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Pregnancy and Cardiovascular Disease (N Scott, Section Editor)

State of the Art Management of Mechanical Heart Valves During Pregnancy

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Abstract

Purpose of the review To review the management of women with mechanical heart valves during pregnancy, from preconception counseling through delivery with a summary of the latest guidelines.
Recent findings The hypercoagulability of pregnancy combined with the imperfect choices of anticoagulant agents contribute to a high risk of complications in pregnant women with mechanical heart valves. Valve thrombosis remains a major concern, much of which occurs during the first trimester transition to heparin-based products. The safest method of anticoagulation, with the best balance of maternal and fetal risk, is use of low-dose vitamin K antagonists, but only if therapeutic anticoagulation can be achieved with warfarin doses of ≤ 5 mg/day.
Summary Management of mechanical heart valves in pregnancy remains fraught with difficult decisions involving balancing of maternal and fetal risks as well as a high risk of maternal and fetal complications. Preconception counseling and planning is imperative. A risk-benefit discussion with the patient will help guide the choice of anticoagulation and outline the plan for safe delivery options. A multidisciplinary approach to management is advisable with close follow-up and care in a tertiary center.

Introduction

Valvular heart disease is the most common form of cardiovascular disease during pregnancy [1], with the most common etiologies being rheumatic heart disease (RHD) and congenital heart disease (CHD) [2]. The increasing prevalence of RHD in the developing world along with advances in medical and interventional therapies has led to an increased number of women of childbearing age considered for valve replacement [3–5]. Additionally, there are an increasing number of women with CHD undergoing valvular interventions [6]. With modernization, increased education, and advanced reproductive techniques, the average age of childbearing has increased significantly over recent years [7, 8], which further increases the proportion of women with prior valve replacement. These factors have led to a larger prevalence of women with mechanical heart valves (MHV) that experience pregnancy, yet the exact percentage of women of reproductive age with MHV is unknown. Among the few available estimates, the overall prevalence of MHV in pregnancies remains low. A recent prospective descriptive population-based study using the UK Obstetric Surveillance System (UKOSS) data collection system revealed that the incidence of MHV in all pregnancies in the UK over a 2-year period was 3.7 per 100,000 [9•].

Pregnancy is a prothrombotic state due to increased levels of fibrinogen, factors VII, VIII, and X, plasminogen activator inhibitor, as well as increased platelet adhesiveness, resistance of activation of protein C, and decreased fibrinolysis [10]. Hence, there is a significantly increased thromboembolic risk during pregnancy for women with MHV. Further, the significant increases in heart rate, stroke volume, and cardiac output combined with increase in plasma volume can lead to decompensation in maternal hemodynamics in women with MHV during pregnancy.

In the UKOSS study [9•], pregnant women with MHV suffered significant morbidity and mortality with 9% maternal death, 41% serious maternal morbidity, and poor fetal outcomes in 47%. In the Registry On Pregnancy and Cardiac disease (ROPAC) [11•], the complication rates were slightly lower with 1.4% maternal mortality, 4.7% valve thrombosis, 23% hemorrhagic complications, and 18.4% fetal loss.

Major adverse events in pregnancy in women with MHV include valve thrombosis, valve failure/dysfunction, endocarditis, cerebral vascular accident (CVA), hemolysis, bleeding, ventricular dysfunction, heart failure, and arrhythmias. In the UKOSS study, four of the five deaths occurred due to valve thrombosis and one occurred due to a CVA. In the ROPAC study, two deaths occurred due to valve thrombosis and one due to preexisting poor LV function exacerbated by H1N1 flu. Serious morbidity occurs primarily due to valve thrombosis, CVA, or bleeding complications of anticoagulation.

This review focuses on the management of women with MHV during pregnancy, from preconception counseling to delivery highlighting the management of complications.

Preconception evaluation, risk assessment, and counseling

Preconception counseling is imperative for any woman contemplating pregnancy with a MHV [12]. In fact, preconception counseling should begin at the time of diagnosis for women with acquired valvular heart disease and during adolescence for those with CHD-associated valvular disease, beginning even prior to valve implantation.

Any woman of childbearing age with a MHV must understand the potential risks of pregnancy to both mother and fetus and if pregnancy is to be pursued; the anticoagulant strategy must be carefully planned. Counseling should include a discussion regarding safe methods of contraception to help with planning the timing of pregnancy or its avoidance. Counseling should be provided by a team of experienced cardiologists and maternal-fetal medicine specialists with expertise in heart disease in pregnancy. It should include a detailed discussion of the maternal and fetal risks of pregnancy including the latest data on the rates of various complications, further individualized based on each

woman's additional risk factors such as history of heart failure, arrhythmias, presence of other cardiac lesions, or ventricular dysfunction.

Each woman should undergo a detailed evaluation at their initial visit including a review of prior records such as operative and procedure notes, a detailed history and physical exam, assessment of functional capacity, electrocardiogram, echocardiogram, and further investigations based on the individual woman's risk factors. An up-to-date assessment of prosthetic valve function as well as ventricular function is preferable prior to planned pregnancy or early in pregnancy if preconception assessment has not taken place. Counseling should address the need for pre-pregnancy intervention to optimize hemodynamics. While a well-functioning MHV with normal biventricular function is often hemodynamically well tolerated during pregnancy; the increased risk is mainly due to the need for anticoagulation and potential for valve thrombosis.

Individualized risk assessment should also be conducted at the initial visit assisted by the use of risk-score calculators for cardiac disease in pregnancy such as cardiac disease in pregnancy (CARPREG) [13], Zwangerschap bij Aangeboren HARtAfwijkingen (ZAHARA) [14], the World Health Organization (WHO) maternal risk classification [15], and the latest CARPREG II risk index [16•]. In addition to the risk factors accounted from by CARPREG, the ZAHARA risk score, which is used specifically to predict pregnancy risk in women with CHD, accounts for risk factors of moderate-to-severe pulmonary or systemic AV valve regurgitation, cyanotic heart disease, and the presence of a MHV [14], and hence may be more applicable to patients with CHD and a MHV contemplating pregnancy. According to the WHO risk calculator [15], which is recommended by the European Society of Cardiology (ESC) [17], women with a MHV fall into WHO III risk class (significantly increased maternal morbidity and mortality) and additionally may fall into WHO IV risk class if there are additional risk factors such as severe left-sided obstruction or left ventricular (LV) dysfunction. The most recent risk index, CARPREG II [16•] incorporates five general predictors (prior cardiac events or arrhythmias, poor functional class or cyanosis, high-risk valve disease/left ventricular outflow tract obstruction, systemic ventricular dysfunction, and no prior cardiac interventions); four lesion-specific predictors (MHV, high-risk aortopathies, pulmonary hypertension, and coronary artery disease); and one delivery of care predictor (late pregnancy assessment). CARPREG II included ~ 2% of patients with MHV and highly weights MHV in the risk calculator. Based on such risk predictors, women with MHV may be at a high enough risk to consider avoiding pregnancy altogether and must be counseled accordingly.

Counseling should include a recommendation for close monitoring by a multidisciplinary team throughout pregnancy. It should also include a discussion of potential complications and outline an approach for anticoagulation at the time of conception through delivery and the postpartum period. Regardless, it is important to emphasize in these discussions, that even with meticulous anticoagulation and thoughtful coordinated care, the risk for MHV thrombosis, and maternal and fetal adverse outcomes, is still high [18].

Multidisciplinary team care

Pregnant women with MHV should be monitored in a tertiary care center with a dedicated heart valve team of cardiologists, surgeons, anesthesiologists, and

maternal fetal medicine specialists with expertise in the management of high-risk cardiac patients [19]. Dedicated nursing staff ideally cross-trained in obstetric and cardiac care are critical members of the team. With the hormonal, hematologic, and hemodynamic changes that occur throughout various stages of pregnancy, in-depth knowledge of the risks and benefits of various approaches to anticoagulation is imperative.

Due to the physiological effects of pregnancy, there are constantly changing requirements for antithrombotic regimens and effective anticoagulation with frequent monitoring (weekly or every 2 weeks) of its systemic effect is critical throughout the pregnancy.

Guidelines recommend monthly visits with physical exam and after baseline transthoracic echocardiogram (TTE), repeat TTE is recommended with the development of any symptoms such as dyspnea or changes in the physical exam. ESC guidelines also recommend monthly echocardiography with clinical follow-up. Furthermore, a TTE must be performed in any woman in whom thrombotic obstruction is suspected or if an embolic event occurs. A transesophageal echocardiogram (TEE) is also indicated to look at disc motion or thrombus burden and is especially important for detection of mechanical mitral valve dysfunction. An apparently normal TTE should not dissuade clinicians from proceeding with TEE if clinically there is suspicion of a complication. Even though radiation exposure should be minimized, valve fluoroscopy may be helpful in the evaluation of disc motion, especially when echocardiographic imaging is insufficient.

With the increase in cardiac output during pregnancy, the pressure gradient across a MHV will increase while the calculated valve area remains stable. Hence, while comparing serial echocardiograms, other parameters such as calculated valve area, dimensionless index (for aortic prostheses), and diastolic half-time (for mitral prostheses) can help in the evaluation of MHV function.

Anticoagulation strategies during pregnancy

Current guidelines on anticoagulation in pregnancy for women with MHV are based on small retrospective series as no randomized clinical trials have been conducted. The lowest maternal risk is with the use of vitamin K antagonists (VKAs), but these pose a significant risk of embryopathy. VKAs cross the placental barrier and have teratogenic effects and also cause stillbirth and miscarriage. Typical features of warfarin embryopathy include but are not limited to cartilage maldevelopment, nasal hypoplasia, depressed nasal bridge, bifid spine, and stippling of epiphyses as well as central nervous system abnormalities such as hydrocephalus, optic atrophy, intellectual disability, blindness, and spasticity [20, 21]. The highest risk of teratogenicity is when VKAs are administered between the 6th to 12th weeks of pregnancy [22], but warfarin fetopathy has been reported throughout all three trimesters in women taking warfarin. Though there is some conflicting evidence, majority of the studies show that fetal effects of warfarin are dose-dependent with doses ≤ 5 mg/day having a relatively safer profile [23–26]. While some studies show no fetal embryopathy at the lower doses of VKAs, there are cases of fetal embryopathy reported and a higher risk of stillbirth/miscarriage still exists [27].

The overall risk of fetal embryopathy with continuation of low dose VKAs during the first trimester is thought to be < 3%, while the risks of stillbirth/miscarriage are relatively similar with any anticoagulation [17–19]. Given this data, both the American Heart Association (AHA)/American College of Cardiology (ACC) and European guidelines recommend continuation of VKAs (or oral anticoagulants) throughout pregnancy at the lower doses of warfarin ≤ 5 mg/day (or phenprocoumon < 3 mg or acenocoumarol < 2 mg daily) after full discussion with the patient of risks and benefits of each strategy [17–19]. If there is a patient preference after full discussion, it is reasonable to consider a switch to unfractionated heparin (UFH) or low molecular weight heparin (LMWH) between weeks 6 and 12 under strict dose control and supervision. If the dose of VKAs to achieve therapeutic anticoagulation exceeds 5 mg warfarin/day (or 3 mg phenprocoumon or 2 mg acenocoumarol) then guidelines recommend this switch after a risk-benefit discussion with the patient. The new ESC guidelines recommended that implementation of changes in the anticoagulation regimen during pregnancy be performed during hospitalization [28•].

Dose-adjusted LMWH is recommended at least two times per day with a target anti-Xa level of 0.8 to 1.2 U/mL, 4 to 6 h post-dose. Alternatively, dose-adjusted continuous intravenous UFH (with an aPTT at least two times control) is reasonable with the caveat that LMWH has the potential advantages of better subcutaneous absorption, more steady bioavailability, longer half-life, and a more predictable anticoagulation response. With meticulous dosing, the incidence of MHV thrombosis is lower with LMWH, but some reports of thrombosis still exist even with newer valves and dosage requirements may increase by as much as 50% over the course of pregnancy. Further, there are unresolved issues around use of peak and trough levels, optimal timing of dosage, and compliance with dosing two times a day and sometimes three times a day.

During the second and third trimesters, both AHA/ACC and European guidelines recommend use of VKAs not LMWH or UFH due to the lower risk of valve thrombosis in combination with low-fetal risk, irrespective of the dosage. The AHA/ACC guidelines recommend addition of aspirin in the second and third trimesters.

Delivery and breastfeeding in women with mechanical valves

Delivery should take place in a tertiary care center with access to multidisciplinary team care. To optimize maternal and fetal outcomes, a structured plan for labor and delivery should be discussed early in pregnancy, based on current guidelines (Table 1). Vaginal delivery is usually preferred. In women with a high risk for MHV thrombosis undergoing a trial of labor, IV heparin can be used in the early part of labor to minimize time off anticoagulation. Intravenous heparin can be discontinued 4 hours prior to initiation of regional anesthesia and then restarted at a low dose. A cesarean delivery should be performed for usual obstetric indications or if there is a need to deliver quickly from a maternal or fetal perspective. Discontinuation of VKAs with initiation of intravenous UFH (with an activated partial thromboplastin time [aPTT] > 2 times control) or LMWH (with a target anti-Xa level of 0.8 to 1.2 U/mL, 4 to 6 h post-dose) is recommended at least 2 weeks before planned vaginal delivery. With

Table 1. Recommended regimen for therapeutic anticoagulation, adapted from 2014 AHA/ACC guidelines for the management of patients with valvular heart disease.

Condition	Management	
Baseline Warfarin dose to maintain therapeutic AC ≤5mg	Options for anticoagulation throughout pregnancy	Continue warfarin to maintain goal INR
		LMWH SQ BID to maintain Anti-Xa levels 0.8 – 1.2 U/mL 4-6 hrs post-dose
		Continuous IV infusion of UFH to maintain aPTT 2x control
Baseline Warfarin dose to maintain therapeutic AC >5mg	Options for anticoagulation in the first trimester	LMWH SQ BID to maintain Anti-Xa levels 0.8 – 1.2 U/mL 4-6 hrs post-dose
		Continuous IV infusion of UFH to maintain aPTT 2x control
	Anticoagulation in the second and third trimesters	Continue warfarin to maintain goal INR + Aspirin 75-100 mg daily
Patients on warfarin or LMWH in third trimester	Prior to delivery (2 weeks prior if warfarin or 12 hours prior if LMWH)*	Switch to continuous IV infusion of UFH to maintain aPTT 2x control**

Class I recommendation
Class IIa recommendation
Class IIb recommendation
*Switching to LMWH only 12 h prior would preclude use of neuraxial anesthesia for an additional 12 h
**In patients with a bileaflet mechanical aortic valve and no other risk factors for thrombosis, one may consider temporary interruption of anticoagulation, without bridging agents

consideration for the increased risk for premature labor in these patients, careful planning by the heart valve team is recommended. If a woman presents in labor fully anticoagulated with a VKA, a cesarean delivery should be performed to minimize the risk to the fetus of intracranial hemorrhage during vaginal delivery. Fresh frozen plasma (FFP) and vitamin K may be administered to both mother and fetus. LMWH should also be switched to intravenous UFH prior to delivery, and for emergent delivery on LMWH, protamine may be considered though this only partially reverses the anticoagulant effects.

UFH should be held during active labor and without bleeding concerns, can usually be restarted 4–6 h after delivery. Time for re-introduction of VKAs varies and bridging may be performed using either LMWH of intravenous UFH. Breastfeeding is safe with all methods of anticoagulation as LMWH and UFH do not transfer to breast milk; and only small quantities of VKAs are expressed in breast milk.

Anesthetic management

During both vaginal delivery and caesarian delivery, neuraxial analgesia/anesthesia is the therapy of choice. However, there is an increased risk of spinal epidural hematoma during neuraxial techniques in the setting of anticoagulation [29], which limits their use. The highest risk of hematoma is when a patient's coagulation system is abnormal either at the time a needle is placed or at the time of removal of a continuous neuraxial catheter [29]. The American Society of Regional Anesthesia (ASRA) guidelines [30] recommend

avoiding neuraxial techniques within 5 days from the last dose of warfarin (with INR < 1.5), 4–6 h after discontinuation of UFH (with normal aPTT), and 24 h of last dose of LMWH. After removal of the neuraxial catheters, UFH can typically be restarted after 1 h in the absence of bleeding complications.

Women who have been transitioned to UFH in a timely fashion are candidates for neuraxial analgesia. If the administration of an epidural analgesia during labor is not possible, other solutions such as morphine administration via patient-controlled anesthesia (PCA) protocols have been proven efficient and safe. A recent retrospective review of 18 cases compared to 36 controls showed underutilization of neuraxial anesthetic techniques in this retrospective cohort of women with MHV who gave birth at their center [31].

Management of valve thrombosis during pregnancy

The most dreaded complication of a MHV in pregnancy is valve thrombosis, and the highest risk occurs in the first trimester, often exacerbated by the transition from VKAs to LMWH/UFH or due to subtherapeutic anticoagulation related to increased requirements of anticoagulants with the larger volume of distribution and increased clearance.

When a MHV thrombosis is suspected, the clinical status of the woman, degree of obstruction, valve involved, size of thrombus, and gestational age are all taken into consideration. Critically ill patients should be taken for urgent surgery if available with awareness of an estimated 11.2% maternal mortality and 33.1% fetal loss with cardiopulmonary bypass [32]. If surgery is not available, fibrinolysis may be considered.

In the setting of left-sided valve thrombosis with minimal symptoms and a small non-mobile thrombus (< 10 mm diameter or 0.8 cm^2 area), it is prudent to reassess after several days of carefully monitored therapeutic intravenous UFH. If thrombus persists, an attempt at fibrinolysis is reasonable. Successful fibrinolysis should be followed by administration of VKAs with increased INR goals of 3.0 to 4.0 for aortic prostheses and 3.5 to 4.5 for mitral prostheses. For right-sided valve thrombosis, fibrinolytic therapy is the treatment of choice as success with normalization of hemodynamics is similar to surgery and the resultant small pulmonary emboli appear to be well tolerated and systemic emboli are uncommon [19].

With high risk of fetal loss with cardiopulmonary bypass, fibrinolysis is a reasonable consideration in many cases. A recent review reported 2.8% maternal mortality, 1.4% fetal death, and 9.9% miscarriage rate with administration of fibrinolytic therapy in pregnancy [33]. While most fibrinolytic agents do not cross the placenta, the risk of embolization (10%), and of subplacental bleeding or placental abruption is a concern [17]. Experience with the use of fibrinolytic agents in pregnancy is limited. However, complication rates of fibrinolytic treatment do not seem significantly higher in pregnant women than in the nonpregnant state. Various low-dose regimens have been proposed including administration of 20 mg intravenous (IV) bolus of tPA followed by 10 mg/h for 3 h or 25 mg slow IV infusion over 6 h. In one of the largest studies of 28 such events (in 25 patients), 100% success rate was reported with the second regimen with one placental hemorrhage with live preterm birth and one complication of

epistaxis [34]. After treatment of the acute thrombotic event, it is important to determine the adequacy of anticoagulation before the event and ensure that there is meticulous follow-up after.

Management of mechanical valve endocarditis in pregnancy

Endocarditis in the setting of a MHV is rare in pregnancy, mostly limited to case reports [35], but one study from Egypt reported two cases among 100 pregnancies [36]. Other larger studies either have not reported its incidence or reported zero cases [11•, 37]. Care must be tailored to culture results with management by a team of cardiologists, cardiothoracic surgeons, infectious disease specialists, and maternal-fetal medicine specialists [38]. Routine prophylaxis for endocarditis during delivery, while controversial, is not recommended in the latest guidelines [39, 40].

Common obstetric and fetal complications

In addition to valve thrombosis and CVA, obstetric and fetal complications are also common in women with MHV. Among the obstetric complications, hemorrhagic complications predominate, often due to secondary hemorrhage (after re-introduction of warfarin postpartum) and include wound hematoma, postpartum hemorrhage, and intra-abdominal bleeding. Rates of hemorrhagic complications were reported as high as 23% in the ROPAC registry and 29% in the UKOSS study. Some bleeding complications may be prevented by avoiding early introduction of warfarin postpartum. Regardless, careful monitoring for obstetric hemorrhage is essential, especially during the period of re-introduction of VKAs.

Fetal outcomes are also poor in these women with high rates of miscarriage, stillbirth or neonatal death, and some fetal anomalies (mostly with use of higher dose warfarin in the first trimester). Preterm labor is also common. In a recent meta-analysis [41•], a composite fetal outcome of spontaneous abortion, fetal death, and the presence of any congenital defect occurred in 39.2% of women on VKAs throughout pregnancy, 13.9% on LMWH throughout pregnancy, 16.4% on a regimen of LMWH in the first trimester followed by VKAs, and 33.6% on a regimen of UFH in the first trimester followed by VKAs. However, in the subgroup receiving low-dose VKAs, the estimated averaged risk of the fetal composite outcome was only 4.8% and was no different from women taking LMWH throughout pregnancy. This supports previous studies showing the highest fetal risk is with VKAs administered early during pregnancy. Fetal risks are mitigated if the required doses are low. The majority of adverse outcomes in women taking VKAs are due to early fetal loss/miscarriage.

Selection of type of heart valve in women of childbearing age

With young patients, when considering the type of valve to implant, much consideration is given to the durability of MHV. However, bioprosthetic valves

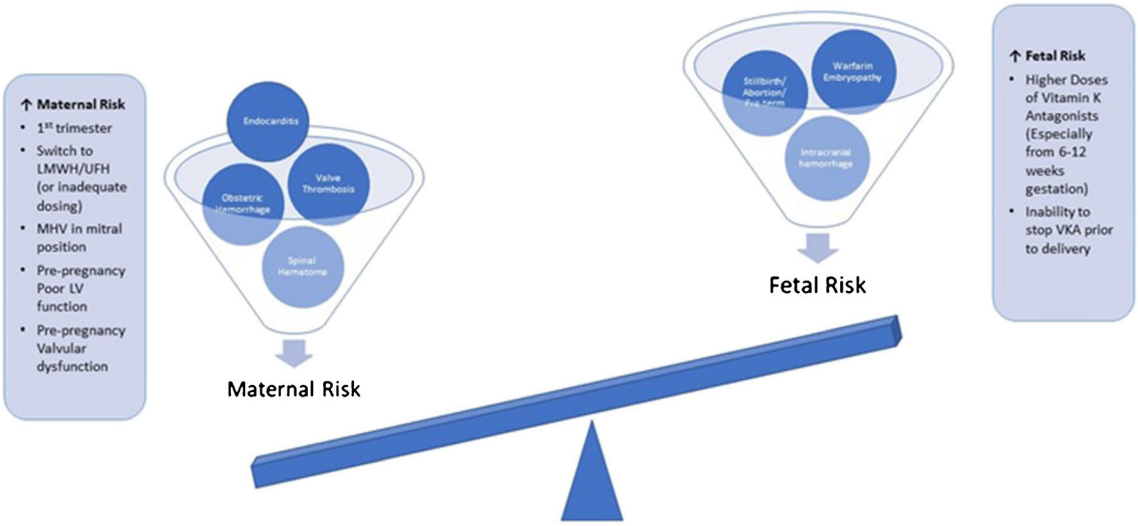

Fig. 1. Difficult balance between maternal and fetal risks in pregnant women with mechanical heart valves.

are often preferred in women planning pregnancy due to the significant (maternal and fetal) morbidity and mortality associated with MHV. This is a difficult choice and must also take into account the availability of resources of re-operation given the finite lifespan of bioprosthetic valves, especially as the rate of deterioration is higher in younger patients. Some have even advocated a preoperative anticoagulation challenge, to guide this choice, in which one would assess the dosage of VKAs required to achieve therapeutic anticoagulation prior to surgery and if achievable on lower doses of VKAs, implantation of a MHV [42].

With the development of newer technology, lower-intensity anticoagulation with MHV has become another possibility. The Prospective Randomized On-X Anticoagulation Clinical Trial (PROACT) study has proven the safety of lower INR goals (1.5–2.0) in patients with the new generation On-X heart valve in the aortic position [43]. This may reduce the dosage of VKAs required to maintain therapeutic anticoagulation, providing a safer option of low-dose VKAs throughout pregnancy. While there is no data available yet regarding pregnancy in women with this newer generation valve, the lower INR goals may be a consideration in women of childbearing age group who opt for a mechanical valve replacement.

Conclusion

Management of women with MHV in pregnancy remains fraught with challenging decisions involving the balancing of maternal and fetal risks and the recognition of the potential maternal and fetal complications (Fig. 1). Preconception counseling is essential with a risk-benefit discussion with the patient to guide the choice of anticoagulation and outline the plan for safe delivery options. A multidisciplinary approach to management is advisable with close follow-up and care in a tertiary center. Finally, in women of childbearing age, at

the time of MHV implant, the decision regarding the type of valve should take into consideration all the risks of pregnancy and potential use of newer technology when applicable.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
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In 2017, Vause et al published a population-based study from the UK showing an incidence of MHVs of 3.7 per 100 000 pregnancies. Their cohort was managed on LMWH throughout pregnancy. Of the 58 women with an MHV they followed through pregnancy, only 28% women had good maternal and fetal outcome. The maternal mortality was as high as 9% and there was a poor fetal outcome in 47% of the pregnancies.

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In 2015, Van Hagen et al published data from a prospective, observational, contemporary, worldwide Registry of Pregnancy and Cardiac disease describing the pregnancy outcome of 212 patients with an MHV compared to 134 patients with a tissue heart valve and 2620 without a prosthetic valve. Only 58% of the patients with an MHV had a pregnancy free of serious adverse events compared with 79% of patients with a bioprosthetic valve and 78% of patients without a prosthetic

valve. There was a 4.7% rate of valve thrombosis, all occurring during the first trimester and half after switching to heparin. There was also a 23.1% rate of hemorrhagic events.

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In 2018, Silversides et al published the latest risk stratification index based on their study of 1938 pregnancies including 43 (2.2%) women with MHV. Based on multivariate analysis, 10 independent predictors of primary maternal cardiac events were included in the final risk score. MHVs are heavily weighted in the score receiving 3 points, automatically increasing the calculated risk for for primary cardiac events during pregnancy in these women to 15% or more.

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