Mechanical Valves and Anticoagulation in Pregnancy

Kentaro Honda, MD; Yoshitaka Okamura, MD, PhD

Management of anticoagulation in pregnant women with mechanical valves is complex. Optimal control is required not only during the entire gestational period but also during delivery, and the choice of the appropriate anticoagulation agent, including warfarin, unfractionated heparin (UFH), or low-molecular weight heparin (LMWH), during pregnancy remains a concern. Moreover, questions exist regarding their specific use: Is it safe to use these agents during the entire gestational period? More specifically, is the use of warfarin safe during the entire gestational period? Should warfarin be discontinued during the first trimester to avoid fetal complications? Furthermore, to determine optimal anticoagulatory control, how often should the effectiveness of the therapy be measured? As a result of these unknowns, consensus has not been reached regarding the optimal anticoagulation strategy.

Warfarin provides the most effective control of anticoagulation with mechanical heart valves. In addition, it is considered to be the best method to prevent maternal thrombotic events. The risks of maternal thromboembolic events and maternal death with the use of warfarin throughout pregnancy are reported to be 3.9% and 2.0%, respectively, based on the results of a systematic review. This is the lowest risk compared with other anticoagulation strategies.

Unfortunately, warfarin also has a 0.6–10% risk of embryopathy, late fetal loss, and fetal bleeding complications, which may limit its use in pregnancy. Reported fetal malformations associated with warfarin use during early gestation, from the 6th to 12th week of gestation, include midfacial hypoplasia, stippled epiphyses, limb hypoplasia, and central nervous system anomalies. The risk of embryopathy with warfarin use during the first trimester is considered to be dose-dependent and dramatically increases with doses >5 mg/day. Recommendations in the European Society of Cardiology (ESC) guidelines indicate that continuation of warfarin throughout pregnancy can be considered when the warfarin dose is <5 mg, and switching to other anticoagulation agents should be considered during the first trimester in cases necessitating warfarin doses ≥5 mg.

Heparin is considered to be the preferable agent for anticoagulation. The use of heparin during gestation weeks 6–12 to avoid warfarin complications has been reported previously. Warfarin’s low molecular weight enables it to readily cross the placenta, increasing the risk of embryopathy, whereas the high molecular weight of heparin does not allow it to cross the placenta. Heparin does not induce fetal hemorrhage or teratogenicity. However, heparin must be given intravenously or subcutaneously, so a longer hospitalization is required. Furthermore, the method of achieving appropriate control of anticoagulation with heparin during pregnancy has not been determined. Heparin dosing is adjusted based on activated partial thromboplastin time (aPTT) after administration; however, the required number of measurements to maintain aPTT at 1.5–2.5-fold longer than control is unknown.

Alternatively, LMWH can be used instead of UFH. The mo...
The circulatory weight of LMWH is 4,000–5,000 daltons, which is smaller than that of UFH (15,000 daltons). The mechanisms are similar to those of UFH, and the benefits of LMWH include a long half-life, increased bioavailability, and decreased incidence of side effects such as thrombocytopenia and osteoporosis. Because of the decreased effect on thrombin, LMWH does not affect the aPTT. Instead, LMWH is monitored using the level of anti-Xa. According to the guidelines issued jointly by the American College of Cardiology and American Heart Association, LMWHs should be administered to maintain peak anti-Xa factor levels between 0.7 and 1.2 U/ml. However, Barbour et al reported that controlling the dose of LMWH using just peak anti-Xa levels is inadequate, because peak levels of 0.75–1.0 U/ml are associated with actual levels <0.5 U/ml in most cases. Furthermore, owing to the renal excretion of LMWH, careful monitoring of anti-factor Xa is recommended in the presence of renal dysfunction (creatinine clearance <30 ml/min). In those patients, UFH is considered to be the first-line therapy.

The use of heparin throughout pregnancy carries the highest risk (>30%) of valve thrombosis. Therefore, after avoiding the use of warfarin until 12 weeks gestation, warfarin should be restarted. In fact, a recent report indicates that the use of warfarin can be safe even after the 8th week following the last menstruation. There are also concerns with the use of anticoagulation therapy during delivery. It may result in increased maternal bleeding in addition to fetal bleeding following delivery trauma. Therefore, it is essential to control anticoagulation at adequate levels and allow its administration appropriately during the entire pregnancy. This includes controlling the timing of delivery. A planned delivery is needed to control the discontinuation of anticoagulants. Warfarin should be discontinued after 34–36 weeks of gestation, and UFH and LMWHs should be discontinued 24 h before induction or cesarean delivery to avoid maternal and fetal bleeding. The method of delivery is also important. Some documents indicate that a planned cesarean delivery is not recommended in pregnant women on anticoagulant therapy and should only be considered in the case of obstetric indications. However, others indicate that a cesarean section is preferred to avoid birth-related trauma. UFH has been used as an alternative anticoagulation strategy, but maternal complications occurred at a high rate, and the authors concluded that a proper treatment strategy is needed. LMWH has been shown to be safe even after the 8th week following the last menstruation. In the study presented in this issue of the Journal, Basude et al compare anticoagulation with LMWH, warfarin, and combination therapy in pregnancy. The number of maternal adverse events was lower in the warfarin group (13.6%) than in the LMWH (100%) and combination groups (50%). Moreover, the incidence of hemorrhage >1 L was higher in the warfarin group than in the other groups.

Although several strategies have been previously reported, controversy remains. We consider that the first priority is the mother’s life, second is the baby’s life, and third is avoiding embryopathy.

Patients on a dose <5 mg/day can be safely maintained on warfarin during the entire gestational period to obtain the lowest maternal and fetal complications. For patients requiring doses ≥5 mg/day, replacing warfarin with LMWH during the first trimester is the safest to avoid fetal embolopathy and hospitalization during the first trimester is recommended to maintain optimal anticoagulation. For delivery, a planned cesarean is the safest method to reduce birth-related trauma (Figure).

References