Mechanical Valves in Pregnancy: A Sticky Business

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Caring for women with mechanical heart valves (MHVs) in pregnancy poses one of the greatest clinical challenges in our specialty. Pregnancy is a prothrombotic state due to relative increases in fibrinogen, plasminogen activator inhibitors, clotting factors, Von Willebrand factor and platelet adhesion molecules, and concomitant decreases in protein S activity. These hypercoaguable changes begin in early pregnancy and persist for at least 6 to 12 weeks postpartum. Evidence from contemporary and historical cohorts of women with mechanical valves in pregnancy suggests increased risk of maternal cardiovascular events, obstetric morbidity such as hemorrhage and preterm birth, and fetal complications including growth restriction, miscarriage, and stillbirth. Owing to these risks, pregnant women with mechanical valves need rigorous control of their anticoagulation; however, the ability to achieve meticulous anticoagulation is hampered by the increased renal clearance and volume of distribution associated with pregnancy. Thus, pregnant women are at the highest risk for complications of mechanical valves at a time when it is the most difficult to maintain adequate anticoagulation. In caring for these women, we strive for a balance between the maternal risk of valve thrombosis, systemic thromboembolism, and hemorrhage with the fetal risk of exposure to oral vitamin K antagonists (VKAs).

Pregnant women with mechanical heart valves have many choices for anticoagulation, but all options carry risk for the mother and fetus. Vitamin K antagonists are the preferred choice for preventing thrombotic complications; however, these medications freely cross the placenta, and exposure in the first trimester may result in warfarin embryopathy characterized by nasal bone hypoplasia and stippled epiphyses.¹ Case series of pregnant women with mechanical heart valves exposed to warfarin in the first trimester suggest an embryopathy rate of roughly 5% to 7%.²³ There also appears to be a dose-dependent relationship with increased
adverse outcomes such as miscarriage, stillbirth, and embryopathy occurring at doses over 5mg daily. Furthermore, warfarin use in the second and third trimester has been associated with neurological sequelae and increased risk of fetal hemorrhage. In the postpartum period, however, warfarin is the preferred choice for its superior anticoagulant properties and its safety in breastfeeding.

Low-molecular weight heparins (LMWHs) are exceedingly safe in pregnancy. They do not cross the placenta, nor do they confer a risk of teratogenicity or neonatal bleeding complications. However, the use of LMWHs for women with MHV in pregnancy is fraught with controversy due to reports of complications including valve thrombosis, hemorrhage, and maternal and fetal mortality.

Finding the delicate balance between adequate anticoagulation of the mother and fetal safety poses a challenging dilemma for maternal fetal medicine specialists, cardiologists, and hematologists who care for women with MHVs. Guidelines, based largely on small retrospective series with incomplete data, are used in an attempt to navigate this difficult field. However, in the preconceptual counseling of women with MHV, it is important to emphasize that even with meticulous anticoagulation and thoughtful coordinated care, the risk for valve thrombosis as well as maternal and fetal adverse outcomes is still high.

In this issue of Circulation, Van Hagen and colleagues report on data from their prospective multi-center registry and add significant numbers to the existing literature on outcomes of pregnancy in women with mechanical and bioprosthetic heart valves. This data was extracted from the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC), initiated in 2008. The authors report the outcomes of 212 women with a MHV who experienced pregnancy, and compare the outcomes to 2620 patients with heart disease and 134
patients with a bioprosthetic valve. Additionally, they stratified outcomes for women by valve type and by emerging or developed country status. Maternal mortality was defined as a death occurring during pregnancy or up to one week after delivery. This definition deviates from the standard definition of maternal mortality that extends up to 42 days postpartum, and may reflect lack of available follow-up data. Given that hypercoagulable changes persist and may even increase postpartum, it is possible that the risk of mortality may therefore be underrepresented in this population.

In women with a MHV, van Hagen and colleagues report a 1.4% risk of maternal mortality and multiple significant morbidities including a 23% risk of hemorrhage and an 18.4% risk of fetal loss. Valve thrombosis occurred in 4.7% of those studied and was associated with a 20% maternal mortality. Strikingly, half of the valve thromboses occurred during the first trimester; notably, all affected women had been switched to some form of heparin. Interestingly, there was no significant difference in the occurrence of valve thrombosis in the mitral or aortic positions.

The authors must be commended on their collaborative efforts to catalogue the factors associated with pregnancy complications in women with heart disease. It is through efforts such as this that we will better understand how to counsel and follow women with heart disease during pregnancy. However, this type of analysis highlights one of the central issues with the management of MHVs in pregnancy, which is the lack of a standard plan of care. The choice of anticoagulant and the management for each varied widely, and the details regarding transition from one anticoagulant to another are unknown. For example, the authors attempted to broadly group the patients into six different anticoagulation regimens (Figure 3); however, despite this, 24 women were on alternative therapies, and for an additional 26 women, the anticoagulation
strategy was not listed due to fetal loss in the first trimester. The diverse management of anticoagulant strategies is further exemplified by the fact that the number of anti-Xa measurements per subject varied between 3 and 42, and that only 57% of women receiving LMWHs had anti-Xa levels documented. This finding is problematic, as a high level of vigilance is needed with anticoagulant management in pregnancy. For example, the requirements of LMWHs increase throughout pregnancy, and anti-Xa levels should be checked 4 to 6 hours after administration if dose-adjusted administration of LMWHs is used.

Current AHA/ACC guidelines suggest that it is reasonable to continue warfarin in the first trimester if the dose necessary to achieve a therapeutic INR is 5mg/day or less (Class IIa). For women whose warfarin dose is above 5mg/day, the guidelines suggest that dose-adjusted LMWHs be used in the first trimester (target anti-Xa level of 0.8–1.2 U/ml, 4–6 hours post-dose). However, the data from van Hagen and colleagues indicates that 50% of the mechanical valve thrombosis occurred in women who were undergoing transition from a VKA to a LMWH in the first trimester. This valuable insight from the study suggests that this may be a particularly vulnerable time in this patient population. As has been noted previously, many of the thromboembolic complications in women with MHVs are associated with anti-Xa levels that are sub-therapeutic; this is more likely to occur if anti-Xa levels are not monitored.

There is also emerging data to suggest that trough values may play as important a role as peak values in maintaining anticoagulation in the pregnant woman with a MHV. Serum levels will vary across gestation due to the increased volume of distribution and increased clearance. In general, pregnant women will need higher than expected doses of LMWHs to achieve target anticoagulation. One small but detailed retrospective study looked at pregnant women with MHV and suggested an overall mean dose increase to 1.3 mg/kg every 12 hours, compared with
1mg/kg every 12 hours, to achieve a peak anti-Xa level of 1.0–1.2 U/ml. In this same population of women, the mean dose needed to achieve peak levels at 1.2 U/ml was not enough to obtain the minimum target trough level for anti-Xa (>0.6 U/mL). This suggests that when transitioning women to LMWHs from VKAs, the dose may need to be increased in order to achieve adequate anticoagulation. There were no adverse clinical outcomes related to the dosing of LMWHs. Larger prospective studies that look at both peak and trough anti-Xa values are essential to understanding the effects of variation in anti-Xa levels on maternal and fetal outcomes.

In registry data such as that presented by van Hagen and colleagues, there is no documentation of INR levels in the women taking VKAs, which also makes it challenging to determine the efficacy and safety of such agents. However, these data do provide insight into the different anticoagulant management strategies in developed versus emerging countries, such as the preferred use of unfractionated heparin in emerging countries. An additional concerning finding is that only 13 of the 212 (6.1%) patients were taking aspirin in the second and third trimesters. Recent guidelines recommend low-dose aspirin daily in the second and third trimesters for pregnant patients with either a mechanical prosthesis or bioprosthesis.

Interestingly, no cases of classic warfarin embryopathy were described by van Hagen and colleagues. Two neonates were born with congenital heart disease and two cases with term hydrocephalus. The findings would lend support to the use of VKA in the first trimester in appropriately selected patients, particularly, as suggested above, in women whose dose is less than 5mg/day.

An important finding was the significant increase in bleeding complications among women with a MHV compared to women without a prosthetic heart valve. The majority of hemorrhages occurred around the time of delivery, and the overall rates of hemorrhage were high...
(23% of MHV patients), findings possibly attributable to the high rate of cesarean sections that occurred in their patient population. Cesarean deliveries and preterm cesarean deliveries were more common in developed countries, which may explain the higher rates of hemorrhage seen. The indications for mode of delivery were not elucidated, but one might wonder if women underwent cesarean delivery for the indication of “cardiac disease.” Current guidelines support that mode of delivery should be guided by standard obstetric indications, for example, failure to progress in labor, malpresentation, or maternal or fetal contraindication to labor. One exception is women on VKAs at the time of delivery, which is due to concern for fetal bleeding risk. Despite systematic support for vaginal delivery in women with cardiac disease, the use of cesarean delivery in this population is widespread and, ultimately, will lead to more complications from hemorrhage during delivery and postpartum. Centralizing the care for these women to appropriate centers with 24-hour availability of cardiology, anesthesia, surgery, and high-risk obstetrics may mitigate the concerns regarding induction of labor and vaginal birth.

In summary, the current study by the ROPAC Investigators reports the outcomes of a large and heterogeneous group of pregnant women with heart disease, and documents that more than 40% of pregnancies in women with MHVs were associated with serious complications. While this data highlights the risks associated with MHVs in pregnancy, it is difficult to draw meaningful conclusions due to the heterogeneous nature of the patient population. However, this manuscript draws attention to several specific areas of concern that may suggest areas of future investigation or changes in our current practice. These include:

1. The meticulous attention needed in transitioning women from VKAs to various forms of heparin, the understanding of the significance of checking both peak and trough anti-Xa levels,
and the reconsideration of the optimal anti-Xa levels in pregnant women at high risk of MHV thrombosis.

2. The realization that the mode of delivery has direct effects on maternal outcomes, with cesarean delivery associated with much greater risks of hemorrhage during delivery and postpartum. Strategies to increase vaginal delivery will likely help decrease hemorrhage rates.

3. The importance of ensuring that women with MHV are on low-dose aspirin in the second and third trimesters of pregnancy.

Registry data such as that provided by van Hagen and colleagues emphasizes the fact that no pregnancy in a woman with a MHV should be considered safe, and that this must be taken into account when counseling women of reproductive age in need of prosthetic heart valve surgery. The risks of various anticoagulation strategies must be acknowledged and the choice of anticoagulant individualized through thoughtful considerations by a dedicated team of cardiologists, high-risk obstetricians, anesthesiologists, and surgeons. A shared responsibility for meticulously monitoring anticoagulant levels and developing a thoughtful delivery plan must be accepted by both the mother and the care team in order to optimize care and decrease risk.

Conflict of Interest Disclosures: None.

References:


