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REVIEW

Clinical update

Management of valvular disease in pregnancy: a global perspective

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Valvular heart disease (VHD) in pregnant women, whether due to congenital or acquired aetiologies, poses a challenge to clinicians and their patients. Significant valve disease, which can affect a single valve or several valves, increases the risk of pregnancy to the mother and foetus and requires a careful preconception risk assessment and, subsequently during pregnancy, specialized care to minimize maternal and foetal morbidity and mortality. The goal of this paper is to provide a guide to risk assessment and to give an overview of the optimal cardiac and obstetric management, including surgical intervention, taking into consideration the resources available in higher and lower-to-middle income countries. This manuscript provides a practical approach and is not replacing comprehensive guidelines on the management of VHD or cardiovascular disease in pregnancy. It focuses on common valvular diseases and does not cover the large variety of aortic disease with and without valve disease or complex congenital heart disease in detail.

Keywords Valve disease • Valve thrombosis • Rheumatic heart disease in pregnancy

General considerations

Both acquired and congenital valve disease are important causes of maternal and offspring morbidity and mortality, going beyond the routinely reported short-term (<42 days) postpartum period.[1] Recent publications showed that the spectrum of the aetiology of valvular diseases differs in lower-to-middle income countries (LMICs) vs. higher income countries (HICs) with congenital heart disease (CHD), including Marfan's disease, being the most common contributing factor in HICs,[2] compared with rheumatic heart disease (RHD), contributing to more than 30% of the burden to cardiovascular disease (CVD) seen in pregnancy in LMICs as Africa.[3,4] Despite a decline in RHD rates in industrialized countries during the course of the last century, RHD remains a major cause of morbidity and premature mortality in LIMCs, with an estimated 250 000 deaths occurring annually in these countries.[5] This estimation of death caused by RHD is based upon relatively poor quality data from a limited number of countries.[5,6] More recent surveys suggest that rates of RHD in LIMCs have been considerably underestimated, including data from Mozambique, Cambodia, and Tonga where prevalence rates of up to 42 cases per 1000 school-aged population have been reported.[7,8] In the European Registry on Pregnancy and Heart Disease (1321 patients), initiated by the European Society of Cardiology, it was found that 25% of the women had valvular heart disease (VHD).[9]

Preconception evaluation

All women with VHD should ideally have preconception evaluation, including advice on risk prediction and contraception (*Table 1*), by a joint cardiac–obstetric team seeking advice from other specialties. Careful counselling on maternal and offspring risk should be done according to the CARPREG (CARdiac disease in PREGnancy) risk score[2] or modified World Health Organization (WHO) classification[10,11] and should include information on complications such as heart failure and valve thrombosis which can occur during, but also beyond the immediate delivery period. A recent article by Balci *et al.*[12] identified that the modified WHO classification is the best available risk assessment model for estimating cardiovascular risk in pregnant women with CHD, comparing the ZAHARA I (Zwangerschapp bij SAangeboren HARtAwijkingen I), the CARPREG, and the WHO classifications. Also the consequences of the medication

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Table 1 Preconception evaluation in any women with valvular heart disease planning a pregnancy or assessment in early pregnancy

Careful history, family history, and physical examination, including screening for connective tissue disorders
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 including maternal risks for complications and mortality, information on choices of therapy (heparin vs. Vitamin K), risk of miscarriage, risk of early delivery, and small for gestational age and, when applicable, risk of foetal congenital defect (inheritance risk)

that may be required (for example warfarin embryopathy) need to be discussed. While optimal counselling is ideal, often women in LMICs only present after 20 weeks of gestation, which has implications for their functional assessment and limits the option for pregnancy termination. Such cases are challenging and should be transferred for ongoing care to a tertiary centre where they can be appropriately assessed and guided/treated. All high-risk patients should be cared for in specialized centres where experienced physicians with expertise in techniques such as mitral balloon valvotomy can perform all diagnostic procedures and interventions.[11]

Pregnancy in women with native valves

In general, stenotic valvular lesions carry a higher pregnancy risk than regurgitant lesions. In valvular stenosis, the increased cardiac output associated with the gestational stage increases the transvalvular gradient and, therefore, upstream pressure.[13] In addition, the fall in the peripheral vascular resistance will provoke fluid retention and volume expansion which may be more marked in women with a stenotic lesion because they are less able to respond to the pressure drop with an increase in cardiac output. Further, the increased heart rate may be poorly tolerated, especially in patients with (severe) mitral stenosis as the left-ventricular filling depends on an adequate diastolic filling time. The consequences are shortness of breath, heart failure, and arrhythmia, commonly seen in women with stenotic lesions. Echocardiography is mandatory for the diagnosis but gradients in mitral and aortic stenosis in the pregnant women need to be evaluated with caution, as an increased heart rate tends to over-estimate, and impaired systolic function underestimate, the degree of stenosis. An increased heart rate per se may affect the peak and mean systolic gradients, as calculated from the Bernoulli transformation, but should not affect the calculated valve orifice area as calculated by the continuity equation (a further way to assess 'degree of stenosis'). The gradient across a valve at any given time is probably the best way to assess the haemodynamic situation; since, even if the valve orifice is relatively good, a high gradient does indicate a clinically significant stenosis in that situation/at that moment.

Left-sided regurgitant valve lesions are in general well tolerated in pregnancy because the fall in systemic vascular resistance leads to a reduction in the regurgitant volume. However, acute regurgitation, as well as regurgitation in the context of poor left- or right-ventricular function, is poorly tolerated. Rheumatic heart disease commonly leads to mixed mitral valve (MV) disease, with a combination of stenosis and regurgitation, but can cause double or even triple valve disease, typically affecting the mitral, aortic, and tricuspid valves. Assessment of the severity of those lesions and risk prediction during pregnancy is complex and requires considerable experience as very little information has been published to date.

Table 2 presents a summary of the aetiology, maternal risks, pregnancy outcome, general management, and preferred mode of delivery for women with valvular lesions. In general, evaluation is preferably performed prior to pregnancy. Severe symptomatic valve disease, in particular, with symptoms or left-ventricular dysfunction should be corrected prior to pregnancy. However, in reality, some women present while pregnant and valve disease needs to be managed, balancing maternal outcome and foetal risk. In general, optimizing the haemodynamic situation of the mother is also beneficial to the foetus. However, cardiac surgery carries high risks for the foetus.[14,15]

Pregnancy in women with prosthetic heart valves

No other aspect of the management of valvular disease shows such a distinct polarization between HICs and LMICs as the replacement or repair of the diseased valves. For one, the underlying pathology in young women is primarily degenerative (e.g. connective tissue diseases such as Marfan's) in HICs and due to the large burden of RHD in LMICs.[16] This creates very different background situations for the spectrum of modern cardiothoracic surgical therapies as opposed to the rather limited choice a few decades ago. Rheumatic heart disease is a condition which has an impact on the cardiac valves over decades, with regurgitant lesions predominant in childhood and leading to mixed regurgitant stenotic lesions later in life.[16] There is also the dynamic of RHD. In Uganda, patients often require surgery at childhood or adolescence, as patients present with pure mitral incompetence in 40% and pure aortic incompetence in another 30% of cases.[17,18] As countries move towards threshold economies and eventually towards HIC status, they show a marked age shift of rheumatic patients, as well as a higher proportion of patients with mitral stenosis. In countries such as South Africa, South Korea, and Thailand, the age of first surgical interventions for RHD has increased to an average of more than 50 years.[16,19,20] Last but not least, access to cardiac surgery further determines the spectrum of treatment options. In most LMICs, populations do not have adequate access to cardiothoracic surgery. While HICs such as Germany provide >1000 open heart operations/million to a largely geriatric population with a diminutive proportion affecting young women, Africa provides one-hundredth of this service level to an overwhelmingly young population with a large proportion of young women.[21]

A large number of prosthetic heart valves (PHV) have been developed and are implanted world-wide, many in women of child-bearing

Table 2 **Risk stratification according to type of valvular lesion and severity**

Lesion	Aetiology[a]	Risk to mother	Risk to foetus	Possible intervention[b]	Preferred mode of delivery
Mitral stenosis	Rheumatic	Mild MS (area >1.5 cm^2/ asymptomatic: low risk Moderate-to-severe MS (area <1.5 cm^2, in AF): may develop heart failure; mortality up to 3%.	Prematurity 20–30%, intrauterine growth retardation 5–20%, still birth 1–3%. Offspring risk higher in women in NYHA class >II.	Non-pregnant: Moderate–severe MS should be counselled before pregnancy and may need intervention. In pregnancy: beta-blockers and duretics; in AF digoxin Percutaneous mitral commissurotomy in NYHA FC III/IV or PAP >50 mmHg on medical therapy	Vaginal delivery in mild MS; Caesarean in moderate–severe MS in FC III/IV or having pulmonary HT on medical therapy.
Aortic stenosis	Congenital bicuspid	Severe AS-Asymptomatic on exercise test: Low risk Severe AS symptoms or drop in BP on exercise test: heart failure in 10% and arrhythmias in 3–25%.	Foetal complications increased in moderate and severe AS as pre-term birth, intrauterine growth retardation, low birth weight in up to 25%.	Non-pregnant: symptomatic severe AS or asymptomatic AS with LV dysfunction or aortic dilatation >45 mm should be counselled against pregnancy or have an intervention first. In pregnancy: restrict activities and in AF beta-blocker or a non-dihydropyrine for rate control. Percutaneous valvuloplasty in severely symptomatic patient despite bedrest and medical therapy.	Non-severe AS vaginal delivery, in selected cases of severe AS Caesarean delivery can be considered.
Mitral regurgitation	Rheumatic, congenital	Moderate-to-severe MR with good LV function: low risk with good care Severe MR with LV dysfunction: high risk of heart failure or arrhythmia	No increased risk of foetal complications has been reported	Non-pregnant: patients with severe regurgitation and symptoms or impaired LV function or dilatation should be referred for pre-pregnancy surgery Pregnant: Symptoms of fluid overload can be managed with diuretics. Surgery in women with intractable HF.	Vaginal delivery is preferable. Epidural anaesthesia and shortened second stage is advisable
Aortic regurgitation	Rheumatic, congenital, degenerative	Moderate-to-severe AR with good LV function: low risk with good care Severe AR with LV dysfunction: high risk of heart failure or arrhythmia	No increased risk of foetal complications has been reported	Non-pregnant: patients with severe regurgitation and symptoms or impaired LV function or severe dilatation should be referred for pre-pregnancy surgery Pregnant: Symptoms of fluid overload can be managed with diuretics and bedrest. Surgery in women with intractable HF, preferably after delivery.	Vaginal delivery is preferable. Epidural anaesthesia and shortened second stage is advisable
Tricuspid regurgitation	Functional, Ebstein's anomaly, endocarditis	Moderate-to-severe TR with good RV function: arrythmias Moderate-to-severe TR with impaired RV function: heart failure	No increased risk of foetal complications has been reported	Non-pregnant: patients with severe regurgitation and symptoms or impaired LV and/or RV function or dilatation should be referred for pre-pregnancy TV repair Pregnant: severe TR can usually be managed medically with diuretics	Vaginal delivery is preferable.

MS, mitral stenosis; AF, atrial fibrillation; MR, mitral regurgitation; AR, aortic regurgitation; TR, tricuspid regurgitation; NYHA, New York Heart Association; AS, aortic stenosis; LV, left ventricular; RV, right ventricular ; TV, tricuspid valve PAP, pulmonary arterial pressure ; FC, function class.

[a]Only most common listed.

[b]Possible intervention could be, e.g. medical, balloon valvotomy, or surgical.

age. The two major groups of artificial heart valves, bioprosthesis/tissue valves (TV) and mechanical valvular prosthesis, have different risk/benefit profiles with regard to need for anticoagulation, valve haemodynamics, incidence of thrombotic events, durability, and impact on foetal outcome. In addition, MVs can be surgically repaired or opened by mitral balloon valvotomy, a procedure that can also be performed in pregnancy as an emergency intervention.[11] These procedures have the advantage of not needing long-term anticoagulation. However, mitral balloon valvotomy or repair can only be done in certain, pliable, not heavily calcified valves.

The biggest change in available options for the surgical treatment of heart valve disease in the past two decades has been the ever growing array of repair procedures preserving the patient's own heart valves, as opposed to the predominant replacement of the diseased valves in the previous era.

There are three key issues related to the need for heart valve replacement in the context of the desire for a future pregnancy: (i) selection of PHV; (ii) management during pregnancy; and (iii) the maternal and foetal risks, as extensively reviewed and summarized by Elkaym and Bitar.[22]

Figure 1 provides algorithms for heart valve surgery for aortic and mitral regurgitation (AR, MR) as well as stenosis (AS, MS) in women of child-bearing age under the circumstances of HICs and LMICs.

Selection of prosthetic valves and repair procedures

Tissue valves

Tissue valves can be separated into three categories: xenografts, homografts, and autografts, with the pericardial xenografts being used most commonly. However, there are marked regional differences in the choice of TV and the treating cardiologist and obstetrician should be certain about the type of valve used as this is important in risk stratification. In general, the use of a TV in women of child-bearing age avoids the use of anticoagulation and its complications, as well as the risk of thromboembolism, but is associated with a high risk of valve deterioration and need for reoperation. Xenografts made of cross-linked porcine leaflets or pericardium have a high risk of clinically significant structural valve deterioration at <5 years post-surgery, reaching 50% at 10 years and 90% by 15 years post-surgery.[23] In a mixed ethnicity study including 74% Maori-Pacific Islanders with RHD from the period 1972–92, North *et al.*[24] reported on a single-centre cohort of 255 women with 394 single-valve replacements using mechanical valves, TVs, and homograft. Valve loss at 10 years was as high as 82% in women with TVs compared with 29% with mechanical valves and 28% at homograft. However, the overall survival in TV was still better, with 84% when compared with mechanical valves translating into a relative risk of death with mechanical valves vs. TVs of 2.17. In that cohort, the relationship between pregnancy and TV functional capacity was analysed separately for each valve type and was not associated with an increased valve loss. Maori and Pacific island women had an eight- and seven-fold relative risk of death, respectively, compared with European women, highlighting the importance of socioeconomic circumstances and also the underlying aetiology of the VHD in assessing outcome.

In many countries, access to regular anticoagulation controls and therefore compliance is an additional factor and TV might still be the best option in the absence of repairs. Moreover, as the baseline mortality of these patients at the first operation is almost 5%,[25] the relatively low re-operation mortality of between 3.8[26] and 8.7%[27] justifies a lower threshold for TVs particularly in selected patients. The deterioration of TV during pregnancy has been reported in a number of studies,[28] but has not been confirmed in others.[22,29] The study by Avila *et al.*[29] suggests that the structural changes found at 5 years after TV are probably attributed to the natural course of xenograft prostheses and independent of any effect of pregnancy. Principally, tissue valves have three modes of failure varying between the makes and whether they are porcine or made of mostly bovine pericardium: (i) calcification; (ii) degradation leading to tears, and (iii) pannus overgrowth from the nearby endocardium leading to leaflet immobilization.[30] As the longevity of TVs largely exceeds the life expectancy of the typically geriatric patients in HICs, together with small markets and lower profit margins in LMICs, there was and remains little incentive for the main players to implement some of the many improvements to tissue preservation which reduced calcific degeneration by up to 95%.[30] Until these improvements have been applied to trans-catheter valves, this accelerated degeneration occurring in young patients of child-bearing age also needs to be taken into consideration when using trans-catheter valves.

Mechanical valves

Mechanical prosthesis are classified into three major groups: caged ball, tilting discs, and bileaflets valves.[22] The bileaflet St Jude valves are currently the most widely employed valves, having replaced the Starr-Edwards cage-ball valves which were previously extensively used in women of child-bearing age.[22] Mechanical prosthesis have an excellent durability and good haemodynamic profile. However, they pose problems, in particular, in pregnancy due to the risk of thromboembolism being increased and the higher level of anticoagulation needed, which might lead to maternal bleeding. *Figure 2* indicates a typical emergency operation for a clotted mechanical mitral bi-leaflet valve prosthesis inserted in a young rheumatic patient from a poor socioeconomic background.

There is very little data on women of child-bearing having valvular changes at two sites (e.g. due to RHD), which has additional implications on the choice of mechanical valves and TVs.

Figure 3 shows echocardiographic images of two women with RHD affecting several valves. *Figure 3A* shows mixed aortic valve disease with mild–moderate mitral stenosis. *Figure 3B* shows mechanical valve prostheses in the mitral and aortic positions with preserved systolic function.

Valve repair procedure and ballon valvotomies

Limited data are available on pregnancy outcome in women who underwent various forms of surgical or percutaneous valve repair procedures. Women who have aortic valve disease have in selected centres the option of aortic valve repair (David's operation), aortic root plus ascending aorta replacement (Bentall repair) and the Ross procedure. The Ross procedure involves the removal of the patient's own pulmonary valve and pulmonary artery, which is then

used to replace the diseased aortic valve with re-implantation of coronary arteries into the graft, as well as insertion of a human homograft into the pulmonary artery. A randomized study by Ismael El-Hamamsky *et al.*[31] reported on 228 patients assigned to aortic homograft vs. Ross procedure, showing excellent haemodynamic results with a 97% survival in the Ross procedure group. However, the procedure is difficult and only performed in major referral centres. Yet, Magdi Yacoub's recent *Lancet* comment[32] addressed previous controversies and highlighted the need to use the Ross Operation more frequently in both HICs and LMICs patients. The reported pregnancies had an overall good maternal and foetal outcome.[33–35]

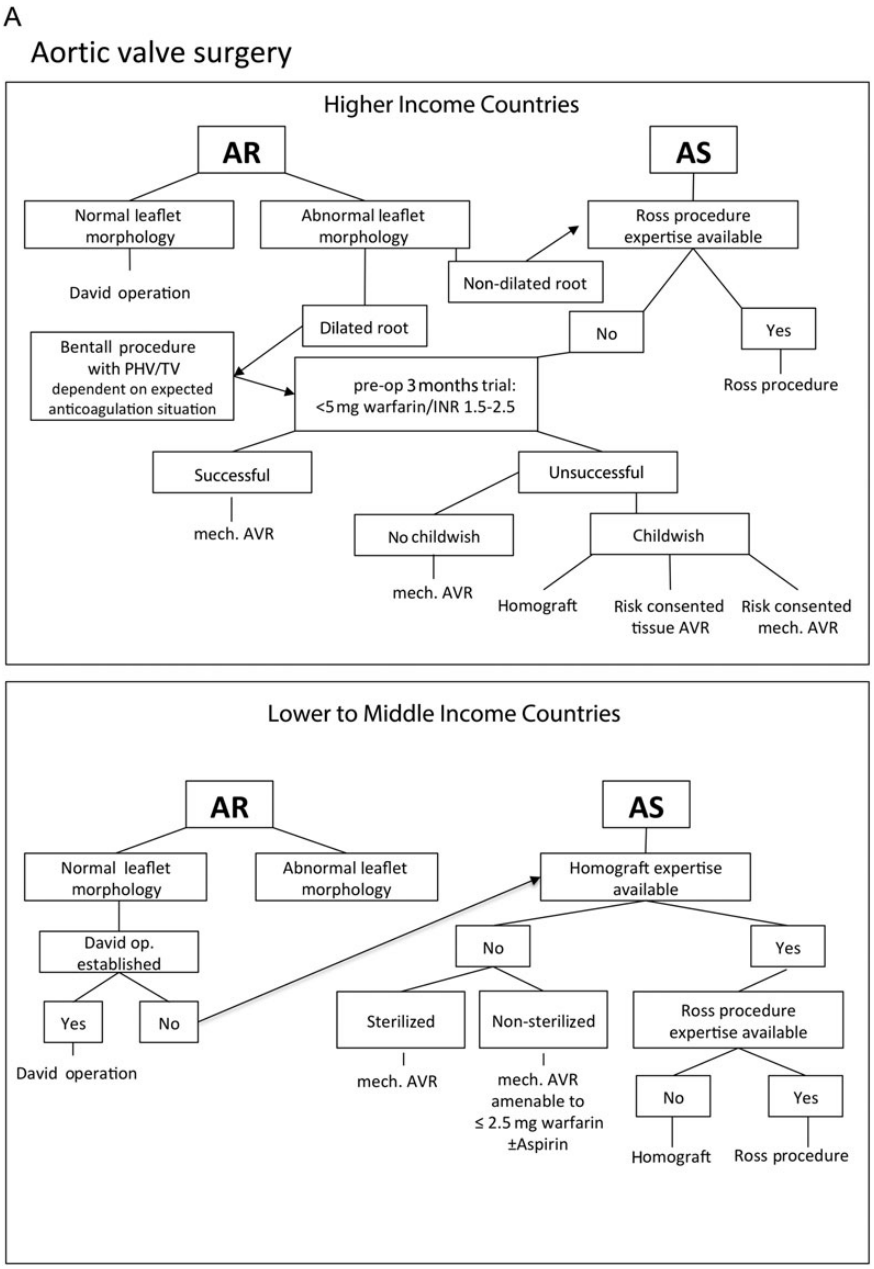

Figure 1 Algorithms for heart valve surgery for aortic and mitral regurgitation (AR, MR) as well as stenosis (AS, MS) in women of child-bearing age under the circumstances of both HICs and LMICs countries. (Bental Procedure: replacement of the aortic valve together with a dilated ascending aorta by a composite Dacron graft with an incorporated aortic valve prosthesis. The coronary arteries are directly inserted with 'aortic buttons' into the proximal Dacron graft; David Operation: incorporation of the patients own aortic valve leaflets into a Dacron tube that supports the leaflets and replaces part of the ascending aorta. The coronary arteries are also re-inserted via 'buttons' into the Dacron graft; Ross Procedure: transposition of the patient's own pulmonary valve into aortic position (with re-implantation of the coronary arteries into the 'neo-aortic' root and replacement of the resected pulmonary trunk by a prosthetic valve, either a homograft or a xenograft). mech. AVR, mechanical aortic valve replacement; PHV, prosthetic heart valves; TV, tissue valve.

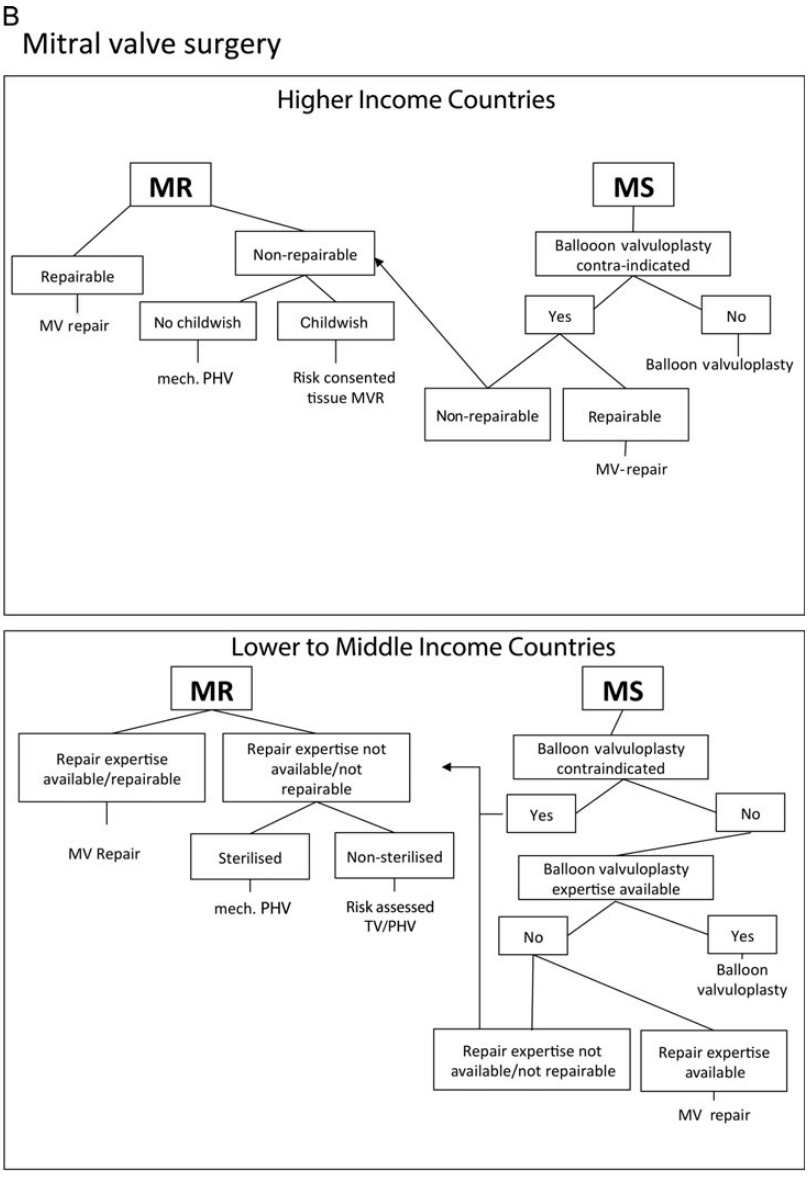

Figure 1 Continued.

Newer devices such as percutaneous repairs for mitral regurgitation (MitraClip) and Transaortic valvular interventions (TAVI) might be of potential use in young women planning pregnancy, but these have not yet been studied in that context. Data from the EVEREST (Endovascular Valve Edge-to-Edge Repair Study trials[37]) and registries in Europe[38]and the USA suggest that a MitraClip procedure success rate of 75% in HICs is relatively safe and generally well tolerated. As such, the procedure can be expected to have acceptable short to mid-term results in primarily incompetent rheumatic MVs once the technology has been simplified to be applicable in LMICs.

For trans-catheter aortic valve therapies, however, most of the currently approved TAVI valves are designed for the old, calcific aortic stenosis patients of HICs and do not qualify for the largely incompetent aortic valves in younger rheumatic patients. Non-occlusive, self-homing systems for the deployment of low-cost synthetic stent-based aortic valve prostheses (*Figure 4*) might expand the reach of cardiac surgery to patients in LMICs.

Management during pregnancy

Antenatal care

Patients with symptomatic significant valvular lesion, in particular those with additional pulmonary hypertension or left-ventricular dysfunction should be seen at a minimum of 4–8 week intervals until 36 weeks and then weekly until delivery. Where there is evidence of cardiac decompensation or significant obstetric complications, such as pre-eclampsia, patients should be admitted early

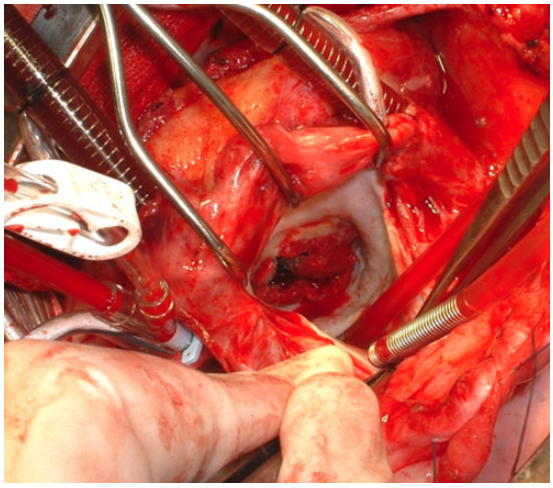

Figure 2 Typical emergency operation for a clotted mechanical mitral valve prosthesis inserted in a young rheumatic patient from a poor socioeconomic background.

and managed aggressively with a low threshold for delivery, particularly in the case of pre-eclampsia where the combination of hypertension, increased vessel permeability, and enhanced thrombotic risk makes the management of women with PHV significantly more complicated.[9]

Anticoagulation

The hypercoagulability of pregnancy causes an increase in mechanical valve thrombosis. Anticoagulation in pregnancy with coumarin derivates reduces the risk of mechanical valve thrombosis with tight control but is linked to an increased risk of miscarriage, foetal embryopathy, and late foetal loss and it has been suggested that the effects are dose-dependent.[38–41] On the other hand, low-molecular weight heparins (LMWHs) have been used during pregnancy and proved to be effective in many conditions, but in patients with an PHV, several cases of valve thrombosis have been reported suggesting that the use of LMWH may be associated with a higher risk of valve thrombosis. The risk of valve thrombosis may improve in the future when adequate measurements of peak and through levels are established and implemented in routine care.[42–45] At the moment, there is not one optimal regimen and an individualized strategy is warranted. Risk factors for having a thromboembolic event include having an PHV in mitral or tricuspid position, suffering from atrial fibrillation or having a history of a thromboembolic event. It is important to understand the risks and benefits of the different strategies and to discuss these risks with the patients. Recent recommendations on options for anticoagulation in pregnancy are summarized in *Table 3*, which has been adapted from the recent ESC Guidelines on Cardiovascular Disease during Pregnancy.

Table 4 presents a practical approach for pregnant women with mechanical prosthetic valves, adapted from Pieper *et al.*[38] In our practice, we consider prescribing low-dose Aspirin, in addition to coumarin derivates or heparin, in high-risk pregnant women who, e.g. have had repeated valve replacements, with impaired function due to pannus ingrowth, double valve replacement or with previous thrombus.

All the recommendations are limited by the paucity of data on pregnancy outcomes in women with the contemporary newer and less thrombogenic valves, such as the St Jude valves, compared with the older types of valves. This means that we are probably overestimating the thrombotic event risk. All anticoagulation regimens are understudied and large prospective comparative studies are needed. Indeed, with the newer valves, it might be possible that Vit K antagonists (coumarin derivates) can be used in lower doses reaching an INR level of only 1.5–2.5,[46] but this remains to be proved. The use of newer anticoagulants is currently contraindicated for PHV. If pregnancy occurs while taking one of these agents it is wise to switch to LMWH (or warfarin).

De Santo *et al.*[46] demonstrated that a 3 months pre-implantation trial period of anticoagulation allowed the identification of those 94% of young women where INRs of between 1.5 and 2.5 could be achieved with a low dose of <5 mg of warfarin which was shown not to cause embryopathies. In this study, more than half of the patients fell pregnant and did not show any need for increasing the warfarin dose beyond 5 mg. All of them delivered healthy babies through Ceasarean section in Week 36 after warfarin was stopped for 2 days. For patients in LMICs, in which the infrastructure for such a high-surveilance approach is not available, there is equally hope for mechanical valves even in mitral position.

Sillesen *et al.*[47] reported on the pregnancy outcome in 79 women who had 155 pregnancies after valve replacement with PHV in Denmark. There were four thromboembolic complications in women with mitral prosthesis on unfractionated heparin. Two women died during pregnancy, one from failure, and one from postpartum bleeding. Compared with healthy women there was significantly more postpartum bleeding ($P<0.0021$), premature birth ($P < 0.00000001$), and congenital malformations (<0.044) in the women with PHV.

Soma-Pillay *et al.*[48] studied the effect of warfarin dosage on maternal and foetal outcomes in pregnant women with PHVs. Of the 52 pregnancies managed, 41 had MV, two aortic valves, and nine double valve prosthesis. There were no maternal deaths or cases of valve thrombosis, but 9.7% had maternal 'near misses'. Forty-one foetuses were exposed to warfarin in the first trimester and there were five (12%) cases of warfarin embryopathy. The authors did not find a significant difference in the live birth rate, average birth weights, or miscarriage rates between the three warfarin dosage groups. The stillbirth rate increased with increasing doses of warfarin.

The decision on appropriate therapeutic regimen for women with single-valve replacement in mitral or aortic position or double valve replacements needs to be based on the individual case scenario taking level of system resources, access of patients to health care, and distance to appropriate testing of INR and anti-Xa into consideration.

Labour and delivery

Induction, management of labour, delivery, and postpartum surveillance require specific expertise and joint management by the obstetrician, cardiologist, and anaesthesiologist, preferably in an experienced tertiary care centre. Specifically, timing and mode of

delivery needs special consideration in women with significant native valve pathology and, in particular, in women with prosthetic valves.

An individualized delivery plan should be documented early and must be available also outside of normal working hours. Due to lack of prospective data and the influence of individual patient characteristics, standard guidelines do not exist and management should therefore be individualized.[11] In general, the preferred mode of delivery is vaginal, with a delivery plan which includes information on the timing of delivery (spontaneous/induced), method of induction, analgesia/regional anaesthesia, level of monitoring, need for postpartum monitoring, and subacute bacterial endocarditis (SBE) prophylaxis. Specific instructions for anticoagulation (discussed subsequently), haemodynamic monitoring, analgesia, the management of the second and third stages of labour, and the postpartum period should be clearly documented.[11]

Delivery in anticoagulated women with prosthetic valves need to follow a certain algorithm of care (*Tables 3* and *4*). At 36 weeks, most patients are converted to either LMWH or UFH (*Tables 3* and *4*). Delivery is usually planned allowing an unfractionated heparin infusion to be started 36 h prior to induction/Caesarean section and for it to be discontinued 6 h before planned delivery. In practice, when labour is being induced with prostaglandins, then

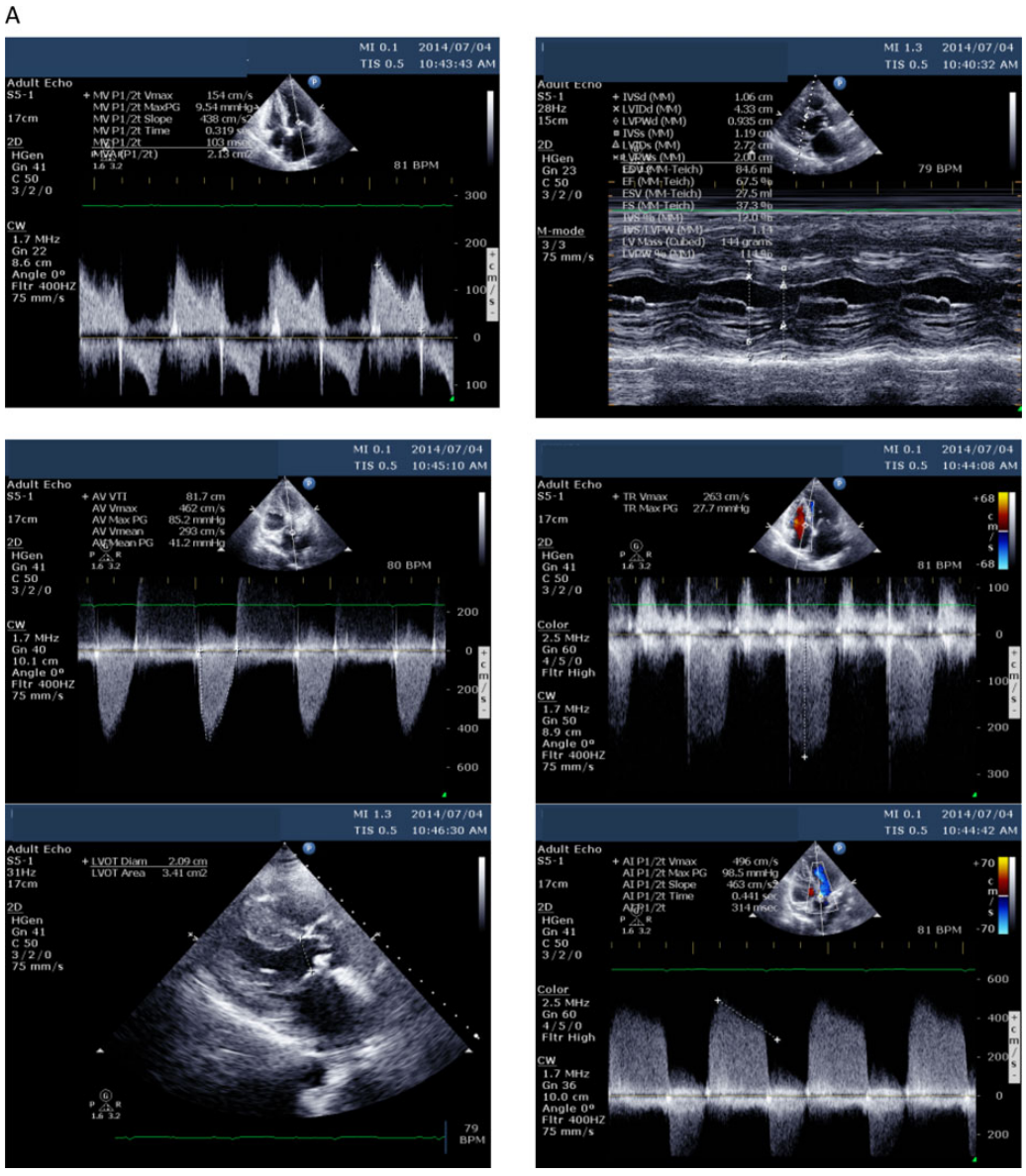

Figure 3 (*A*) 26-year-old female with rheumatic heart disease—mixed aortic valve disease and mild–moderate mitral stenosis. Figure shows continuous wave Doppler of the mitral valve lesion, left-ventricular parameters assessed by M-mode, 2-D images and pressure gradients of the aortic valve. (*B*) 24-year-old female with double valve replacement (mitral and aortic position) with post- operative preserved left-ventricular systolic function.

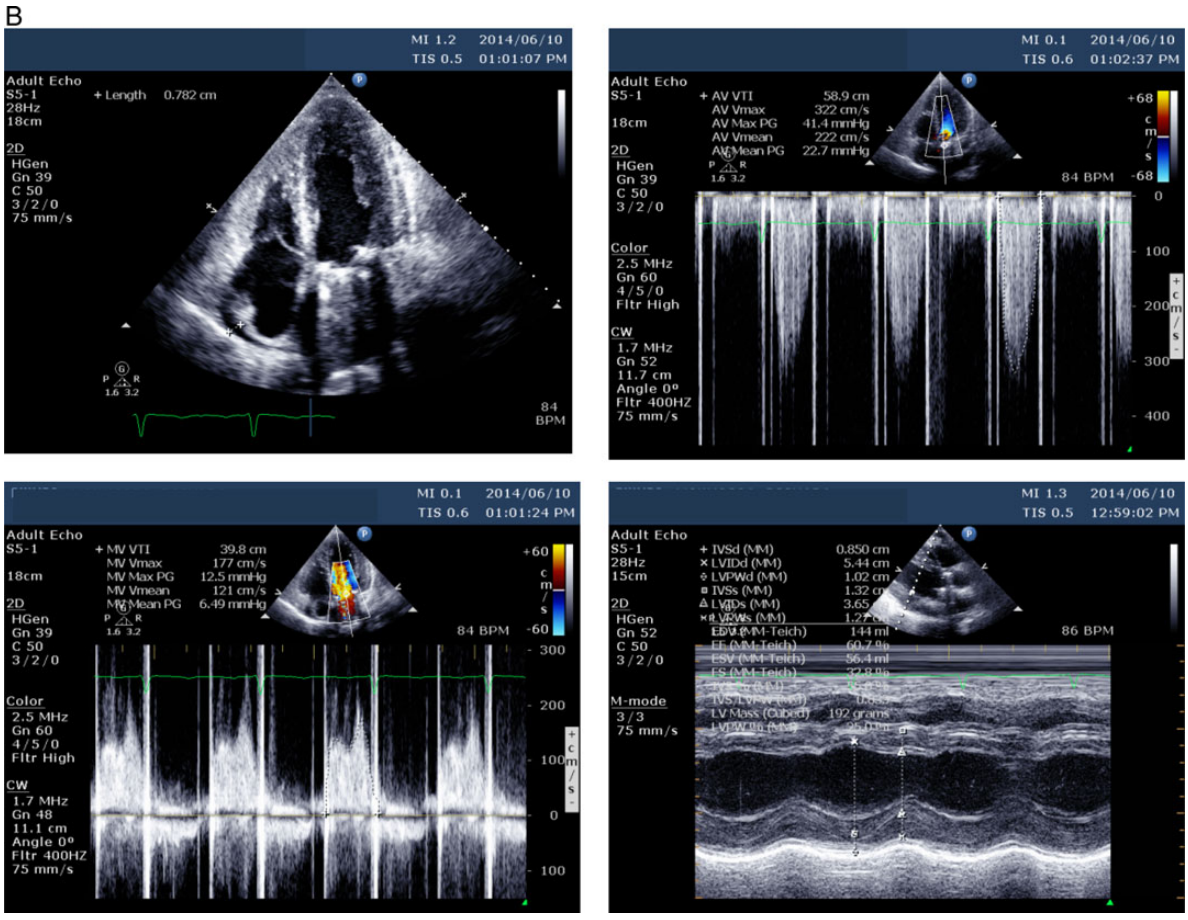

Figure 3 Continued.

it is wise to continue with the infusion until either it is possible to perform an artificial rupture of membranes or contractions are becoming regular (≥2 times in 10 min). If pain relief is required before 6 h has elapsed, then patient controlled analgesia with remifentanil may be considered. If there are no bleeding complications during the delivery, then unfractionated heparin infusion can be restarted 4–6 h after delivery. In the case of significant vaginal tears, haematoma, or PPH, a later start of heparin could be considered depending on the clinical situation and the risk of valve thrombosis (higher risk for mitral position), Supplementary material online, *Table S1*.

Caesarean delivery could be considered for patients with valvular lesions presenting in pre-term labour on oral anticoagulants, in patients with symptomatic severe stenotic lesions (AS, MS) or an ascending aorta >45 mm, severe pulmonary hypertension or acute heart failure.[49] If labour starts or an emergency delivery has to be carried out while the patient is taking warfarin, then Caesarean section should be performed under general anaesthetic with fresh frozen plasma cover and prothrombin complex concentrate added if necessary to reverse anticoagulation. If the patient is on a heparin infusion, where possible, stopping the infusion and waiting as long as possible is the best approach as the half-life of heparin is 60–90 min. Avoiding these emergency situations where anticoagulation may be compromised is key, and Caesarian delivery may be considered in situations where foetal distress is more likely, e.g. induction with foetal growth restriction or when the cervix is unfavourable and induction is unlikely to succeed. Where delivery has been by Caesarean section and early re-introduction of anticoagulation is planned, then placing a prophylactic brace (uterine compression) suture and the insertion of pelvic and sub-rectus drains may be wise.

Peripartum and postpartum obstetric complications are more common in patients with VHD and can include postpartum haemorrhage (PPH) defined as blood loss >500 mL (vaginal delivery) or >1000 mL (Caesarian section), which required transfusion or is accompanied by a drop in haemoglobin >2.0 g/L. The impact of PPH in context of heart disease is greater than in the normal population. In the context of PHV, this problem is compounded by the need for anticoagulation. Consequently, effective management of the third stage is critical.[50]

Ergometrine is relatively contraindicated due to its effects on blood pressure and potential to cause coronary artery spasm while oxytocin can also have adverse effects, inducing vasodilatation in the subcutaneous vessels, vasoconstriction in the splanchnic bed

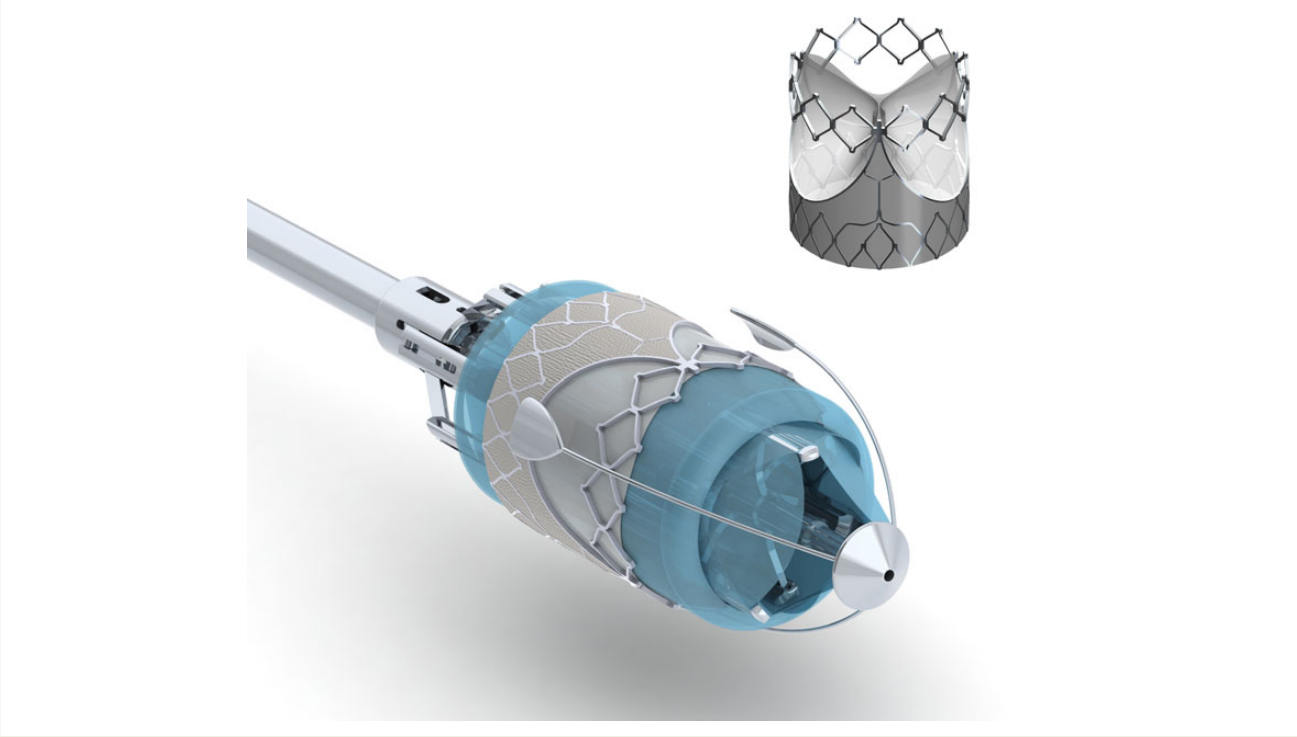

Figure 4 Non-occlusive, self-homing, backflow-protected trans-apical system for the deployment of low-cost synthetic stent-based aortic valve prostheses emulating principles of closed mitral valvotomy with Tubbs dilator for preventing the hollow-balloon from encroaching the outflow lumen (University of Cape Town Strait Access Technologies).

Table 3 Anticoagulation regimen for mechanical valves in the peripartum period. Adapted from Elkayam *et al.* *JACC* 2012;59:1110–1115 and Pieper *et al.*[39]

Pre-pregnancy
– Discuss anticoagulation regimen with the patient
– Continue coumarin derivative until pregnancy is achieved
– When menstruation does not occur at expected day, perform pregnancy tests every 3 days until positive or until menstruation, in order to detect pregnancy at early stage
– Instruct patient to contact physician responsible for anticoagulation as soon as pregnancy is achieved
– Give patient and physician responsible for anticoagulation written instructions about anticoagulation regimen during pregnancy
6th to 12th week of pregnancy
– If warfarin daily dose is <5 mg or acenocoumarol dose <2.0 mg, continuation of coumarin derivative throughout pregnancy can be considered especially in high-risk patients (mechanical valve in mitral or tricuspid position, atrial fibrillation or history of TE on Heparin)
– Otherwise, substitute coumarin derivative with subcutaneous LMWH/UFH twice daily
– Adjust LMWH dose to achieve peak anti-Xa levels of 0.6–1.2 U/L mL 4 h post dose
– If trough levels are <0.6 IU/mL with therapeutic peak levels, dose three times daily
– Check peak and trough levels and anti-Xa levels weekly
13th to 35th week of pregnancy
– Coumarin derivatives are preferred but in low-risk patients LMWH can be considered
36th week of pregnancy
– Substitute coumarin derivative with subcutaneous LMWH/UFH twice daily
– Adjust LMWH dose to achieve peak anti-Xa levels of 0.7–1.2 U/L mL 4 h post dose
– If trough levels are <0.6 IU/mL with therapeutic peak levels, dose three times daily
– Check anti-Xa levels weekly
Onset of Labour and postpartum
– Temporary i.v. heparin but withholding heparin during delivery for a few hours
– Restart LMWH/UFH a few hours post delivery
– Continuing the LMWH until coumarin have at least $\times 2$ an adequate INR level
– Careful INR level assessment in the weeks postpartum

LMWH, low-molecular weight heparin; UFH, unfractionated heparin.

Table 4 Recommendations for the management of mechanical valves in pregnancy. Adapted from ESC guidelines on the management of cardiovascular disease in pregnancy[11]; Table 12.

Recommendations	Class[a]	Level[b]
Mechanical valves		
OACs are recommended during the second and third trimesters until the 36th week.	I	C
Change of anticoagulation regimen during pregnancy should be implemented in hospital.	I	C
If delivery starts while on OACs, caesarean delivery is indicated.	I	C
OAC should be discontinued and dose-adjusted UFH (a PTT $\geq 2\times$ control) or adjusted-dose LMWH (target anti-Xa level 4–6 h post-dose 0.8–1.2 U/mL) started at the 36th week of gestation.	I	C
In pregnant women managed with LMWH, the post-dose anti-Xa level should be assessed weekly.	I	C
LMWH should be replaced by intravenous UFH at least 36 h before planned delivery. UFH should be continued until 4–6 h before planned delivery and restarted 4–6 h after delivery if there are no bleeding complications.	I	C
Immediate echocardiography is indicated in women with mechanical valves presenting with dyspnoea and/or an embolic event.	I	C
Continuation of OACs should be considered during the first trimester if the warfarin dose required for therapeutic anticoagulation is <5 mg/day (or phenprocoumon <3 mg/day or acenocoumarol <2 mg/day), after patient information and consent.	IIa	C
Discontinuation of OAC between Weeks 6 and 12 and replacement by adjusted-dose UFH (a PTT $\geq 2\times$ control; in high-risk patients applied as intravenous infusion) or LMWH twice daily (with dose adjustment according to weight and target anti-Xa level 4–6 h post-dose 0.8–1.2 U/mL) should be considered in patients with a warfarin dose required of >5 mg/day (or phenprocoumon >3 mg/day or acenocoumarol >2 mg/day).	IIa	C
Discontinuation of OACs between Weeks 6 and 12 and replacement by UFH or LMWH under strict dose control (as described earlier) may be considered on an individual basis in patients with warfarin dose required for therapeutic anticoagulation <5 mg/day (or phenprocoumon <3 mg/day or acenocoumarol <2 mg/day).	IIb	C
Continuation of OACs may be considered between Weeks 6 and 12 in patients with a warfarin dose required for therapeutic anticoagulation >5 mg/day (or phenprocoumon >3 mg/day or acenocoumarol >2 mg/day).	IIb	C
LMWH should be avoided, unless anti-Xa levels are monitored.	III	C

aPTT, activated partial thromboplastin time; AS, aortic stenosis; LMWH, low-molecular weight heparin; LVEF, left-ventricular ejection fraction; MS, mitral stenosis; OACs, oral anticoagulants; UFH, unfractionated heparin.
[a]Class of recommendation.
[b]Level of evidence.

and coronary arteries, direct effect on cardiac receptors increases heart rate, with the overall effect of hypotension, tachycardia, and myocardial ischaemia.[51–53] However, in some situations where cardiac function is uncompromised, ergometrine can be used.

These problems have meant that the use of bolus oxytocin has declined and been largely replaced by the use of low-dose oxytocin infusions, although the benefit of this approach is not clear.[54] If a PPH does occur, oxytocin should be given and prostaglandins are generally well tolerated, but early intervention is key to keep control of the situation, with a greater emphasis on mechanical approaches including an intrauterine balloon and uterine compression sutures.

Infective endocarditis in pregnancy is rare and has been reported with an incidence of 0.5% in patients with known valvular lesions.[11] Breastfeeding is associated with low-risk of bacteraemia, secondary to mastitis. In highly symptomatic and unwell patients, bottle-feeding could be considered if milk formula is readily available.[11] Endocarditis prophylaxis is recommended for high-risk patients (prosthetic valve) with high-risk procedures such as, e.g. dental procedures. During delivery, the indication is controversial and at present antibiotic prophylaxis is not routinely recommended during vaginal or Caesarian delivery.[55] However, in our practice, we are using prophylaxis with any mode of delivery other than an uncomplicated vaginal delivery, especially in patients with a mechanical valve.

Management of complications

Diagnosis and treatment of mechanical valve thrombosis

New onset of dyspnoea, reduced exercise tolerance, dizziness or new-onset palpitations or an embolic event in a pregnant or peripartum woman with an MV must raise the suspicion of valve thrombosis. Often the women will have noted palpitations or the 'disappearance of the clicks' in those who are aware of them. This should lead to careful clinical examination and auscultation, followed by echocardiography. An increase in the mean prosthetic valvular gradient, compared with the pre-pregnancy gradient or increased turbulence are suggestive but the presence of visible thrombus is diagnostic. Additional transoesophageal echocardiography (TEE) is usually necessary.[56] However, this is often not tolerated in pregnant women with advanced gestation or those presenting in heart failure. If there is any remaining doubt, fluoroscopy must be performed.[56] The radiation dose to the foetus is limited and very unlikely to have adverse effects. The ESC Guidelines recommend that in selected asymptomatic cases (in particular when inadequate anticoagulation can be documented or if the thrombus is very small), anticoagulation can be optimized first. If the thrombus disappears, no other intervention is necessary. Success has been reported in up to 85% of cases.[57]

For critical PHV thrombosis, the treating physician has the option of fibrinolysis or surgery. The successful use of fibrinolytics has been recently reported during pregnancy in a series by Özkan *et al.*[58] Between 2004 and 2012, tissue-type plasminogen activator was administered to 24 consecutive women in 25 pregnancies with 28 prosthetic valve thrombosis episodes (obstructive, $n = 15$; non-obstructive, $n = 13$). Thrombolytic therapy sessions were performed under TEE guidance. The mean dose of tissue-type plasminogen activator used was 48.7 ± 29.5 mg (range, 25–100 mg). All episodes resulted in complete thrombus lysis after thrombolytic therapy. No patient died and complications were minimal. The authors concluded that the protocol applied was safer than cardiac surgery or other medical strategies.

Thrombolytics do not cross the placenta, but the risk of embolization (10%) and placental abruption is a concern.[11] Fibrinolysis is the therapy of choice in all critically ill patients when surgery is not immediately available and is the therapy of choice in right-sided thrombosis.[36] Surgery in pregnant women has a reported foetal loss of 20–30%,[59,60] but the risk for the mother is similar to the risk outside the pregnancy. It remains the treatment of choice if thrombolysis has failed or is contraindicated.

Diagnosis and management of heart failure in women with prosthetic valves

In patients with sub-optimal TV (e.g. pannus ingrowth) or mechanical valves, in particular with small valve sizes due to prosthesis mismatch, arrhythmias, left-ventricular dysfunction, and the physiological haemodynamic changes in pregnancy might result in cardiac decompensation. Development of severe heart failure and death have been reported.[22,61,62] The treatment follows guidelines on managing heart failure in pregnant women with diuretics, nitrates, and hydralazine for reduction in pre-and afterload and digoxin and beta-blockers to reduce heart rate.[11] ACE-inhibitors are contraindicated.

Conclusion

The number of pregnant women with valvular disease presenting to individual physicians is generally small. Knowledge of the risks associated with specific valvular conditions or types of prosthetic valves and need for anticoagulation in pregnancy is of fundamental importance for advising the patient before pregnancy. In managing pregnant women, we should remain mindful of the fact that all treatments have an impact on both the mother and the foetus. Consequently, all treatment choices need to be optimized for both. Data from prospective or randomized studies are absent and guidelines for the optimal management in a given situation are based on consensus and/or opinion of experts in the field, together with data derived from small prospective studies, retrospective studies, and registries (Level C). Until successful prevention programmes will have eradicated RHD in LMICs, their main challenge will be access to heart valve surgery followed by replacement valves that are suitable for the young rheumatic patients of LMICs. Percutaneous valve lesion mitigation (e.g. use of MitraClip for mitral regurgitation), or the placement of low-cost synthetic stented valves for other lesions through a non-occlusive, self-homing approach may also hold hope for that majority of young women in LMICs that currently have no access to surgery.

Altogether, careful planning and a multi-disciplinary approach to the management of women with complex valvular disease mean that most complications can be avoided.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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