Use of therapeutic dose low molecular weight heparin during pregnancy in women with mechanical heart valves

Management of anticoagulation in women with mechanical heart valves (MHV) is one of the most challenging issues faced by obstetric physicians who manage pregnant women with cardiac problems. The already high risk of valve thrombosis is increased further during pregnancy because of the prothrombotic changes of pregnancy. The safest option for the mother, to reduce the risk of valve thrombosis leading to valve failure or systemic thromboembolism, is to remain on oral anticoagulants such as warfarin. However, warfarin crosses the placenta with a 5–6% risk of warfarin embryopathy if taken between six and nine weeks gestation.¹ In addition, warfarin anticoagulates the fetus and there is a high rate of late fetal loss, up to 40% in some studies,² which further increases women's reluctance to continue taking this form of anticoagulation. Heparin, which does not cross the placenta, is an effective alternative to warfarin for treatment and prevention of venous thrombosis during pregnancy, but there are concerns relating to its efficacy as an anticoagulant in women with MHV. Subcutaneous unfractionated heparin, even when given in high and monitored doses, is associated with an unacceptably high rate of maternal thrombosis. The more predictable anticoagulant effect of low molecular weight heparin (LMWH) makes it an attractive agent for use in this clinical situation but there are limited data relating to its safety and efficacy. In 2004, Oran and co-workers³ reviewed published case reports and case series of LMWH use in pregnant women with MHV. The overall rate of thromboembolic complications in 81 pregnancies was 11.1% but four of these events were reported in single case studies. Monitoring of anti-Xa levels was not carried out in all centres and women received LMWH for variable periods during pregnancy. Such discrepancies make it difficult to extrapolate these data to other situations.

In 2009, four studies were published reporting maternal and fetal outcomes in women treated with therapeutic dose LMWH. A summary of outcomes from the studies is shown in Table 1.

Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin

McLintock *et al.*

BJOG 2009;**116**:1585–92

The largest series from McIntock and co-workers in Auckland, New Zealand, reported maternal and fetal outcomes in 47 pregnancies in 31 women who had taken enoxaparin (starting dose 1 mg/kg twice daily) with low-dose aspirin in two centres from 1997 to 2008. The majority of women (87%) in this series had mechanical heart valves inserted for previous rheumatic fever. A large proportion of pregnancies (45%) were in women with Starr-Edwards (ball and cage) valves. In 34 pregnancies low molecular weight heparin was prescribed from the time pregnancy was diagnosed and throughout the pregnancy, and in

the remaining 13 pregnancies, enoxaparin was taken in the peridelivery period and/or the first trimester with warfarin at other times. Enoxaparin doses were adjusted to maintain trough anti-Xa levels between 0.4 and 0.7 IU/mL and four-hour peak anti-Xa levels between 0.7 and 1.2 IU/mL. Seven thromboembolic complications (14.9%) were reported, five (10.6%) in association with enoxaparin, but poor-compliance with therapy or sub-therapeutic anti-Xa levels were described as major contributing factors in all events. Of the 34 women who took enoxaparin throughout pregnancy, the live birth rate (excluding miscarriages and terminations of pregnancy) was 95%, with a single late loss in this group unrelated to anticoagulant therapy. Both stillbirths and the infant death in this cohort were complications of warfarin.

Use of low molecular weight heparin in pregnant women with mechanical heart valves

Yinon *et al.*

Am J Cardiol 2009;**104**:1259–63

The Canadian Study by Yinon and co-workers reported 23 consecutive pregnancies in 17 women from a single centre. All women chose to take therapeutic dose low molecular weight heparin (LMWH) and low-dose aspirin throughout pregnancy, and this was started by six weeks' gestation in 19 pregnancies and by nine weeks' gestation in the remaining four pregnancies. All women had either tilting disc or bileaflet valves and only one woman had both aortic and mitral valve replacements. The indication for valve replacement was congenital heart disease in 50% of the pregnancies. Peak (4-hour) anti-Xa levels were measured with a target range of 1–1.2 IU/mL. Thromboembolic complications occurred in one woman with a Medtronic-Hall aortic valve who presented with a transient ischaemic attack at 24 weeks gestation and, despite an increase in the LMWH dose, valve thrombosis occurred at 26 weeks gestation resulting in cardiac arrest and death, with an early neonatal death of the infant who was born by perimortem caesarean section. Peak anti-Xa levels ranged between 0.99 and 1.4 IU/mL throughout her pregnancy. Other cardiac complications occurred in five (22%) of pregnancies. Two miscarriages were reported and there were two fetal deaths at 21 and 34 weeks gestation thought to be due to placental insufficiency.

Management of pregnant women with mechanical heart valve prosthesis: thromboprophylaxis with low molecular weight heparin

Abildgaard *et al.*

Thromb Res 2009;**124**:262–7

This study by Abildgaard and co-workers reported outcomes of 12 pregnancies in 11 women treated with dalteparin and low-dose aspirin throughout Norway between 1997 and 2008. All women had either tilting disc or bileaflet valves and two women had both mitral and aortic valve replacements. Again only peak anti-Xa levels were measured with a target range of 0.7–1.2 IU/mL except for the first two pregnancies in

Table 1 Summary of anticoagulation and monitoring during pregnancy and fetal outcomes from studies

Study	McLintock ⁴	Y'inon ⁵	Abildgaard ⁶	Quinn ⁷	Total
Pregnancies (women) / N	47 (31)	23 (17)	12 (11)	12 (11)	94 (70)
LMWH (starting dose)	Enoxaparin (1 mg/kg bd)	Not reported in paper	Dalteparin (100 U/kg bd)	Dalteparin (100 U/kg bd) [n = 8] Enoxaparin (1 mg/kg bd) (n = 4)	
Low-dose aspirin advised	Yes	Yes	Yes	High-risk patients only	
Frequency of anti-Xa monitoring	Monthly	Every 2–4 weeks	Every 2–4 weeks	Every 2–4 weeks	
Peak anti-Xa (IU/mL)	0.7–1.2	1–1.2	0.7–1.2	1–1.2	
Trough anti-Xa (IU/mL)	0.4–0.7	Not done	Not done	Not done	
Maternal complications					
Thromboembolic complications related to LMWH	5	1	2	1	9 (10%)
Major antenatal bleeding	4	0	0	2	6 (6%)
Major postpartum bleeding	12**	3	4	2	21 (22%)
Fetal outcome					
Live births, N (% excluding losses <20 weeks)	31† (89%)	19 (90%)	13† (100%)	11 (92%)	73 (91%)
Miscarriage	8	2	0	0	10
Stillbirth	2†	2	0	1	3
Neonatal/infant death	2†	1	0	0	2

LMWH = low molecular weight heparin

*Postpartum haemorrhage in six women

†Both stillbirths and one infant death were attributable to warfarin

‡One set twins

women with mechanical aortic valves where the peak anti-Xa target range was 0.4–0.8 IU/mL. In two pregnancies from early in the study period, women received subtherapeutic doses of dalteparin (110 IU/kg once daily and 55 IU/kg twice daily initially). All other women received 100 IU/kg twice daily. Thromboembolic complications occurred in the two pregnancies where women initially received subtherapeutic doses of dalteparin. Anti-Xa levels in these women were 0.67 and 0.71 IU/mL. Both women made complete recoveries. No fetal complications were reported and 13 healthy babies were delivered, including one set of twins.

Use of high intensity adjusted dose with low molecular weight heparin in women with mechanical heart valves during pregnancy: a single-center experience

Quinn *et al.*

Haematologica 2009;**94**:1608–12

This study by Quinn and co-workers reports outcomes in 12 pregnancies in 11 women in a single centre in London from 2001 to 2007. Women were treated with either therapeutic dose dalteparin or enoxaparin, eight women (nine pregnancies) had single prosthetic valves and three had both aortic and mitral valve replacements. Again only peak anti-Xa levels were measured and low-dose aspirin was only given to women ($n = 4$) at 'high risk' who had either atrial fibrillation, enlarged right atrium or a systemic right ventricle. A single episode of valve thrombosis at 26 weeks gestation occurred in a woman whose geographical location made it difficult for her to have regular anti-Xa levels measured and these were subtherapeutic in the weeks prior to the event. She was also not taking aspirin. The patient required an emergency caesarean section at the time of the valve thrombosis and had a live born infant. The authors also described an intrauterine fetal death at 37 weeks in one woman but no further details are provided.

What these studies show us:

- (1) Experience with managing pregnant women with mechanical heart valves (MHV) with therapeutic dose low molecular weight heparin (LMWH) continues to grow;
- (2) Women with MHV have high-risk pregnancies;
- (3) The risk of thromboembolism is higher in women who are non-compliant and do not have regular monitoring of anti-Xa levels, but the risk remains even in women who are compliant with therapy. Eight of the nine (89%) thromboembolic complications reported in women who were prescribed LMWH, occurred in women who either had subtherapeutic anti-Xa levels or who were non-compliant with therapy;
- (4) Use of LMWH during pregnancy is associated with good fetal outcomes;
- (5) Bleeding complications, in particular postpartum (see Table 1) are common in these women who require prompt reinstitution of anticoagulant therapy following delivery.

There will continue to be a demand for alternatives to warfarin in pregnant women with MHV. Data from these studies are

encouraging but reinforce the high risk these women face during pregnancy and the importance of a dedicated multi-disciplinary team to ensure compliance with treatment and monitoring.

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