Is there a safe anticoagulation protocol for pregnant women with prosthetic valves?

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Summary

We studied the outcome of 41 pregnancies in an attempt to identify an appropriate and safe anticoagulant regimen for pregnant women with cardiac valve prosthesis. The cumulative number of events: (neonatal death, premature deliveries, intrauterine fetal death and spontaneous abortion) was 66.6%, 20%, 12.5% and 20% in the Coumadin, Fraxiparine, Heparin and porcine valve groups, respectively.

We conclude that in pregnant women with mechanical heart valves, low molecular weight heparin therapy is a superior strategy compared to warfarin.

Key words: Pregnancy; Prosthetic valves; Anticoagulant.

Introduction

Treatment of valvular heart disease in women of child bearing potential is difficult because it requires long-term anticoagulant therapy to prevent thromboembolic phenomena. Pregnancy is a hypercoagulable state due to an increase in coagulation factors II, VII, VIII, IX and an inhibition of fibrinolysis, and is associated with increased risk of maternal thromboembolic complications [1, 2]. Oral anticoagulants easily cross the placenta and enter the fetal circulation. There is convincing evidence that warfarin therapy in pregnancy causes fetal loss as well as development of several congenital malformations [3-6], in addition to causing bleeding complications at delivery. On the contrary, heparin does not cross the placenta and its effect can be promptly neutralized. In a study of a large number of patients receiving heparing during pregnancy, normal fetal and neonatal outcome were noted without increase in maternal bleeding complications. Heparin therapy in pregnancy, may be associated with osteoporosis, sub-clinical reduction in bone density, and a small risk of symptomatic bone fracture [7]. Thrombocytopenia is another rare but potentially dangerous side-effect of heparin use. These side-effects are usually reversible and it is not surprising that the use of heparin has been preferred during pregnancy in patients requiring anticoagulation therapy [8]. Subcutaneous heparin is easy to administer on an out-patient basis, and seems to be an attractive therapy with a safe outcome. Low molecular weight heparin, produced by the enzymatic or chemical breakdown of the heparin molecule [9] may offer advantages over the standard unfractioned heparin especially in obstetrics where the time scale of prophylaxis is much longer than in surgery [10-12].

The aim of this study is to report our experience with a series of 41 pregnancies with different types of mechanical valves, on different types and routes of anticoagulant therapy including low molecular weight heparin (Nadroparine calcique, Sanofi-Winthrop, laboratoire Choay-94258 Gentilly, Cedex-France), during the periods when the use of oral anticoagulants is most hazardous.

Patients and Methods

Review of the medical records of women of reproductive age who underwent cardiac operations for prosthetic valve replacement at the American University of Beirut, Medical Centre, between January 1981 and March 1996 was undertaken. Most of these patients were followed-up postoperatively in the same hospital for cardiac and obstetric care. Patient data were taken from medical records and follow-up evaluation in the out-patient high risk pregnancy clinic.

In our hospital women of child bearing age who receive artificial prosthetic heart valves are advised about the added risk of anticoagulant therapy during gestation. We reviewed retrospectively 52 pregnancies in 31 females with prosthetic heart valves. The age of patients at conception ranged from 18-39 years, with a mean of 27±4.3 years. Eleven women (21.1%) had elective induced-abortion and were excluded from the study and only 41 patients (78.9%) continued pregnancy and were comprised in the data base. Verbal informed consent was obtained from each patient. Pregnancies were divided into two groups according to the type of valvular surgery. Group I included 36 women with mechanical valves and Group II included 5 women with biological valves.

Methods of Anticoagulation

In Group I, 18 out of 36 women (50%) failed to stop the oral anticoagulant therapy (coumadin) during the first trimester, while the oral anticoagulant was stopped and replaced by fraxiparine in 10 women (27.7%) and heparin in the remaining 8 (22.3%). The mean gestational stage (MGA) of stopping coumadin was 5.9 weeks. Eight pregnancies in Group I were maintained on subcutaneous (S/C) and intravenous (IV) heparin (16.5%) in a dose range of 5000 units (U) twice per day to 7500

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U three times per day through the S/C route and 24000 U per day in the IV route. Ten were given low molecular weight heparin (24.4%) in a dose of 7500 U (0.3 ml) S/C twice per day. The remaining (12.2%) constitute the non-anticoagulant group (5 women with biological valves) (Group II). The mean gestational age of starting heparin was 6.6 weeks with a mean period of treatment of 6.6 weeks. Mean gestational age at starting fraxiparine was 5.4 weeks for a mean duration of 8.7 weeks. Treatment with coumadin was resumed in all cases after the end of 12th week (mean of 14.1 weeks). In this period, the patients were seen at a high-risk pregnancy clinic every two to three weeks. All women were readmitted to our hospital for delivery.

Control of Anticoagulation

In patients receiving coumadin the target prothrombin ratio (international normalised ratio) was 2.0 to 2.5. Heparin was administered either by subcutaneous injection, every eight hours to twelve hours, or by continuous intravenous infusion according to partial thromboplastin time (PTT), which was maintained at 1.5 to 2.5 times the control value. Aspirin (325 mg once daily) and Dipyridamole (75 mg twice per day) orally were given in four pregnancies in Group II.

Definition of terms

Abortion was defined as fetal loss before 28 weeks of gestation. Stillbirth was fetal death after the 28th week of gestation. The definition of premature labor was delivery of a fetus before the 37th completed week of gestation. Antepartum haemorrhage was defined as bleeding from the genital tract after the 28th week of gestation, and peripartum haemorrhage as bleeding from the genital tract from the first stage of labor until 12 hours postpartum.

Results

The implanted valves were: Bjork-Shiley (46.4%), ST-Jude (36.6%), Starr-Edwards (4.8%) and the Hancock Porcine valve in 12.2% of pregnancies. Most of the women in this study were in New York Heart Association Functional Class I and II. Only two pregnancies were in class III. Thirty-three patients were in sinus rhythm (80.5%) and 8 pregnancies were in chronic atrial fibrillation (19.5%). Twenty-eight patients (68.3) received treatment with digitalis and 9 (21.9%) were on diuretics. The clinical data on the subjects in each group is summarised in Table 1.

There were no statistically significant differences among patients who continued pregnancy and those in which abortion was induced in regard to age, underlying disease and presence of atrial fibrillation (Table 1). The incidence of complications is shown in Table 2. Spontaneous abortion was noted in 38.9% of the coumadin group, 10% in the fraxiparine group, 10% in the heparin group and none in the porcine valve group. Neonatal death occurred in one pregnancy (5.5%). Two premature deliveries (11.1%) were noted in the coumadin group, but none in the other groups. One of the two stillbirths in the coumadin group was attributed to anencephaly with atrial septal defect. Intrauterine fetal death was noted in 10% of the fraxiparine group, 12.5% in the heparin group and none in the porcine valve group.

Table 1. — *Basic characteristics of pregnant women with mechanical and biological valve prostheses.*

Characteristics	Number of pregnancies N = 41	Induced abortion N = 11
Age	27±4.3 years	29±3.4 years
Valve type		
Mechanical	36 (87.8%)	11 (100%)
Biological	5 (12.2%)	0
Site of insertion		
Mitral	25 (61%)	9 (80.8%)
Aortic	6 (14.6%)	0
Mitral and aortic	10 (24.4%)	2 (18.2%)
Functional Class during pregnancy		
Class I	32 (78%)	9 (81.85%)
Class II	7 (17.2%)	1 (9.1%)
Class III	2 (4.8%)	1 (9.1%)
*Medication**		
Digoxin	28 (68.3%)	6 (54.5%)
Diuretics	9 (21.9%)	3 (27.3%)
Underlying disease		
Rheumatic	41 (100%)	11 (100%)
Cardiac rhythm		
Sinus rhythm	33 (80.5%)	9 (81.8%)
Atrial fibrillation	8 (19.5%)	2 (18.2%)
Surgery to pregnancy interval	54.5±35.5 months	59.5±48.8 months

*Four pregnancies (9.8%) were off medication.

Table 2. — *Pregnancy outcome and complication of 41 pregnancies with cardiac valve prostheses.*

Pregnancy outcome	Coumadin N = 18	Fraxiparine N = 10	IV ±S/C heparin N = 8	Porcine valve none N = 5
Neonatal Death	1 (5.5%)	0	0	0
Premature deliveries	2 (11.1%)	0	0	0
Stillbirth+IUFD	2 (11.1%)	1 (10%)	1 (12.5%)	0
Spontaneous abortion	7 (38.9%)	1 (10%)	0	1 (20%)
Total	14 (66.6%)	2 (20%)	1 (12.5%)	1 (20%)
Maternal outcome				
Vaginal bleeding	1 (5.5%)	1 (10%)	1 (12.5%)	0
Valve malfunction	1 (5.5%)	2 (20%)	0	1 (20%)
Death	0	0	0	0
Live Births	6 (33.4%)	9*(80%)	7 (87%)	4 (80%)
Body weight in grams	3152±374	3070±417	3229±488	2905±304
Apgar score (1 Minute)	7.6 ± 1.5	8.1 ± 1	7.1 ± 3.7	6.7 ± 2.5
Apgar score (5 Minutes)	9.5 ± 0.8	9.3 ± 0.7	8.2 ± 1	8.7 ± 0.5

Maternal complications consisted of peripartum haemorrhage, 5.5% in the coumadin group, 10% in the

fraxiparine, 12.5% in the heparin and none in the porcine valve group. All patients in these pregnancies required transfusion of more than one unit whole blood. Valve malfunction was noted in 5.5% in the coumadin group, 20% in the fraxiparine, none in the heparin group and 20% in the non-anticoagulant group (porcine valve). Only 33.4% of pregnancies in the coumadin group resulted in normal live babies in comparison to 87% in the heparin group and 80% in each of the fraxiparine and non-anticoagulant groups. Neonatal birth weight and Apgar scores at one minute and five minutes are summarised in Table 2. Thrombosis related valve malfunction was noted in one case (5.5%) in the coumadin group and two in the fraxiparine group (20%). The clinical characteristics of these patients can be seen in Table 3.

Discussion

In this retrospective study of 41 pregnancies, three different approaches to anticoagulant therapy were used during the first trimester, according to the time when the pregnancy was diagnosed. All patients received coumadin during the second and third trimester and in the majority of cases the oral anticoagulant was replaced by heparin during the peripartum period.

Previous reports have shown that intake of coumadin during the first trimester of pregnancy is associated with increased incidence of spontanous abortion, ranging from 28.1 percent [14] to 44 percent [6]. In our study the patients who had been on coumadin during the first trimester had a spontaneous abortion rate in 38.9 percent of the cases. When pregnancy was detected early and heparin was substituted for coumadin before the sixth week of gestation, the incidence of complications decreased significantly. No maternal thromboembolic complications were encountered in 36 patients with mechanical prostheses. In previous reports of maternal thromboembolic complications during pregnancy in patients with mechanical prosthetic valves, most prostheses were of the Starr-Edwards and Bjork-Shiley types [4, 6, 14, 15]. It is likely that the nature of the prosthesis used, in addition to an effective therapeutic anticoagulation target contributed to the absence of thromboembolism. Other factors that may have contributed to the lack of thromboembolism in this study include the low rate of chronic atrial fibrillations (19.5%), stable hemodynamic status of the patients (78% were in class I, 17.2% in class II and only 4.8% in class III) and the continuation of the anticoagulation therapy during labor. The teratogenic effect of coumadin in live births is well-documented [3]. The incidence of coumadin embryopathy in this study was 5.5 percent (a stillbirth boy delivered at 29 weeks of gestation with anencephaly and atrial septal defect). Premature labor and neonatal death were noted mainly in the coumadin group with an incidence of 11.1 percent and 5.5 percent, respectively. The incidence of maternal hemmorrhagic complications was low with no major difference among the three anticoagulation groups.

This retrospective study presents an early experience with the use of low molecular weight heparin (fraxiparine) in pregnant women with prosthetic valves. The drug had been used safely to treat deep vein thrombosis during pregnancy [16, 17], but no available data exist regarding its safety in patients with valve prosthesis. There is concern about pregnancy-related accelerated bioprosthetic valve failure [13, 18]. It occurred in 35 percent of valves in the study by Sbarouni *et al.* [17] and 47 percent of valves in the study by Badduke *et al.* [19]. Our experience revealed similar results. No maternal mortalities were reported in our study. More live babies were reported in the fraxiparine, heparin and porcine valve groups (80%, 87.5 and 80%, respectively) in comparison to the coumadin group (33.4%).

Table 3. — *Basic characteristics of pregnant women with valve malfunction.*

Characteristics	Coumadin (n = 1)	Fraxiparine (n = 2)	None (n = 1)
Age	22	27	30
Duration of therapy	—	12 weeks	—
Valve Type	Bjork-Shilly	St-Jude	Hancock (porcine)
Site of insertion	Mitral	Mitral	Mitral
Surgery to pregnancy interval	36 months	32 months	108 months
Functional Class during pregnancy	III	II	I
Underlying disease	Rheumatic	Rheumatic	Rheumatic
Anti-phospholipid antibodies titers	—	positive	—
INR	1.8	—	—
Surgical intervention	MVR (St-Jude)	Valve declotting*	MVR (St-Jude)

*St-Jude valve was inserted first time.

Conclusion

The present study underscores the difficult issue of anticoagulation in patients with mechanical heart valves during pregnancy. We observed that low molecular weight heparin (fraxiparine) is safe, easy to administer, and seems to result in low incidence of fetal as well as maternal complications. However, a large, prospective, randomised and well-controlled study is needed to evaluate the efficacy and safety of low molecular weight heparin in women with prosthetic heart valves during pregnancy.

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