Risks and Pregnancy Outcome in Women With Prosthetic Mechanical Heart Valve Replacement

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Background Pregnancy after mechanical heart valve replacement is highly risky for both mother and child because of the aggravation of maternal heart function and adverse effects of anticoagulation therapy. In Japan, however, the risks and pregnancy outcomes in women with prosthetic mechanical heart valve replacement remain to be elucidated.

Methods and Results In the present study 16 pregnancies in 12 women with prosthetic mechanical heart valve replacement were identified between 1983 and 2005. At 6–13 weeks of gestational age, warfarin, an anticoagulant agent, was changed to heparin and administration was continuously adjusted according to the activated partial thromboplastin time level up to the time of delivery. Major maternal complications and pregnancy outcomes were retrospectively investigated. The valve replaced was mitral (n=7), tricuspid (n=7), and aortic (n=2). Eight (50%) of 16 had cesarean live births. One case was delivered at full term, and 7 cases were delivered preterm (26–36 weeks) because of maternal indications. Two babies died in the neonatal period. Therapeutic abortion was performed in 3 cases, 4 cases ended in early miscarriage, and 1 case ended in intrauterine fetal death (30 weeks). Three mothers developed valve (mitral, tricuspid, aortic) thrombosis. There was 1 maternal death from heart failure.

Conclusions Pregnancy after mechanical heart valve replacement requires strict control of coagulation. Special attention should be paid to the occurrence of complications during anticoagulation therapy. (Circ J 2007; 71: 211–213)

Key Words: Fetal outcome; Heparin; Maternal complication; Mechanical heart valve replacement; Pregnancy outcome; Warfarin

Although the recent decrease in the prevalence of rheumatic heart disease in young women has decreased the prevalence of mechanical heart valve replacement, and developments in cardiac surgery have replaced mechanical heart valves with biological heart valves, these same advances in cardiac surgery have enabled women with mechanical heart valves after surgery for complex cardiovascular anomalies to survive long term. For such women, long-term management of coagulation is essential.

Pregnancy after mechanical heart valve replacement has the potential risks of maternal heart failure, arrhythmia, infectious endocarditis, and maternal death with advancing gestational age! For such cases, obstetricians have sometimes chosen therapeutic abortion or premature birth to save the mother's life. In addition, anticoagulation therapy using warfarin throughout the pregnancy carries risks of inducing congenital fetal anomaly, abortion, and early neonatal death, as well as maternal hemorrhage.² However, inadequate anticoagulation therapy may induce thromboembolism. Thus, pregnancy in women with prosthetic

mechanical heart valve replacement remains problematic and troublesome even now. In Japan, however, only limited data are available with regard to the impact of mechanical heart valve replacement and anticoagulation therapy on pregnancy outcome and risks.

Methods

We retrospectively identified 16 pregnancies in 12 women with prosthetic mechanical heart valve replacement managed between 1983 and 2005 at the Department of Perinatology, National Cardiovascular Center, Osaka, Japan. Warfarin, an anticoagulation agent, was changed to heparin around 6–13 weeks of gestational age, and administration of heparin was continued to parturition. The dose of heparin was regulated from 20,000 to 30,000 IU/day, according to the circulating activated partial thromboplastin time (APTT) levels. APTT in patients was maintained 2–3-fold higher than in controls. Except for those who strongly desired to

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Table 1 Fetal Outcomes for the Enrolled Subjects (n=16*)

Live birth	8
Term	1
Preterm	7
Spontaneous abortion	4
Therapeutic abortion	3
Intrauterine fetal death	1

*Sixteen pregnancies in 12 women.

Table 2 Details of the Live Births

Case no.	Valve site	Mode of delivery	Birth weight (g)	Fetal outcome	Change to heparin (weeks of gestation)	Heparin delivery	Warfarin	Complications
1	Mitral	38W·CS	2,458	Alive	6	SC	–	–
2	Mitral	33W·elective CS	1,730	Alive	8	SC	–	Valve thrombosis
3	Mitral (marfan syndrome)	33W·CS	1,968	Alive	6	SC	–	Dissection of carotid artery
4	Tricuspid (functional MV)	33W·CS	1,620	Alive	13	SC	–	Subchorionic hematoma
5	Tricuspid (functional MV)	27W·CS	1,063	Alive (hydrocephalus)	4–15, 26	DIV	+	Fetal hydrocephalus
6	Tricuspid (functional MV)	36W·elective CS	2,104	Alive	5	DIV	–	–
7	Aortic	26W·CS	797	Dead (IVH)	5	DIV	–	ICH
8	Tricuspid	27W·CS	1,063	Dead (pulmonary hemorrhage·IVH)	6	DIV/SC/DIV	–	ICH, Valve thrombosis

W, weeks; CS, cesarean section; SC, subcutaneous; MV, mitral valve; DIV, drip infusion; IVH, intra ventricular hemorrhage; ICH, intracranial hemorrhage. Cases 5 and 6 were the same mother; cases 4, 13, 14, and 15 were the same mother.

Table 3 Details of Fetal Loss

Case no.	Valve site	Change to heparin (weeks)	Abortion or IUFD (weeks)	Outcome
9	Mitral	5	7	SA
10	Mitral	9	9	SA
11	Mitral	10	10	SA
12	Mitral	10	10	SA
13	Tricuspid (functional MV)	9	9	Therapeutic abortion
14	Tricuspid (functional MV)	10	19	Subchorionic hematoma/Therapeutic abortion
15	Tricuspid (functional MV)	5	15	Subchorionic hematoma/Therapeutic abortion
16	Aortic	27	30	IUFD during extracorporeal circulation

IUFD, intrauterine fetal death; SA, spontaneous abortion. Other abbreviation see in Table 1.

Cases 4, 13, 14, and 15 were the same mother.

Table 4 Comparison of Complications Between Women Receiving Subcutaneous and Intravenous (Drip Infusion) Heparin

Anticoagulation regimen	Valve thrombosis	Bleeding			Maternal death
		Subchorionic hematoma	ICH	Perinatal bleeding	
Heparin (SC) (n=7)	2	3	0	2	0
Heparin (DIV) (n=4)	0	0	2	2	0

Abbreviations see in Table 2.

remain as outpatients, patients was hospitalized in principle throughout pregnancy. For the patient who hoped to be managed at home, heparin was administered by subcutaneous injection, and APTT for 6 h afterward was controlled to 2–3-fold the normal value. Continuous intravenous infusion of heparin was given to all cases before labor, and administration of heparin was stopped at delivery. Six to 12 h after parturition, heparin was administered again and then changed to warfarin after the decrease in postpartum uterine bleeding. Pregnancy outcomes, including maternal complications and fetal outcomes, were retrospectively investigated. Valvular thrombosis, subchorionic hematoma, maternal intracranial hemorrhage, and perinatal bleeding were compared between the women receiving subcutaneous injections and those receiving drip infusions.

Results

Table 1 shows the fetal outcomes for 16 pregnancies in

12 women with mechanical heart valve replacement: there were 8 live births (50%) and 8 cases of fetal loss.

Table 2 shows the details of the 8 live births. The gestational ages of these infants ranged from 26 to 38 weeks. One case (case 1) was delivered at full term, and 7 cases (cases 2–8) were delivered preterm because of maternal indications. All cases were delivered by cesarean section. Two neonates died (cases 7, 8). Two patients (cases 2, 8) who had received subcutaneous heparin therapy developed valvular (mitral, tricuspid) thrombosis, and thrombolytic therapy was performed during pregnancy. Patient 5 who had received heparin from 4 to 15 weeks and then warfarin from 16 to 26 weeks, underwent termination because of fetal hydrocephalus associated with intracranial hemorrhage.

Table 3 shows the details of the women with fetal loss. Four pregnancies (cases 9–12) resulted in spontaneous abortion at an early stage. Therapeutic abortion was performed in 3 cases (cases 13–15). In case 13, abortion was performed at the patient's request. Case 14 ended in thera-

peutic abortion because of intrauterine infection associated with the enlarged subchorionic hematoma. In case 15, aggravation of maternal anemia from massive subchorionic hemorrhage resulted in therapeutic abortion. Case 16 was a very severe case. The patient did not receive anticoagulation therapy at her own request 26 weeks of gestational age, and she then developed aortic valve thrombosis. At 30 weeks, the aortic valve was surgically replaced, but intrauterine fetal death occurred during intraoperative extracorporeal circulation and the mother also died of heart failure 3 days after cardiac surgery.

Table 4 is a comparison of complications in the patients receiving subcutaneous and those receiving intravenous (drip infusion) heparin. Valvular thrombosis formation occurred more frequently in the subcutaneous group, but the risk of bleeding was comparable between the 2 groups. Mean gestational age at the change to heparin in the cases of early miscarriage was 8.5 weeks (5–10 weeks), compared with 6.6 weeks (5–13 weeks) in the cases of continuing pregnancy. It appears that in cases of early miscarriage the change to heparin was often delayed. There was no heparin-induced thrombocytopenia.

Complications occurred in 3 patients with prosthetic mechanical heart valve replacement (cases 2, 8, 16) because of valve thrombi formation, in 4 cases (cases 3–6) because of bleeding after surgery, and in 3 cases (cases 4, 14, 15) because of subchorionic hematoma.

Discussion

Currently, biological heart valve replacement is being performed in young women because it does not require anticoagulation therapy,³ but biological valves require replacement after 10–15⁴ whereas mechanical valves do not, although they require long-term anticoagulation therapy to minimize the high risk of associated thromboembolic complications. Pregnancy is a physiologic hypercoagulable state that further increases the risk of functional deterioration of the valve. There are several reports of the risks and pregnancy outcomes in women with mechanical heart valve replacement in Western countries,^{1–3,6,7} but only limited data are available in Japan.

Although warfarin is an easily administered and controllable drug, switching to heparin in the early weeks of gestational age is recommended because warfarin carries a potential risk of teratogenicity and higher rate of fetal loss.^{6,7} We have conventionally performed anticoagulation with subcutaneous heparin administration, but it can sometimes be difficult to control maternal coagulability with this technique because of the drug's narrow therapeutic range. In fact, in the present study, 2 patients developed valve thrombosis during subcutaneous heparin therapy, but this was not observed in women receiving intravenous heparin. Intravenous drip infusion of heparin may be superior to conventional subcutaneous administration.

The rate of healthy babies born to these mothers was 37.5% (6/16), which appears to be lower than that reported by Nassar et al.² It is possible that the anticoagulation therapy we administered was inappropriate. Two mothers in the intravenous heparin therapy group developed intracranial hemorrhage, but in both cases the APTT was extended

approximately 2-fold, so it is unlikely that drip infusion of heparin contributed to the maternal intracranial hemorrhage. Recently, in Japan, there have been several reports that lower doses of warfarin are recommended for non-pregnant Japanese patients with atrial fibrillation or prosthetic heart valves, in order to maintain anticoagulability and reduce side-effects.^{8–11}

Vitale et al demonstrated dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves and they concluded that a dose less than 5 mg of warfarin does not have a major impact on the fetus.¹² However, it remains unclear whether warfarin at less than 5 mg/day would be appropriate for pregnant Japanese women because of racial differences in lifestyle, food intake, drug metabolism, body size, and bleeding tendency. Thus, further data for Japanese women should be gathered.

In the present study the rate of healthy babies born to women with mechanical heart valve replacement was lower than that reported from Western countries. Anticoagulation therapy using heparin might be inappropriate, so it is necessary and warranted to determine the appropriate dose and route of heparin therapy for pregnant Japanese women with prosthetic mechanical heart valve replacement.

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