Valvular Heart Disease in Pregnancy: Anticoagulation and the Role of Percutaneous Treatment

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Abstract: Valvular heart disease is present in about 1% of pregnancies, and it poses a management challenge as both fetal and maternal lives are at risk of complications. Pregnancy is associated with significant hemodynamic changes, which can compromise the cardiac status in women with underlying valvular disorders. Management of valvular heart diseases has undergone considerable innovation and advancement with newer techniques, approaches and devices being employed. The decision regarding the management of anticoagulation, especially in patients with prosthetic valves, raises distinct questions and challenges. In this review, we describe the management of common valvular heart diseases encountered during pregnancy, role of percutaneous catheter based therapeutic interventions, the importance of a team-based approach, and the challenges given existing gaps in the literature. (Curr Probl Cardiol 2021;46:100679.)

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Introduction

Cardiovascular disease contributes to almost 50% of the total maternal mortality. Maternal mortality is defined as death during or soon after pregnancy and the United States is one of eight countries where maternal mortality is on the rise. Valvular heart disease (VHD) is present in 1% of total pregnancies and approximately 1 in 3 of pregnant women with heart diseases have VHD.[1-3] Significant hemodynamic changes occur in pregnancy, including an increase in cardiac output (CO), stroke volume, heart rate and physiological anemia. It is imperative to understand the cardiac physiology of pregnancy in order to predict which valvular lesions may do poorly with the hemodynamic stress of pregnancy. In addition, the hypercoagulable state of pregnancy increases thromboembolic risk associated with certain valvulopathies. Due to major surgical and medical advances, there has been an increase in the number of women with congenital and acquired cardiac disease who reach childbearing age.[4] Congenital heart disease is the most common etiology of VHD in western countries, while rheumatic heart disease remains more common in developing countries.[5,6] Other causes of VHD include connective tissue disorders, myxomatous valve disease, infective endocarditis, Marfan's syndrome, systemic lupus erythematous and prosthetic heart valve disorders.[7]

The risk of decompensation in pregnant women due to VHD varies based on the type and severity of the underlying condition. Generally, stenotic lesions carry a higher risk of complications than regurgitant pathologies, as the increased CO increases the transvalvular gradients.[8] In addition, increased heart rates associated with pregnancy causes increased gradients in women with mitral stenosis. In contrast, the afterload reduction and decrease in systemic vascular resistance (SVR) of pregnancy may be beneficial for women with regurgitant lesions.

Pregnancy in itself is a hypercoagulable state associated with increased risk of thromboembolism.[9] There are accelerated rates of thrombus formation and fibrinolysis that is required to achieve hemostasis within the placenta to minimize blood loss during delivery.[10] Valve thrombosis in pregnancy is a potentially life-threatening complication, and maintaining adequate anticoagulation is essential to reduce the risk of thromboembolic events.[11]

The management of VHD is challenging in pregnancy given the need to balance maternal and fetal effects of therapies. Despite the advances in diagnostics and therapeutic options, there are challenges and potential for adverse events to the mother and the fetus. It is crucial that an

experienced multi-disciplinary team care for these patients to help ensure the best possible outcomes. This article will focus on the common VHDs encountered during the pregnancy, management strategies, potential role of percutaneous, catheter-based therapeutic interventions and anticoagulation management.

Risk Assessment

With close observation, prenatal counseling, and careful titration of cardiac medications, most women with VHD tolerate pregnancy without complications. However, some of these VHDs are poorly tolerated in pregnancy and require aggressive management. Ideally, women with known VHD should have pre-conception counseling with experts familiar with heart disease management in pregnancy. Women benefit from careful evaluation, management and counseling before, during and after their pregnancy (Table 1). The European Society of Cardiology (ESC) guidelines on the management of heart disease during pregnancy recommend risk assessment of all women of childbearing age, using the Modified World Health Organization (mWHO) classification of maternal risk (Table 2).[12] Management recommendation ranges from simple surveillance in a patient with mWHO class I to contraindication or termination of pregnancy in patients with mWHO class IV. Other notable risk scores commonly used include CAPREG II (Cardiac Disease in Pregnancy) risk score and ZAHARA (Zwangerschapp bij SAangeboren HARtAwijkingen I) risk score.[13] Although risk assessment can be performed with available risk scores, the WHO classification allows for lesion-specific assessment and should be utilized for women with VHD.

ESC guidelines recommend that women with a moderate or high risk of complications during pregnancy (greater than mWHO class II) should be referred for preconception counseling and management to a multi-disciplinary pregnancy heart team, including a cardiologist, an obstetrician, and anesthesiologist, with expertise in the management of high-risk

Table 1. Preconception evaluation in women with valvular heart disease

- Careful history and physical examination
- 12 lead electrocardiogram
- Echocardiogram including assessment of left and right ventricular and valve function
- Exercise test to be considered for objective assessment of functional classification
- Careful counselling for maternal risks of complications and mortality, information on choices of therapy, risk of miscarriage, risk of early delivery, and small for gestational age and when applicable, risk of fetal congenital defect

Table 2. Modified World Health Organization classification of maternal valvular heart diseases

	mWHO I	mWHO II	mWHO II-III	mWHO III	mWHO IV
Diagnosis	- Small MVP - Trivial AR - Mild PS - Mild TR	- Mild MR - Mild AS - Moderate PS - Moderate TR	- Mild MS - Moderate AS - Severe PR - Mild left ventricular impairment (EF > 45%)	- Moderate MS - Severe asymptomatic AS - Severe PS - Severe TR - Moderate left ventricular impairment (EF 30-45%)	- Severe MS - Severe symptomatic AS - Pulmonary arterial hypertension - Severe systemic ventricular dysfunction (EF < 30% or NYHA Class III-IV)
Risk	No detectable increased risk of maternal mortality and no/mild increased risk of morbidity	Small increased risk of maternal mortality or moderate increase in morbidity	Intermediate increased risk of maternal mortality or moderate to severe increase in morbidity	Significant increased risk of maternal mortality or severe morbidity	Extremely high risk of maternal mortality or severe morbidity

MVP = Mitral Valve Prolapse; AR = Aortic Regurgitation; PS = Pulmonary Stenosis; TR = Tricuspid Regurgitation; MR = Mitral Regurgitation; AS = Aortic Stenosis; MS = Mitral Stenosis; PR = Pulmonary Regurgitation

pregnancies in women with heart disease. Additional experts such as geneticists, cardiothoracic surgeons, pediatric cardiologists, pulmonologists, maternal-fetal medicine specialists, neonatologists, hematologists, and nurse specialists may be involved as appropriate. The patient should be counseled about the severity of the valvular lesion, maternal and fetal risks, and consideration of percutaneous intervention or surgical replacement of valve prior to pregnancy. Women with mWHO IV high-risk VHD should be counseled against pregnancy unless the valvular lesion can be corrected. During pregnancy, consideration should be made regarding timing and mode of delivery, risk of anesthesia, and predicted success of medical therapy. For high-risk pregnancies, serial echocardiography and regular follow up is routinely required.

Intervention during pregnancy

Indications for percutaneous or surgical intervention in women is similar to non-pregnant patients with VHD. If deemed necessary, most of the interventions are performed during the fourth month of pregnancy as the organogenesis is complete and the uterine volume is low. However, during pregnancy, cardiac surgery should be avoided if possible due to the significant adverse risk associated with non-pulsatile blood flow and decreased placental perfusion during cardiopulmonary bypass.[14] Surgery is usually reserved for life threatening situations when medical interventions have failed and percutaneous options are not feasible.

Stenotic lesions

In stenotic lesions such as mitral and aortic stenosis, increased cardiac output causes an increase in the transvalvular gradient, thereby increasing risk of maternal complications such as volume overload and pulmonary edema.

Mitral stenosis (MS) and Percutaneous Transvenous Mitral Commissurotomy (PTMC). Rheumatic heart disease is the most common cause of MS among women of childbearing age worldwide. In developed countries, congenital heart disease is more common. Pulmonary edema and arrhythmias, primarily valvular atrial fibrillation with potential thromboembolic events, are the most common complications during pregnancy.[8,15] Moderate to severe MS is usually poorly tolerated during pregnancy due to increased mitral gradients due to the volume load of pregnancy and the increased heart rates that further worsen the gradients.

Percutaneous Transvenous Mitral Commissurotomy (PTMC), also known as percutaneous mitral balloon valvuloplasty, was developed in 1984 for the treatment of selected patients with MS.[16,17] It is a minimally invasive procedure performed under local anesthesia. Balloon dilation of the stenotic mitral valve improves hemodynamics by decreasing the transmitral gradient and thereby, reducing pulmonary artery and pulmonary capillary wedge pressure.[18] It is associated with significantly less maternal and fetal complications and mortality compared to open mitral valve commissurotomy.[19] Wilkins score is used to determine anatomic suitability for PMBV. In women with unfavorable anatomy, PTMC may be considered as the initial method of treatment in women with mild to moderate calcifications or impaired sub-valvular apparatus with other favorable characteristics. Potential complications of the procedure include mitral regurgitation (most common), atrial perforation, cardiac tamponade, arrhythmias and emboli formation. Presence of left atrial thrombus is a contraindication for PTMC due to the risk of dislodging the thrombus during the procedure. Therefore, transesophageal echocardiogram (TEE) is mandatory prior to PTMC to exclude the thrombus.[20,21]

Women with significant MS should be counseled against pregnancy, especially if the valve area is $< 1.0\ cm^2$. However, in women with a desire for pregnancy with moderate to severe MS, PTMC should be considered before pregnancy if valve morphology is favorable for intervention and valve area is $\leq 1.5\ cm^2$, even if the patient is asymptomatic.[22] If hemodynamic compromise (NYHA class III/IV symptoms and/or systolic pulmonary artery pressure $\geq$ 50 mmHg) persists during pregnancy despite optimal medical management such as diuretics and beta blockers, PTMC may be performed, ideally after 20 weeks of gestation in the absence of other contraindications.[12] Patients with severe mitral stenosis should be managed in tertiary care facilities with a valve team and cardio-obstetrics team familiar with the hemodynamic changes of pregnancy. Other possible sequelae of mitral stenosis such as pulmonary hypertension and atrial arrhythmias such as atrial fibrillation need to be considered and managed carefully.

Aortic stenosis (AS) - Transcatheter Balloon Aortic Valvuloplasty (BAV) and Transcatheter Aortic Valve Implantation (TAVI). Congenital bicuspid aortic valve is the most common cause of AS in women of childbearing age, followed by rheumatic heart disease.[7] Mild to moderate AS is usually well tolerated in pregnancy. However, severe AS is associated with increased maternal and fetal morbidity.[23] Women with severe, symptomatic AS should be strongly considered for valve intervention prior to pregnancy due to high risk of complications such as heart failure, arrhythmias,

and adverse fetal outcomes such as preterm birth and low birth weight.[24,25] Pregnant women with severe symptomatic unstable AS may require more acute intervention and can be considered for transcatheter BAV as a bridge.[25] BAV may provide a small increase in valve area which helps improve stroke volume and allows time for pregnancy to progress. It avoids the risk of valve replacement during pregnancy and may reduce hemodynamic complications of labor, and delivery.[26,27] However, it must be performed cautiously by an experienced operator to mitigate the risk of potential complications, particularly acute aortic regurgitation. Data on BAV for severe symptomatic AS in pregnancy is sparse.

The presence of aortic coarctation and associated congenital valve abnormalities such as bicuspid aortic valve should be excluded, given the associated risk of aortic dissection.[28] In asymptomatic women with severe AS without left ventricular dysfunction, pregnancy can be managed with close surveillance and close attention to volume status. The hemodynamic stress of labor and delivery requires pre-delivery anesthesia and obstetric planning as epidural anesthesia and the subsequent drop in SVR can cause hemodynamic instability. Close monitoring of blood pressure and volume status are needed during and after delivery.

TAVI is an alternative method of treating symptomatic severe AS and may be considered as an alternative to surgical replacement in select patients. TAVI during pregnancy is a possible alternative to surgical valve replacement considering the high fetal risk of surgery, including placental hypoperfusion caused by cardiopulmonary bypass. However, the data on TAVI in pregnant women is still very limited.[29] Pre-TAVI evaluation should be performed by a multidisciplinary heart team. Consideration must be given to the cardiac and extracardiac characteristics of the patient, risk of contrast injection, radiation, the feasibility of TAVI, and local experience and outcome data. In addition, etiology of AS in young women is more likely to be from bicuspid valves and there is limited data on use of TAVI in this population. Potential limitations of TAVI in pregnancy include suboptimal result, conduction abnormality which might require a pacemaker, increased risk of aortic dissection in a patient with aortopathy, and unknown long-term durability. However, with careful assessment and planning, TAVI can be a treatment option for severe symptomatic AS during pregnancy who remain symptomatic despite medical therapy.[30]

Regurgitant lesions

Regurgitant lesions such as mitral regurgitation (MR) and aortic regurgitation (AR), tend to be well tolerated during pregnancy due to the

decrease in SVR associated with pregnancy. The most common causes of MR during pregnancy are rheumatic heart disease and mitral valve prolapse. Chronic MR is usually well tolerated in pregnancy due to a fall in SVR and subsequent reduced left ventricular afterload which occurs during pregnancy. Patients with chronic mitral regurgitation rarely need acute intervention in pregnancy.[31-33] Women with severe, symptomatic MR, and women with acute MR (usually due to papillary muscle rupture after myocardial infarction) during pregnancy are at risk of decompensated heart failure.[34] Efforts should be made to stabilize the patient medically with diuretics and possibly with additional afterload reduction with medications. Although percutaneous mitral valve repair, or mitral clip, is a less invasive alternative to surgery, it has not been studied or approved for clinical use in pregnant patients in the United States.

The most common cause of AR during pregnancy is bicuspid aortic valve. AR is also well tolerated in pregnancy. Chronic severe aortic regurgitation usually does not lead to clinical decompensation as the drop in SVR and the increased heart rate associated with pregnancy decrease the hemodynamic effect of the regurgitation. In rare cases of acute AR, such as due to aortic dissection or aortic valve endocarditis, patients may develop acute heart failure.[26] TAVI may be considered for patients with acute AR to avoid the risk of surgical complications. It is not uncommon to have patients with mixed complex valve disease. These patients need to be followed with frequent clinical follow up, echocardiogram, and serial brain natriuretic peptide (BNP) levels.[12,35] Care of these patients must be individualized as the combination of AS and AR can lead to challenges in assessing valve gradients by echocardiogram, especially given the increased cardiac output of pregnancy. Lastly, bicuspid aortic valve can be associated with aortopathies and multi-modality imaging with echocargiogram and cardiac MRI may be needed to assess aortic dimension and changes over time.

Bioprosthetic valve degeneration and role of valve-in-valve implantation

Pregnant women with bioprosthetic valve degeneration can worsen during pregnancy. Hanania et al. reported valvular degeneration in 7 of 74 bioprosthetic heart valves in pregnant patients, while Sbarouni and Oakley et al. reported valvular degeneration in 17 of 49 women.[36,37] Sadler et al. reported valvular degeneration in 10% of pregnant patients with mitral bioprosthetic valves.[38] Until a few years ago, redo open heart surgery was the only feasible option. Recently, transcatheter valve-in-

valve implantation has been employed with some success in improving maternal and fetal outcomes. There have been several cases reported with a high procedural success rate with bioprosthesis degeneration and valve-in-valve implantation in single and multiple heart valves during pregnancy.[39-41] However, there is a possibility of developing patient-prosthesis mismatch with this procedure if the effective orifice area of the prosthetic valve is not appropriate for the patient's body surface area.[42] The data on valve-in-valve implantation is still very limited, and further research is required to explore its use in pregnant patients.

Risks and benefits of percutaneous treatment during pregnancy

While still invasive, transcatheter-based interventions present a relatively lower risk therapeutic approach compared with open cardiac surgery.[43] However, these interventions do pose specific risks both to maternal and fetal well-being. Fetal risk of complications is mainly due to the radiation and contrast exposure as well as hemodynamic instability that may occur during intervention. The effects of radiation exposure depend on the radiation dose and the gestational age of the fetus. The radiation dose below 50 mGy is considered safe for the fetus, while doses above 100-150 mGy may result in adverse effects including miscarriage, growth reduction and mental retardation at birth.[44] Percutaneous interventions performed during pregnancy generally deliver radiation that is below this threshold. The fetus is most susceptible to the adverse effects of radiation at the time of organogenesis during the first trimester. The second trimester is considered the most ideal time to perform a percutaneous intervention. This is when organogenesis is complete, the fetal thyroid is still inactive, and there is greater distance between the fetus and the chest of the mother resulting in a lower risk of cancer.[45] Measures to reduce radiation exposure include using the radial approach, minimizing fluoroscopy time, small collimated beam sizes, using echo guidance whenever possible, and using a shield to protect the fetus.[46]

Anticoagulation for mechanical heart valves during pregnancy

Pregnancy is a prothrombotic state that is associated with a higher thromboembolism risk, especially in patients with VHD. Maintaining adequate anticoagulation is essential to reduce this risk. However, the choice of anticoagulation and maintaining optimal anticoagulation remains challenging due to adverse maternal and fetal risks. Data from randomized prospective controlled trials is lacking in this population.[47]

Recent report from Registry of Pregnancy and Cardiac Disease (ROPAC) compared outcomes in pregnant patients with mechanical, bioprosthetic and with no prosthetic valves.[48] Patients with mechanical valves had valvular thrombosis in 4.7% of patients, with higher rate of fetal loss. The rate of valve thrombosis is higher in mechanical valves in the mitral or tricuspid positions.[47]

Anticoagulation in patients with mechanical heart valves during pregnancy is a challenging problem that requires careful shared decision making and close monitoring. The annual risk of a thrombotic event in patients not taking anticoagulation is approximately 4%, whereas the risk in those on appropriate anticoagulation is 1%.[49] The risks of various anticoagulation strategies must be discussed with the patient, and a shared responsibility for meticulous anticoagulation monitoring should be accepted both by the patient and the physician to optimize care and balance the risks of bleeding and thrombosis.

Vitamin K antagonists

Vitamin K antagonists (VKAs) remain the most effective anticoagulation regimen to prevent mechanical valve thrombosis.[50] However, it crosses the placental barrier and has been known to cause embryopathic effects, with a reported incidence between 0.6%-10%.[51] Controversy exists between balancing the risk of valve thrombosis versus potential teratogenic effects to fetus. Current guidelines of the European Society of Cardiology and the American College of Cardiology recommend continuing VKAs in the first trimester of pregnancy if the therapeutic dose is less than 5 mg/day as the risk of fetal embryopathy appears to be dose related(class IIa).[23,52] Alternatively, change to unfractioned heparin (UFH) or low molecular weight heparin (LMWH) can also be made in the hospital setting (class IIb). In second and third trimester, current guidelines support VKAs as the preferred choice (class Ic). At 36 weeks of pregnancy, VKA is switched in a hospital setting to UFH or LMWH (class Ic), with switch to UFH 36 hours prior to the planned delivery[20] (figure 1). If the dose of VKA exceeds 5 mg, then consideration of changing to UFH or LMWH (with careful monitoring of anti-factor Xa levels) in the first trimester is suggested (class IIa).[53] During second and third trimester, switch to VKA should be made in the hospital setting (class IIa) (figure 2). Women must be counseled that even though the fetal risk seems to be dose related, low dose does not completely eliminate the risk of embryopathic effects. Also, use of VKAs in the second and third trimester has been associated with neurological sequelae and increased risk

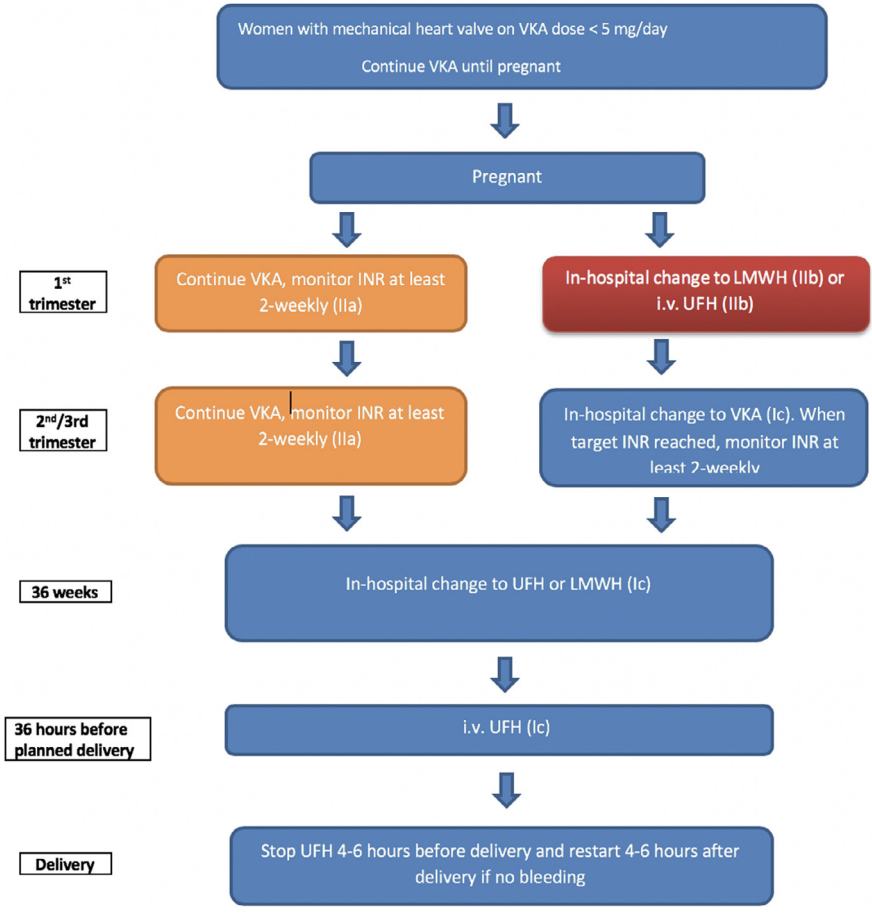

Figure 1. Flowchart on anticoagulation in mechanical valves and low-dose VKA

of fetal hemorrhage in a dose-dependent manner, especially in patients requiring higher doses to maintain therapeutic anticoagulation.[54,55]

Unfractionated heparin

Unfractionated heparin (UFH) does not cross the placenta, however, it can cause heparin-induced thrombocytopenia (HIT) and osteoporosis during pregnancy.[56] Subcutaneous dosing of unfractionated heparin is not reliable to prevent prosthetic valve thrombosis, but IV heparin is recommended around the time of delivery. At 36 weeks of pregnancy, UFH or LMWH are the preferred choice of anticoagulation, and the switch should be made in the hospital setting. However, switch to UFH must be made

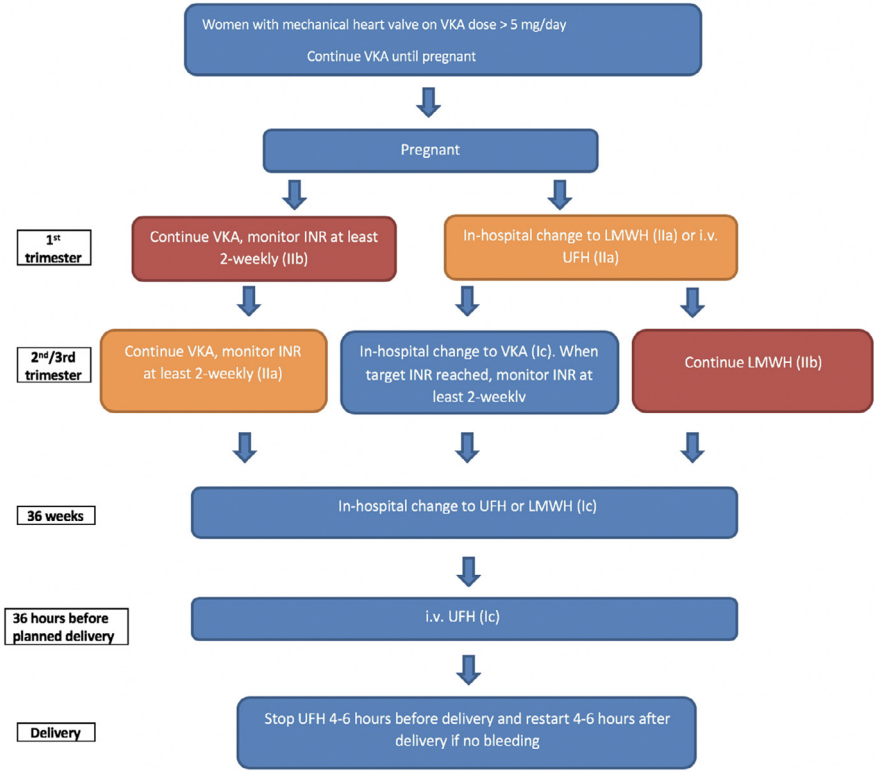

Figure 2. Flowchart on anticoagulation in mechanical valves and high-dose VKA

36 hours before planned delivery with aPTT target of $\geq$ 2 times the normal. Transitioning from VKA to UFH around the time of delivery is recommended due its short half-life and the ability to quickly reverse its anticoagulant effects with protamine.[57] It is also preferred over LMWH in patients with renal insufficiency.

Low molecular weight heparin (LMWH)

LMWH does not cross the placenta and is safe in pregnancy. It provides a more predictable anticoagulant response and the incidence of HIT and heparin-induced osteoporosis is markedly lower compared to UFH.[58] ESC and ACC suggest that patients on VKA > 5 mg/day can be switched to LMWH during the first trimester to decrease the risk of embryopathy (class IIa). Switching from one anticoagulation to another poses a serious risk of therapeutic failure, and needs to be done cautiously and ideally in an inpatient setting.[48] Most of the reported cases of mechanical heart

valve thromboses in LMWH treated patients have been due to inadequate dosing, lack of monitoring, or subtherapeutic anti-factor Xa levels.[59] The potential switch from VKA to LMWH should be done in a hospital setting where patients can be closely monitored. In a patient on LMWH, twice-daily dosing with weekly peak anti-factor Xa level of 0.8-1.2 IU/mL, 4-6 hour post-dose, and trough level of $>$ 0.6 IU/mL is recommended in low risk patients (bileaflet prosthetic valve in aortic position without additional risk factors) and $>$ 0.7 IU/mL in high risk patients (prosthetic valve in mitral and tricuspid positions, and additional hypercoagulable conditions).[20,60,61] Elkayam et al. suggested that the dose of LMWH should be guided by the trough anti Xa levels, while the peak should be used to avoid over anticoagulation.[62] After the first trimester, patients can either be continued on LMWH throughout the pregnancy (class IIb) or switched to VKA during the second and third trimester (class IIa). Considering there is no reversal agent, LMWH should be switched to UFH prior to delivery (class Ic).

Direct-acting oral anticoagulants

Direct oral anticoagulants (DOACs) have replaced VKA for certain conditions in the general population. However, they are contraindicated in pregnancy as they can cross the placenta and result in embryopathy.[63] If a patient on a DOAC is planning to conceive, it should be switched to VKA or LMWH prior to conception.[64]

Anticoagulation for valvular atrial fibrillation

Women with MS have an increased risk of atrial fibrillation (AF), thereby causing systemic embolization. Anticoagulation is recommended in pregnant patients with MS and AF. LMWH is the preferred mode of anticoagulation in the first trimester to minimize teratogenic risk, followed by VKAs or LMWH in the second and third trimester, with switch to UFH before delivery.[12,65] Cardioversion is also a safe option during pregnancy, but the choice depends on patient tolerance of severity of the underlying valve disease.

General considerations for labor and delivery in women with valvular heart disease

Expertise in cardiac physiology during pregnancy allows the obstetrician, anesthesiologist and cardiologist to appropriately counsel and manage labor and delivery. General management strategies for women with

cardiac disease include monitoring of strict input and output of fluids, maternal positioning in left lateral tilt, careful control of bleeding, oxygen supplementation, and adequate pain control.[66] Decisions regarding mode of delivery must consider the patient's valvular lesion and severity, symptom status, concomitant pathology such as aortopathies, and fetal indications. Most maternal cardiac pathology allows for careful vaginal delivery with consideration for assisted second phase of labor. In general, cesarean delivery is reserved for obstetric indications. Delivery planning should be discussed in advance with a multi-disciplinary labor team with experience in labor hemodynamics.

There are particular considerations for labor management for specific valve diseases. Women with severe mitral stenosis require careful monitoring of vitals to avoid tachycardia, which can result in shortening diastolic filling time and precipitate pulmonary edema. Strict monitoring of fluids and surveillance for atrial fibrillation, pulmonary edema and right ventricular failure are also important.[67] In women with severe mitral stenosis and secondary severe pulmonary hypertension, expertise in management of pulmonary hypertension is critical as the hemodynamic stressors of labor and delivery can precipitate decompensation and acute right ventricular failure. In women with aortic stenosis, decrease in systemic vascular resistance from placement of regional anesthesia or blood loss during the third stage of labor can lead to severe refractory hypotension. Aortic or mitral insufficiency is usually well tolerated, but increases in systemic vascular resistance may worsen regurgitation and careful pain management and monitoring of fluid intake and output is indicated. Myocardial depressant drugs should be avoided.

Conclusion

With increased utilization of assistive reproductive technologies and pregnancies at a later age, there is an increase in the number of pregnant women with VHD. Stenotic lesions are less well-tolerated due to hemodynamic alterations described earlier in this review. Percutaneous interventions can be considered for stenotic valve lesions in symptomatic pregnant women. Regurgitant lesions typically fare better. Due to advances in treating congenital heart disease and transcatheter based valve interventions, it is expected that there will be an increase in the number of pregnant women with prosthetic valves. This will continue to pose new challenges in terms of the long-term valve durability and management of thrombotic risks. The risk-benefit of any approach would need to be carefully discussed with the patient and shared-decision making

utilized in developing management strategies. More data is needed, especially in the rapidly evolving field of transcatheter-based therapies, for the treatment VHD in pregnancy. The safety of various anticoagulants in mitigating the risks of both bleeding and thromboembolic complications also needs further investigation. A team-based approach, through collaborative cardio-obstetric programs play a key role in optimizing the personalized management of this special patient population with VHD. Consideration of timing and mode of delivery, safety of cardiac medications and safety and appropriateness of imaging modalities should be made by clinicians with expertise and experience in management of cardiac disease in pregnancy.

REFERENCES

1. Khanom M, HA. Valvular heart disease in pregnancy: A review. *J Indian Coll Cardiol* 2015;5(3):177–82.
2. Stout KK, Otto CM. Pregnancy in women with valvular heart disease. *Heart* 2007;93 (5):552–8.
3. Lima FV, Yang J, Xu J, Stergiopoulos K. National Trends and In-Hospital Outcomes in Pregnant Women With Heart Disease in the United States. *Am J Cardiol* 2017;119 (10):1694–700.
4. Soler-Soler J, Galve E. Worldwide perspective of valve disease. *Heart* 2000;83 (6):721–5.
5. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001;104(5):515–21.
6. Diao M, Kane A, Ndiaye MB, et al. Pregnancy in women with heart disease in sub-Saharan Africa. *Arch Cardiovasc Dis* 2011;104(6-7):370–4.
7. Nanna M, Stergiopoulos K. Pregnancy complicated by valvular heart disease: an update. *J Am Heart Assoc* 2014;3(3):e000712.
8. Hameed A, Karaalp IS, Tummala PP, et al. The effect of valvular heart disease on maternal and fetal outcome of pregnancy. *J Am Coll Cardiol* 2001;37(3):893–9.
9. Battinelli EM, Marshall A, Connors JM. The role of thrombophilia in pregnancy. *Thrombosis* 2013;2013:516420.
10. Brenner B. Haemostatic changes in pregnancy. *Thromb Res* 2004;114(5-6):409–14.
11. Gupta R, Ranchal P, Harburger J. Mechanical Valve Thrombosis in a Pregnant Patient: A Case of Therapeutic Failure. *Cureus* 2019;11(9):e5615.
12. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2018;39 (34):3165–241.
13. Balci A, Sollie-Szarynska KM, Van Der Bijl AG, et al. Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. *Heart* 2014;100(17):1373–81.

14. John AS, Gurley F, Schaff HV, et al. Cardiopulmonary bypass during pregnancy. *Ann Thorac Surg* 2011;91(4):1191–6.
15. Silversides CK, Colman JM, Sermer M, Siu SC. Cardiac risk in pregnant women with rheumatic mitral stenosis. *Am J Cardiol* 2003;91(11):1382–5.
16. Inoue K, Owaki T, Nakamura T, Kitamura F, Miyamoto N. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* 1984;87(3):394–402.
17. Lock JE, Khalilullah M, Shrivastava S, Bahl V, Keane JF. Percutaneous catheter commissurotomy in rheumatic mitral stenosis. *N Engl J Med* 1985;313(24):1515–8.
18. Dev V, Shrivastava S. Time course of changes in pulmonary vascular resistance and the mechanism of regression of pulmonary arterial hypertension after balloon mitral valvuloplasty. *Am J Cardiol* 1991;67(5):439–42.
19. De Souza JA, Martinez EE, Jr., Ambrose JA, et al. Percutaneous balloon mitral valvuloplasty in comparison with open mitral valve commissurotomy for mitral stenosis during pregnancy. *J Am Coll Cardiol* 2001;37(3):900–3.
20. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63(22):e57–185.
21. Salem DN, O'gara PT, Madias C, Pauker SG. Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133(6 Suppl):593S–629S.
22. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38(36):2739–91.
23. 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(23):2440–92.
24. Silversides CK, Colman JM, Sermer M, Farine D, Siu SC. Early and intermediate-term outcomes of pregnancy with congenital aortic stenosis. *Am J Cardiol* 2003;91(11):1386–9.
25. Orwat S, Diller GP, Van Hagen IM, et al. Risk of Pregnancy in Moderate and Severe Aortic Stenosis: From the Multinational ROPAC Registry. *J Am Coll Cardiol* 2016;68(16):1727–37.
26. Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society Of C. Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J* 2003;24(8):761–81.
27. Banning AP, Pearson JF, Hall RJ. Role of balloon dilatation of the aortic valve in pregnant patients with severe aortic stenosis. *Br Heart J* 1993;70(6):544–5.
28. Mckellar SH, Macdonald RJ, Michelena HI, Connolly HM, Sundt TM, 3rd. Frequency of cardiovascular events in women with a congenitally bicuspid aortic valve in a single community and effect of pregnancy on events. *Am J Cardiol* 2011;107(1):96–9.
29. Cauldwell M, Johnson M, Jahangiri M, Roos-Hesselink J. Cardiac interventions and cardiac surgery and pregnancy. *Int J Cardiol* 2019;276:43–7.

30. Hodson R, Kirker E, Swanson J, Walsh C, Korngold EC, Ramelli S. Transcatheter Aortic Valve Replacement During Pregnancy. *Circ Cardiovasc Interv* 2016;9(10).
31. Whitlow PL, Feldman T, Pedersen WR, et al. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. *J Am Coll Cardiol* 2012;59(2):130–9.
32. Fattouch K, Guccione F, Sampognaro R, et al. POINT: Efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation: a randomized trial. *J Thorac Cardiovasc Surg* 2009;138(2):278–85.
33. Smith PK, Puskas JD, Ascheim DD, et al. Surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med* 2014;371(23):2178–88.
34. Van Hagen IM, Thorne SA, Taha N, et al. Pregnancy Outcomes in Women With Rheumatic Mitral Valve Disease: Results From the Registry of Pregnancy and Cardiac Disease. *Circulation* 2018;137(8):806–16.
35. Tanous D, Siu SC, Mason J, et al. B-type natriuretic peptide in pregnant women with heart disease. *J Am Coll Cardiol* 2010;56(15):1247–53.
36. Hanania G, Thomas D, Michel PL, et al. [Pregnancy in patients with heart valve prosthesis. A French retrospective cooperative study (155 cases)]. *Arch Mal Coeur Vaiss* 1994;87(4):429–37.
37. Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. *Br Heart J* 1994;71(2):196–201.
38. Sadler L, Mccowan L, White H, Stewart A, Bracken M, North R. Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. *BJOG* 2000;107(2):245–53.
39. Chengode S, Shabadi RV, Rao RN, Alkemyani N, Alsabti H. Perioperative management of transcatheter, aortic and mitral, double valve-in-valve implantation during pregnancy through left ventricular apical approach. *Ann Card Anaesth* 2018;21(2):185–8.
40. Berry N, Sawlani N, Economy K, et al. Transcatheter Aortic Valve Replacement for Bioprosthetic Aortic Stenosis in Pregnancy. *JACC Cardiovasc Interv* 2018;11(19):e161–2.
41. Herbert KA, Sheppard SM. Not Your Typical Dyspnea of Pregnancy: A Case Report of Transcatheter Valve-in-Valve Replacement During Pregnancy. *A A Pract* 2019;12(6):202–4.
42. Pibarot P, Magne J, Leipsic J, et al. Imaging for Predicting and Assessing Prosthesis-Patient Mismatch After Aortic Valve Replacement. *JACC Cardiovasc Imaging* 2019;12(1):149–62.
43. Elassy SM, Elmidany AA, Elbawab HY. Urgent cardiac surgery during pregnancy: a continuous challenge. *Ann Thorac Surg* 2014;97(5):1624–9.
44. Yoon I, Slesinger TL. Radiation Exposure In Pregnancy. StatPearls; Treasure Island (FL).
45. Presbitero P, Prever SB, Brusca A. Interventional cardiology in pregnancy. *Eur Heart J* 1996;17(2):182–8.

46. Orchard E, Dix S, Wilson N, Mackillop L, Ormerod O. Reducing ionizing radiation doses during cardiac interventions in pregnant women. *Obstet Med* 2012;5(3):108–11.
47. Elkayam U, Bitar F. Valvular heart disease and pregnancy: part II: prosthetic valves. *J Am Coll Cardiol* 2005;46(3):403–10.
48. 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(2):132–42.
49. Mclintock C. Anticoagulant therapy in pregnant women with mechanical prosthetic heart valves: no easy option. *Thromb Res* 2011;127(Suppl 3):S56–60.
50. Beyer-Westendorf J, Michalski F, Tittl L, et al. Pregnancy outcome in patients exposed to direct oral anticoagulants - and the challenge of event reporting. *Thromb Haemost* 2016;116(4):651–8.
51. European Society Of G. Association for European Paediatric C. German Society for Gender M. 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 (24):3147–97.
52. 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(10). 1248 e1241-1248 e1249.
53. Elkayam U, Singh H, Irani A, Akhter MW. Anticoagulation in pregnant women with prosthetic heart valves. *J Cardiovasc Pharmacol Ther* 2004;9(2):107–15.
54. Economy KE, Valente AM. Mechanical Heart Valves in Pregnancy: A Sticky Business. *Circulation* 2015;132(2):79–81.
55. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. 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(2 Suppl):e691S–736S.
56. Hawkins D, Evans J. Minimising the risk of heparin-induced osteoporosis during pregnancy. *Expert Opin Drug Saf* 2005;4(3):583–90.
57. Mclintock C. Thromboembolism in pregnancy: challenges and controversies in the prevention of pregnancy-associated venous thromboembolism and management of anticoagulation in women with mechanical prosthetic heart valves. *Best Pract Res Clin Obstet Gynaecol* 2014;28(4):519–36.
58. Goland S, Elkayam U. Anticoagulation in pregnancy. *Cardiol Clin* 2012;30(3):395–405.
59. 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(4):747–51.
60. Alshawabkeh L, Economy KE, Valente AM. Anticoagulation During Pregnancy: Evolving Strategies With a Focus on Mechanical Valves. *J Am Coll Cardiol* 2016;68 (16):1804–13.
61. Goland S, Schwartzenberg S, Fan J, Kozak N, Khatri N, Elkayam U. Monitoring of anti-Xa in pregnant patients with mechanical prosthetic valves receiving low-molecular-weight heparin: peak or trough levels? *J Cardiovasc Pharmacol Ther* 2014;19(5):451–6.

62. Elkayam U. Pregnancy in the Patient with Prosthetic Heart Valves. doi:https://doi.org/10.1002/9781119409861.ch7 (2019).
63. Scheres LJJ, Bistervels IM, Middeldorp S. Everything the clinician needs to know about evidence-based anticoagulation in pregnancy. *Blood Rev* 2019;33:82–97.
64. Cohen H, Arachchillage DR, Middeldorp S, Beyer-Westendorf J, Abdul-Kadir R. Management of direct oral anticoagulants in women of childbearing potential: guidance from the SSC of the ISTH. *J Thromb Haemost* 2016;14(8):1673–6.
65. Lip GYH, Collet JP, Caterina R, et al. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Europace* 2017;19(11):1757–8.
66. Ramin KD. Management of Labour and Delivery in the High−risk Patient. In: Celia Oakley CaW, ed. *Heart Disease in Pregnancy*; 2007Second Edition, .
67. Hameed AB, FMR. Cardiac disease in pregnancy. In: Foley MR, STH, Garite TJ, eds. *Obstetric Intensive Care Manual*, 2nd ed., New York, NY: McGraw-Hill; 2004:96–112.