Perspective

Interventional Cardiology

# Should we offer a bioprosthetic valve to women of child-bearing age who need valve replacement?

Rafael Hirsch
Adult Congenital Heart Unit, Dept. of Cardiology, Rabin Medical Center – Beilinson Campus, Petah Tikva, 49100 Israel
and
The Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
rafaelh@clalit.org.il

Pregnancy is associated with hypercoagulability and hemodynamic instability. Mechanical valves pose a special problem during pregnancy. Warfarin, the most effective drug for preventing valve complications, is teratogenic and also increases fetal loss. Other anticoagulant regimens are less effective and therefore increase the risk of maternal and fetal complications. Chronic anticoagulation can also significantly affect young patient's quality of life. Biological valves do not require maintenance of any kind and do not pose special risk during pregnancy. However, they degenerate with time, requiring reintervention. Practice guidelines are gradually moving toward recommending biological valves in the majority of young women. There are emerging solutions for valve degeneration that will further tilt the balance in favor of these valves.

**Keywords:** bioprosthesis • enoxaparin • heart valve • mechanical valve • practice guidelines • pregnancy • thromboembolism • valve-in-valve • valve sparing procedures • warfarin

In this perspective, I will try to persuade the reader that the answer should be 'yes' for the question in the title for most women.

The first mechanical heart valve was the Starr–Edwards ball valve, introduced in 1960. Single tilting disk valves came several years later and bileaflet valves in 1979. The latter have an improved hemodynamic profile, reduced incidence of mechanical hemolysis and a lower incidence of catastrophic stuck valve. However, all of them require regular treatment with effective doses of anticoagulants, vitamin K antagonists (VKA; warfarin, acenocoumarol) being the most effective and almost universally used for this purpose. The biggest advantage of mechanical valves is their durability. In theory, they could be as effective as on the day of their implantation throughout a patient's lifetime, even when implanted in the very young. In reality, there is need for reoperation due to valve thrombosis, thromboembolism, tissue ingrowth and infective endocarditis. Also, the chronic use of VKA has its toll in the form of bleeding complications at a rate of around 0.5–1% per year [1].

The need for anticoagulation is particularly problematic during pregnancy. At this procoagulant and physiologically unstable period, when protection of the mechanical valve requires the most effective drugs, the use of VKA antagonists is hampered by a specific and severe embryopathy when given during the first trimester. Later in pregnancy, embryopathy is not common but other fetal complications including stillbirth, prematurity and brain hemorrhage remain a significant problem [2].

Replacement tissue valves behave in many ways like native valves. They do not require regular maintenance. They have a good hemodynamic profile initially but are subject to structural deterioration with time, resulting in stenosis, regurgitation or a combination of both. The degenerative process is faster in young patients compared with older ones with the same prosthesis. The need for reoperation is almost certain when implanted in the young [3].

Future Medicine part of fsg

My interest in heart disease in pregnancy began more than 20 years ago, when I established an adult congenital heart service in my hospital and became consultant to the obstetrics and high-risk pregnancy departments.

At that time, replacement of heart valves with mechanical prostheses in young women was the rule, most young ladies with valve replacement had rheumatic heart disease and practice guidelines were not yet available.

Over the years I have witnessed many complications of mechanical heart valves in pregnancy, maternal and fetal. These can be devastating. There is fatality, need for urgent reoperation or thrombolytic therapy, massive bleeding and fetal loss [4,5]. In the literature, balanced reviews of the choice of valve for women of childbearing age can be found [6]. Personally, I have been an advocate of tissue valves for women of childbearing age for many years. It was a difficult position to defend at those early days. However, as cardiology is a rapidly evolving field of medicine, many things have changed, and I believe it is easier to defend this stance nowadays.

## Optimal anticoagulation for mechanical valves during pregnancy

Mechanical heart valves have been used for over 50 years now. Still, there is no consensus regarding optimal anticoagulation in pregnancy. There is a need to balance between, on the one side, optimal maternal outcome requiring the use of VKA throughout pregnancy with a significant compromise of fetal health and high incidence of fetal loss, and, on the other side, alternative anticoagulation with a better chance for a successful pregnancy and delivery of a healthy child, while risking maternal health. It is beyond the scope of this perspective to go into the details of the numerous anticoagulant regimens suggested by the different bodies and institutions dealing with this complex subject [7–9].

It is recommended to add aspirin, beginning from the second trimester, to all patients with prosthetic valves, bioprosthetic and mechanical ones, regardless of anticoagulant regimen [9,10].

What is the incidence of pregnancy complications in patients with mechanical valves? There is an abundance of case reports and several larger series dealing with this issue. One such series [11] was published in 2000 and included 1234 pregnancies in 976 women with mechanical valves that were subject to one of several different anticoagulant regimens. Maternal mortality was 2.9%, valve thrombosis occurred in 3.9% of women taking VKA throughout pregnancy and 9.2% in those with heparin replacement. Major bleeding occurred in 2.5%, mostly around delivery. Although this reflects a previous era of prosthetic valves (only 7% were bileaflet), and newer approaches to anticoagulation (e.g., low molecular weight heparin) were not practiced at that time, the numbers are frighteningly high.

Most studies on anticoagulants for prosthetic valves in pregnancy included small numbers, were retrospective and nonrandomized. It comes without surprise that there is no consensus regarding the preferred regimen. For comparison, when the pharmaceutical companies wanted to test the hypothesis that the recently introduced novel anticoagulant drugs, dabigatran, rivaroxaban and apixaban, were a suitable substitute for warfarin in the prevention of stroke in atrial fibrillation, they conducted randomized trials that together included 50,000 patients [12].

It has been advocated, based on small-scale studies, that warfarin treatment throughout pregnancy is safe in patients who require only low-dose warfarin (up to 5 mg/day) to sustain a therapeutic level of INR (International Normalized Ratio) per day [13]. These recommendations have been adopted recently by the AHA/ACC (American Heart Association/American College of Cardiology) guidelines as class IIa recommendation, preferring it to other anticoagulant alternatives [9]. Others advocate warfarin for most patients regardless of the dose, considering maternal safety as a first priority [14]. This may also be the only treatment available in certain under-resourced societies and countries [15]. Some advocate reducing the warfarin dose to achieve what is usually considered a subtherapeutic INR level for mechanical valves, even for nonpregnant patients, in order to reduce the risk to the fetus. In one report, this approach was shown not to increase thrombotic complications [16]. However, considering the fact that pregnancy is known to have a much increased thromboembolic complications risk, I find this approach risky and unjustified.

In recent years, many centers including ours, have adopted the policy to give low molecular weight heparin throughout pregnancy, replacing it with continuous unfractionated heparin only toward term or planned induction of labor. In order to achieve maximal protection and minimize bleeding complications, anti Xa monitoring is required, with predefined peak and trough levels. If two daily injections fail to achieve the target levels, three injections may be required. This regimen seems to balance well between the risks of pregnancy to the mother and the fetus. However, it is a very costly and time-consuming regimen for both patient and caregivers. It requires a high degree of patient compliance and understanding of the entire process. It needs physician input almost around the clock [17–20]. In the recent AHA/ACC guidelines [9], this method of anticoagulation had only a class IIb recommendation in patients who could be treated with a low-dose warfarin.

It was hoped that newer anticoagulants would become available to replace the problematic VKAs and inconvenient injections of low molecular weight heparins, but the recently introduced so-called novel anticoagulants are not safe in pregnancy as they cross the placenta [21]. Also, one of them, dabigatran, a factor II inhibitor, was compared with warfarin for mechanical valves in a randomized trial, which was stopped prematurely due to excessive complications [22].

## Bioprosthetic valves

A bioprosthetic valve does not require regular maintenance and servicing. From the day it is implanted it serves the patient very much as if it was his own native valve, until it degenerates to a degree that hemodynamic deterioration and clinical events take place. In young patients, this typically occurs after around 10 years, although rarely, early degeneration, sometimes as soon as 2 years after implantation, has been known to occur.

For some time, it was 'common knowledge' that pregnancies contribute to accelerated valve degeneration. This was supported by several studies and constituted a strong argument against implanting tissue valves in young women planning to become pregnant. However, other studies failed to support this hypothesis, and showed that the relatively rapid degeneration of these valves was due to the young age of these women, unrelated to the pregnancies [23,24].

In the past, many patients had rheumatic fever and atrial fibrillation. Such patients require anticoagulants anyway, and the advantage of bioprosthetic valves is less obvious. Nowadays, the incidence of rheumatic heart disease is lower, and many women requiring valve replacement have congenital heart disease with a relatively low incidence of atrial fibrillation.

There is consensus that bioprosthetic valves are safer than mechanical valves in pregnancy. Those who favor mechanical valves argue that the rapid degeneration of bioprosthetic valves in the young requires early reoperation with a high surgical risk. Nevertheless, most studies on reoperation for valve replacement deal with older and sicker patients. When using the surgical scores of calculating surgical risk, the Euroscore II for a 40-year old lady undergoing valve replacement, with one previous heart operation, NYHA FC II and no other comorbidities, is 2.1% and STS (Society of Thoracic Surgeons) score 1.2%. This risk is similar if not lower than the risk of maternal death in a single pregnancy with a mechanical valve. If a tissue valve is implanted, the patient can have two or three pregnancies before the valve needs replacing, thus reducing mortality per pregnancy by half or two-thirds. If we take into consideration that in addition to the risk during pregnancies, anticoagulation imposes a yearly risk of 0.5–1% of major bleeding between pregnancies, the risk reduction by the bioprosthetic valves is even larger.

## Quality-of-life issues

The above discussion related to the risk incurred to mother and fetus by mechanical versus tissue valves. However, this debate has much more to it, if we also consider quality-of-life issues.

A mechanical valve in a young woman means she has to adhere to anticoagulation without compromise. Compliance must be absolute. She has to understand the constant threat of death or stroke imposed by forgetting to take the medication, even for only one or two days. She needs to have her blood tested every fortnight to three weeks, observe dietary restrictions, find out about drug interactions with warfarin and refrain from contact sports. She has to report pregnancy immediately, start painful injections twice or three times a day, and worry constantly about her own health and that of the fetus she is carrying.

On the other hand, a tissue valve will allow this patient, after recovering from the operation, to lead an entirely normal life.

It has been my experience in recent years that even young men often choose to have a tissue valve replacement because of those important quality-of-life issues. If this is true in men, undoubtedly, the possibility of future pregnancies in women should by far tilt the scale in favor of a tissue valve.

## What do the official guidelines say?

Discussing this topic is much easier nowadays, as practice guidelines are here to help us decide. The European ones have shifted rapidly toward supporting tissue valves for young women. The recent AHA/ACC guidelines do not approach this question directly.

The European Society of Cardiology (ESC) guidelines on the management of cardiovascular disease during pregnancy from 2011 [7] state that 'the desire for pregnancy is considered a class IIb indication for a biological valve'.

One year later, the ESC guidelines from 2012 on the management of valvular heart disease [8] upgraded this recommendation to class IIa – 'a bioprosthesis should be considered in young women contemplating pregnancy'.

Quote from the 2012 ESC guidelines on the management of valvular heart disease:

In women who wish to become pregnant, the high risk of thromboembolic complications with a mechanical prosthesis during pregnancy – whatever the anticoagulant regimen used – and the low risk of reoperation are incentives to consider a bioprosthesis, despite the rapid occurrence of SVD in this age group.

In the AHA/ACC guidelines on valvular heart disease from 2014, like in the ESC ones, there is a class I recommendation to implant the kind of valve the patient chooses, after being properly informed. The patient's inability or wish not to take anticoagulants will result in implantation of a tissue valve.

### Class I

The choice of valve intervention, that is, repair or replacement, as well as type of prosthetic heart valve, should be a shared decision-making process that accounts for the patient's values and preferences, with full disclosure of the indications for and risks of anticoagulant therapy and the potential need for and risk of reoperation. *(Level of Evidence: C)*

A bioprosthesis is recommended in patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired. *(Level of Evidence: C)*

However, if the patient is under 50 years old and does not object to anticoagulation, there is a class IIa recommendation for mechanical prosthesis, even for a woman of childbearing age.

But further down the same guidelines, there is a section regarding pregnant patients with prosthetic mechanical valves.

And here are quotes from these guidelines for the reader to judge.

### Class I

Pregnant patients with a mechanical prosthesis should be monitored in a tertiary care center with a dedicated Heart Valve Team of cardiologists, surgeons, anesthesiologists and obstetricians with expertise in the management of high-risk cardiac patients. *(Level of Evidence: C)*

### Class I

Therapeutic anticoagulation with frequent monitoring is recommended for all pregnant patients with a mechanical prosthesis. *(Level of Evidence: B)*

There is a high risk of valve thrombosis in patients with mechanical prostheses who are pregnant due to the hypercoagulable state that occurs during pregnancy. All anticoagulant regimens carry an increased risk to the fetus, with fetal abnormalities, an increased risk of miscarriage, and hemorrhagic complications, including retroplacental bleeding, leading to premature birth and fetal death. However, without any anticoagulation, maternal mortality is high (up to 5%), and there is a high risk of thromboembolic events (up to 24%) and valve thrombosis. Because of the physiological effects of pregnancy, there are constantly changing requirements for antithrombotic regimens. Effective anticoagulation with frequent monitoring of its systemic effect is critical throughout the pregnancy.

The only mention of bioprosthetic valves in the entire section on pregnancy with prosthetic valves related to the need for aspirin. It is hard not to be impressed by how much easier and safer it is for a woman of childbearing age to go through pregnancy with a tissue valve.

## Important present advances and a look to the future

The manufacturers of bioprosthetic valves are steadily working on improving the durability of their valves, thus the rate of deterioration of valves implanted these days may be slower than that reported in the literature.

Until several years ago, a degenerated tissue valve causing hemodynamic and/or clinical problems had to be replaced surgically. In recent years, we have a promising alternative to redo surgery in the form of a valve-in-valve procedure. For the aortic position this can be achieved percutaneously. For the mitral valve, a transapical approach is required, but this is relatively minor surgery and does not involve cardiopulmonary bypass [25–27]. These procedures enable us to prolong the period in which our young female patients can enjoy a safe and maintenance-free valve and sustain pregnancies, before requiring another open heart operation. At the fast pace these technologies are evolving, valve-in-valve procedures will most probably become even easier to perform and safer, and it is almost certain that in the future we shall be able to further prolong the lifespan of the original valve by re intervening with a 'valve-in-valve-in-valve' procedure and so on.

## Alternatives to bioprosthetic valves

If we accept the concept that mechanical valves are not desirable in women of childbearing age, but do not want to replace the valve with a bioprosthetic one, there are some alternatives to consider.

For many years, the rheumatic stenotic mitral valve could be repaired with surgical commisurrotomy or balloon valvuloplasty. Nowadays, many more valve problems can be solved without replacing the valve. This includes repair of a prolapsing or flail mitral valve, repair of a leaking trileaflet left atrioventricular valve in atrioventricular septal defect, repair of the displaced tricuspid valve of Ebstein's anomaly, valve sparing operations of the aorta for Marfan syndrome and other aortopathies, repair of a ventricular septal defect with a prolapsing aortic valve, repair of valves affected by infective endocarditis and many more.

Before deciding between repair and replacement, we should find out what is the risk, success rate and durability of valve repair compared with valve replacement,

including the possibility of extending the lifespan of the tissue valve in the future with a valve-in-valve procedure.

An alternative approach to aortic valve replacement with a tissue valve is to perform the Ross procedure, where the patient's own pulmonary valve is implanted in the aortic position, and is itself replaced with a tissue valve. The advantage of this approach is that the patient's autograft aortic valve does not deteriorate over time like tissue valves, and can perform satisfactorily for many years. This is a complex and lengthy operation, requiring surgeons with expertise. The tissue valve in the pulmonary position (often a homograft) does deteriorate with time, but can nowadays be replaced percutaneously in most instances. Our experience with this operation has been very good, including many pregnancies [28].

Homograft valves, either pulmonary or aortic, harvested from cadavers, have been used for many years for valve replacement, especially in the pulmonary position. They degenerate over the years, getting heavily calcified, stenotic or regurgitant. It has been suggested that, at least in part, this degenerative process is caused by immune reaction to the foreign tissue. There is already some clinical evidence that decellularized homografts do better than regular ones [29], and it is speculated that coating the decellularized homograft scaffold with the patient's derived cells will further improve durability and performance of these valves [30].

In case a patient is willing to have only one child, one pregnancy with the patient's native valve disease may have a lower risk to the mother and fetus than would a pregnancy with a mechanical prosthesis. In such a case, it is sometimes possible to allow a well-observed pregnancy and delivery, and replace the valve with a mechanical prosthesis after delivery of the baby.

## In whom should we still consider a mechanical prosthesis?

Despite being an advocate of bioprosthetic valve in most cases, there are some circumstances in which I would consider a mechanical valve.

Mitral valve replacement in childhood is exceptionally rare, but, if required, a mechanical prosthesis should be implanted in order to avoid repeated operations. The Ross procedure should be the choice for aortic valve disease, as the pulmonary autograft has been shown to grow with the child.

Bioprosthetic valves deteriorate very fast in patients with renal dysfunction. Even without heart disease, those patients have a markedly increased pregnancy risk. It is probably advisable to discourage patients with chronic renal failure who are in need of valve replacement from having children and choose a mechanical prosthesis.

Which valve is better for patients on anticoagulants for atrial fibrillation or other reasons, requiring valve replacement, especially a mitral valve? Some of the advantages of a bioprosthetic valve are lost because of the need to anticoagulate anyway. Still, it would be reasonable to assume that the thromboembolic risk of pregnancy in a patient with a tissue valve taking low-dose anticoagulation is lower than with a mechanical prosthesis.

If a patient who is in need of valve replacement wishes to have only one child, the advantage of having a tissue valve during pregnancy from the mother's safety aspect is negated by the risk of later reoperation. Still, I would recommend a tissue valve for the better chance of completion of the pregnancy and delivering a healthy child.

We often encounter young women who are not planning to become pregnant in the coming years. If we recommend a tissue valve, we might find ourselves replacing this valve 10 years later without the patient having had any pregnancies. It is crucial to have the patient understand the full meaning of her choice of valve.

Finally, patients who have an increased risk at reoperation should be considered for a mechanical prosthesis. For many of those, pregnancy poses too high a risk anyway.

## Future perspective

In recent years, a significant progress has been made in treating native valve disease. We have at our disposal more and more effective valve sparing operations and catheter interventions, better, longer lasting bioprosthetic valves and the possibility to extend the time before reoperation is required by further catheter interventions. Also, the risk at reoperation is lower than it was when prosthetic valves have been introduced many years ago.

Patients who do not receive a mechanical valve enjoy a much improved quality of life. Therefore, avoiding mechanical valves altogether seems more realistic today than ever before.

It is my belief that over the next decade or two, mechanical valves will gradually cease to be a viable option, rendering the subject of this paper, the choice of valve in young women, irrelevant.

## Conclusion

I liken a pregnancy in a patient with a mechanical prosthesis to an acrobat walking on a string. You have to be skilled, well equipped, brave and lucky to succeed. And there are no safety nets.

I believe that nowadays there is strong support from literature and practice guidelines for bioprosthetic valves in women of childbearing age. Having heart disease can pose problems in pregnancy even without having to deal

obsessively with anticoagulation. The volume overload, increased cardiovascular demand and metabolic and endocrine changes may require careful attention and appropriate pharmacological and other forms of intervention. Nevertheless, it has been our experience that most pregnancies in heart patients end well. Most fetal losses, severe bleeding, thromboembolic complications and death I have witnessed were in patients with severe pulmonary vascular disease or those with mechanical valves.

Not only is a tissue valve safer than a mechanical valve, it carries with it a much improved quality of life.

The future seems even more promising, when we may have more resilient tissue valves, and will be able to prolong the time to reintervention significantly with valve in valve procedures.

Occasionally there will be a patient with valve disease that will require a mechanical prosthesis. For those, it is important to continue searching for the optimal anticoagulation regimen in order to improve both maternal and fetal outcome.

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### Executive summary

- Despite mechanical heart valves being in use for over 50 years, optimal anticoagulation during pregnancy is still debated.
- There is considerable maternal morbidity and mortality during pregnancy with mechanical valve, whatever the anticoagulant regimen.
- Warafarin is the safest drug but is teratogenic and causes fetal loss.
- Recent publications endorse treatment with enoxaparin throughout pregnancy, strictly monitoring anti Xa levels, at least peak level, preferably also trough levels.
- Bioprosthetic valves deteriorate with time. Rate of degeneration is more rapid in young patients. Contribution of pregnancies to valve dysfunction is debated.
- Reoperation for a degenerated bioprosthetic valve is low risk for most young patients.
- Quality of life with a bioprosthetic valve is much improved compared with patients on chronic anticoagulation for a mechanical valve.
- European practice guidelines have shifted toward supporting a biological valve in most women of childbearing age.
- American practice guidelines are more conservative and do not address this issue directly.
- A lot of effort is put into improving bioprosthetic valve durability. Emerging catheter techniques are very promising in their ability to extend the time before valve replacement is required, namely, valve-in-valve procedures.
- Surgical and transcatheter valve sparing techniques should always be considered before a decision to replace a valve is taken.
- Rarely, we will encounter patients for whom a mechanical prosthesis is the preferred choice.
- In the future, it is speculated that mechanical valves will be abandoned for most patients in favor of bioprosthetic ones, obviating the need to discuss young women separately.

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