Pregnancy Outcomes Compared in Women with Mechanical Heart Valve Replacements Anticoagulated with Warfarin and Enoxaparin in Pregnancy

Vijayan Valayatham, Obstetric Medicine Fellow(Lond), Rachel Thundyil, MRCP

Sabah Women & Children Hospital, Kota Kinabalu, Sabah, Malaysia

SUMMARY

The anticoagulation of choice for mechanical heart valves is the oral anticoagulant warfarin. Warfarin is associated with increased risk of miscarriage, intrauterine fetal deaths and warfarin embryopathy. This longitudical cross-over study of 5 women observed all 5 having livebirths of healthy infants after heparin-managed pregnancies. Their earlier 8 pregnancies had all resulted in perinatal losses or miscarriages when on regimes based on warfarin.

KEY WORDS:
Mechanical Heart Valve, Pregnancy, Heparin, Low Molecular Weight Heparin, Warfarin

INTRODUCTION

Pregnant women with mechanical heart valves carry higher morbidity and mortality risks regardless of anticoagulation therapy used. This is due to the increased coagulable state of pregnancy contributing towards as inherent risk of valve thrombosis. Anti-coagulation is mandatory after mechanical valve replacement and warfarin is the anti-coagulant of choice. Pregnancy poses therapeutic dilemmas. While warfarin is the anticoagulation of choice it increases the risk of miscarriage, malformations and perinatal deaths. Heparin is the alternative.

MATERIALS AND METHODS

The Sabah Women and Children Hospital is a tertiary referral centre. It has dedicated high risk and combined (obstetric-medical) clinics. This is a longitudinal observational study of 13 pregnancies in a cohort of 5 women with mechanical heart valves in pregnancy managed by the combined team. The standard anticoagulation strategy recommended by the national clinical practice guideline (CPG) (heparin-warfarin-heparin) was recommended to the five women for their eight pregnancies prior to the year 2007. Patients were converted to heparin upon confirmation of pregnancy, converted to warfarin at 14 week and finally re-converted to heparin at 36 weeks. In 2007 the option of heparin (low molecular weight heparin, Enoxaparin) through the duration of pregnancy was offered to these five women. We describe the 13 pregnancies of five women (labeled A-E). Eight pregnancies prior to the year 2007 were anticoagulated with warfarin. From the year 2007 five pregnancies were anticoagulated with the low molecular weight heparin (LMWH) enoxaparin (Sanofi-Aventis: pregnancy category B [no known human risk]).

The local protocol for the use of LMWH in mechanical heart valves in pregnancy is as follows:
Patients who are keen or are given the option of heparin through pregnancy are subjected to detail counseling by a joint obstetrics-physician team. Written consents were obtained. Their coagulation profiles are monitored on a weekly basis until therapeutic targets are achieved. A 1-hour pre-dose (trough) anti-Xa level of 0.7/ml and a 4-hour post dose (peak) level of approximately 1.0-1.2/ml is targeted for enoxaparin and an activated partial thromboplastin time (aPTT) of 2.5-3.5 times the control is targeted for UFH. Monitoring was continued 2-3 weekly once targets were achieved. All women were also prescribed low dose aspirin of 75mg daily as an adjunct. Clear anticoagulation plans are outlined in the event of admissions or if they present in labour. Detailed peripartum care pathways are outline in the event of the latter. Platelet counts were monitored at 2 and 4 weeks after commencement of treatment to detect heparin-induced thrombocytopenia (HIT). A Level 2 anomaly scan was performed at 20-22 weeks gestation. Fetal growth scans were performed every 2 weeks from the 28th week of gestation. All women had an echocardiogram planned per trimester to detect evidence of pre-clinical valve thrombosis.

Patients were not encouraged on the option of heparin through pregnancy if they had one of the following:

1. Older generation more thrombogenic valves such as the ball and socket Bjork-Shiley.
2. Multiple valve replacements.
3. Previous thromboembolic complications.
4. Other cardiac co-morbidities such as atrial fibrillation, dilated chambers or cardiac failure.

The patient's informed decision was, however, final.

RESULTS

There were 13 pregnancies by these five women from 2006 up until 2010. Eight pregnancies prior to 2007 were anticoagulated with warfarin. There were no livebirths with all ending in miscarriages. The 5 pregnancies since 2007 anticoagulated with the LMWH enoxaparin resulted in livebirths for each of the 5 subjects A-E. Table I summarizes pregnancy outcome prior to and after 2007 in subjects A-E.

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Corresponding Author: Vijayan Valayatham, Sabah Women & Children Hospital, Kota Kinabalu, Sabah, Malaysia
Email: vj1vela@gmail.com

Table I: Outcomes of all pregnancies prior to and after the introduction of LMWH for mechanical heart valves in pregnancy in 2007

Prior to 2007 (Heparin-Warfarin-heparin)			2007	LMWH Enoxaparin through duration of pregnancy		
Subject	**N**	**Outcome**		**Subject**	**N**	**Outcome**
A	1	Miscarriage at 15 weeks	INTRODUCTION OF LMWH AS TREATMENT OPTION	A	4	Normal vaginal delivery at term
	2	Intrauterine fetal death at 22 weeks				
	3	Miscarriage at 14 weeks				
B	5	Miscarriage at 17 weeks		B	7	Normal vaginal delivery at term
	6	Miscarriage at 10 weeks				
C	8	Miscarriage at 10 weeks		C	10	Normal vaginal delivery at term
	9	Miscarriage at 11 weeks				
D	NA	NA		D	11	Induced vaginal delivery at term
E	12	Intrauterine fetal death at 20 weeks		E	13	Normal vaginal delivery at term

Table II: Anticoagulation description and pregnancy outcomes after warfarin and heparin anti-coagulation in subjects A-E

N	Subjects A-E	Valve Replaced	Pre-Pregnancy Dose / medication	Regime	Pregnancy stabilized dose	Final Outcome	Complications
1	A	Sorin Mitral	Warfarin 7 mg	Converted to UFH at 8 weeks. Reconverted to warfarin at 13 weeks.	Warfarin 8-9mg day weeks	Miscarriage at 16	Blood transfusion after ERPOC
2				Converted to UFH at 6 weeks then re-warfarinized at 14 weeks	Warfarin 8-9 mg	Perinatal death at 22 weeks gestation of normally formed fetus	Induction of labour necessary.
3				Heparinized at 7 weeks. Re-warfarinized at 14 weeks.	Warfarin 8-9 mg	Miscarried at 14 weeks while being re-warfarized	ERPOC necessary
4				**Presents at 16 weeks still on warfarin. Converted to enoxaparin**	**Enoxaparin 80mg bid**	**NVD**	
5	B	St Jude Aortic	Warfarin 2.5-3 mg	Converted to UFH at 6 weeks. Re-warfarinized at 16 weeks.	Warfarin 5-6 mg	Miscarriage at 17 weeks	ERPOC necessary. Blood product transfused for abnormal coagulation profile pre-operatively
6				Converted to UFH at 6 weeks	UFH 14000 bd	Complete miscarriage at 10 weeks	
7				**Converted to enoxaparin at 7 weeks**	**Subsequently required UFH 16000 bd**	**NVD**	
8	C	Sorin Mitral	Warfarin 4-5 mg	Warfarin	Warfarin 6-7 mg	Miscarriage at 10 weeks	ERPOC required
9						Miscarriage at 11 weeks	Transfusion of blood products for abnormal coagulation profile. ERPOC required
10				**Converted to UFH at 6 weeks**	**Enoxaparin 70mg bd**	**NVD**	
11	**D**	**Carbomedic Mitral**	**Warfarin 3-4 mg**	**Converted to enoxaparin at 6 weeks**	**Enoxaparin 100 + 80 mg (bd)**	**Term vaginal delivery**	**IOL required**
12	5	Carbomedic Mitral	Warfarin 2-3 mg	Converted UFH at 10 weeks. Re-warfarinized at 15 weeks	Warfarin 4-5 mg	Perinatal death at 20 weeks	IOL required
13				**Converted to enoxaparin at 9 weeks gestation**	**Enoxaparin 80mg bd**	**NVD**	

N=pregnancies
Subject column represents the five women involved
UFH= unfractionated heparin
NVD= normal vaginal delivery at term
ERPOC= evacuation of retained products of conception
IOL= induction of labour
In bold: successful pregnancy outcomes

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Table III: Description of LMWH pregnancies

	Valve type / Position	NYHA at outset	Starting dose / stabilized dose	Therapeutic problems	Complications	Labour	Mode of delivery	Fetal growth & Birth weight	Postpartum complications
4	SORIN Mitral	I	60mg bid 80mg bid	NA	Minimal site bruising. Tolerable	Spontaneous	NVD	Normal growth Birth weight 2.8kg	NIL
7	St Jude Aortic	I	Enoxa 60mg bid converted UFH 16000 U bid	Unable to achieve therapeutic targets on enoxaparin (max 100mg bid). Converted to UFH at 20 weeks gestation	Subchorionic hematoma at 14 weeks Threatened miscarriage at 18 weeks	Spontaneous	NVD	Normal fetal growth Birth weight 3.55kg	NIL
10	SORIN Mitral	I	10,000 U bid Max 17000 U bid converted enoxa 60mg bid Stable at 60+80mg (bid)	Unable to achieve therapeutic doses on UFH hence converted to LMWH	NIL	Spontaneous	NVD	Normal fetal growth Birth weight 3.0kg	NIL
11	Carbomedic Mitral	I	Stable on bid dosing of 100mg am + 80 mg pm		NIL	Induced for IUGR	NVD	IUGR 2.5kg	NIL
13	Carbomedic Mitral	I	Stable on 80mg bid of enoxaparin	Therapeutic target achieved after 5 weeks	NIL	Spontaneous	NVD	Normal fetal growth 3.2kg	NIL

All pregnancies conceived on warfarin and converted to LMWH unless specified otherwise
NVD= normal vaginal delivery at term
UFH = unfractionated heparin
LMWH: low molecular weight heparin

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Table II lists the 13 pregnancies and provides salient anticoagulation management points and events. The pregnancy listing is by the subjects A-E and not in chronological order. It also provides information on morbidity. Three of the pregnancies ending with miscarriages while on warfarin required transfusion of blood or blood products.

Table III further describes the 5 LMWH pregnancies. All except one had stable therapeutics dosing through pregnancy. In subject B there was difficulty achieving in-vivo targets by conventional anti-Xa testing. Subject A reported site-bruising but was able to continue with relevant advise. All had livebirths at term with no postpartum complications, especially those expected with anti-coagulation at therapeutic levels such as hematomas and birth canal bleeding.

DISCUSSION

The use of oral anticoagulation (OA) throughout pregnancy is associated with warfarin embryopathy in 6.4% (95% confidence interval [CI], 4.6%-8.9%) of livebirths. The regimen associated with the lowest risk of valve thrombosis (3.9%; 95% CI, 2.9-5.9%) was the use of OA throughout; using heparin between 6 and 12 weeks' gestation was associated with an increased risk of valve thrombosis (9.2%; 95% CI, 5.9%-13.9%). Maternal mortality was 2.9%[1]. The leading cause of mortality is acute valvular failure due to thrombosis.

The management of women with mechanical heart valve in pregnancy poses challenges. The local clinical practice guideline issued in 2001 outlines 3 options for this select group of mothers: (i) warfarin through pregnancy (ii) heparin through pregnancy (iii) heparin in the first trimester, warfarin in the second trimester and heparin back in the third. The reviewers go on to suggest that the best option is warfarin through pregnancy with option (iii) an acceptable compromise for fetal benefits[2].

Prior to the index enoxaparin pregnancies described we routinely managed women with mechanical heart valves in pregnancy using option (iii). Warfarin would be re-commenced at 14 weeks through to 36 weeks gestation when heparin would be recommenced. The pregnancy outcomes however were unacceptable. It would appear from the series that a warfarin maintenance dose of 4mg or more is associated with adverse pregnancy outcomes. No comparison was possible where lower doses of warfarin were used. It is also our observation that warfarin requirements are increased in pregnancy. Apart from subject A who perpetually required high pre-pregnancy doses of 7 mg all others required dose increments of 40-50%in pregnancy.

The option of heparin through pregnancy, option (i), was offered to these five women in their subsequent pregnancies after the year 2007. All five women (5 pregnancies) on LMWH had livebirths after normal vaginal deliveries. This is encouraging although we do take note that the number is too small to draw conclusions. The doses of LMWH did not increase with advancing gestation. It is of the authors' experience that LMWH produced more reliable and stable anticoagulation responses when compared to UFH in pregnancy.

There were no cases of warfarin embryopathy in babies born in this series despite the majority converted to heparin beyond the 6th week of gestation and of warfarin doses higher than 5 mg per day. There were, however, two early

prenatal loss at 20 and 22 weeks. The 5 babies born after LMWH anticoagulation were normal and healthy at birth.

There were concerns regarding compliance in a report among women opting for heparin leading to deaths[3]. Subjects A-E were taught to self inject and monitored by a dedicated team. Site bruising was sought as a clinical sign of compliance. Excessive bruising led to technique re-appraisal and coagulation profile checks for over anti-coagulation. All were able to self inject regardless of socio-economic background.

There were no significant adverse events in the LMWH pregnancies. A point of note is all but one patient went into spontaneous labour while on therapeutic enoxaparin doses. There were no postpartum hemorrhages or other anticoagulation related complications. Serial echocardiograms per trimester did not pick up pre-clinical valve thrombosis, a criteria for immediate conversion to OA. All women had subdermal implants inserted for contraception at 3 months postpartum. This was performed while on therapeutic doses of warfarin without any complications.

The decision of utilizing LMWH as the heparin of choice drew debate. LMWH, in a large retrospective series in 2000, was associated with a higher maternal mortality rate [1]. It should be noted that the review was conducted at a time when valves were more thrombogenic. It was also not the norm then to achieve target anti-coagulation levels when utilizing LMWH. However authorities persist in cautious and guarded recommendations on the use of LMWH in mechanical heart valve in pregnancy as the argument still lacks robust comparative evidence [1].

The Royal College of Obstetrics and Gynaecology Study Group Consensus on Heart Disease in Pregnancy recommended the following on the use of LMWH in women with mechanical heart valves in pregnancy [4].

1. Enoxaparin as the drug with the most available data.
2. Twice a day dosing as opposed to once daily dosing.
3. The use of low dose aspirin as an adjunct.

Heparin, precisely the LMWH, is a safe option for women with mechanical heart valve in pregnancy. However we still urge caution when opting for LMWH. Strict inclusion and exclusion criteria must be outlined. Care should be multi-disciplinary and consultant led. In short all aspects of care should be optimized to avoid failure of therapy.

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