, small sample sizes, and lack of control arms. Dose adjustments of LMWH have been inconsistent and often based on peak effect with insufficient concern for trough effect. The purpose of this consensus statement is to assist providers in preconception and early pregnancy counseling, so that our message is consistent across disciplines and to help the patient make an informed decision about anticoagulation choice over the course of her pregnancy.

PRECONCEPTION

The preconception period offers an important opportunity for initial discussions regarding reproductive plans and risks associated with carrying a pregnancy in the setting of a mechanical heart valve. Initial counseling should be with the patient's cardiologist in preparation for valve replacement. The decision for type of valve replacement (mechanical vs. bioprosthetic) is complex and based on individual circumstances. The patient, in consultation with the cardiologist and cardiothoracic surgeon, should weigh the risks and benefits of each option prior to replacement. Since bioprosthetic valves do not require life-long anticoagulation and mechanical heart valves do, these decisions impact the patient's reproductive management.

- Hemodynamically stable women with bioprosthetic valves are considered to be low to moderate risk with a mild increase risk in maternal mortality and moderate increase in morbidity (7). Bioprosthetic valves have a limited life span. Women of reproductive age would often need at least one additional valve surgery during their lifetime.
- Pregnant women with mechanical heart valves are at significantly increased risk of mortality and morbidity due to thrombotic profile associated with these valves. The longevity of mechanical valves represents a significant advantage over the lifetime of the patient.
- The potential impact of Transcatheter Aortic Valve Replacement (TAVR) after a bioprosthetic valve replacement may, in time, impact this decision making.

ACCP & ACC/AHA guidelines recommend life-long anticoagulation with a VKA in patients with mechanical heart valves. Multiple trials have demonstrated the clear effectiveness at reducing thrombotic risks in patients with mechanical heart valves (8, 9).

Choice of anticoagulation strategies during pregnancy involve an inherent conflict between maternal and fetal well-being. There is no ideal anticoagulant for pregnant patients with a mechanical heart valve. VKAs have a preferable maternal anticoagulation profile, but cross the placenta and pose a risk to the fetus. LMWH does not cross the placenta, but treatment is associated with increased maternal risk for serious complications. While some risk is likely mitigated by fastidious care and achieving appropriate trough effect, fundamental maternal risk remains elevated above management with VKA. Noncompliance probably elevates the risk associated with treatment with LMWH compared to VKA due to the shorter duration of action of LMWH compared to VKA. VKA dose likely impacts fetal survival and teratogenicity.

Counseling patients with mechanical heart valves should highlight the risks to both the mother and fetus so that the patient can weigh the risks that the pregnancy poses to her and her future child's health. Data that has been used to estimate risk in the literature is based from imperfect studies that limit our ability to quote the true risks

of each anticoagulation regimen. Below are points to raise with patients when discussing how to move forward with anticoagulation in the setting of a mechanical heart valve.

Key counseling points for preconception:

- Coordinated preconceptional counseling should occur with Cardiology and Maternal-Fetal Medicine.
- Care should be concentrated in a team experienced with management of anticoagulation and care of valve disease in pregnancy.
- Bioprosthetic valves are preferable in pregnancy.
- Mortality rates for women with mechanical valves may be increased, regardless of whether VKA or LMWH is used during pregnancy. The potential impact of noncompliance cannot be overestimated.
- The risk of thromboembolism and valve failure is increased in the setting of warfarin or LMWH use during pregnancy. The potential impact of noncompliance cannot be overestimated.
- Treatment with a VKA is associated with the lowest rate of maternal thromboembolism and valve dysfunction.

Treatment with VKA is associated with higher risk of pregnancy loss. This risk is increased in women who need >5mg/day of warfarin.

Warfarin crosses the placenta and leads to anticoagulation of the fetus. Therefore, urgent delivery in the setting of warfarin use requires delivery by cesarean section due to the risk of bleeding in the anticoagulated fetus.

- LMWH does not cross the placenta and does not anticoagulate the fetus or increase the risk of birth defects.
- Anticoagulation with LMWH is not as effective as warfarin, placing the mother at an increased risk of maternal mortality, valve failure and thromboembolic complications.
- Data on use of LMWH is limited to experiences with conservative dosing strategies based on peak, rather than trough, anti-Xa goals.
- Anticoagulation with LMWH in the setting of a mechanical heart valve requires frequent evaluation of mid-interval and trough anti-Xa levels and appropriate dose adjustment.
- Risk of thromboembolism and valve failure are increased during the first trimester and during times of transition between anticoagulation regimens.
- Not all insurers cover the cost of LMWH fully, so some patients may not be able to afford it.
- Some patients, based on their individual circumstances, may benefit from hospitalization during transitions.
- A specific plan of anticoagulation in very early pregnancy should be established prior to pregnancy.
 - Establish anticoagulation strategy
 - Train for injections if planning to use LMWH
 - Give patient a prescription for LMWH, so she has it on hand to start with a positive home pregnancy test (to avoid pharmacy delays once pregnant)

MANAGEMENT DURING PREGNANCY

There are 4 distinct management strategies for VKA and heparin use during pregnancy (Table 1). Considerations for each management strategy are discussed below. Table 2 compares the two most commonly used management strategies.

Table 1. Anticoagulation Strategies

Anticoagulant(s)	Strategy	Monitoring
A) Vitamin K Antagonist (VKA)*	No change in anticoagulation strategy during pregnancy regardless of VKA dosing.	INR – anticipate possible need to increase dose (10)
B) Low-Dose VKA*	No change in anticoagulation strategy as long as VKA daily dose not >5mg/day.	INR – anticipate possible need to increase dose, potentially beyond 5mg/day (10)
C) Low Molecular Weight Heparin (LMWH)*	Transition to LMWH as soon as + pregnancy test	Anti-Xa levels –trough, mid-interval
D) LMWH + VKA*	Transition to LMWH as soon as + pregnancy test. Transition back to VKA after 13 weeks gestation.	Anti-Xa levels while on LMWH – trough, mid-interval, INR when using VKA

* Transition to IV or Subcutaneous UFH at 36 weeks in preparation for delivery

General Approaches to Implement Strategies A-D

A) VKA to 36 weeks: In limited studies of a VKA only regimen, the range of maternal mortality has been shown to be between 0-4.3%, the range of valve thrombosis 4-10.5% and thrombotic events 2.2-6%. A recent meta-analysis stated an overall maternal composite risk (maternal death, prosthetic valve failures, or thromboembolism) of 5% in women treated with VKA throughout (6). The same meta-analysis demonstrated 39% of pregnancies treated with VKA throughout will have an adverse fetal outcome (spontaneous abortions, fetal death, congenital defects) (6). The “window of VKA (warfarin) embryopathy” is greatest when exposure occurs between 6-12 weeks and at high therapeutic doses. However, congenital anomalies have been reported at low dose VKA (< 5 mg) (11-13).

- INR goal remains the same during pregnancy as outside of pregnancy
- Warfarin dose to be managed by anticoagulation clinic.
- Recommend ultrasound at 11-13 weeks for NT and early anatomy US at 16-18 weeks in addition to scan at 20 weeks.
- Transition to UFH at 36 weeks
- The time frame for correction of fetal anticoagulation by VKA is unknown but, based on general principles of fetal and neonatal drug clearance, it should be anticipated to be substantially longer than the mother’s (the adult terminal elimination half-life is about 1 week).

B) Low-Dose VKA to 36 weeks: When doses of VKA remain <5mg/day maternal mortality rates were shown to be low (0-1.3%). Prosthetic valve thrombosis ranged from 0.3-2% and total thromboembolic events were shown to be 1.1-3.6%. Fetal loss, spontaneous abortions and fetal embryopathy were shown to be 8.1%, 7.3%, and 0.6%, for a combined adverse fetal outcome rate of 16%. (10) Women initially at <5mg/day may require a dose increase to >5mg/day. (10)

- Same regimen as detailed in the VKA throughout protocol.

C) LMWH + VKA to 36 weeks: The composite risk of maternal death, prosthetic valve failure or thromboembolism has been demonstrated to be 15.9%. (6) The composite fetal risk has been demonstrated to be 16.4% (6).

- With positive pregnancy test, patient should stop VKA and start LMWH at 1mg/kg q12hrs.(11)
- Add/continue Low dose ASA
- Obtain trough anti-Xa level in 2-3 days adjusting dose as INR falls*.
- Goal trough: 0.6-0.8.
- If trough is within goal, obtain mid-interval anti-Xa (goal 0.8-1.2) within 48 hours. (14)
- Check trough and mid-interval regularly through completion of 13 weeks gestation
- At 14 weeks transition back to VKA through coordination with the anticoagulation clinic.
- Transition to UFH at 36 weeks.

* Initially titrating to an appropriate mid-interval anti-Xa is also a reasonable approach

D) LMWH to 36 weeks. Maternal mortality has been shown to range from 0-9% in women treated with LMWH throughout the pregnancy. Valve thrombosis rates range from 0-1.58% and 0-5.2% for thrombotic events. The overall composite maternal risk has been shown to be 15.5% (6). In the meta-analysis of Steinburg et al, this risk is comparable to the LMWH + VKA regimen, (15.9%). The composite fetal risk has been shown to be 13.9% (6).

- With positive pregnancy test, patient should stop VKA and start LMWH at 1mg/kg q12hrs.
- Low dose ASA
- Obtain trough anti-Xa level in 2-3 days adjusting dose at INR falls.*
- Goal trough: 0.6-0.8.
- If trough is within goal, obtain mid-interval anti-Xa (goal 0.8-1.2) within 48 hours.
- Check trough and mid-interval regularly through completion of 13 weeks gestation.
- If trough remains stable through 13 weeks decrease testing to every two weeks.
 - If dose of LMWH is increased to meet goal troughs, but mid-interval becomes supratherapeutic consider changing dosing interval to q8hrs (divide total daily dose by 3).
- Transition to UFH at 36 weeks
- * Initially titrating to an appropriate mid-interval anti-Xa is also a reasonable approach

Some patients who are anticoagulated with VKA will need an urgent delivery. Fetal anticoagulation with VKA places the fetus and neonate at risk of intracranial bleeding (17), particularly in the setting of a vaginal delivery. We recommend a cesarean delivery in patients who need to be delivered while anticoagulated with a VKA. The ACCP, AHA, and the ACC have developed evidence-based medicine guidelines for the reversal of warfarin with FFP and/or Vitamin K (18). Management options should be tailored to the specific clinical scenario. Treatment options include:

- Fresh Frozen Plasma
 - Volume 200-250cc per unit
 - Replacement need depends on INR. 2-4 units (or more) may be needed to reverse VKA.
 - Most pregnant women can tolerate volume load in context of anticipated blood loss associated with delivery
- 4-Factor Prothrombin Complex Concentrates
 - Volume 10-15cc
 - Replacement need depends on INR.
- Mid-line vertical skin incision to reduce risk of subfacial hematoma.
- Electrocautery used to aid dissection.
- Anticipate the need to re-dose correction after uterine closure based on intraoperative INR.

Fetal anticoagulation will not be impacted by maternal correction. The neonatal team should be informed of the anticipated status. The time course to fetal correction is unknown and likely to be substantially longer than spontaneous correction in the mother.

Table 2. Comparison of 2 Most Common Strategies During Pregnancy

<p style="text-align: center;"><u>Preconception VKA →</u> <u>LMWH in 1st trimester with + uPregTest →</u> <u>Return to VKA 2nd and 3rd trimesters →</u> <u>UFH at 36 weeks</u></p>	<p style="text-align: center;"><u>Preconception VKA →</u> <u>LMWH in 1st trimester with + uPregTest →</u> <u>Continue LMWH in 2nd and 3rd trimesters →</u> <u>UFH at 36 weeks</u></p>
<p><u>Benefits</u></p> <ul style="list-style-type: none"> • Lower maternal mortality rate. (15,16) • Lower thromboembolic complication rate. (6,15,16) • Oral medication as opposed to twice daily injections for a majority of the pregnancy. • If VKA dose is <5mg/daily, option of not changing to LMWH in first trimester. 	<p><u>Benefits</u></p> <ul style="list-style-type: none"> • LMWH does not cause birth defects. • Limited transition periods. • Lower miscarriage and fetal loss rate. (6,15)
<p><u>Risks/Disadvantages</u></p> <ul style="list-style-type: none"> • Risk of thromboembolic complications during multiple transition periods • Anticoagulation of the fetus creates risk of fetal intracranial hemorrhage. • Need for cesarean delivery if delivery is indicated in the setting of VKA anticoagulation (risk of fetal intracranial hemorrhage during labor with anticoagulated fetus) • Increased risk of late fetal death • Only 60% chance of having an uncomplicated pregnancy (15) • Low risk for birth defects (<0.6%) even with low 1st trimester dose 	<p><u>Risks/Disadvantages</u></p> <ul style="list-style-type: none"> • Increased risk of maternal thromboembolic complication. (15,16) • Increased risk of maternal mortality. • Twice daily injections needed throughout pregnancy. • Need for frequent monitoring throughout pregnancy.

POSTPARTUM

Patients are likely to be at their highest risk for thrombosis during the postpartum period.

IV-UFH should be initiated in the immediate postpartum period. Timing of IV-UFH should be based on post-op assessment of bleeding risk. For example, after an uncomplicated vaginal delivery IV UFH might be started at 6-8 hours after delivery. After a complicated cesarean section treatment might be delayed for 24-36 hours. In either case, a no bolus protocol should be used. The aPTT goal should be 90-100 sec. Continue IV UFH, with appropriate downward titration), until INR is greater than the lower limit of the therapeutic range. In some patients at low risk for bleeding, a LMWH bridge could be considered to shorten hospital stay.

Vigorous efforts should be made to insure postpartum uterine tone.

VKA therapy should be initiated in the immediate postpartum period, 12-24 hours after delivery at 1 to 1.5 times usual maintenance dose. Timing should be based on post-op assessment of bleeding risk in context of the slow onset of action of VKA

Patients should be informed that breastfeeding is safe while on VKA.

UNIVERSITY OF WASHINGTON ANTICOAGULATION RESOURCES

UW IV Heparin Protocols

Please refer to the UW Anticoagulation Website for further details.

<https://depts.washington.edu/anticoag/home/content/heparin-infusion-guidelines>

<https://depts.washington.edu/anticoag/home/content/heparin-infusion-algorithms>

<https://depts.washington.edu/anticoag/home/sites/default/files/UW%20Medicine%20Heparin%20Infusion%20Algorithms%202017.pdf>

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