The Heart Surgery Forum #2007-1024
10 (4), 2007 [Epub May 2007]
doi: 10.1532/HSF98.20071024

Online address: http://cardenjennings.metapress.com

Anticoagulation in Pregnant Women with a Bileaflet Mechanical Cardiac Valve Replacement

Kyung-Hwan Kim, MD, Dong Seop Jeong, MD, Hyuk Ahn, MD

Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

ABSTRACT

Background. We investigated the risk and outcome of anticoagulation in pregnant women who had a mechanical valve.

Materials and Methods. This retrospective study was undertaken for 41 pregnancies (27 women, 33.1 ± 4.7 years old) from January 1990 to December 2005. Patients were divided into 3 groups: group I (n = 5) took warfarin throughout the pregnancy, group II (n = 18) took heparin throughout the pregnancy, and group III (n = 18) took heparin in the 1st trimester and warfarin from a gestational age of 12 to 20 weeks.

Results. Twenty-three pregnancies (56.1%) resulted in live births, 11 (26.8%) in stillbirths, and 8 (19.5%) in spontaneous abortions (SA). In group I, there were 2 live births (40.0%), 2 stillbirths (40.0%), and 1 SA (20.0%); in group II, there were 10 live births (55.6%), 1 stillbirth (5.6%), and 7 SA (38.9%); and in group III, there were 10 live births (55.6%), 8 stillbirths (44.4%), and no SA. No significant difference was observed between the 3 groups in terms of successful delivery rates ($P = .826$).

Conclusion. The probability of successful delivery was low. No single reliable anticoagulation protocol in pregnant patients with mechanical valves emerged from the collated data.

INTRODUCTION

Whereas the management of pregnant women who have a tissue valve is relatively clear, anticoagulation for pregnant patients who have a mechanical valve presents many problems; for example, it was found that warfarin is safer for pregnant women but that heparin is safer for the fetus [Sbarouni 1994]. However, no randomized controlled trial data is available to guide adequate anticoagulation treatment decision making. Prospective randomized trials are needed to resolve this issue, but clinical research in pregnant patient presents serious ethical and medico-legal issues.

Recent estimates of mortality in pregnant patients with prosthetic valves range from 1% to 4% [Vitale 1999], and the overall risk of thromboembolic complications is 4% to 24% [Iturbe-Alessio 1986]. Other risks during pregnancy include the effect of anticoagulants on the developing fetus and the association of both warfarin and heparin with high rates of fetal loss (16% to 44%) because of spontaneous abortion (SA) or stillbirth [Sareli 1989; Salazar 1996]. In addition, exposure to warfarin during the first trimester has been associated specifically with embryopathy, characterized by stippled epiphyses and nasal and limb hypoplasia [Hirsh 1991], and warfarin exposure throughout pregnancy has been associated with rare developmental abnormalities of the central nervous system and eyes [Hall 1980]. Moreover, the effectiveness of heparin at preventing valve thrombosis has been brought into question with respect to therapy failures and adverse maternal outcomes [Elkayam 1996; Chan 1999].

Currently, the recommended regimens are: (1) warfarin throughout pregnancy, (2) the replacement of warfarin with unfractionated heparin between gestation weeks 6 and 12 and near term, and (3) unfractionated heparin throughout pregnancy [Ginsberg 1989]. Although the USA guideline is the most popularly accepted regimen, some authors have suggested that oral anticoagulation is preferable, especially in countries with certain socioeconomic backgrounds [Hall 1980]. A previous systemic review of the literature [Hirsh 1991] provides estimates of maternal and fetal risks associated with these 3 regimens, but does not offer an ideal therapy. In this study, we sought to evaluate risks and outcomes in pregnant women with mechanical valves who were treated with the above 3 regimens.

MATERIALS AND METHODS

A retrospective study was conducted of 41 pregnancies in 27 women with mechanical valves who registered at our institution between January 1990 and December 2005. Average patient age was 33.1 ± 4.7 years (range, 23 to 44 years). The replaced valves were mitral (70.7%), aortic (7.3%), or both

Received January 19, 2007; accepted March 26, 2007.

Correspondence: Kyung-Hwan Kim, MD, Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul, 110-744, Korea; 82-2-2072-3971; fax: 82-2-765-7117 (e-mail: kkh726@snu.ac.kr).

Table 1. List of Mechanical Valve Types

Valve Brands	Number of Replaced Valves
Carbomedics (bileaflet)*	20
St. Jude (bileaflet)†	22
Duromedics (bileaflet)‡	1
On-X (bileaflet)§	2
Total	45

*Carbomedics, Austin, TX, USA.
†St. Jude Medical, St. Paul, MN, USA.
‡Baxter, Chicago, IL, USA.
§MCRI, Austin, TX, USA.

(22.0%). The mechanical valves used are listed in Table 1, and Table 2 provides details of multiple pregnancies.

Methods of Anticoagulation

Pregnancies were divided into 3 groups according to the anticoagulation regimen used. Physicians explained the advantages and disadvantages of warfarin and heparin for mothers and fetuses. After detailed discussion, patients individually selected one of the 3 regimens.

Group I. Oral anticoagulants were given throughout pregnancy (until just before delivery), including the 1st trimester with a target international normalized ratio (INR) of 2.0 to 3.0. No significant oscillations in INRs were noticed in this group, which included 5 pregnancies. The patients of group I did not know that they were pregnant and the physician did not detect pregnancy until the 1st trimester.

Group II. Eighteen pregnancies with heparin administration throughout pregnancy were included. Subcutaneous unfractionated heparin was used in 11 patients and low molecular weight heparin (LMWH) in 7.

Group III. For the remaining 18 pregnancies, oral anticoagulant (warfarin) was replaced by heparin when pregnancy was confirmed. Heparin doses were adjusted according to activated partial thromboplastin times, which were maintained at twice the control level. Heparin was replaced with warfarin before delivery, and warfarin was stopped no later than the end of the 36th gestational week and replaced with heparin.

Oral anticoagulants (warfarin) were recommenced 24 hours after delivery when bleeding stopped, and the patients were kept in hospital for 3 or 4 days until INRs were within the therapeutic range.

Table 2. Multiplicity of Pregnancies

Number of Pregnancies	Number of Patients
1	18
2	5
3	3
4	1
Total	27

All clinical results were analyzed according to the guidelines for reporting morbidity and mortality after cardiac valve surgery suggested by Ian and associates [2006]. Clinical outcomes were reviewed retrospectively.

Statistical Analysis

Statistical analysis was performed using a commercially available software package (SPSS for Windows, version 11.01, SPSS, Chicago, IL, USA). Descriptive statistics are reported as mean ± SD for continuous variables and as frequencies and percentages for categorical variables, unless otherwise stated. The significances of differences were assessed using the unpaired Student t test, the χ^2 test, or the Fisher exact test. P values less than .05 were considered statistically significant.

RESULTS

Twenty-two pregnancies (56.1%) resulted in live births, 11 (26.8%) in stillbirths, and 8 (19.5%) in SA. Gestational age for SA averaged 7.8 ± 1.3 weeks. With the exception of 2 cases, stillbirths occurred in the 2nd trimester and 10 patients were receiving warfarin at diagnosis.

In group I, there were 2 live births (40.0%), 2 stillbirths (40.0%), and 1 SA (20.0%); in group II, 10 live births (55.6%), 1 stillbirth (5.6%), and 7 SA (38.9%); and in group III, 10 live births (55.6%), 8 stillbirths (44.4%), and no SA. Outcomes for the 3 groups are listed in Table 3. The successful delivery rates of the 3 groups were not significantly different ($P = .826$, the Fischer exact test). The mean gestational age of live births was 38.5 weeks (range, 34 to 42 weeks). Gestational age distributions are listed in Table 4. There were 12 pregnancies resulting in live births (54.5%) before the 39th week of gestational age.

There were no premature or low–birth weight babies (below 2.4 kg) among the live births. In group I, there was 1 fetal ventriculomegaly due to cerebral palsy. In group II, there was 1 fetal pleural effusion. In this case, induction delivery was performed at a gestational age of 36 weeks, and the baby is currently in good condition. In group III, there were 1 fetal ventriculomegaly and 2 fetal intracranial hemorrhages, which resulted in stillbirths. There were no maternal deaths. In group II, valve thrombosis requiring re-replacement of a pre-existing mechanical valve occurred in 1 patient and postpartum bleeding was found in another patient. There were no maternal complications in the other groups.

Table 3. The Outcomes of Pregnancies in 3 Different Groups*

	Live Birth	Stillbirth	SA
Group I	2/5 (40.0%)	2/5 (40.0%)	1/5 (20.0%)
Group II	10/18 (55.6%)	1/18 (5.6%)	7/18 (38.9%)
Group III	10/18 (55.6%)	8/18 (44.4%)	0/18 (0%)
Total	22/41 (53.7%)	11/41 (26.8%)	8/41 (19.5%)

*$P = .826$. P values were calculated using the Fisher exact test for live births for the 3 groups. SA indicates spontaneous abortion.

Table 4. Distribution of Gestational Ages in Live Births

Gestational Age, wk	Number of Babies
34	1
35	1
36	2
37	5
38	3
Total	12/22 (54.5%)
39	4
40	4
41	1
42	1
Total	10/22 (45.5%)

DISCUSSION

The anticoagulant treatment for pregnant women with a mechanical valve remains a dilemma for patients and doctors. Physicians have been treating these women with warfarin and/or heparin during pregnancy; however, no adequate prospective randomized trial has been conducted to resolve this issue. Some authors [Hirsh 1991; Elkayam 1996; Chan 1999; Choi 2000] have suggested heparin during the 1st trimester, warfarin until full term, and a return to heparin just before delivery, whereas others [Al-Lawati 2002; Conti 2003] have recommended warfarin only after having considered socioeconomic statuses and medical circumstances in their countries. LMWH was considered to be a potential alternative to warfarin, and it has been shown to be safe and effective [Nelson-Percy 1997]. But recently, Rainer et al reported on the treatment failure of LMWH for anticoagulation in a pregnant woman with a mechanical valve [Rainer 2002]. There was only little evidence regarding the effect of LMWH for long-term anticoagulation in pregnant women with mechanical heart valves [Berndt 2000; Lev-Ran 2000].

We usually discuss this situation with these patients and explain advantages and disadvantages of warfarin and heparin. Clearly, warfarin is safer for the patient in terms of preventing valve thrombosis and fatal valve-related complications, but heparin is safer for the fetus because of the risk of warfarin-related embryopathy during the 1st trimester and the risk of fetal hemorrhage throughout pregnancy. The ACC/AHA guidelines recommend full discussion with patients and partners before choosing an anticoagulation strategy, the guidelines state, "If a patient chooses to change to heparin for the first trimester, she should be made aware that heparin is less safe for her and presents a higher risk of thrombosis and bleeding, and that any risk to the mother also jeopardizes the baby." Many obstetricians and cardiologists/cardiac surgeons have different ideas concerning regimen choice, which is a reflection of the lack of a recognized safest regimen. Our data also show similar successful live birth rates for the 3 study groups. In the present study, we used 3 anticoagulation regimens, and the regimen adopted in any particular case was decided upon after thorough discussion with the patient concerned.

SA was more frequent in group II and stillbirth more frequent in group III. All patients in these 2 groups received heparin. Ginsberg et al [1989a] reported that the complication rate for heparin for pregnant patients was similar to that for healthy pregnancies and that bleeding complications were predominant in mothers rather than fetuses. They emphasized the safety of heparin, but its bioavailability may have differed from that in the present study, and in their study SA was also more predominant in the heparin-only group. Whereas warfarin presents a substantial risk of bleeding in the anticoagulated fetus, especially at the time of delivery, heparin does not cross the placenta, and thus has not been associated with the teratogenic effects of fetal bleeding [Ginsberg 1989b; Dahlman 1990]. The disadvantages of heparin include the need for twice-daily subcutaneous injections and the development of osteoporosis [Ginsberg 1989a]. LMWH heparin may be an attractive option for heparin therapy during pregnancy. However, because of limited data, management remains controversial about the substitution of LMWH for unfractionated heparin [Ian 2006]. In our study, we used LMWH in 7 patients and we intend to analyze these data to clarify the effects of LMWH after collecting more cases. Many physicians recommend tissue valves in these patients; however, even after tissue valve replacement [Lee 1999], if a patient has atrial fibrillation or history of thromboembolism, warfarin should be prescribed.

Premature labor frequently occurs in women with mechanical cardiac valves. Salazar et al [1996] reported that 36% of neonates were born before the 37th gestational week, and 1 neonate died of a cerebral hemorrhage that occurred during labor due to warfarin medication. This data suggest the need for heparinization no later than gestation weeks 35 or 36 to avoid the onset of labor during warfarinization. Our study revealed 4 pregnancies (18.2%) that concluded before the 37th gestation week.

If a patient has been administered warfarin during the first trimester, most doctors favor changing to heparin. Our data showed single cases of ventriculomegaly in groups I and III, and 2 fetal intracranial hemorrhages in group III. The ventriculomegaly fetus in group I was found to have cerebral palsy after successful caesarean section, and the pregnancies with fetal ventriculomegaly or fetal intracranial hemorrhage concluded with stillbirths. In our series, the patients of group I did not know that they were pregnant and the physician did not detect pregnancy until the 1st trimester.

There were limitations in our analysis such as age factors, small numbers in each group, and patient selection. Age factors should be considered when assessing abortion data and we did not correct the age-related bias. The small number was an important limitation of this study, especially because there were only 5 patients in group I. More patients are required to gain statistical power. We decided on delivery based only on the obstetrician's decisions, and did not attempt caesarean sections because of the lower risk of bleeding during vaginal delivery.

One valve thrombosis occurred in group II and required urgent valve re-replacement. Although the occurrence of

valve thrombosis during heparin medication was low in the present study (5.6%, 1/18), the frequent monitoring of therapeutic levels is required to lower the risk of valve thrombosis. Moreover, practically, it is difficult to achieve adequate and constant anticoagulation using subcutaneous heparin because of its narrow therapeutic window.

In the present study, the probability of successful delivery for women with a bileaflet mechanical cardiac valve was found to be low. Our results show that the 3 anticoagulation regimens had similar outcomes in terms of successful delivery. In the heparin group, abortion and stillbirth were more frequent, and in the warfarin group 1 embryopathy occurred. Although there was no statistical significance, warfarin therapy during the 1st trimester was very dangerous in terms of the low success rate (40%) of live birth.

In conclusion, our data show that anticoagulation during pregnancy in patients with mechanical valve replacement remains difficult and falls short of enabling us to recommend a single reliable anticoagulation protocol. But the avoidance of warfarin during 1st trimester is mandatory. The use of LMWH instead of warfarin during the 1st trimester is worth consideration.

REFERENCES

Al-Lawati AM, Venkitraman M, Al-Delaime T, Valliathu J. 2002. Pregnancy and mechanical heart valves replacement; dilemma of anticoagulation. Eur J Cardiothorac Surg 22:223-7.

Berndt N, Khan I, Gallo R. 2000. A complication in anticoagulation using low-molecular weight heparin in a patient with mechanical valve prosthesis. A case report. J Heart Valve Dis 9:844-6.

Chan WS. 1999. What is the optimal management of pregnant women with valvular heart disease in pregnancy? Hemostasis 29(suppl 1): 105-6.

Chan WS. 2000. Anticoagulation of pregnant women with mechanical heart valves: a systematic review. Arch Intern Med 160:191-6.

Choi SH, Ko KP, Han JO, Chui JB, Kim GH. 2000. Anticoagulation therapy in pregnant women with mechanical cardiac valve prosthesis. Korean J Thorac Cardiovasc Surg 33:502-6.

Conti RC. 2003. Anticoagulation for mechanical valve prostheses during pregnancy. Clin Cardiol 26:303-4.

Dahlman T, Lindvall N, Hellgren M. 1990. Osteopenia in pregnancy during long-term heparin treatment: a radiological study postpartum. Br J Obstet Gynadecol 97:221-8.

Edmunds Jr HL, Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. 1996. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ann Thorac Surg 62:932-5.

Elkayam UR. 1996. Anticoagulation in pregnant women with prosthetic heart valves: a double jeopardy. J Am Coll Cardiol 27:1704-6.

Ginsberg JS, Hirsh J, Turner DC, Levine MN, Burrows R. 1989. Risks to the fetus of anticoagulant therapy during pregnancy. Thromb Haemost 61:197-203.

Ginsberg JS, Kowalchuk G, Hirsh J, Brill Edwards P, Burrows R. 1989. Heparin therapy during pregnancy: risks to the fetus and mother. Arch Intern Med 149:2233-6.

Hall JG, Pauli RM, Wilson KM. 1980. Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med 68:122-140.

Hirsh J. 1991. Oral anticoagulant drugs. N Engl J Med 324:1865-75.

Ian AG. 2006. Anticoagulation in pregnancy. J Thromb Thrombolysis 21:57-65.

Iturbe-Alessio I, Fonseca MC, Mutchinik O, Santos MA, Zajarias A, Salazar E. 1986. Risks of anticoagulant therapy in pregnant women with artificial heart valves. N Engl J Med 315:1390-93.

Lee SY, Jang BC, Park HG, et al. 1999. Pregnancy in patients with prosthetic heart valve. Korean J Thorac Cardiovasc Surg 32:1023-30.

Lev-Ran O, Kramer A, Gurevitch J, Shapira I, Mohr R. 2000. Low-molecular-weight heparin for prosthetic heart valves: treatment failure. Ann Thorac Surg 69:264-5.

Nelson-Percy C, Letsky EA, de Swiet M. 1997. Low molecular weight heparin for obstetric thromboprophylaxis: experience of 69 pregnancies in 61 women at high risk. Am J Obstet Gynecol 176:1062-8.

Rainer GL, Stefan F, Arjang R, Axel H. 2002. Anticoagulation for prosthetic heart valves during pregnancy: is low-molecular weight heparin an alternative? Eur J Cardiothorac Surg 21:577-9.

Salazar E, Iziguirre R, Verdego J, Mutchinick O. 1996. Failure of adjusted doses of subcutaneous heparin to prevent thromboembolic phenomena in pregnant patients with mechanical cardiac valve prostheses. J Am Coll Cardiol 27:1698-1703.

Sareli P, England MJ, Berk MR, et al. 1989. Maternal and fetal sequelae of anticoagulation during pregnancy in patients with mechanical heart valve prostheses. Am J Cardiol 63:1462-5.

Sbarouni E, Oakley CM. 1994. Outcome of pregnancy in women with valve prosthesis. Br Heart J 71:196-201.

Vitale N, De Feo M, De Santo LS, Pollice A, Tedesso N, Cotrufo M. 1999. Dose-dependent fetal complications of warfarin in pregnant women with mechanical valves. J Am Coll Cardiol 33:1637-41.