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Management of Anticoagulation in Pregnant Women With Mechanical Heart Valves

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Abstract

Importance: Mechanical heart valves (MHVs) pose significant thrombogenic risks to pregnant women and their fetuses, yet the choice of anticoagulation in this clinical setting remains unclear. Various therapeutic strategies carry distinct risk profiles that must be considered when making the decision about optimal anticoagulation.

Objective: We sought to review existing data and offer recommendations for the anticoagulation of pregnant women with MHVs, as well as management of anticoagulation in the peripartum period.

Evidence Acquisition: We performed a literature review of studies examining outcomes in pregnant women receiving systemic anticoagulation for mechanical valves, and also reviewed data on the safety profiles of various anticoagulant strategies in the setting of pregnancy.

Results: Warfarin has been shown to increase rates of embryopathy and fetal demise, although it has traditionally been the favored anticoagulant in this setting. Low-molecular-weight heparin,

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Off-Label Usage: Dr. Thomas G. DeLoughery has disclosed that use of enoxaparin and heparin in pregnancy has not been approved by the U.S. Food and Drug Administration as discussed in this article. Please consult the product's labeling for approved information.

This manuscript has not been presented or submitted elsewhere.

when dosed appropriately with close therapeutic monitoring, has been shown to be safe for both mother and fetus.

Conclusions and Relevance: We favor the use of low-molecular-weight heparin with appropriate dosing and monitoring for the anticoagulation of pregnant women with MHVs. Data suggest that this approach minimizes the thrombotic risk associated with the valve while also providing safe and effective anticoagulation that can be easily managed in the peripartum period.

Target Audience: Obstetricians and gynecologists, family physicians.

Learning Objectives: After completing this activity, the learner should be better able to: describe the clinical considerations in choosing an anticoagulation strategy for a pregnant patient with an MHV; evaluate the existing data about the safety profile of various anticoagulation strategies and the potential benefits and risks of each approach to the mother and fetus; and discuss one recommended approach to management of mechanical valves in the pregnant patient and assess the clinical nuances associated with each individual patient's decision.

Mechanical heart valves (MHVs) increase the risk of thromboembolism, and systemic anticoagulation is required to prevent adverse outcomes including valve thrombosis, stroke, and death. In pregnancy, the hemostatic equilibrium is further disrupted by physiologic changes including production of procoagulant serum factors, acquired protein C resistance, reduced protein S levels, and decreased fibrinolysis.[1] The choice of optimal anticoagulation in pregnant women with mechanical valves, however, remains a source of controversy.

All major guidelines currently recommend vitamin K antagonists (VKAs), with the addition of low-dose aspirin in those with low bleeding risk, as the primary prophylactic strategy in the general patient population with MHVs.[1–3] However, warfarin, the dominant VKA in clinical use, carries significant risks of warfarin-induced embryopathy and fetal demise.[4] These adverse fetal outcomes must be weighed against limited data suggesting a potentially increased incidence of maternal thromboembolic events with heparin-based anticoagulation.[5] Direct oral anticoagulants are currently contraindicated in patients with MHVs in light of a prospective trial showing increased rates of both thromboembolic and bleeding complications.[5] Although low-molecular-weight heparin has proven to be safe for the fetus in pregnancy, small studies of unmonitored therapy have questioned whether it is as effective as warfarin for stroke prophylaxis in patients with MHVs.[2]

To date, there is no clear consensus in the ideal anticoagulation strategy in pregnant women with MHVs as evidenced by variability among different professional groups' recommendations (Table 1). There are various proposed protocols for anticoagulation of MHVs in pregnant women using warfarin, low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), or a combination of medications, typically favoring the use of heparin products for the first trimester in order to mitigate fetal risks.[5,7] Unfortunately, none of these protocols have been prospectively trialed in a head-to-head comparison study, and there is a high degree of variability in the choice of anticoagulation in this patient population. In this review, we will outline the current understanding of the risks and benefits of each approach, with the hope of empowering women to make informed decisions in this complex clinical setting.

EPIDEMIOLOGY

Mechanical heart valves are rare in women of childbearing age. Data from a large national health survey from 1988 reported a prevalence of valve prostheses in the United States ranging from 0.2 per 1000 in people aged 44 years or younger to approximately 5.3 per 1000 in people aged 75 years or older.[8] Approximately two-thirds of these valves were mechanical.[7] At the time of the study, the most common reason for prosthetic valve implantation in younger patients was rheumatic heart disease. Although the incidence of rheumatic heart disease has been declining for decades, advances in cardiovascular medicine allow more patients with congenital heart disease to survive into adulthood, resulting in a growing population of young adults with prosthetic heart valves, the majority of whom will have mechanical valves requiring long-term anticoagulation.[8,9] As outlined in detail later in this review, major society guidelines currently recommend consideration of mechanical over bioprosthetic heart valves in younger patients, given their predicted longevity and decreased need for surgical replacement.[10]

ANTICOAGULATION OPTIONS

The various anticoagulation strategies proposed by professional societies each carry their own risks and benefits (Table 2). Potential protocols include LMWH throughout all 3 trimesters (LMWH-LMWH-LMWH), warfarin throughout (War-War-War), LMWH in the first trimester in an attempt to mitigate fetal risks, followed by warfarin (LMWH-War-War), or low-dose warfarin throughout in women who maintain therapeutic drug levels on doses of warfarin less than 5 mg/d (LD-War-LD-War-LD-War). Unfractionated heparin has many limitations including the need for multiple injections or continuous intravenous therapy, risk of osteoporosis, and delayed elimination in pregnancy. Our practice has been to avoid its use in pregnancy, and as such, we have excluded it from this review. In the following section, we outline the current data on maternal and fetal risk with each approach.

Warfarin

Warfarin has the strongest evidence for stroke prophylaxis in MHVs. Consensus guidelines consistently recommend warfarin for anticoagulation of MHVs in nonpregnant patients.[2–4] Although these guidelines are designed to preserve maternal health, they do not account for the significant risks to the fetus with warfarin exposure during pregnancy. Rates of embryopathy and fetal demise with warfarin exposure during pregnancy are significant.

Efficacy of Warfarin—A meta-analysis of 13,088 patients with MHVs reported a rate of embolism of 8.6 per 100 patient years without systemic anticoagulation, which is reduced to 1.8 with warfarin.[11] Compared with aortic valves, mitral valves and combined aortic/mitral valves have increased rates of thromboembolism.[11] Another major meta-analysis of pregnant women with mechanical valves found that VKA treatment was associated with the lowest rate of adverse maternal outcomes compared with LMWH, LMWH and VKA, and UFH and VKA.[1] The addition of aspirin to warfarin has been shown to significantly decrease the rate of stroke and improve mortality,[12] and this has led to the majority of professional guidelines recommending aspirin in addition to oral anticoagulation therapy in patients with

low bleeding risk.[6] Our practice is to add low-dose aspirin to systemic anticoagulation in pregnant patients with low bleeding risk, as well.

Risks of Warfarin

Fetal Demise.: Although warfarin has the most data in preventing thromboembolic events in patients with MHVs, there are numerous adverse effects in the fetus that must be taken into account. Warfarin is a small molecular weight compound that readily crosses the placenta.[13] Due to reduced fetal hepatic synthetic function, the levels of vitamin K–dependent clotting factors in fetal circulation are low. Consequently, warfarin's effects on fetal blood are amplified and result in microhemorrhages that can cause fetal demise and characteristic embryopathies.[13]

A recent meta-analysis including 2113 pregnancies and 1538 women found the rate of fetal demise was 33% in women who took warfarin throughout their pregnancies.[7] Furthermore, subgroup analysis based on warfarin dosing (high dose >5 mg/d versus low-dose warfarin ≤5 mg/d) revealed the rate of fetal demise rose to 63% in the high-dose warfarin (HDW) group, compared with 19% in the low-dose group. Given the magnitude of risk of fetal demise with warfarin, it is understandable that many women seek alternatives.[7]

Warfarin Embryopathy.: In addition to fetal demise, a significant number of fetuses exposed to warfarin during gestation develop a classic embryopathy characterized by limb and nasal hypoplasia, congenital heart defects, stippled epiphyses, and growth retardation. There are also various neurological defects associated with VKA exposure including microcephaly, mental retardation, hypotonia, corpus callosum agenesis, and optic nerve atrophy.[7]

The true incidence of fetal embryopathy is disputed and appears to be dependent on both dose and timing of gestational exposure. In a review of 418 pregnancies anticoagulated with warfarin, one sixth of pregnancies resulted in congenital abnormalities, one sixth in spontaneous abortions or stillbirths, and two-thirds in normal infants.[13] Other studies report embryopathy rates ranging from as low as 0.45%[7] to as high as 29%.[14] One prospective study of 72 pregnancies exposed to warfarin during different periods of gestation found the incidence of embryopathy to be 29% in the group exposed to warfarin throughout pregnancy, 25% in the group exposed to warfarin during the first 6 weeks of pregnancy, and 0% in the group exposed to warfarin after the 12th week of pregnancy.[14] This study suggests that fetal warfarin exposure is most damaging during the early stages of development and provides rationale for the combination regimen (LMWH-War-War) discussed previously.

Low-Dose Warfarin

The therapeutic dose of warfarin varies significantly between patients due to differences in a variety of factors including coadministered medications, diet, and genotype.[15] Some patients require relatively low-doses of warfarin (≤5 mg/d) to achieve therapeutic anticoagulation. The safety profile of low-dose warfarin in pregnancy has been investigated in several studies.

As mentioned previously, a recent large meta-analysis on the safety and efficacy of various anticoagulation strategies in pregnant women with MHVs found that the risks

of warfarin-associated fetal demise and embryopathy were markedly higher in the group on HDW compared with LDW. The rates of fetal demise were 63.92% in the high-dose group compared with 19.23% in the low-dose group (risk ratio, 7.4; confidence interval, 4.6–11.9).[7] In addition, the rates of embryopathy were significantly higher in the HDW group compared with the LDW group (8.25% vs 0.45%; $P < 0.001$).[7] The rates of major thromboembolic events and maternal hemorrhagic events were not statistically significantly different. These data suggest that the toxic effects of VKAs on the fetus are significantly reduced—but not fully mitigated—at warfarin doses 5 mg/d or less.[7,16] This strategy, however, is not an option for many women. In one series, nearly 40% of women required doses higher than 5 mg/d to remain therapeutic, making low-dose warfarin an unsafe anticoagulation strategy.[17]

Low-Molecular-Weight Heparin

Low-molecular-weight heparin is the first-line anticoagulant for pregnant women without mechanical valves who require anticoagulation due to lower reported rates of bleeding, predictable pharmacokinetics in pregnancy, and significantly lower risks of osteoporosis and heparin-induced thrombocytopenia (HIT) compared with UFH.[6] Unlike warfarin, LMWH does not cross the placenta and has not been shown to increase the risk of congenital defects in large observational studies of pregnant women.[18,19]

Despite the excellent fetal safety profile of LMWH compared with warfarin, there is significant controversy surrounding its efficacy in patients with mechanical valves. In 2002, the Food and Drug Administration issued an alert for enoxaparin cautioning that the drug may lead to an increased risk of thrombosis in pregnant women with MHVs.[20,21] This warning was based on a study of 7 pregnant women on therapeutic enoxaparin for MHVs, 2 of whom developed valve thrombosis resulting in maternal and fetal death.

Despite this early warning, many professional societies have since endorsed LMWH as a treatment option for pregnant women with MHVs. The 2012 American College of Clinical Pharmacy (ACCP) guidelines recommend consideration of dose-adjusted LMWH throughout pregnancy for women with lower-risk MHVs,[6] as do the 2014 American Heart Association (AHA) guidelines.[3] We believe the data leading to this Food and Drug Administration warning were flawed given the small number of patients included and the lack of therapeutic monitoring. Although subsequent data are also lacking, dose-adjusted LMWH seems to be an acceptable protocol in pregnant women with mechanical valves and leads to significantly improved fetal outcomes compared with warfarin.[6]

Efficacy of LMWH—Although there are no prospective trials comparing the efficacy of LMWH, UFH, and warfarin in pregnant women with MHVs, some data can be gleaned from retrospective series.

One systematic review of 81 pregnant women with MHVs managed with LMWH reported thromboembolic complications in 12.3% of study participants.[22] However, a majority of these patients were undergoing unmonitored therapy, and when a subgroup analysis of the women who received therapeutic doses of LMWH was performed, rates of thromboembolism dropped to 2.7%.[22]

A second case series of 76 pregnancies found the rate of thrombosis with LMWH to be as high as 22%. The validity of this evidence is questionable given the high risk of bias associated with the large number of single case reports that were included.[23] Another study suggested that many thrombotic events on LMWH were related to subtherapeutic doses of LMWH, suboptimal anti-Xa levels, and poor patient compliance, suggesting optimal compliance and close monitoring could lead to more acceptable outcomes.[24] High-quality studies of dose-monitored LMWH are needed to determine the true efficacy of LMWH in the setting of MHVs.

Risks of LMWH—More recently, a systematic review and meta-analysis of 51 studies including 2113 pregnancies attempted to compare outcomes in women with MHVs managed with LMWH compared with a combination regimen of LMWH-War-War. Patients with inadequate LMWH dosing and those without monitoring were excluded from the study. In this population, the analysis found lower rates of fetal complications with LMWH versus LMWH-War-War.[6] Compared with the LMWH-War-War group, rates of fetal demise (22.65% vs 12.24%) and spontaneous abortion (12.73% vs 5.10%) were significantly lower in the LMWH group. Maternal outcomes, including major thromboembolic events (7.42% vs 4.42%) and antenatal bleeding (0.61% vs 4.08%), were similar. The authors concluded that LMWH throughout pregnancy may be a reasonable strategy for women with lower-risk mechanical valves who prefer to avoid VKAs.[6]

Other Risks Associated With Heparin Products

Osteoporosis.: Transient osteoporosis is an uncommon complication of pregnancy.[25] It is worth mentioning that UFH appears to increase the risk of osteoporosis significantly. A small prospective study of 14 pregnant women receiving UFH suggests approximately a third of them will lose 10% or greater femur bone mineral density from their prepregnancy baseline.[26] As many as 3% of pregnant women receiving long-term UFH develop vertebral compression fractures.[27] Fortunately, LMWH does not carry the same osteoporotic risk, with several studies suggesting no effect on bone mineral density in women who received LMWH during pregnancy.[28,29]

Heparin-Induced Thrombocytopenia.: Heparin-induced thrombocytopenia is extremely uncommon during pregnancy, with some large retrospective series failing to identify a single case.[30] A systematic review of the literature identified 12 cases of HIT during pregnancy, with a wide variety of nonheparin anticoagulants being reported as therapy including argatroban, danaparoid, fondaparinux, and lepirudin.[31] If HIT does develop, UFH and LMWH must be stopped immediately and replaced with an alternative, nonheparin anticoagulant. Unopposed warfarin can provoke severe thrombosis in the acute phase of HIT and is therefore contraindicated.[32] There is no consensus on the optimal nonheparin anticoagulant for the management of pregnant women who develop HIT, nor are there recommendations in the literature on the ideal agent for patients with MHVs who develop HIT. Data are extremely limited on potential therapeutic options with the combination of HIT and MHV in pregnancy. Notably, fondaparinux has been successfully used in pregnancy, and there are reports of safe use with MHVs.[33,34]

MANAGEMENT OF ANTICOAGULATION IN THE PERIPARTUM PERIOD

Management of anticoagulation in the peripartum period in women with MHVs is controversial and without consensus. Anticoagulation near the time of delivery is challenging for a number of reasons. There is a high bleeding risk associated with both vaginal and cesarean deliveries, and the unpredictable nature of natural births makes this extremely challenging to mitigate. In addition, some anesthesia procedures, such as epidurals, are contraindicated in the presence of therapeutic anticoagulation given the risk of a spinal epidural hematoma.[35] It is important to note that epidurals are not required for every delivery, and the risks and benefits of such a procedure need to be carefully considered in patients with MHVs on anticoagulation. Current guidelines do not mandate discontinuation of aspirin monotherapy before epidural placement.[36]

These risks can best be mitigated with scheduled induction of labor or elective cesarean delivery and by appropriately modifying the anticoagulation regimen in women with MHVs who are close to term.[35]

For women who choose to use LMWH throughout their pregnancy, some centers routinely change anticoagulation to unfractionated heparin (UFH) near delivery. This method has drawbacks, however, as UFH is associated with erratic pharmacokinetics during pregnancy. The unpredictably prolonged half-life of UFH in this patient population can preclude epidurals in up to 50% of cases.[37] Our recommended approach is to hold LMWH 24 hours before planned delivery to allow safe use of epidural anesthesia.[36] In the event of premature labor, LMWH levels can help guide therapy. As the half-life of LMWH is shorter in pregnancy, it is preferable to use anti-Xa levels to determine candidacy for epidural placement rather than arbitrary timing guidelines. Our practice is to check an anti-Xa level 24 hours after the last dose of LMWH, just before planned delivery. After delivery, we recommend restarting LMWH within 24 hours and bridging to warfarin. Professional guidelines concur with our approach to hold LMWH 24 hours before delivery to allow for regional anesthesia. Low-molecular-weight heparin may be resumed as soon as 4 to 6 hours after vaginal delivery and 6 to 12 hours after caesarean delivery.[6] Postpartum hemorrhage rates do appear to be slightly increased in women who received treatment dose anticoagulation,[38] as do surgical complications.[39] If significant bleeding occurs and precludes the reinitiation of anticoagulation, all attempts should be made to achieve prompt and adequate hemostasis to allow resumption of anticoagulation as soon as possible.

Women who choose to remain on warfarin throughout pregnancy should be instructed to hold the drug at least a week before their scheduled delivery and then bridge back to warfarin with LMWH. Management during the postpartum period is the same as it is for women who chose to use LMWH throughout.

Breastfeeding can be safely initiated immediately postpartum while women are still on the LMWH bridge. Although anti-Xa activity has been detected in breast milk ranging from less than 0.005 to 0.037 IU/mL in women taking prophylactic dose dalteparin, this amounts to a milk/plasma ratio of less than 0.025 to 0.224. In such low concentrations, this is unlikely to have harmful effects in the child.[40] Warfarin appears to lack breast milk excretion.[41]

OUR PREFERRED ANTICOAGULATION STRATEGY

As discussed previously, the early literature surrounding LMWH in pregnancy includes several studies confounded by inconsistent LMWH dosing, inadequate monitoring, and failure to make proper dose adjustments. Studies suggest that the rate of thromboembolic events in pregnant patients with MHVs is lower when therapeutic dosing and intensive anti-Xa monitoring combined with dose adjustments are implemented.[42]

Although all potential strategies that have been suggested have benefits and risks, it is our belief that LMWH-LMWH-LMWH is a reasonable management strategy for women with lower-risk mechanical valves as it offers the best fetal outcomes and has an acceptable maternal safety profile (Table 3). We include 81 mg of aspirin in addition to anticoagulation in all women who do not have a significant risk of bleeding.

There is no consensus on the ideal monitoring of LMWH in pregnancy. CHEST guidelines recommend a target anti-Xa level of 1.0 to 1.2 IU/mL[42] and, more recently, recommend titration to the manufacturer's peak anti-Xa levels (approximately 1.0 IU/mL), whereas the 2014 American Heart Association and American College of Cardiology (AHA/ACC) valve guidelines recommend anti-Xa levels between 0.8 and 1.2 IU/mL.[3] We attempt to reach the more conservative range of 1.0 to 1.2 IU/mL and monitor levels every other week during pregnancy due to significant possibility of the need for dose adjustment as the pregnancy progresses.

We manage peripartum anticoagulation, as described previously, by holding LMWH 24 hours before surgery and using anti-Xa levels to guide the time of epidural placement. We restart LMWH 4 to 6 hours after vaginal delivery and 6 to 12 hour after cesarean delivery, and bridge to warfarin in the postpartum period.

PATIENT PREFERENCES

As decisions about the choice of anticoagulant in pregnancy carry complex risks for both a woman and her fetus, patient preference must factor heavily into the decision. Ultimately, the physician's role is to describe the risks and benefits of each therapeutic option, make recommendations based on clinical experience and the provider's understanding of the current available data, and allow space for shared decision-making.

There are some data describing the current prevalence of the different anticoagulation protocols. A prospective registry of European women with mechanical valves (n = 212, 2008–2011) found that most women were managed with heparin products in the first 14 weeks of gestation. Between 14 and 36 weeks, the most common choice by far was VKA, whereas UFH was the preferred anticoagulant in the peripartum period.[43] Unfortunately, only 58% of the women with MHVs in this study experienced an uncomplicated live birth, compared with 79% of women with tissue valves and 78% of women without a prosthetic valve.[43]

ALTERNATIVE OPTIONS

Women of childbearing age requiring heart valve replacement must be informed of the risks associated with anticoagulation in pregnancy. The risk of bleeding, thrombosis, and fetal loss or morbidity is significant. Given the extent of complications reviewed, some women will seek alternative management strategies. We will review several alternative options below.

Bioprosthetic Valves

Traditionally, mechanical valves, which carry a higher thrombogenic risk and require lifelong anticoagulation, have been preferred in younger patients due to prosthetic longevity and lower replacement rates (~10% vs 25% replacement rate for mechanical vs bioprosthetic valves at 15 years).[10,44] Bioprosthetic valves—which require only 3 months of anticoagulation—have been preferred in older patients who often have contraindications to long-term anticoagulation and who are not expected to require a valve replacement during their lifetime.[44]

Although controversy persists about the choice between mechanical or bioprosthetic aortic valve replacement (AVR), overall trends in the United States have shown an increase in the use of bioprosthetic valves compared with mechanical valves over the past 2 decades.[45] The current AHA/ACC guidelines state that bioprosthetic valves are reasonable in patients greater than 70 years of age (class IIa) and recommend mechanical AVRs or mechanical MVRs for patients less than 60 years of age without a contraindication to anticoagulation (class IIa).[3] The guidelines also recommend bioprosthetic valves for patients of any age in whom anticoagulation is contraindicated or not desired (class I).[3]

It is known that women who have well-functioning bioprosthetic heart valves and who do not have other cardiac risk factors often have uncomplicated pregnancies.[46] Bioprosthetic valves are increasingly being considered in women of childbearing age as a way to circumvent the risks to mother and fetus associated with anticoagulation during pregnancy. Although this is a potential solution to one problem, it has its own drawbacks. Overall, about 50% of women of childbearing age will require valve replacement due to valve deterioration within 10 years of the original operation.[47] Thus, there is a high likelihood of repeat valve replacement surgery, and the risks associated with this should be discussed with patients who are considering this option.

Surrogacy and Adoption

Women may decide that the risks of anticoagulation during pregnancy are unacceptably high and may opt for alternative fertility strategies. One such option is surrogacy, a procedure in which fertilized eggs from the patient and her partner are implanted into another woman’s uterus, who then carries the pregnancy to term. This allows patients with MHVs to remain on warfarin, decreasing their risk for thromboembolism, and protects the fetus from exposure to warfarin or heparin products during the critical gestational period. A major barrier to surrogacy is the financial cost, as the procedure tends to be prohibitively expensive for many.

Elective Termination

Women who enter an unplanned pregnancy before understanding the associated risks may choose to undergo elective termination rather than carry the fetus to term. Although we recognize that this is an extremely difficult decision and may not be available to all, it remains an option for certain patients.

CONCLUSIONS

Women with MHVs require lifelong anticoagulation to reduce their risk of thromboembolic events. The management of MHVs in pregnancy is complicated by questions about the risks to both mother and fetus of various anticoagulation strategies. Data to guide the optimal strategy in this scenario are limited, and the possibility of morbidity and mortality for both mother and fetus remains high. To minimize adverse outcomes, we favor anticoagulation with dose-adjusted LMWH throughout pregnancy. During the peripartum period, we recommend holding LMWH 24 hours before delivery and monitoring anti-Xa levels to determine appropriate timing of regional anesthesia. Within 24 hours postpartum, we recommend resuming therapeutic LMWH while bridging to warfarin. Warfarin can be continued thereafter as monotherapy or with the addition of low-dose aspirin if bleeding risk is felt to be low.

Communication with women of childbearing age who require valvular replacement is paramount, as alternatives such as bioprosthetic valves carry their own unique set of risks and benefits, but may allow for superior pregnancy outcomes.[43,46] All women of childbearing age who may require cardiac valve replacement should receive preconception counseling about the risks of systemic anticoagulation and various therapeutic strategies. After mechanical valve replacement, the risks of childbirth must be explained to women before conception as they may impact reproductive choices. Here we presented a number of alternatives including surrogacy, adoption, and elective termination, which should be included as part of a shared decision-making conversation as appropriate.

There are many limitations that prevent strong recommendations as evidenced by the wide range of variation among professional guidelines. High-grade evidence comparing various anticoagulation strategies is lacking. Patients, their families, and providers alike will benefit from more robust evidence in this complex clinical scenario.

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REFERENCES

1. Steinberg ZL, Dominguez-Islas CP, Otto CM, et al. Maternal and fetal outcomes of anticoagulation in pregnant women with mechanical heart valves. J Am Coll Cardiol. 2017;69:2681–2691. [PubMed: 28571631]
2. Whitlock RP, Sun JC, Fremes SE, et al. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(suppl 2):e576S–e600S. [PubMed: 22315272]

3. Nishimura RA, Otto CM, Bonow RO, 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;129:2440–2492. [PubMed: 24589852]
4. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. European Society of Gynecology (ESG); Association for European Paediatric Cardiology (AEPC); German Society for Gender Medicine (DGesGM), ESC Committee for Practice Guidelines. ESC guidelines on the management of cardiovascular diseases during pregnancy: the task force on the Management of Cardiovascular Diseases during pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:3147–3197. [PubMed: 21873418]
5. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369:1206–1214. [PubMed: 23991661]
6. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(suppl 2):e691S–e736S. [PubMed: 22315276]
7. 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;32:1248.e1241–1248.e1249. [PubMed: 26927861]
8. Garver D, Kaczmarek RG, Silverman BG, et al. The epidemiology of prosthetic heart valves in the United States. Tex Heart Inst J. 1995;22:86–91. [PubMed: 7787476]
9. Jeejeebhoy FM. Prosthetic heart valves and management during pregnancy. Can Fam Physician. 2009;55:155–157. [PubMed: 19221073]
10. Stassano P, Di Tommaso L, Monaco M, et al. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. J Am Coll Cardiol. 2009;54:1862–1868. [PubMed: 19892237]
11. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation. 1994;89:635–641. [PubMed: 8313552]
12. Massel DR, Little SH. Antiplatelet and anticoagulation for patients with prosthetic heart valves. Cochrane Database Syst Rev. 2013; CD003464.
13. Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med. 1980;68:122–140. [PubMed: 6985765]
14. Iturbe-Alessio I, Fonseca MC, Mutchinik O, et al. Risks of anticoagulant therapy in pregnant women with artificial heart valves. N Engl J Med. 1986;315:1390–1393. [PubMed: 3773964]
15. Li J, Wang S, Barone J, et al. Warfarin pharmacogenomics. P T. 2009;34:422–427. [PubMed: 20140106]
16. Hassouna A, Allam H. Limited dose warfarin throughout pregnancy in patients with mechanical heart valve prosthesis: a meta-analysis. Interact Cardiovasc Thorac Surg. 2014;18:797–806. [PubMed: 24595247]
17. Vitale N, De Feo M, De Santo LS, et al. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. J Am Coll Cardiol. 1999;33:1637–1641. [PubMed: 10334435]
18. Forestier F, Daffos F, Capella-Pavlovsky M. Low molecular weight heparin (PK 10169) does not cross the placenta during the second trimester of pregnancy study by direct fetal blood sampling under ultrasound. Thromb Res. 1984;34:557–560. [PubMed: 6740572]
19. Lepercq J, Conard J, Borel-Derlon A, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. BJOG. 2001;108:1134–1140. [PubMed: 11762651]
20. Food and Drug Administration. Package insert for low-molecular-weight heparin. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020164s085lbl.pdf. Accessed January 31, 2020.
21. Hung L, Rahimtoola SH. Prosthetic heart valves and pregnancy. Circulation. 2003;107:1240–1246. [PubMed: 12628941]

22. 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;92:747–751. [PubMed: 15467905]
23. James AH, Brancazio LR, Gehrig TR, et al. Low-molecular-weight heparin for thromboprophylaxis in pregnant women with mechanical heart valves. J Matern Fetal Neonatal Med. 2006;19:543–549. [PubMed: 16966122]
24. McLintock C, McCowan LM, North RA. Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin. BJOG. 2009;116:1585–1592. [PubMed: 19681850]
25. Maliha G, Morgan J, Vrahas M. Transient osteoporosis of pregnancy. Injury. 2012;43:1237–1241. [PubMed: 22464203]
26. Barbour LA, Kick SD, Steiner JF, et al. A prospective study of heparin-induced osteoporosis in pregnancy using bone densitometry. Am J Obstet Gynecol. 1994;170:862–869. [PubMed: 8141217]
27. Hawkins D, Evans J. Minimising the risk of heparin-induced osteoporosis during pregnancy. Expert Opin Drug Saf. 2005;4:583–590. [PubMed: 15934862]
28. Galambosi P, Hiilesmaa V, Ulander VM, et al. Prolonged low-molecular-weight heparin use during pregnancy and subsequent bone mineral density. Thromb Res. 2016;143:122–126. [PubMed: 27236710]
29. Le Templier G, Rodger MA. Heparin-induced osteoporosis and pregnancy. Curr Opin Pulm Med. 2008;14:403–407. [PubMed: 18664969]
30. Fausett MB, Vogtlander M, Lee RM, et al. Heparin-induced thrombocytopenia is rare in pregnancy. Am J Obstet Gynecol. 2001;185:148–152. [PubMed: 11483919]
31. Chaudhary RK, Nepal C, Khanal N, et al. Management and outcome of heparin-induced thrombocytopenia in pregnancy: a systematic review. Cardiovasc Hematol Agents Med Chem. 2015;13:92–97. [PubMed: 26695420]
32. Srinivasan AF, Rice L, Bartholomew JR, et al. Warfarin-induced skin necrosis and venous limb gangrene in the setting of heparin-induced thrombocytopenia. Arch Intern Med. 2004;164:66–70. [PubMed: 14718324]
33. De Carolis S, di Pasquo E, Rossi E, et al. Fondaparinux in pregnancy: could it be a safe option? A review of the literature. Thromb Res. 2015;135:1049–1051. [PubMed: 25912931]
34. Willenborg KL. Successful use of Fondaparinux early after mechanical aortic valve replacement in a patient with a history of heparin-induced thrombocytopenia. Pharmacotherapy. 2014;34: e55–e59. [PubMed: 24644124]
35. Marik PE, Plante LA. Venous thromboembolic disease and pregnancy. N Engl J Med. 2008;359:2025–2033. [PubMed: 18987370]
36. Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (third edition). Reg Anesth Pain Med. 2010;35:64–101. [PubMed: 20052816]
37. Anderson DR, Ginsberg JS, Burrows R, et al. Subcutaneous heparin therapy during pregnancy: a need for concern at the time of delivery. Thromb Haemost. 1991;65:248–250. [PubMed: 2048050]
38. Romualdi E, Dentali F, Rancan E, et al. Anticoagulant therapy for venous thromboembolism during pregnancy: a systematic review and a meta-analysis of the literature. J Thromb Haemost. 2013;11:270–281. [PubMed: 23205953]
39. Limmer JS, Grotegut CA, Thames E, et al. Postpartum wound and bleeding complications in women who received peripartum anticoagulation. Thromb Res. 2013;132:e19–e23. [PubMed: 23735589]
40. Richter C, Sitzmann J, Lang P, et al. Excretion of low molecular weight heparin in human milk. Br J Clin Pharmacol. 2001;52: 708–710. [PubMed: 11736885]
41. Orme ML, Lewis PJ, de Swiet M, et al. May mothers given warfarin breast-feed their infants? Br Med J. 1977;1:1564–1565. [PubMed: 871666]

42. Quinn J, Von Klemperer K, Brooks R, et al. Use of high intensity adjusted dose low molecular weight heparin in women with mechanical heart valves during pregnancy: a single-center experience. Haematologica. 2009;94:1608–1612. [PubMed: 19880782]

43. van Hagen IM, Roos-Hesselink JW, Ruys TP, 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;132:132–142. [PubMed: 26100109]

44. Chiang YP, Chikwe J, Moskowitz AJ, et al. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. JAMA. 2014;312:1323–1329. [PubMed: 25268439]

45. Isaacs AJ, Shuhaiber J, Salemi A, et al. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. J Thorac Cardiovasc Surg. 2015;149:1262.e3–1269.e3. [PubMed: 25791947]

46. Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. Br Heart J. 1994;71:196–201. [PubMed: 8130033]

47. Elkayam U, Bitar F. Valvular heart disease and pregnancy part I: native valves. J Am Coll Cardiol. 2005;46:223–230. [PubMed: 16022946]

TABLE 1

Professional Society Guidelines for Anticoagulation of Mechanical Valves in Pregnancy

Chest Guidelines[6]	AHA/ACC Guidelines[3]	ESC Guidelines[4]
Recommend any of the following (grade 1A): A. Dose-adjusted LMWH twice daily throughout pregnancy (adjusted to achieve goal peak anti-Xa LMWH 4 h post dose) B. Dose-adjusted UFH throughout pregnancy, administered subcutaneously twice daily (adjusted to keep the mid-interval aPTT ≥ twice control or to attain an anti-Xa heparin level of 0.35 to 0.70 U/mL) C. UFH or LMWH (as above) until the 13th week, with substitution by vitamin K antagonists until close to delivery when UFH or LMWH is resumed	For women whose baseline warfarin dose is ≤5 mg/d (class 2A): A. Continue warfarin with close INR monitoring throughout pregnancy after a full discussion of risks. B. Dose-adjusted LMWH twice daily for the first trimester (peak anti-Xa 0.8–1.2 U/mL, 4–6 h post dose) followed by warfarin in second and third trimesters C. Dose-adjusted continuous infusion UFH for the first trimester (PTT goal ≥2× control) followed by warfarin in second and third trimesters	For women whose baseline warfarin dose is <5 mg/d (class 2A): A. Continuation of OACs should be considered during the first trimester if the therapeutic warfarin dose is ≤5 mg/d
For higher-risk patients (grade 2C) (ie, older generation prosthesis in the mitral position or history of VTE) A. Vitamin K antagonists throughout pregnancy with replacement by UFH or LMWH (as above) close to delivery rather than one of the regimens above B. Consider the addition of low-dose aspirin (75 to 100 mg/d) for high-risk women	For women whose baseline warfarin dose is >5 mg/d (class 2A): A. Dose-adjusted LMWH twice daily in the first trimester (peak anti-Xa 0.8–1.2 U/mL 4–6 h post dose) followed by warfarin in second and third trimesters B. Dose-adjusted continuous infusion UFH in the first trimester (PTT goal ≥2× control) followed by warfarin in second and third trimesters	For women whose baseline warfarin dose is >5 mg/d (class 2B): A. Dose-adjusted UFH (PTT ≥2× control) or LMWH twice daily (dose adjustment according to weight and peak anti-Xa level 0.6–1.2 IU/mL, 4–6 h post dose) for the first trimester in high-risk patients, given as intravenous infusion B. Continuation of OACs may be considered between weeks 6 and 12 in patients with a therapeutic warfarin dose >5 mg/d C. LMWH should be avoided, unless anti-Xa levels are monitored

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TABLE 2

Advantages and Disadvantages of Anticoagulation Strategies for Pregnant Women With Mechanical Valves

Protocols	LMWH-LMWH-LMWH	LMWH-War-War	LD-War-LD-War-LD-War	War-War-War
Advantages	• Lowest rates of fetal demise without teratogenicity • Strong track record of fetal safety. Most recommended anticoagulant in women without MVs. • Rates of HIT and osteoporosis appear negligible or nonexistent. • Peripartum management simplified	• Omitting first trimester warfarin appears to significantly reduce fetal complications. • Endorsed by many practitioners • Rates of HIT and osteoporosis appear negligible or nonexistent.	• Warfarin has the most robust data on maternal safety • Decreased rates of fetal complications compared with full dose warfarin	• Most robust data on maternal safety
Disadvantages	• Maternal safety data are limited. Unmonitored studies report high complication rates. • Requires close Xa monitoring and adjustment	• Still has a notable rate of fetal complications • More complex peripartum management then LMWH	• Not an option for many women • Still has a notable rate of fetal complications (less embryopathy, but still significant rates of fetal demise) • More complex peripartum management then LMWH	• Significant rates of fetal demise and embryopathy • More complex peripartum management then LMWH
Society endorsement	• ACCP grade 1A for women without high-risk mechanical valves	• ACCP grade 1A for women without high-risk mechanical valves • AHA class 2A • ESC class 2B	• ACCP grade 2C • AHA class 2A • ESC class 2A	• ACCP grade 2C • ESC class 2A

TABLE 3

Potential Anticoagulation Strategies for Pregnant Women With Mechanical Valves

	First Trimester	Second Trimester	Third Trimester	Peripartum
LMWH-LMWH-LMWH	LMWH	LMWH	LMWH	Hold LMWH 24 h before delivery Resume LMWH: • 4–6 h after vaginal deliverty • 6–12 h after cesarean delivery Bridge to warfarin
LMWH-War-War	LMWH	Warfarin	Warfarin	Hold warfarin 7 d before delivery Bridge to warfarin with LMWH as above
LD-War-LD-War-LD-War	Low-dose warfarin	Low-dose warfarin	Low-dose warfarin	Hold warfarin 7 d before delivery Bridge to warfarin with LMWH as above
War-War-War	Warfarin	Warfarin	Warfarin	Hold warfarin 7 d before delivery Bridge to warfarin with LMWH as above

Notes: LMWH dosed twice daily with monitoring; target anti-Xa level 1.0 to 1.2 U/mL at 4 to 6 h post-dose. Monitor every other week. Aspirin 81 mg daily can be added to all regimens in patients without significant bleeding risk.

Low-dose warfarin ≤ 5 mg/d.