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

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ABSTRACT

The use of standard dose low molecular weight heparin (LMWH) to anticoagulate women with mechanical valves in pregnancy is associated with morbidity and mortality. We conducted a prospective audit of the use of adjusted dose high intensity LMWH in 12 pregnancies in 11 women with prosthetic heart valves. LMWH ± low-dose aspirin was started at therapeutic-dose with monitoring of anti-Xa levels to achieve a target level of 1.0-1.2 IU/mL (0.8-1.2 in the first 3/12 pregnancies). This necessitated a mean increase in the dose of LMWH of 54.4% (SD±33.2) over initial dose. Eleven of 12 pregnancies resulted in live births, with one intrauterine fetal death at 37 weeks. One non-fatal valve thrombosis occurred at 26 weeks gestation associated with subtherapeutic anti-Xa levels. Three patients experienced major bleeding. This regime provides a therapeutic option for women with mechanical heart valves during pregnancy, provided anti-Xa levels are kept within the target range. These patients require close surveillance for bleeding and thrombotic complications within a multidisciplinary setting.

Key words: pregnancy, low molecular weight heparin, mechanical heart valves.

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Introduction

Provision of safe and effective anticoagulation for pregnant women with mechanical heart valves is a challenging management problem. All current anticoagulation regimens are associated with maternal thromboembolism (TE) and/or bleeding. Vitamin K antagonist (VKA) therapy throughout pregnancy results in the lowest observed risk of TE (3.9%). However, VKA use is associated with fetal anomaly rates of 6.4%, fetal death of 12% and neurodevelopmental problems.[1,2] The rate of TE with unfractionated heparin (UFH) is high at 25% if used throughout pregnancy and 9% if used for the first trimester.[1]

Therapeutic dose LMWH is an attractive alternative to VKAs and UFH. However, in the HIP-CAT study which compared enoxaparin with sequential UFH and warfarin in pregnant women with mechanical valves, 2/7 women receiving therapeutic dose enoxaparin 1 mg/kg 12 hourly developed fatal valve thrombosis.[3] The incidence of TE using LMWH in this setting is not known because of the limited data available, but James *et al.* found an overall TE rate of 22% and a maternal mortality of 4%.[4] In another review, Oran *et al.* found an overall incidence of valve thrombosis of 8.64% (8/81) and the overall TE rate 12.35% (10/81).[5] However, 9 of these 10 patients received a fixed dose of LMWH, and in 2 of these a low fixed dose was used. Among 51 pregnancies where anti-Xa levels were monitored, only one patient was reported to have had TE. The American College of Chest Physicians (ACCP) advises that there are insufficient data for definitive recommendations on how best to anticoagulate women with mechanical valves in pregnancy, in view of concerns for fetal well-being with warfarin therapy and the possible poorer efficacy of subcutaneous UFH and LMWH in preventing maternal TE.[6] Recommendations have included adjusted dose LMWH throughout pregnancy to keep a 4 h post-dose anti-Xa level of 1.0-1.2 IU/mL although updated ACCP guidelines recommend adjusted dose LMWH to achieve the manufacturer's peak anti-Xa level 4 h post subcutaneous injection (approximately 1.0 IU/mL) with consideration of LDA in women with prosthetic heart valves at particularly high risk of thrombosis.[7] Against this background, we conducted a prospective audit of our experience with the use of our dose-adjusted regimen of high intensity LMWH in pregnant women with mechanical heart valves, and documented TE and bleeding complications, pregnancy outcome, as well as anti-Xa levels throughout their pregnancies.

Design and Methods

All pregnancies in women with mechanical heart valves between 2001 and 2007 who received LMWH were included.

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The audit was carried out in accordance with United Kingdom regulations.[8,9] Since 2004, all women receiving therapeutic dose LMWH were managed in a multidisciplinary clinic for high-risk obstetric patients. Self-administered LMWH was commenced at full therapeutic dose, based on current weight; dalteparin at 100 units/kg and enoxaparin at 1 mg/kg, 12 hourly subcutaneously (SC) when warfarin had been discontinued. All women received counseling regarding the risks and benefits associated with warfarin, UFH and LMWH as thromboprophylaxis in this setting. Warfarin was stopped before six weeks gestation and LMWH started when the INR was <2.0. LMWH was self-administered in the majority of cases. Aspirin 75 mg (LDA) daily was added in women who were felt to be at particularly high risk of thrombosis (atrial fibrillation, enlarged right atrium and systemic right ventricle). In 6 out of 12 cases, peridelivery anticoagulation was managed according to a regimen using fixed dose UFH 15,000 IU/24 h by continuous intravenous infusion peridelivery, and recommencement of LMWH 24 h post-delivery.[10]

Anti-Xa levels were measured on samples taken 4 h post-injection using a chromogenic assay (Coamatic Heparin, Chromogenix), with adjustment of the LMWH dose to achieve anti-Xa levels 1.0-1.2 IU/mL (0.8-1.2 in the first 3/12 pregnancies). Platelet counts were monitored weekly for the first three weeks and thereafter every four weeks. From 2004 onwards patients were offered calcium supplements, together with vitamin D (calcichew D3 500mg bd), in those with suboptimal or low vitamin D levels (normal 15-120 IU, optimal >70 IU). The following outcomes were recorded: TE and bleeding complications, and pregnancy outcome.

Results and Discussion

Past obstetric and cardiac history

Twelve pregnancies in 11 women (9 Caucasian) who received LMWH during pregnancy were audited. The mean age was 29.8 (SD±7.4) years. Details of the pregnancies are outlined in Table 1. Mechanical valve sites were as follows: mitral (MVR) 4, aortic (AVR) 2, dual aortic and mitral (DVR) 3, and systemic right atrioventricular valve (SRAVV) 2 (Table 1). The median age of the valves in relation to each pregnancy was eight (range 1-19) years. Past obstetric history included 6 fetal losses: 2 first trimester miscarriages and 4 terminations of pregnancy (TOP), including one therapeutic TOP at 22 weeks gestation because of an intracerebral fetal hemorrhage during maternal warfarin therapy.

LMWH and anti-Xa Levels

LMWH heparin was commenced at or before six weeks gestation in 11 pregnancies with one remaining patient switching from warfarin to LMWH at eight weeks gestation. Anticoagulation in 8 pregnancies was with dalteparin and 4 patients received enoxaparin. One of twelve patients discontinued LMWH at the end of the first trimester and was anticoagulated with warfarin for the 2nd and 3rd trimesters. Four patients also received low-dose aspirin. Self-administered LMWH was commenced at full therapeutic dose SC based on weight (dalteparin 100 IU/kg or enoxaparin 1 mg/kg 12 hourly). Mean weight at booking was 76.1 kg (range 50-97). Considerable stepwise increases in the doses of LMWH were required to maintain target or near–target 4-hour post-dose anti-Xa levels, with mean LMWH doses pre-delivery of 11,194 IU (range 8,750–15,000) 12 hourly for dalteparin and 90mg (80-95) 12 hourly for enoxaparin, representing a mean increase of 54.4% (SD±33.2) over initial dosage. The mean anti-Xa level between 32 and 37 weeks was 1.09 IU/mL compared to 0.66U/mL between four and seven weeks. Anti-Xa levels (mean and SD) throughout pregnancy are demonstrated in Figure 1. One-hundred and eighty-six anti-Xa levels were measured during a total of 355 weeks gestation (mean duration between measurements, 1.9 weeks). Of the 12 pregnancies, there were 11 live births with a mean birth weight of 2.33kg (SD 0.95) at a mean gestation of 35.3 weeks (SD±3.84), and one IUFD at 37 weeks.

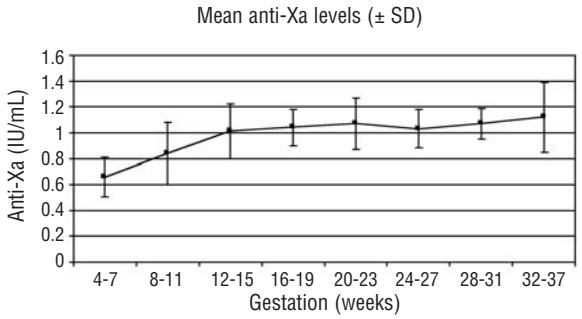

Figure 1. Mean anti-Xa levels during all pregnancies (±SD)

Thrombotic complications

There was one valve-related thrombosis, which occurred at 26 weeks gestation in a 25-year old patient (Patient 9, Table 1) who had undergone mitral-valve replacement (Bjork-Shirley) at the age of six years for left atrio-ventricular valve regurgitation. She had a past history of subclavian vein thrombosis at the age of 21. Thrombophilia testing showed that she was heterozygous for the G20210A prothrombin gene mutation (PGM). This was her second pregnancy, the first ending in an early spontaneous miscarriage one year previously whilst on warfarin treatment. She switched to therapeutic dose LMWH, dalteparin 5000 IU 12 hourly (weight 50 kg) at eight weeks gestation. Optimal anti-Xa monitoring at our center was not possible due to geographical remoteness. By week 26, her dalteparin dose was 8,750 IU 12 hourly (peak dose during pregnancy) and she developed progressive dyspnea. Pulmonary edema secondary to mitral valve thrombosis was diagnosed. She underwent emergency CS with delivery of a female infant weighing 1.0 kg followed by emergency mitral valve replacement. Importantly, anti-Xa levels at 14 and 20 weeks gestation were subtherapeutic (0.6 and 0.64 IU/mL, respectively). There were no transient ischemic

attacks, strokes, cases of heparin-induced-thrombocytopenia or bone fractures. Three patients have undergone bone mineral densitometry (BMD) imaging since delivery and all had normal T-scores.

Bleeding complications

Three patients experienced major bleeding complications. In the antenatal period, there were 2 episodes of antepartum hemorrhage, one with placenta previa (patient 10), associated with a 4 h post-dose anti-Xa level of 1.53 IU/mL. In the other case (patient 4), pregnancy was uneventful until week 27 when she developed bleeding per vagina (PV) which was of small volume (<100 mL). There was no hemodynamic compromise or fall in hemoglobin concentration. At this time the anti-Xa level 4 h post-dose was 1.07 IU/mL and her total daily dalteparin dose was 24,000 IU. Over the next four weeks she continued to have intermittent low-volume PV bleeding which was managed conservatively and low-dose aspirin was discontinued. The anti-Xa range at 4 h post dose was reduced to 0.8-1.0 IU/mL to achieve a balance between adequate thromboprophylaxis and bleeding risk. The peak anti-Xa level was 1.46 IU/mL at 18 weeks gestation. Ultrasound scan demonstrated a 6 cm hematoma over the cervical opening above the cervical os. Persistent vaginal bleeding eventually necessitated caesarian section at 31 weeks with delivery of a female infant (birth weight 2.3 kg). Postpartum she was commenced on intravenous UFH 15,000 IU/24 h by continuous IVI. The dose of UFH was increased after 24 h to attain a therapeutic APTR of 2.0-3.0. Three days post-CS she developed a wound hematoma, which required surgical evacuation and transfusion of 4 units of red cells. The APTR had been labile and more than 5.0 on 2 occasions despite close monitoring.

She was switched to LMWH and subsequently to warfarin, making a full recovery. Post-delivery there was one further major bleeding episode; a major post-partum hemorrhage (PPH) (during LMWH treatment) which necessitated a red cell transfusion of 8 units but no surgical intervention Three patients had minor bleeding: one per-rectum secondary to hemorrhoids and also epistaxis, one secondary PPH and one placental hematoma. The median estimated blood loss was 500 mls (300-900 mls) excluding the deliveries complicated by major hemorrhage (n=2). Median hemoglobin concentrations at day 1 and day 5 post-delivery were 10.7 g/dL (range 8.5-14.5) and 9.8g/dL (range 6.6-12.0), respectively. Median platelet counts at day 1 and day 5-post delivery were 199×10^9/L (range 145-325) and 225×10^9/L (150-400$\times10^9$/L). There were no transient ischemic attacks, strokes, cases of heparin-induced-thrombocytopenia or bone fractures. Three patients have undergone bone mineral densitometry (BMD) imaging since delivery and all had normal T-scores.

Table 1. Details of pregnancies.

Case	Age	Valve site	Past obstetric losses	Mode of delivery and gestation	Birth weight	Fetal outcome	Aspirin	LMWH	Complications
1	19	AV and MV	–	ELCS 39w	1.94kg	Alive	Y	Dalteparin	No
2	21	MV	T1 TOP on warfarin	EMCS 38w	2.9kg	Alive	Y	Dalteparin	Epistaxis and bleeding PR secondary to hemorrhoids (minor)
3	18	MV	T2 TOP on warfarin	ELCS 35w	1.1kg	Alive	Y	Dalteparin	Placental hematoma (minor)
4	31	AV	T1 TOP on warfarin	EMCS 32w	2.3kg	Alive	Y	Dalteparin	APH, postnatal wound hematoma (major) (*see text*)
5	35	MV	–	EMCS 38w	3.7kg	Alive	N	Enoxaparin	Secondary PPH (minor)
6	35	SRAVV	T1 miscarraige on LMWH	ELCS 32w	1.5kg	Alive	N	Enoxaparin (Warfarin in T2 and T3)	No
7	35	SRAVV	–	ELCS 38w	2.9kg	Alive	N	Enoxaparin	No
8	26	AV	T1 miscarraige on warfarin	EMCS 37w	N/A	IUFD	N	Dalteparin	IUFD
9	34	MV	T1 TOP on warfarin	EMCS 26w	1kg	Alive	N	Dalteparin	Mitral Valve thrombosis at 26w
10	38	AV and MV	-	EMCS 33w	2.0kg	Alive	N	Enoxaparin	APH with placenta previa (major)
11	27	AV	As per case 8 (same patient)	ELCS 36w	2.5kg	Alive	N	Dalteparin	N
12	41	AVand MV	-	ELCS 38w	3.84kg	Alive	N	Dalteparin	PPH (major)

APH: antepartum hemorrhage; ELCS: elective caesarean section; EMCS: emergency caesarean section; PPH: post-partum hamorrhage, weeks; LMWH: low molecular weight heparin; T2: 2nd Trimester, T3: 3rd Trimester, TOP: termination of pregnancy, AV: aortic Valve, MV: mitral valve; TV: tricuspid valve; SRAVV: systemic right atrioventricular valve; Y: yes, N: no.

Results and Discussion

This single-center experience has demonstrated that an adjusted-dose high intensity LMWH regimen in pregnant women with prosthetic heart valves provides effective anticoagulation provided anti-Xa levels are kept within a tight therapeutic range of 1.0-1.2 IU/mL. The importance of meticulous anti-Xa monitoring with appropriate LMWH dose adjustment is underlined by the occurrence of a mitral valve thrombosis in one patient whose monitoring was not well maintained and the anti-Xa level was sub-therapeutic albeit transiently, although there were other contributory factors. There were live births in 11/12 pregnancies and no maternal mortality. Large increases in the doses of LMWH were required to achieve effective anticoagulation during pregnancy, with mean doses pre-delivery showing an approximately 54% increase over initial dose. Interestingly, we did note a minor reduction (which was not statistically significant) in LMWH dose required to maintain target anti-Xa levels in the 3rd trimester in comparison with the 2nd trimester (Figure 2).

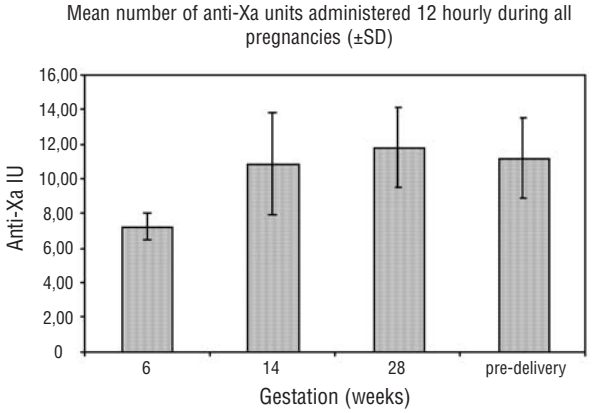

Figure 2. Mean number (±SD) of anti-Xa IU LMWH administered 12 hourly SC during all pregnancies

Our findings that achievement of target anti-Xa levels required stepwise LMWH dose increases during pregnancy concurs with observations in patients with venous thromboembolism treated with dalteparin where 85% of pregnancies (11/13) required upward dose adjustments to maintain anti-Xa levels.[11] As LMWHs undergo renal clearance, the increase in glomerular filtration rate (GFR) and expansion of plasma volume during pregnancy may explain the large doses of LMWH required to achieve therapeutic anti-Xa levels.[12]

The number of TE complications in this audit (one in 12 pregnancies) is lower than that documented by James *et al.*[4] in their review, where they reported 17 TE complications in 72 pregnancies (22%). It is notable that we observed no TE complications in those patients whose anti-Xa levels were well maintained. Major bleeding episodes occurred in 3 patients; however, there was a good maternal and fetal outcome in all cases. In their review, James *et al.*[4] report a 10.9% rate of hemorrhage including one fatal, whereas Rowan *et al.*[13] in their audit, report a rate of 14.3%. Predictably, bleeding occurs; particularly if there are compounding obstetric complications, such as placenta previa.

The anti-Xa assay is the most informative available assay for monitoring LMWH treatment, even though it is recognized that the assay has its limitations.[14] For example, Leizorovicz *et al.* found a weak correlation between thrombosis and anti-Xa levels and no significant correlation with hemorrhage in a large cohort of patients receiving LMWH thromboprophylaxis for general surgery.[15] However, another study has shown that most major bleeds occurred in those patients receiving the highest doses of LMWH[16] and those with mean anti-Xa levels greater than 0.8 IU/mL. Other studies have shown that the pharmacokinetics of LMWH are altered during pregnancy.[17,18] In 2002, the Control of Anticoagulation Subcommittee of the Scientific and Standardisation Committee of the International Society for Thrombosis and Haemostasis made the following recommendation on monitoring LMWH: *Use of anti-Xa assays may provide some clue to the pharmacokinetics of LMWH when used to treat thrombosis in those in whom standard or weight-adjusted dosing is likely to be unreliable, especially subjects with severe renal failure, the obese, the pregnant, neonates and infants.*[19] Therefore, given the very high doses of LMWH prescribed to our patients, added to the altered LMWH pharmacokinetics in pregnancy and the ACCP recommendation regarding dose adjustments of LMWH according to anti-Xa levels when treating pregnant women with mechanical heart valves, it would seem that anti-Xa monitoring is necessary in these high-risk patients.[7]

The risk of osteoporotic fracture associated with long-term use of LMWH in pregnancy is very low, estimated at 0.04%.[20] Rodger *et al.* reported normal bone-density six weeks after completion of dalteparin thromboprophylaxis during pregnancy in a cohort of 62 patients.[21] However, our patients received higher doses of LMWH in comparison with patients in these studies, and the risk of osteopenia in this situation remains to be defined.

This regime provides a therapeutic option for women with mechanical heart valves during pregnancy, who should be considered *highly complex* when antenatal care is being planned. They require specialist multi-disciplinary care with early intervention to overcome complications.

Authorship and Disclosures

JQ, KVK, and RB analyzed the data and wrote the paper; DP, FW and MC were responsible for the clinical management of patients; all authors were involved in the final revision of the paper.

The authors declare no potential conflict of interest.

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