Outcome of surgery in critically ill patients presenting with mechanical mitral valve thrombosis during pregnancy.

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Abstract

OBJECTIVES: Prosthetic valve thrombosis during pregnancy is associated with serious maternal complications and considerable fetal loss. We report and analyze the outcome of surgery in critically ill patients referred to our tertiary center between January 2009 and January 2015.
METHODS: Twenty-eight pregnant patients with median age of 28 years (range: 20-40 years) presented with thrombosed bileaflet mechanical mitral valve prostheses, 48 (15-192) months after implantation. Twenty-two patients (78.6%) were on fixed dose LMWH (1 mg/kg twice daily) and six patients were on warfarin, with an INR <1.4 in four cases (66.6%). Patients were reported as being critically ill since 4 (1-12) days and presented in NYHA class IV (III-IV), with median gestational age (GA) of 31 (8-40) weeks. We had six cases of confirmed stillbirth (21.4%) on admission. The remaining were 14 patients presenting with GA ≥28 weeks (Group 1) and 8 patients with GA <28 weeks (Group 2). Delivery was planned before bypass in Group 1. Measures of fetal protection during surgery included: ≥2.7 L/m2/min high flow normothermic bypass maintaining mean perfusion pressure ≥ 70mm Hg and keeping hematocrit >28%.
RESULTS: All mitral prostheses were emergency replaced with same-sized mechanical valves. Median aortic cross clamp and bypass times were 57 (34-106) and 93 (48-140) minutes. We had two maternal mortalities (7.1%) and one preoperative regressive stroke (3.6%). Thirteen fetuses (59.1%) were successfully delivered before surgery (92.8% of Group 1) and nine were submitted to bypass: one rapidly deteriorating Group 1 patient and all eight patients in Group 2. Only three fetuses (GA =10, 21 and 31 weeks) survived bypass (33.3%) and were delivered at term. Outcome of the 22 live fetuses on admission was: 14 live births in Group 1 (100%; 9 healthy babies and 5 prematures) versus two in Group 2 (25%; P<0.001), with a total fetal loss of 27.3%.
CONCLUSION: Maternal outcomes are comparable to those of non-pregnant subjects. Unless the fetus is delivered before bypass, the heavy fetal loss, especially in patients presenting with GA <28 weeks, calls for applying more safety bypass measures. Controlled randomized trials are equally needed to evaluate the alternative fibrinolytic therapy.
Keywords: mitral valve, heart valve prosthesis, thrombosis, pregnancy, gestational age, cardiopulmonary bypass.

INTRODUCTION:

Prosthetic valve thrombosis (PVT) is a major complication of mechanical valve replacement, which risk is expected to increase during pregnancy. Besides being a hypercoagulable state, expecting mothers often lose the privilege of the effective thromboprophylaxis offered by oral anticoagulants when they are shifted to Heparin, in order to improve fetal

outcomes and to avoid the risk of warfarin induced embryopathy [1-3]. Two large systematic reviews involving 2577 pregnant patients with mechanical valve prostheses (MVP) have clearly shown that the incidence of prosthetic valve thrombosis during pregnancy (PVTP) in patients still following oral anticoagulants (1.2%-3.9%) was tripled in those shifting to Heparin derivatives during the first trimester (5.3-9.2%) and finally reached as much as 10.2%-33.3% in patients continuing parenteral anticoagulation till term [4,5].

Patients with PVTP are usually referred to our tertiary center in NYHA class III-IV and after a considerable time delay from the onset of alarming symptoms. Following the current guidelines [1-3], we managed those critically ill patients surgically and herein we report and analyze the outcomes.

MATERIAL AND METHODS

In the period between January 2009 and January 2015, patients referred to the department of cardiothoracic surgery of Ain Shams University hospitals with a preliminary diagnosis of PVTP represented an exclusive surgical emergency. After reviewing their surgical and obstetrical history, patients were investigated for recent shortness of breath, palpitation, muffling of mechanical valve clicks, symptoms suggesting thromboembolic events or other prosthetic valve related complications. All patients benefited from a full clinical as well as transthoracic echocardiographic examination and, in case of suspicion, they were further subjected to transesophageal echo (TEE) or fluoroscopy for better assessment of leaflet mobility. An obstetrician checked fetal viability and confirmed gestational age (GA). All examinations and investigations were conducted on an emergency basis. Once PVTP was confirmed, mothers were admitted to the intensive care unit (ICU) for full hemodynamic monitoring and support, while all measures were taken for emergency surgery. This report only concerns critically ill pregnant patients presenting with PVTP and fulfilling the following criteria: (i) Patient presenting with NYHA class III-IV due to PVTP and not due to any other comorbidity. (ii) Echocardiographic examination showing that the thrombus is either obstructive or otherwise large ($\geq$1 cm in diameter) or mobile with recent systemic embolization.

In the cardiac operation room, patients with GA $\geq$28 weeks were scheduled for an emergency Cesarean section, unless spontaneous delivery has already occurred. The neonate was transferred to the neonatal ICU. Mother was infused with Oxytocin for two-hours and the uterus was packed before commencing emergency valve surgery. Patients were routinely positioned supine, except still gravid mothers with GA $\geq$ 20 weeks who were positioned on a left lateral decubitus to reduce aorto-caval compression by the enlarged uterus. Our operative technique included femoral artery exposure before reopening sternotomy with an oscillating sternal saw. Adhesions were dissected first. Patients were fully heparinized and non-pulsatile cardiopulmonary bypass (CPB) was instituted. Gravid patients were kept normothermic with a flow rate $\geq$ 2.7 L/m^2/min and a mean perfusion pressure $\geq$ 70mm Hg was maintained by increasing flow and avoiding the use of vasoconstrictors as much as possible. Other patients benefited from routine mild hypothermic CPB, with a flow rate of 2.4 L/m^2/min. Excessive hemodilution was avoided and hematocrit was kept above 28% by adding packed red blood cells when needed. Myocardial protection was achieved with antegrade cold blood cardioplegia, given intermittently every 30 minutes. There were no attempts for simple thrombectomy and all malfunctioning valves were replaced by the same size mechanical prosthesis. In patients benefiting from Cesarean section before bypass, the abdominal wound was then inspected and closed after chest hemostasis was established.

Statistical analysis: Data were presented as numbers (%) or median (range). The distribution of fetal mortality between patients

presenting before GA of 28 weeks and those presenting afterwards was analyzed by a bilateral Fisher's exact test, with the P value of 0.05 as the limit of statistical significance.

RESULTS

In the period between January 2009 and January 2015, 28 patients fulfilled the inclusion criteria for this report. The common main presenting symptom was progressive shortness of breath over the last few days (median 4; range 1-12 days). It was associated with palpitation in 18 cases (64.3%), by the patient noticing muffling or absence of valve clicks in 7 cases (25%) and a cerebrovascular stroke with left sided hemiparesis in one case (3.6%). Table 1 shows patients and fetus main demographics and outcomes. Median maternal age was 28 years (range: 20-40 years). Median GA was 31 weeks (range: 8-40 weeks): 18 patients were in GA $\geq$28 weeks and 10 patients in GA <28 weeks. The majority of patients were in NYHA class IV (range: III-IV) and 13 cases (46.4%) were in atrial fibrillation (AF) on admission. Twenty-two patients (78.6%) were following unadjusted 1mg/kg LMWH, given twice daily and six patients (21.4%) remained on warfarin throughout pregnancy, targeting an INR between 2.5 and 3.5. Four out of the latter (66.6%) were neglecting regular prothrombin time check-up and their median international normalized ratio (INR) was 1.2 (1.1 – 1.38). The other two patients had managed to keep their INR within the target range.

As shown in Table 1, the malfunctioning mitral valve prostheses were: 12 Carbomedics valves (42.9%), 10 St. Jude Medical (35.7%), 5 Sorin bileaflet (17.9%) and one On-X valve (3.6%). Median valve size was 27mm (range: 25-31 mm) and median duration of implantation was 48 months (range: 15–192 months). In addition, two patients (7.1%: Patients number 20 and 25) had the same type aortic valve prosthesis and 7 cases (25%) had previously benefited from DeVega tricuspid valve annuloplasty. Diagnosis was made by transthoracic echocardiography that needed further confirmation by TEE in 4 cases (14.3%) and by fluoroscopy in another 2 cases (7.1%). Median mitral valve area was 1cm (range: 0.9-1.5cm) and median transprosthetic gradient 16mm Hg (11-28mm Hg). The thrombus was shown to be obstructive in all cases, except one patient who had an embolising highly mobile thrombus (3.6%). Median left atrial size was 54.5mm (range: 47-65mm) and median EF% was 45 (range: 35-55). The two aortic valve prostheses were properly functioning and 12 patients (42.9%) had moderate to severe tricuspid valve regurgitation.

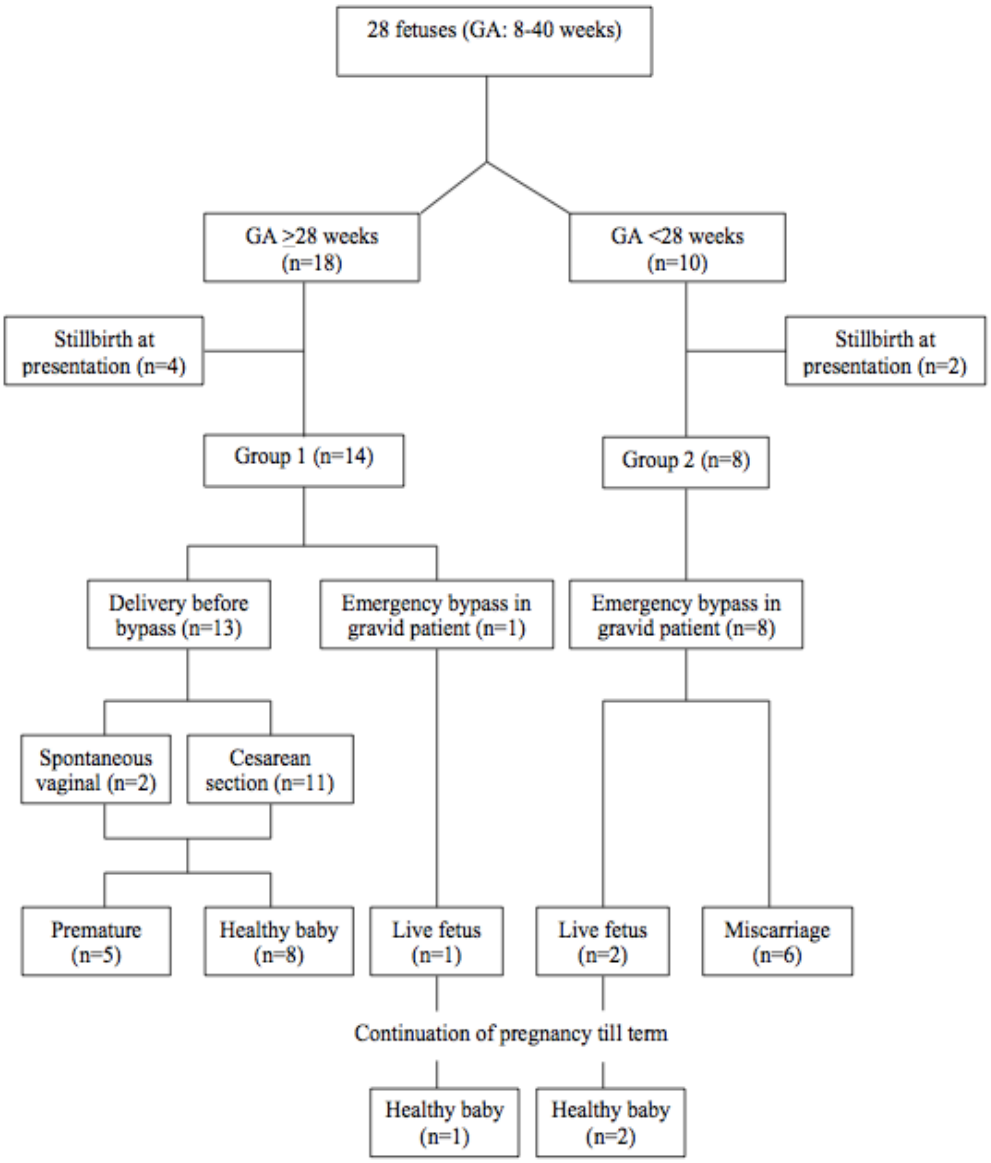
Maternal outcome: All thrombosed prostheses were replaced with the same size mechanical prosthesis: 12 Carbomedics valves (42.9%), 9 On-X valves (32.1%) and 7 St. Jude Medical prostheses (25%). In addition, 12 patients (42.9%) benefited from DeVega tricuspid valve repair. Median aortic cross clamp time and bypass times were 57 minutes (range: 34-106 minutes) and 93 minutes (range: 48-140 minutes). We had two maternal mortalities (7.1%) and one patient already presenting with a cerebrovascular stroke was discharged with regressive left-sided hemiplegia (3.6%). Both mortalities were initially following unadjusted fixed dose LMWH, presented before 28 weeks of gestation and were due to multi organ failure after prolonged bypass in one case (patient 21) and postoperative cerebral hemorrhage in the other case (patient 25 in Table 1). In total, median amount of blood loss was 600 ml (100-800 ml) and no cases were re explored for bleeding. Median durations of mechanical ventilation, positive inotropic support, ICU and total hospital stays were: 12 hours (range: 6-144 hours), 6 hours (range: 2-96 hours), two days (range: 1-12 days) and 11 days (range: 8-17 days); respectively. Twenty-five patients were discharged in NYHA class I (96.1%), with only one patient being in NYHA class II (Patient number 20). Three patients continued their pregnancy after bypass (patients number 9, 19 and 20) and were placed on warfarin therapy, with the INR being closely checked out weekly. Follow-up was uneventful till term, with the delivery of three healthy babies by elective Cesarean section.

Table 1: Patients and fetal demographics and outcomes

n	Age (yrs)	GA	ACR	NYHA Class	Valve type	Valve size (mm)	Implantation (months)	ACC (min)	CPB (min)	Fetal outcome
A) Patients presenting in GA ≥ 28 weeks:										
1	29	40	LMWH	4	Sorin	29	78	60	100	Healthy[a]
2	27	39	LMWH	4	CM	29	24	60	123	Healthy[a]
3	21	38	LMWH	3	SJM	25	48	77	110	Healthy[b]
4	36	37	LMWH	3	SJM	27	88	68	121	Healthy[b]
5	30	37	LMWH	4	CM	27	75	55	77	Healthy[b]
6	31	37	LMWH	4	CM	27	48	66	90	Healthy[b]
7	20	37	LMWH	4	SJM	27	62	52	80	Healthy[b]
8	28	40	Warfarin	4	Sorin	27	46	34	127	Healthy[b]
9	24	31	Warfarin	4	Sorin	27	66	56	93	Healthy[b]
10	23	35	LMWH	3	CM	29	59	50	106	Premature
11	33	35	LMWH	3	SJM	27	24	47	93	Premature
12	40	31	LMWH	3	CM	27	15	58	113	Premature
13	26	30	LMWH	4	CM	29	55	52	110	Premature
14	28	30	LMWH	4	SJM	29	79	48	89	Premature
15	37	35	Warfarin [d]	4	CM	29	57	58	76	Still birth [e]
16	29	33	LMWH	4	SJM	27	63	37	66	Still birth [e]
17	29	31	UFH	4	Sorin	27	38	77	88	Still birth [e]
18	20	30	Warfarin [d]	3	Sorin	29	33	65	89	Still birth [e]
B) Patients presenting in GA < 28 weeks:										
19	26	21	LMWH	3	CM	31	9	49	95	Healthy[c]
20	32	10	LMWH	4	On-X [f]	25	192	106	125	Healthy[c]
21[g]	35	22	LMWH	4	CM	27	108	45	127	Still birth [e]
22	29	19	LMWH	4	CM	29	18	67	120	Still birth [e]
23	37	18	LMWH	4	CM	29	22	60	117	Miscarriage [h]
24	23	12	LMWH	3	SJM	27	38	65	77	Miscarriage [h]
25 [g]	23	10	LMWH	3	CM [f]	27	75	52	77	Miscarriage [h]
26	23	9	LMWH	4	SJM	27	36	37	48	Miscarriage [h]
27	23	10	Warfarin [d]	3	SJM	27	38	60	105	Miscarriage [h]
28	25	8	Warfarin [d]	4	SJM	27	25	49	60	Miscarriage [h]

n= patient number, Cesarean section, GA= gestational age in weeks, ACR=anticoagulation regimen, ACC = aortic cross clamp time, CPB = cardiopulmonary bypass time, LMWH = low molecular weight heparin, UFH = unfractionated heparin, CM = Carbomedics valve, SJM= St. Jude Medical valve, Sorin= Sorin bileaflet valve, On-X= On-X valve, IUFD = intra uterine fetal death, (a)= spontaneous vaginal delivery before bypass, (b)= Cesarean section before bypass, (c) = patients continued pregnancy and babies were delivered by Cesarean section at term (d) = INR below 1.4 at presentation, (e) = before bypass, (f) = additional well functioning same type aortic valve prosthesis, (g)=maternal mortality, h = post bypass. Patient number: 2, 4, 10-14, 19 and 21-23 were included in a previous report [17].

Figure 1: Fetal outcome flow chart



GA= gestational age, n = number, Group 1= patients presenting with live fetus with GA ≥28 weeks, Group 2= patients presenting with live fetus with GA <28 weeks.

Fetal outcome (Figure 1, Table 1)**:** Among the 18 patients presenting with GA ≥ 28 weeks, there were already four cases of stillbirth on admission (22.2%; patients 15-18). In the remaining 14 cases (Group 1), we managed to perform Cesarean section before bypass in 11 cases only (78.6%), two patients had spontaneous vaginal delivery before section (14,3%) and one last patient developed cardiac arrest that left no time but to go on bypass before delivery (7.1%). This 31 weeks' baby survived bypass and was later on delivered by Cesarean section at full term (Patient number 9). Fetal outcome for Group 1 patients was: nine full term healthy babies (64.3%) and 5 prematures (35.7%).

We had two cases of miscarriage on admission (20%: patients 21 and 22) among the 10 patients presenting with GA <28 weeks. The remaining eight cases (Group 2) underwent emergency bypass and only two fetuses (25%: patients 19 and 20) survived and were later on delivered by Cesarean section at full term. In total, 9 fetuses (Patient number 9 in Group 1 and all eight patients of Group 2) were submitted to emergency bypass and only 3 survived the procedure (33.3%). Out of 22 fetuses with proven viability before surgery (Group 1 and 2), a total of six fetuses were lost (27.3%), all belonging to Group 2 (75%; P<0.001). Overall fetal loss was significantly higher in the 10 patients presenting with GA <28 weeks, compared to the 18 patients presenting with GA ≥28 weeks (80% versus 22.2%; P = 0.005).

DISCUSSION

Oral anticoagulants offer the best thromboprophylaxis for patients with MVP. Pregnant patients failing to achieve INR target with a relatively safe dose of warfarin not exceeding 5 mg/day [1] as well as those wishing to avoid oral anticoagulant-related embryopathy and fetal loss can shift to heparin either during the first trimester [1, 3] or continuously until term [1-3]. Heparin given in a fixed dose according to the body weight has been shown to provoke the highest rates of thromboembolic complications during pregnancy, including valve thrombosis [4, 5] and both: UFH or LMWH have to be adequately monitored and adjusted to ensure better prophylaxis[6]. However, a recent prospective European report of 220 pregnant patients with MVP showed an overall incidence of PVTP of 4.7%, half of which occurring during the first trimester, while switching to some sort of Heparin [7]. The majority of our patients were on fixed dose LMWH and two-thirds of the patients who were still following oral anticoagulants during pregnancy had a sub therapeutic INR on admission. Such poor compliance has been observed in as much as 93% of the cases of PVTP reported by Ozkan and colleagues [8] and, at least on our side, it was due to poor socioeconomic conditions.

The current guidelines for managing patients with PVTP are a replica of those originally designed for PVT, with few recommendations concerning fetal protection during and early after bypass [1-3, 9]. In brief, hemodynamically stable patients presenting with a recent onset small non-obstructive thrombus can benefit from a short period of anticoagulation adjustment and IV heparinotherapy under strict Doppler echocardiographic control [1-3]; which has been reported to restore valve function in the majority of these cases [10]. None of our cases fitted those criteria, being a tertiary center most of our patients are usually referred after a considerable time delay from the onset of alarming symptoms or even the confirmation of diagnosis in another hospital; with all patients being admitted in NYHA class III or IV. Major American and European societies agree on the primary role of surgery in those critically ill patients with left-sided PVT [1-3], with few detailed differences. American societies recommend surgery for all patients presenting with NYHA class III to IV symptoms [3], as well as for those case with a mobile [3] or large thrombus ≥0.8 cm^2 on TEE [2, 3]. European societies recommend surgery to critically ill patients, when the thrombus is shown to be obstructive on TEE or ≥10 mm in diameter and embolising [1]. All our patients fitted in one of those criteria. Due to the high risk of maternal

and fetal complications after surgery, the society of heart valve disease recommends fibrinolytic therapy (FT) to all patients with left-sided PVT, limiting the role of surgery to cases where FT is contraindicated [9].

In the actual era, maternal outcomes are comparable to those of non-pregnant subjects undergoing bypass for similar diseases [11-14]. Two recent systematic reviews involving 690 [15] and 2302 cases presenting with PVT [16] have shown that surgery was associated with better complete restoration of valve function (82-87% versus 70-81%), reduction in thromboembolic events (1.6-8.9% versus 11-16%) bleeding episodes (1.4-4.6% versus 5-6.8%) and recurrence of PVT (7.1% versus 25.4%) but higher mortality (13.5-18% versus 6.6-9%), compared to FT [15, 16]. Our 7.1% mortality and 3.6% stroke rates are quite matching with those calculations as well as with higher mortality rates (8.7%-13.3%) reported for critically ill pregnant patients undergoing cardiopulmonary bypass for different cardiac pathology [12, 17]

In contradiction, fetal outcome raises a lot of concerns. There is a general agreement that hypothermia has a deleterious effect on the fetus [11-14, 17-21]. The institution of CPB activates eicosanoid products, which increase placental vascular resistance and lead to malperfusion [21]. Uterine excitability is also increased during bypass, most probably for progesterone being diluted [18] The additional use of hypothermia further reduces O2 exchange through the placenta, aggravating placental malperfusion and provoking more contractions of an already excitable uterus [18]. The end result is fetal hypoxia manifesting by fetal bradycardia that appears at the beginning of bypass and usually ends by its termination [22]. In one study, the use of hypothermia was associated with 24% fetal mortality, compared to none in patients operated under normothermic bypass [19]. This process has turned out to be reversible by increasing the perfusion [23]. Experimental studies have shown that both hypothermia at any flow rate and low flow rate at normothermia were associated with significant hypoxia, compared to normal flow under normothermia [21]. Our measures to improve fetal condition during bypass included: maintaining uterine displacement to avoid aorto-caval compression, the use of normothermic high flow bypass (>2.7L/m^2/min), maintaining mean arterial pressure >70 mm Hg and minimizing bypass time, intraoperative blood loss and maintaining hematocrit >28%. We have missed the benefits of pulsatile flow and fetal monitoring during and early after bypass. Pulsatile flow is thought to improve placenta perfusion by decreasing both: uterine contraction through enhancing the release of endothelium–derived growth factor from the vascular endothelium [24] and placental vascular resistance through reducing the activation of fetal renin-angiotensin-aldosterone axis [25]. Monitoring uterine contraction and fetal heart rate during bypass allow adjustments to the flow and pharmacologic manipulations to ensure adequate placental perfusion [11, 13, 14, 19, 20].

Fetal mortality after cardiopulmonary bypass shows a wide variation form 14% to as much as 41% [11-14, 17, 19], reflecting the limited size of reported series as well as the large spectrum of patients with variable seriousness of illness and associated comorbidities. The lowest mortality was presented in a series of 21 patients: 50% were elective cases and only one patient presented with PVTP [14]. Surgery was quite quick with a short median bypass time of 53 minutes [14]. The highest mortality figures (38,5% and 41%) were presented in 2 series of 15 [12] and 23 patients [17]. In one study, 74% of the cases had a stuck mitral valve [17]. Eighty percent of the patients in both studies were in NYHA class III-IV and surgery appeared to be time consuming for necessitating relatively long bypass (median 95 and mean 89 minutes) [12, 17]. Our corresponding 27.3% fetal mortality reflects the seriousness of maternal condition however, one has to acknowledge the deleterious effect of cardiopulmonary bypass. No fetal mortality was recorded among Group 1 patients, where 93% of the fetuses escaped bypass by being delivered before surgery; which is considered to be the

best available option in PVTP [11, 14, 17]. On the other hand, fetal mortality was as much as 66.6% among the nine cases subjected to bypass, all belonging to Group 2 patients; confirming the fact that the heavy costs of bypass are usually paid by the younger fetuses [11, 14; 17].

In order to avoid the serious fetal and maternal complications associated with surgery, FT has been suggested as first line management in all patients presenting with PVTP [8-10]. A recent literature review involving 38 cases reported over three decades has shown: 76% thrombolytic success, 10% maternal mortality, 14% major complication and 28% fetal mortality [8]. Ozkan and colleagues have recently reported the use of TEE-guided slow infusion of a small dose of tissue type plasminogen activator (t-PA) in a series of 25 PVTP; regardless of the thrombus being obstructive or not and irrespective to the patient's NYHA class [8]. There was no maternal mortality but three cases of recurrence during the same pregnancy (12%) and five fetal mortalities (20%). Like in our series, fetal mortalities were exclusively recorded among patients presenting with young GA <28 weeks, resulting in as much as 29.4% fetal loss among the latter group [8], which is still much lower than our corresponding rate. Surprisingly, Ozkan and colleagues recorded a single mortality among the "high-risk group" of 13 patients presenting with NYHA class III-IV and obstructive thrombus on TEE, compared to as much as 4 mortalities among the "low-risk group" of 12 patients presenting with NYHA class I-II and mostly (92%) having non-obstructive thrombus on TEE. In other words, FT achieved good fetal outcome (7.7% mortality) in surgical candidates but the worst results (33.3% mortality) in candidates for FT; being defined as such according to the current guidelines [1-3]. In consequence, and despite that the use of FT was associated with considerable 60% reduction of fetal mortality among the subgroup of patients presenting with gestational age <28 weeks, the neutralization of the effect of maternal hemodynamic deterioration and serious TEE findings needs to be investigated.

Conclusion: Prosthetic valve thrombosis during pregnancy was mainly noted in patients with unmonitored and/or unadjusted anticoagulation, especially those receiving LMWH. Maternal mortality is comparable to those recorded in non-pregnant patients. Unless delivery can be carried out before surgery, fetal loss is majored after cardiopulmonary bypass, especially among younger gestation age and hence, more protective measures should be investigated. There is not enough evidence in the literature to recommend alternative FT for this group of high-risk patients and randomized clinical trials are needed to validate the best option according to the patient's clinical and echocardiographic finding and the fetal gestational age.

Study limitations: Eleven of our cases (39.3%) were previously reported among a series of 23 pregnant patients undergoing emergency surgery for different valve pathology [17]. The previous report did not show relevant information for each patient namely; NYHA class, duration of valve implantation and type of anticoagulation regimen. The high post bypass fetal mortality among patients presenting with GA <28 weeks may have been improved if we managed to use pulsatile flow and applied effective fetal monitoring during and early after bypass. Being a tertiary referral site, long-term clinical follow-up was not available for many patients.

Conflicts of interest: none declared

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