Prosthetic Valve Thrombosis in Pregnancy:
A Promising Treatment for a Rare and Mostly Preventable Complication

Running title: Casais et al.; Valve thrombosis in pregnancy

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Prosthetic heart valve thrombosis (PVT) is a rare complication, with an estimated incidence of 0.1-5.7% per patient-year\(^1\). However, during pregnancy, changes in the hemostatic system lead to a pro-coagulant state that increases the risk of PVT up to 10%\(^2\). This maternal and fetal life-threatening complication is mostly preventable with long-term adequate anticoagulation therapy. When anticoagulation fails, treatment focuses on choosing between cardiac surgery and thrombolysis, two therapeutic strategies whose risks and benefits for the mother and fetus are difficult to assess.

The study by Ozkan et al.\(^3\), in this issue of *Circulation*, is the largest series of pregnant patients with prosthetic mitral valve thrombosis reported to date and offers interesting results in a scenario where randomized clinical trials are not feasible. A protocol of low-dose, slow infusion of t-PA with repeated doses as needed and transesophageal echocardiography guided, was associated with a successful thrombolysis in all episodes, with no maternal deaths and a fetal mortality rate of 20%, results that seem to be better than other thrombolytic strategies reported.

Authors’ conclusions regarding the superiority of thrombolysis over surgery and the redefinition of the lytic option as a first-line therapy in pregnant patients with PVT require careful evaluation. Prior studies of cardiac surgery showing maternal and fetal mortality rates of 6% and 30% respectively, were published a decade ago, and mostly based on coronary revascularization procedures. Since then, some recommendations have been included such as appointing the procedure during the second trimester of pregnancy when possible, monitoring intra-operative fetal heart rate and uterine contractions, and maintaining normothermia during the surgery. In fact, results of more recent series of surgical management of valvular diseases in pregnant women seem to have improved\(^4\,5\). It is noteworthy that four of the 28 events were re-thrombosis; three of them were recurrent obstructive thrombi occurring during the same
pregnancy. The intervals between the first PVT treated with thrombolysis and the recurrence were 3, 6 and 10 weeks; the doses of t-PA used in the first event ranged from 25 to 100 mg. These observations raise the question of whether the first treatment should be considered indeed successful, or if the definition of thrombolytic success should include some “time free of thrombosis” besides the echocardiography and clinical criteria. However, an adequate anticoagulant treatment after thrombolysis is essential to achieve “time free from thrombosis”. After thrombolysis, anticoagulant treatments in these three patients were warfarin, LMWH at a lower dose (than the dose at the time of the first event) and no anticoagulation at all. For clinicians this is an important learning point from this study, PVT either “de novo” or recurrent require optimizing anticoagulation after thrombolysis.

The observations by Ozkan et al.3 are in agreement with previous reports showing that risk factors for valve thrombosis during pregnancy are the same as in non-pregnant women, which are prosthetic valve in mitral position and sub-therapeutic anticoagulation. These facts highlight the need for careful evaluation of the thrombotic risks in each particular patient and the importance of prevention with adequate anticoagulation.

Even though evaluation of the efficacy of an anticoagulant treatment requires the assessment of time spent within therapeutic range during follow-up –data not provided in the present study-, anticoagulation was sub-therapeutic in 93% of the patients at the time of PVT diagnosis, regardless of the regimen used. Moreover, three episodes occurred in patients receiving no anticoagulant treatment at all; one of them a 25 year-old woman with a prior PVT while on low molecular weight heparin (LMWH) at 6 weeks of gestation who recurred at the 12th week.

There is no optimal anticoagulation regimen during pregnancy for patients with
mechanical heart valve prostheses, because every therapeutic option has its drawbacks.

Anticoagulant regimens in pregnant patients with prosthetic heart valves are associated with similar risk of maternal bleeding but with different embolic risk.

Warfarin through the entire pregnancy with an intended International Normalized Ratio (INR) 2.5-3.5 is the safest for the mother, with an incidence of PVT < 4%. LMWH twice daily with a target anti-Xa level of 0.7-1.2 IU/mL at 4 hours after injection is associated with an embolic risk of 7-16%. Unfractionated heparin (UFH) twice daily to maintain APTT values twice the control or to achieve an anti-Xa level of 0.35-0.70 anti-Xa/mL is associated with the highest risk of thromboembolic complications (33%)\(^6\). However, published reports include very heterogeneous populations, with different risk factors for thromboembolism, different valve types and position, time in therapeutic range is usually not provided, and compliance with anticoagulation was not assessed in many studies\(^7-9\).

Even though warfarin was associated with the lowest risk of PVT, there is concern regarding its safety for the fetus. Unlike heparins, warfarin crosses the placenta and is associated with early fetal loss and with teratogenesis (0.6–10%); though embriopathy and spontaneous abortions might be dose-dependent with a very low risk when the dose is less than 5mg/ day. Even though some authors recommend intravenous heparin before delivery (week 35-36\(^{th}\))\(^10\), currently, one of the most accepted anticoagulant regimens for pregnant patients with prosthetic valves is to switch to therapeutic doses of LMWH during the first trimester and re-start warfarin in the 13\(^{th}\) week, until the 35\(^{th}\)-36\(^{th}\) week when it is substituted with LMWH again.

Still, American and European recommendations for anticoagulation in this scenario are not in full agreement. European Society of Cardiology guidelines discourage the use of LMWH during the entire pregnancy because of the thrombotic risks, and consider the use of warfarin
throughout pregnancy when the dose is <5 mg/daily (or phenprocoumon < 3 mg/daily or acenocoumarol < 2 mg/ daily)\textsuperscript{11}.

The American College of Chest Physicians, Antithrombotic Therapy and Prevention of Thrombosis Evidence-Based Clinical Practice Guidelines (ACCP) and American College of Cardiology/American Heart Association Guidelines recommend (grade 2 recommendations) that low dose aspirin be added in pregnant patients with mitral valve prostheses and with other high risk factors (such as prior thrombo-embolic event, or atrial fibrillation)\textsuperscript{6, 12}. In the study by Ozkan, only 2 patients were receiving low dose aspirin, and none the patients with recurrent PVT were on aspirin after the first event.

Patients should be informed about risks and benefits of each alternative and they should be aware that compliance with the chosen treatment is essential to prevent complications. Factors to be considered when deciding the best anticoagulant treatment include patients’ preferences, physicians’ expertise, costs, and availability of monitoring\textsuperscript{13}.

Neonatal mortality in the series by Ozkan et al.\textsuperscript{3} was 20%, similar to the incidence reported in other studies. All abortions occurred before the 11\textsuperscript{th} week of gestation (weeks 6, 9 and 11\textsuperscript{th}), in patients both on warfarin and on LMWH, and between 1 to 5 weeks after thrombolysis. Only five early abortions preclude from drawing any conclusions regarding a causal effect of anticoagulation or thrombolysis. In addition, as early spontaneous miscarriages occur in 15-25\% of pregnancies and are caused by random karyotype abnormalities of the embryo in 50\% of the cases, chance cannot be ruled out\textsuperscript{14}.

In conclusion, the low-dose slow-infusion regimen of t-PA is promising because it seems safe for the mother and the fetus but further research is warranted to determine its efficacy. So, currently there is no evidence to recommend it as the first therapeutic choice in PVT since other
factors such as gestational age at diagnosis, contraindications for thrombolytics, and hospital resources should be considered. Finally, focus on an adequate anticoagulation treatment, probably including low dose aspirin in mitral valves, and patient compliance are crucial to avoid this severe complication.

Conflict of Interest Disclosures: None.

References:


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