Methods

We examined outcomes after mechanical valve replacement in 25 pregnancies (16 women) between 1983 and 2013 at the Department of Perinatology, National Cerebral and Cardiovascular Center, Japan. Of these, 10 livebirths from 9 pregnancies (8 women) were managed with unfractionated heparin and 1 pregnancy was managed with warfarin (Figure 1). Two of the 9 neonates died in the postnatal period.

Conclusions: Each group showed a high rate of maternal complications, so a review of current anticoagulant treatment strategies is necessary. (Circ J 2014; 78: 878–881)

Key Words: Anticoagulant therapy; Mechanical valve replacement; Pregnancy; Unfractionated heparin
The types of mechanical valve were as follows: 27-mm St. Jude Medical (SJM) valve (cases 1–3, 6, 9), 25-mm SJM valve (cases 4, 8), 21-mm SJM valve (case 5), 27-mm Carbomedics valve (case 7). Case 1 had Marfan syndrome and underwent the Bentall Operation for annuloaortic ectasia.

Table 2 shows the complications in all groups. In cases 3 and 7, valve thrombosis and CS occurred simultaneously, and both patients developed perinatal bleeding. Intracranial hemorrhage occurred in cases 5 and 6 during emergency CS. Further complications arose in case 6, as detailed later.

Table 3 lists the neonatal outcomes. Birth weight ranged from 797 to 2,458 g. The pH of the umbilical artery ranged from

| Table 1. Perinatal Outcomes of 9 Pregnancies After Mechanical Valve Replacement |
|---------------------------------|-----------------|--------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Case no. | Age (years) | Valve replacement | Change to heparin (week) | Heparin administration | Delivery mode | GA | Blood loss at delivery (ml) |
|---------|-------------|-------------------|--------------------------|------------------------|---------------|----|---------------------------|
| I       | 33          | Aortic            | 6                        | SC                     | CS            | 33w4d         | 610            |
| II      | 25          | Aortic            | 5                        | DIV                    | CS            | 26w4d         | 1,400          |
| III     | 36          | Mitral            | 5                        | DIV                    | CS            | 34w6d         | 1,100          |
|         | 33          | Mitral            | 5                        | DIV                    | CS            | 33w5d         | 1,000          |
|         | 36          | Tricuspid         | 5                        | DIV                    | CS            | 36w0d         | 1,260          |

CS, cesarean section; d, days; DIV, intravenous drip; GA, gestational age; w, weeks.
therapy to unfractionated heparin and admitted her to hospital at 5 weeks’ gestation, whereupon we immediately switched her to CRI of 5.75 mg/day since the operation. She visited hospital at 6 weeks gestation, we immediately switched her to CRI of unfractionated heparin (4.5 mg/day) after the operation. When she visited our clinic at 26 weeks gestation, we began administration of verapamil hydrochloride because paroxysmal atrial fibrillation had developed. The frequency of thrombosis with unfractionated heparin administered by CRI of 28,000 units/day, on average, and APTT was measured twice weekly, with a goal of 80s. We shifted her to outpatient status when we judged that APTT was stable. She was rehospitalized for odontotherapy at 26 weeks’ gestation. She suddenly lost consciousness and underwent emergency CT, which identified a left brain intracranial hemorrhage. CS and surgical removal of the hematoma were performed. She was discharged 2 months later, unaffected by the operation. She received a tissue valve at 34 weeks gestation, but a brain hemorrhage occurred. Fortunately, she lived without the sequelae.

**Case 7**
This 36-year-old woman had her mitral valve replaced with a mechanical valve at 21 years of age. She took warfarin (4.5 mg/day) after the operation. When she visited our clinic at 6 weeks gestation, we immediately switched her to CRI of 20,000 unit/day unfractionated heparin in hospital and APTT was measured daily. Pregnancy management while hospitalized included ultrasonography of the patient’s heart every 2 weeks. At 26 weeks gestation, we began administration of verapamil hydrochloride because paroxysmal atrial fibrillation had developed. It later disappeared, but at 34 weeks gestation, she complained of feeling “stifled” and ultrasonography revealed valve thrombus. Her APTT was 68s and the PG of the mitral valve was 10 mmHg. We conferred with specialist cardiologist, and decided to perform simultaneous CS and valve replacement. She was discharged from hospital at 1 month after the operation.

7.25 to 7.35. Two neonates in Group II had IVH (grade IV) and neither survived. All neonates in Groups I and III survived.

**Table 2. Maternal Complications of Anticoagulant Therapy With Unfractionated Heparin**

| Group   | Valve thrombosis | ICH | Perinatal hemorrhage | Maternal death |
|---------|------------------|-----|-----------------------|----------------|
| I (n=4) | 1                | 0   | 1                     | 0              |
| II (n=2)| 0                | 2   | 0                     | 0              |
| III (n=3)| 1               | 0   | 1                     | 0              |

ICH, intracranial hemorrhage.

In each group, the rate of maternal complications was high. The probability of thrombus in this cohort is reported to be approximately 10%. In all of the present cases, patients were treated with unfractionated heparin administered at doses 2–3-fold the normal value, which was considered sufficient but thrombosis developed. The frequency of thrombosis with unfractionated heparin therapy was approximately 33% in the report of Chan et al.

APTT is a trough value and its peak value cannot be reviewed. Intracranial hemorrhage is caused by excessive anticoagulant therapy, although the dose of heparin was sufficient in each group. The anticoagulant action may have been too strong, and related to a lack of accurate evaluation or because APTT is 50% more variable during the night. Therefore, accurate evaluation must be done. Protection of the mother is the primary consideration in anticoagulant therapy using unfractionated heparin.

Warfarin is considered to be the best anticoagulant therapy from the viewpoint of thrombosis prevention. In the report by Chan et al, thrombosis frequency was approximately 4%. In our hospital, warfarin was used during 1 pregnancy and caused fetal intracranial hemorrhage at 26-weeks gestational age. It is reported that the fetal complication rate with warfarin is approximately 10% and the effect is dose-dependent. It is reported that the frequency of embryopathy decreases with dosages ≤5 mg/day. However, racial differences for the gene concerning the effect of warfarin are reported. The frequency of the H1 and H2 types of the VKORC1 gene is reportedly approximately 90% in Europeans, 40% in Asians and 10% in Africans. The Japanese population has the possibility of showing high receptivity to warfarin, so it is essential to examine this issue in a Japanese population. After experiencing that case of fetal intracranial hemorrhage, we no longer use warfarin.

Low-molecular-weight (LMW) heparin does not cross the placenta, so the side effects of heparin-induced thrombocytopenia, osteoporosis, and hemorrhage are infrequent, and it is also unnecessary to monitor it closely because of its long half-life.

**Table 3. Neonatal Outcomes for Pregnancies After Mechanical Valve Replacement**

| Case no. | Birth weight (g) | Apgar score (1 min) | Apgar score (5 min) | UApH | Outcome |
|----------|------------------|---------------------|---------------------|------|---------|
| I 1      | 1,968            | 3                   | 3                   | 7.324| Alive   |
| 2        | 2,458            | 7                   | 9                   | 7.303| Alive   |
| 3        | 1,730            | 2                   | 7                   | 7.303| Alive   |
| 4        | 1,620            | 4                   | 6                   | 7.303| Alive   |
| II 5     | 797              | 7                   | 9                   | 7.356| Died    |
| 6        | 1,063            | 2                   | 7                   | 7.341| Died    |
| III 7    | 1,838            | 8                   | 9                   | 7.333| Alive   |
| 8        | 2,182            | 8                   | 9                   | 7.251| Alive   |
| 9        | 2,104            | 9                   | 10                  | 7.275| Alive   |

UApH, pH of umbilical artery.
Therefore, it might be the best anticoagulant therapy. However, there has not been a randomized control study, and the appropriate blood level of anti-Xa factor is unknown. With such knowledge, LMW heparin could potentially be a gentle anticoagulant therapy for both fetus and mother. It is necessary to overcome the difficulty of measuring anti-Xa factor measurement in Japan, and the lack of authorization for use of LMW heparin during pregnancy.

**Conclusions**

We managed pregnancy in 8 women after mechanical valve replacement by unfractionated heparin therapy, but it was not completely efficacious. The establishment of anticoagulant therapy that is safe for both mother and the fetus is hoped for.

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