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Maternal, fetal outcome, and anticoagulant management in pregnant women with prosthetic heart valves

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Summary

Introduction: Cardiac disease in maternity is a great problem particularly in developing countries. Pregnant patients with prosthetic heart valves (PHV) may suffer therapeutic difficulty, as the need for anticoagulation is fraught with risk of hemorrhagic or thromboembolic complications and structural valve deterioration. The present study aimed to evaluate the maternal, fetal outcome, and anticoagulant management in pregnant women with PHV. *Materials and Methods:* This study is prospective observational research. The medical archives of pregnant patients with PHV from September 2010 to January 2015 were scanned. Data collected from Yuzuncu Yıl University Hospital Cardiology clinics archives included demographic characteristics, anticoagulant, presence or absence of obstructive or non-obstructive thrombus, and maternal-fetal outcome. *Results:* The authors evaluated the outcomes of 56 pregnant patients with PHV. The age at the time of pregnancy ranged between 19 and 37 (mean 28.7 ± 8.4) years. Most common preferred anticoagulation therapy was heparin during the first trimester, followed by oral anticoagulation up to the 36th week, with subsequent replacement by heparin until delivery. Most common encountered complication was preterm birth. Death occurred in one patient due to obstructive valve thrombosis. *Conclusion:* Ideal PHV is not accessible for women during childbearing age. The risk of adverse event during pregnancy depends on valve position, symptoms, valve type, cardiac function, and functional capacity in patients with PHV. The active collaboration among an obstetrician, a cardiologist, and a cardiothoracic surgeon is required for optimal outcome patient with PHV.

Key words: Pregnancy; Prosthetic heart valve; Anticoagulation.

Introduction

Cardiac disease in maternity is a great problem particularly in developing countries. Frequency of cardiac disease in the course of pregnancy is approximately 2%, but it maintains an important cause of maternal and fetal death [1, 2].

Pregnancy is related with hypercoagulation, due to three main factors: the increased thrombocyte aggregation capacity, increased activity of coagulation factors, and decreased fibrinolytic activity of plasma. Pregnant patients with prosthetic heart valves (PHV) may suffer therapeutic difficulty, as the need for anticoagulation is fraught with risk of hemorrhagic or thromboembolic complications and structural valve deterioration [3-5]. These factors increase the vital risk of both the mother and the fetus. The active collaboration among an obstetrician, a cardiologist, and a cardiothoracic surgeon is required for optimal outcome patient with PHV [6].

The choice of PHV is still a challenge in women during childbearing age, because an ideal PHV is not accessible [7]. There are two different groups of PHV including mechanical and bioprostheses. Each provides different advantages and disadvantages. Important areas of difference of these valves include durability or structural valve deterioration (SVD), incidence of thromboembolism, valve hemodynamics, and effect on fetal outcome [8].

High structural valve deterioration was reported during pregnancy or after delivery in patient with bioprotheses [8]. Pregnant women with mechanical valves are at a high risk of thromboembolism. Warfarin use during pregnancy is related with a low risk thromboembolic complications but a high risk of fetal complication such as embryopathy or haemorrhagic complication for fetus [9, 10]. Antithrombotic therapy with unfractioned heparin (UFH) or low molecular weight heparin (LMWH) significantly decreased of fetal complication, but up to a third of pregnant women with mechanical valves have thromboembolic complications [10] The American College of Cardiology and European Society of Cardiology have recommended strategies for anticoagulation during pregnancy in patients with PHV [11, 12].

The present study aimed to evaluate the maternal, fetal outcome, and anticoagulant management in pregnant women with PHV who were hospitalized or followed by the Department of Cardiology Yuzuncu Yil University.

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Materials and Methods

This prospective observational search was affirmed by the Yuzuncu Yil University Faculty of Medicine Ethics Committee for suitable to the Declaration of Helsinki. The medical archives of pregnant patients with PHV from September 2010 to January 2015 were scanned. Data's collected from Yuzuncu Yıl University Hospital Cardiology clinics archives included demographic characteristics, anticoagulant, presence or absence of obstructive or non-obstructive thrombus, and maternal-fetal outcome. Pregnant patients with PHV were graded according to the New York Heart Association (NYHA) classification [13].

The echocardiographic assessment was done at rest, the patient left lateral decubitis position, using available echocardiographic device with a 3.0-MHz transducer, by senior fellow echocardiographer according to established standards [14]. Spectral Doppler and color flow evaluation was examined for assessing the prosthetic valve morphology, gradient on PHV, and function. Transesophageal echocardiography was done for suspicion of PHV deterioration, obstructive or non-obstructive thrombus, and changes in clinical status of pregnancy.

After initial examination, pregnant women who were in NYHA functional class I and II were followed as outpatients and examinated monthly up to 32 weeks, then weekly until subsequently delivery. Those who were in NYHA class III and IV were hospitalized mainly due to worse social condition and the fact that most were referred from far areas of the source.

Experienced cardiologist with an obstetrician assessed all pregnant women with PHV and reviewed treatment regimens. If pregnancy was planned, they advised two strategies for anticoagulation. According to The European Society of Cardiology and American College of Cardiology two strategies were advised for anticoagulation during pregnancy in patients with PHV [11, 12] Strategy one: UFH throughout first trimester (to avoid warfarin embryopathy), followed by warfarin up to the 36th week, with subsequent replacement by heparin until delivery. Strategy two: oral anticoagulation until the 36th week, followed by heparin until delivery. Choice of anticoagulant therapy during pregnancy was done clinically (example corcondance follow for anticoagulation, thromboemboli history) and choice of the pregnant women and her husband. If pregnancy was unplanned, women with PHV and her husband was informed about pregnancy, hazards of anticoagulation at pregnancy, and possible embryopathy as a result of warfarin therapy in first trimester.

At each examination, anticoagulation was monitored by checking the international normalized ratio (INR). All patients were given five mg oral warfarin sodium, adjusted to give an INR of 2.5–3.5. If a patient was found to have an INR outside the target range, she was admitted until the optimal INR was achieved, and followed up weekly until control of the INR was ensured.

If antenatal care was uneventful, decisions on mode of delivery and review by obstetrician was taken at approximately 36 weeks' gestation. Vaginal delivery was the principle mode of delivery but cesarean section (C/S) was performed if vaginal delivery was contraindicated for obstetric reasons or if delivery begins under warfarin therapy [12].

All neonates were examined for fetal embryopathy by a neonatologist. Spontaneous abortion was defined as spontaneous fetal loss before 28 weeks of gestation [10] Therapeutic abortions included all medically indicated terminations before 28 weeks of gestation [15]. Warfarin embryopathy was defined as facial abnormalities, optic atrophy, digital abnormalities, epithelial changes, or mental impairment [15]. Warfarin was restarted 24 hours after delivery at the pre-delivery dosage, along with intravenous heparin until the INR was > 2.

All statistical analyses were conducted using SPSS system version 15.0. Descriptive statistics are presented as means ± standard deviation (SD) or by frequency percentages.

Table 1. — *Characteristics of pregnant women with prosthetic heart valve.*

Age (years)	Mean (SD): 28.7 ± 8.4 Range: 19 to 37
Location of valve n (%)	Mitral: 38 (66.7%) Aortic: 18 (31.7%) Multiple: 1 (MVR+TVR) (1.6%)
Type of PHV n (%)	Bi-Leaflet: 43 (75.4%) St. Jude: 23 (40.4) CarboMedics: 16 (28.1%) Sorin-Bicarbon (only aortic): 4 (7%) Heterograft and other: 14 (24.6%) Carpenter-Edwards: 13 (22.8%) Sorin: 1 (1.6%);
Time since valve repair (months)	Mean (SD): 34.2±13.6 Range: 18 to 40
NYHA class at onset n (%)	Class I: 27 (48.2%) Class II: 16 (28.6%) Class III: 9 (16.1%) Class IV: 4 (7.1%)
Additional risk factors at the onset of pregnancy n (%)	Atrial fibrillation: 13 (23.2%); Prior thrombosis: 1 (1.8%);
Labour and delivery n (%)	Vaginal delivery: 21 (37.5%); Cesarean section: 35 (62.5%);
Gravidity n (%)	Primigravida: 23 (41.1%) Parity 1: 17 (30.4%) Parity 2: 4 (7.1%) Previous miscarriage: 12 (21.4%)

Results

The present authors evaluated the outcomes of 56 pregnant patients with PHV. The age at the time of pregnancy ranged between 19 and 37 (mean 28.7 ± 8.4) years. Characteristics of pregnant women with PHV are shown in Table 1. Most common preferred anticoagulant therapy was heparin during the first trimester, followed by oral anticoagulation up to the 36th week, with subsequent replacement by heparin until delivery. Throughout warfarin alone usually was selected in unplanned pregnancy. Anticoagulant regimen for pregnant women with PHV in Table 2. Most common encountered complication was preterm birth. Death occurred in one patient due to obstructive valve thrombosis. Outcomes and results of pregnant with PHV are shown in Tables 3 and 4.

Discussion

In this paper the authors evaluated the consequence of pregnancies with PHV 56 patients. Prosthetic mitral valve is the most common PHV, most common preferred anticoagulant therapy is heparin during the first trimester, fol-

Table 2. — *Anticoagulant regimen for pregnant women with prosthetic heart valve.*

Anticoagulant regimen	Warfarin alone pregnancy 19 (33,9%) (commenced prior to pregnancy and continued until 36 weeks): • Mechanical prosthetic heart valve 17 (30.4%) • Bioprosthetic heart valve 2 (3.5%) • Planned pregnancy 3 (5.4%) • Unplanned pregnancy 16 (28.6%) • Target INR: 2.5-3.5 • Time to INR in therapeutic range, n (%): 87 warfarin (trimester 2 and 3) + therapeutic heparin 25 (44.6%) • T2&3 Warfarin INR adjusted: 2.5 – 3.5 • Warfarin commenced 12 weeks continued until 36 weeks • Trimester 1 UFH aPTT-adjusted: 2 – 2.5 times • Heparin commenced 0 weeks; continued until 12 weeks and after 36 weeks
Antiplatelet agents	Proportion using antiplatelet agents, n (%): 13 (23.2%); • Type of antiplatelet agent: low-dose aspirin (75 – 150mg), 11 (19.4%) • High dose ASA (325 mg) 2 (3.5%) • Mechanical prosthetic heart valve 1 (1.8%) • Bioprosthetic heart valve 12 (21.4%)

Table 3. — *Outcomes and results.*

	Warfarin alone (n= 19)	Warfarin + heparin (n=25)	Antiplatelet alone (n=12)
Maternal deaths, n (%)	1 (1.8%)	0	0
Valvular thrombosis, n (%)	3 (5.4%)	4 (7.1%)	1 (1.8%)
Major bleeding requiring transfusion/ discontinuation of anticoagulation	0	0	0
Adverse drug events (HIT/ hypersensitivity), n (%)	0	2 (3.6%)	
Maternal cardiac event(s), n (%)	4 (7.1%)	5 (8.9%)	0
(a) Preterm birth < 37 weeks	3 (5.4%)	11 (19.6%)	1 (1.8%)
(b) Small for gestational age (<10th centile)	2 (3.6%)	3 (5.4%)	1 (1.8%)
Fetal loss – miscarriage (< 20 weeks), n (%)	2 (3.6%)	7 (12.5%)	0
Fetal loss – stillbirth (>20 weeks), n (%)	1 (1.8%)	3 (5.4%)	0
Neonatal deaths, n (%)	0	1 (1.8%)	0
Fetal intracranial bleeding, n %	0	0	0
Fetal malformations, n (%)			
(a) Warfarin embryopathy	0	0	0
(b) Other malformations	0	0	0

Table 4. — *Outcomes and results.*

Timing and cause of maternal death(s)	1 (1.8%), not planned pregnancy, mechanic mitral valve thrombosis, and pulmonary edema, 24 gestational weeks
Timing and site of thromboembolic event(s)	8 (14,3%) patients had thromboembolic events (3 warfarin group, 4 warfarin + heparin group, 1 aspirin group), all of them second trimester
Details and timing of maternal cardiac event(s)	5 obstructive thrombus, 3 non-obstructive thrombus on PHV, 1 patient had pulmonary edema

lowed by oral anticoagulation up to the 36th week, and most common encountered complication is preterm birth in this study.

A great number of PHVs are being implanted every year in worldwide. Many of them in women of childbearing age who implanted PHV want to have children [16]. A selection of PHV in women during childbearing age is still problematic, because an ideal PHV is not available. The two main groups of prosthetic heart valves (i.e., the mechanical prostheses and the bioprostheses) both provide advantages and disadvantages. Important areas of difference in these valves are durability or structural valve deterioration, incidence of thromboembolism, valve hemodynamics, and effect on fetal outcome [8].

The use of bioprostheses valves in the course of childbearing age reduces the risk of anticoagulation and thromboembolism during pregnancy, but is related with a high risk of SVD in young women. Patients between the age of 16 and 39 years at the time of surgery, with either Carpentier-Edwards porcine bioprostheses or Hancock showed a high risk of SVD, which became noticeable as early as two to three years after operation and was as high as 50% at ten years and 90% at 15 years [17]. Moreover, North *et al.* [7] reported prosthetic valve loss ten years in 82% of 73 women at the time of PHV replacement with bioprosthetics of various types (Carpentier-Edwards, Hancock, and Medtronic.

Born *et al*. [18] reported higher incidence re-operation during pregnancy or the puerperium in 14% of 20 patients. Badduke *et al.* [19] reported long-term performance of biological prostheses valve in 87 women at less than 35 years of age; 17 of these experienced 37 gravidities. SVD was recorded in 47% of patients with pregnancy, compared with only 14% in the non-pregnant group ($p < 0.05$). Lee *et al.* [20] reported SVD during pregnancy in only four out of 95 pregnancies with bioprosthesis, although a lower ten-year graft survival incidence was noted in women with two subsequent pregnancies after their valve surgery (17%), compared with only one subsequent pregnancy (55%). In addition, re-operation, due to SVD, which presented as obstruction and calcification, was applied in 59% of the pregnancy group and 19% of the non-pregnancy group ($p < 0.05$).

Although some reports make a strong case for pregnancy-related accelerated SVD of valves, other reports have failed to support these findings. Jamieson *et al.* [21]

published 53 women who experienced pregnancy and 202 who did not. The rate of SVD and valve-related re-operation at the seven years follow up was slightly higher in the pregnancy group (51% *vs*. 41%, and 51% *vs*. 42%, respectively). Avila *et al*. [22] reported five-year prospective follow-up of 48 pregnancy with bioprosthetic valves and 37 women who did not become pregnant and found a comparable rate of SVD (27% and 30%, respectively) and re-operation (8% in both groups). The risk of SVD was seven-fold greater in the mitral position bioprothesis than the aortic or tricuspid position [8].

As a result of these reports, SVD at bioprosthetic heart valves during gravidity has been reported in some studies, but could not be confirmed by others. In this study, 14 (24.6%) patients with bioprothesis were present (Table 1). This ratio is higher than other case reports series with PHV because of desire to have children in the present study group. SVD was not seen during pregnancy or postpartum period in the present patients with bioprothesis valves.

Other major group of artificial heart valve is the mechanical heart valve. Mechanical PHV are classified into three groups: caged-ball, tilting-disc, and bileaflet valves [23]. The most widely used mechanical PHV are the bileaflet valves (St. Jude valve). The old generation prosthesis is no longer used and has a historical importance [18]. Mechanical PHVs, offer excellent long-term durability [24] and superior hemodynamic profile; however, their need for life-long anticoagulation and thrombogenicity are associated with a hazard of thromboembolism and maternal bleeding during pregnancy. In addition, available information on fetal outcome suggests an increased risk of fetal loss as well as birth defects, low birth weight, prematurity, and neonatal mortality in patients with mechanical PHVs [18, 20, 25].

Pregnancy is related with hypercoagulation, due to three main factors; the increased thrombocyte aggregation capacity, increased activity of coagulation factors, and decreased fibrynolytic activity of plasma [3-5]. Even with anticoagulation, 7.5–23% of pregnant patients with a mechanical prosthesis have a thromboembolic event, mostly valve thrombosis, with a resultant mortality rate of 40% [15, 26]. Mechanical valves at the mitral position have the highest risks of thromboembolism [27]. The American College of Cardiology and European Society of Cardiology has recommended strategies for anticoagulation during pregnancy in patients with PHV [11, 12]; these are shown in Table 5.

Geelani *et al.* [28] reported on 250 pregnancies with mechanic PHV. First group took warfarin throughout pregnancy and second group subcutaneous UFH by the end of the first trimester and warfarin up to 36 weeks. Similar frequencies of spontaneous abortion were found in both groups. Nassar *et al.* [29] reviewed 82 pregnancies retrospectively: there were 54 live births, nine stillbirths, 12 spontaneous, and seven therapeutic abortions. The ratio of spontaneous abortion was higher in women that were on warfarin during pregnancy, but spontaneous abortion was higher in warfarin+heparin group in the present study (5.4% *vs*. 17.9%).

Table 5. — *Recommendation for anticoagulant therapy during pregnancy with prosthetic heart valve.*

Recommendation	Class of recommendation	Level of evidence
Warfarin is recommended during the second and third trimesters until the 36th week	I	C
If delivery starts while on warfarin, cesarean delivery is indicated.	I	C
Warfarin should be discontinued and dose-adjusted UFH (a PTT ≥ 2× control) or adjusted-dose LMWH (target anti-Xa level 4–6 hours 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
Continuation of warfarin should be considered during the first trimester if the warfarin dose required for therapeutic anticoagulation is 5 < mg/day after patient information and consent.	IIa	C
LMWH should be avoided, unless anti-Xa levels are monitored.	III	C

If warfarin dosage does not exceed five mg daily, the risk of fetal warfarin embryopathy is small [11,12]. Vitale *et al.* [10] reported that 58 pregnancies in with PHVs who took warfarin ≤ five mg or > five mg (target INR, 2.5–3.5) until labor. There were clearly fewer fetal undesirable events in women taking ≤ five mg warfarin. Authors were recommended that warfarin at doses below five mg to achieve a target INR may be safe throughout the first trimester. In the present study, the dose of warfarin before, during, and after pregnancy was approximately 7.8 ± 2.4 mg and the present results were similar as previous study.

Mechanical PHV have the risk of thrombosis which is increased throughout pregnancy. In a review, this adverse event was 3.9% with warfarin alone, 9.2% when UFH was used in the first trimester, and warfarin in other trimester, and 33% with UFH throughout pregnancy [4]. Maternal death seen in warfarin alone group in 2.4%, and 15%, in warfarin + UFH group, and death was usually related to valve thrombosis [4]. In the present study, there were three (5.4%) thrombosis cases in warfarin group (one of them with obstructive thrombus and the patient died, while the other two patients with non-obstructive thrombus treated with tissue plasmingen activator), four (7.1%) developed thrombosis in warfarin + UFH group (all of them non-obstructive thrombus treated by tissue plasmingen activator).

One death (1.8%) was seen in the present study related o obstructive thrombosis in patient with unplanned pregnancy with poor functional capacity. In the present study, the ratio of thrombosis was similar to the aforementioned review.

The patient with PHV and her family should be informed on potential adverse events that might occur throughout pregnancy, including: symptomatic and hemodynamic deterioration, growing risk of thromboembolism, structural deterioration of bioprosthetic valves, and potential detrimental effects to the fetus due to cardiac medications (increased risk of prematurity, fetal loss, and growth retardation), because clinical deterioration often occurs during pregnancy [30].

This study had some limitations. Small size of the study population is major limitation for this study. Real incidence of PHV thrombosis, especially non-obstructive thrombus was not defined due to echocardiographic examination because transesophageal echocardiography was not a routine examination.

Conclusions

Ideal PHV is not accessible for women during childbearing age [7]. Mechanical PHV provide a better durability, and with careful anticoagulation relatively, there is small risk of thrombotic adverse event. In women who are not compliant in anticoagulation or for those in which close follow-up is not possible, a tissue valve is preferred [30]. The risk of adverse event during pregnancy depends on position, symptoms, type, cardiac function, and functional capacity in patient with PHV. Pregnancy with PHV evaluation should include a careful physical examination, and cardiac and valvular function assessment [30].

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