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Chitsike, Rufaro Saeed

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The Efficacy of Low Molecular Weight Heparin in the Prevention of Thromboembolic Disease in Pregnant patients with Mechanical Prosthetic Heart Valves.



RUFARO SAEED CHITSIKE

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master in Medicine in the branch of Haematology and Molecular Medicine.

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DECLARATION

I, Rufaro Saeed Chitsike, declare that this research report is my own work. It is being submitted as partial fulfilment for the degree of Master of Medicine in the branch of Haematology and Molecular Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at this or any other university.

Signature:

On this 10th day of March 2011.

Dedication

To Jesus.

To my wife, Samukele.

To my son, Tawana.

To my parents, Langford and Inam Chitsike.

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Publication:

- Chitsike RS, Jacobson BF, Manga P, Rhemtula HA, Moodley S, Toweel GD. A Prospective Trial Showing the Safety of Adjusted Dose Enoxaparin for Thromboprophylaxis of Pregnant Women with Mechanical Prosthetic Heart Valves. *Clinical and Applied Thrombosis and Hemostasis* 2010 Jun 13. [epub]

Poster Presentations:

- "Is Dosage Adjustment of Low Molecular Weight Heparin Necessary and Safe for Pregnancies at Greatest Risk of Thrombosis?" at the International Society of Thrombosis and Haemostasis, Boston, July 2009

- "Intrapartum Bridging Therapy in Pregnant Patients at the Highest Risk of Thrombosis" at the International Society of Thrombosis and Hemostasis, Boston, July 2009

- "Is Dosage Adjustment of Low Molecular Weight Heparin Necessary and Safe for Pregnancies at Greatest Risk of Thrombosis?" at the South African Society of Haemostasis and Thrombosis Conference Johannesburg in November 2007;

- "Intrapartum Bridging Therapy in Pregnant Patients at the Highest Risk of Thrombosis" at the South African Society of Haemostasis and Thrombosis Conference Johannesburg in November 2008

Oral presentations:

- "The Safety of LMWH in Pregnancy Complicated by Mechanical Prosthetic Heart Valves" at the Department of Medicine Chris Hani Baragwanath Hospital October 2009
- "The Safety of LMWH in Pregnancy Complicated by Mechanical Prosthetic Heart Valves" at the Department of Medicine Charlotte Maxeke Johannesburg Academic Hospital September 2009
- "Anticoagulation in Pregnant Patients with Mechanical Prosthetic Heart Valves" Department of Obstetrics and Gynaecology September 2008
- "Anticoagulation in Pregnant Patients with Mechanical Prosthetic Heart Valves" at the Department of Haematology and Molecular Medicine Seminar Johannesburg August 2008

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Abstract

Objective: To determine whether dosage adjustment of enoxaparin during pregnancy, in order to maintain a peak anti-Xa of 1.0-1.2 U/ml, is safe for women with mechanical prosthetic heart valves (MPHV).

Methods: This was a prospective observational study performed at Charlotte Maxeke Johannesburg Academic Hospital from 2007 to 2009. 15 women with MPHVs were treated with enoxaparin with dosage adjustment throughout pregnancy to achieve a peak anti-Xa of 1.0-1.2 U/ml. Main outcomes measured were prosthetic valve thrombosis, bleeding and maternal mortality.

Results: There was no maternal mortality. None of the women developed valvular thrombosis during pregnancy. Two women developed epistaxis and another developed spotting per vagina. There was no foetal mortality.

Conclusion: Our data show that enoxaparin may be administered safely during pregnancy to pregnant women with mechanical prosthetic heart valves when there is dosage adjustment throughout pregnancy in order to maintain an anti-Xa of 1.0-1.2 U/ml.

Introduction:

Physiological adaptation to pregnancy is the most rapid and profound change that a woman's body undergoes in her life time. One of the changes that occur is the generation of a state of hypercoagulability. This thrombogenicity is due to a number of reasons, such as changes affecting the coagulation factors, the rate of blood flow and the development of endothelial damage. Levels of coagulation factors such as factors VII, VIII, X and fibrinogen increase as pregnancy progresses, peaking at delivery[1]. Factors II, V and IX remain essentially stable throughout pregnancy. Markers of thrombin (Factor IIa) generation, such as prothrombin fragments 1 and 2, as well as thrombin-antithrombin complexes are also elevated during pregnancy[2]. In addition fibrinolysis is suppressed in the second and third trimesters of pregnancy due to elevated levels of plasminogen activator inhibitor type 1 (PAI-1), which may increase fivefold, and to increased levels of PAI-2 which is produced by the placenta and has peak concentrations produced in the third trimester[2, 3]. Maximal suppression of fibrinolysis occurs 3 hours post delivery[3]. Similarly levels of soluble, active and unbound, protein S decrease as the pregnancy progresses with the lowest levels being recorded an hour post delivery [4]. Other reasons that predispose pregnant women to thrombosis include the reduction in venous flow in pregnancy and the trauma to the endothelium of the pelvic veins which occurs at delivery. The hypercoagulable state begins to revert back to the pre-pregnancy state hours after delivery but only fully returns to normal about six weeks post delivery[3, 4]. Notable physiological changes occurring in other systems in pregnancy include changes in the cardiovascular and genitourinary and systems.

Cardiovascular changes include an enlarged circulatory volume, a rise in the cardiac output and a drop in blood pressure. Circulatory volume changes comprise an increased red cell volume (about 20%) and an increased plasma volume (about 40%). Cardiac output rises in the first trimester as a result of an increased heart rate and stroke volume. The heart rate and stroke volume increase as a compensatory response to a drop in the systemic vascular resistance which in turn is caused by peripheral vasodilation occurring in pregnancy. The heart rate increases by up to 20% in the third trimester, and the stroke volume begins to increase at 8 weeks of gestation, reaching a plateau by 16-20 weeks gestation. The cardiac output rises to 30-50% of non-pregnant values, peaking at the end of the second trimester. Despite the increased cardiac output in the first trimester, the blood pressure still falls due to the low systemic vascular resistance. The blood pressure falls by 10% at the 8th week of gestation and reaches its lowest level at 24 weeks gestation and then rises to normal pre-pregnancy levels by term. The cardiac output increases at the onset of labour then drops rapidly postpartum[5]. In the third stage of labour fluid shifts occur resulting in an increased venous return to the heart. This involves the addition of about 500ml of blood from the uterus into the peripheral circulation, the removal of the compression of the inferior vena cava by the gravid uterus and fluid shifts from the extravascular to the intravascular space. The changes put a strain on the heart but this only results in cardiac decompensation when the cardiac function is already compromised.

Genitourinary system changes include an increase in the renal plasma flow rate at the end of the first trimester resulting in an increased glomerular filtration rate of about 50%. This increased glomerular filtration rate is maintained until the 36th week, dropping down towards pre-pregnancy levels thereafter[6].

The prevalence of rheumatic heart disease (RHD) is significantly higher in developing countries than in developed countries with quoted prevalence rates being 100-200 times greater[7]. The current prevalence of RHD in South Africa is unknown however a survey conducted in Soweto in 1975 showed the prevalence to be 6.9/1000[8]. For this reason RHD is a common underlying cause of cardiac disease in pregnancy in South Africa despite it being a preventable disease. RHD accounted for 63.5% of all recorded maternal cardiac disease at Pretoria Academic Hospital between 2002 and 2005[9]. RHD is a common indication for mitral or aortic valve replacement. Options for valve replacement include either a bioprosthetic valve or a mechanical prosthetic heart valve (MPHV). Bioprosthetic valves, despite having the significant advantage over mechanical prosthetic heart valves of not requiring thromboprophylaxis during pregnancy[10], are not ideal for young females of child bearing age. This is because porcine bioprosthetic valves have been associated with a high rate of structural valvular damage (SVD) with a 10 year survival rate of 50%[10,11]. Pregnancy has been shown to accelerate the rate of SVD with damage occurring in 10-35% of such pregnancies[12,13,14] and reoperation mortality is quoted as 3,8% in one study[15] and 8,7% in another[16]. Furthermore one study, done in a South African population, showed that patients with mechanical prosthetic heart valves are able to cope well with the cardiac demands of pregnancy[17] and other studies have shown these valves to have excellent long term durability[18]. For these reasons mechanical prosthetic heart valves are still in use and are commonly used in young women especially in developing countries. Mechanical prosthetic heart valves are of three main types: the cage-ball valves such as the Starr-Edwards valve, the tilting disc valves, such as the Bjork-Shiley and the Medtronic valves, and the bileaflet valves such as the St Jude's Medical valve. Compared to the bioprosthetic valves however, mechanical

prosthetic heart valves require long term anticoagulation due to their increased thrombogenicity. Greater thrombogenicity is associated with the older generation valves (Starr-Edwards and Bjork-Shiley) compared to the newer generation valves (St Jude's Medical and Medtronic) and with a prosthetic valve in the mitral as opposed to the aortic position[19].

Patients with mechanical prosthetic heart valves who fall pregnant are at an even greater risk of thromboembolic disease. The options available for anticoagulation during pregnancy may however be associated with significant foetal and maternal morbidity and mortality. Risks of treatment include the teratogenicity of the oral anticoagulant warfarin, and the possibility of treatment failure of unfractionated heparin (UFH) and Low Molecular Weight Heparin (LMWH) resulting in maternal valvular thrombosis. Furthermore there is a risk of excessive bleeding with any of the aforementioned options.

When it occurs, prosthetic valve thrombosis may be a fatal complication. Symptoms include (of) acute dyspnoea and chest pain which may often be retrosternal or subscapular and orthopnoea. Typical signs include muffled prosthetic valve heart sounds on auscultation, particularly muffling of the opening snap, or there may be absence of prosthetic valve sounds altogether[20] in the clinical setting of congestive cardiac failure. Clinical features of peripheral arterial thromboembolic disease, such as cerebrovascular accidents and transient ischaemic attacks, may also be a feature of valvular thrombosis. The diagnosis is confirmed by fluoroscopy, and echocardiography which may be either trans-thoracic or ideally trans-oesophageal.

Warfarin therapy throughout pregnancy is believed to be most efficacious in the prevention of the maternal thromboembolic disease for patients with mechanical prosthetic heart valves. Unfortunately evidence has shown that this drug may be associated with foetal morbidity and mortality described in the literature as "warfarin embryopathy"[21]. The incidence of warfarin embryopathy has been shown to be highest between the sixth and twelfth week of gestation[21]. The documented incidence of warfarin embryopathy has been a subject of much debate. Estimates have ranged from as low as 1,6% [22] to 6,4% [23]. A recent authoritative text has however, suggested that such figures probably represent an underestimation given the retrospective nature of the reports and the lack of pathological assessment of the aborted foetuses of most series[24]. This is supported by a prospective study in which reported facial defects suggestive of warfarin embryopathy accounted for 29% of viable offspring[25]. Oral anticoagulants have a molecular weight of approximately 1 000 and readily cross the placenta to the foetus. Therapeutic doses for the mother will unfortunately result in a considerable overdose for the foetus due to the immaturity of foetal liver enzyme systems and the low levels of vitamin K – dependent clotting factors[26]. The features associated with warfarin embryopathy due to warfarin exposure during the 1st trimester include spontaneous abortions, still births, facial abnormalities such as nasal hypoplasia, and chondrodysplasia punctata[23]. Chondrodysplasia punctata is diagnosed by observing epiphyseal calcification on X-rays of the new born, also called epiphyseal stippling. Warfarin blocks the regeneration of reduced vitamin K by inhibiting vitamin K epoxide reductase. Vitamin K is an essential cofactor for post translational carboxylation of glutamic acid residues of osteocalcin and matrix glutamic acid protein, which modulate calcium deposition. This failure of synthesis of osteocalcin and glutamic acid matrix protein results in epiphyseal stippling and nasal hypoplasia[27]. Stippling occurs primarily in the axial skeleton at the proximal

femurs and in the calcanei. This may result in scoliosis[21]. Central nervous system abnormalities and eye abnormalities are also noted and are likely to be due to warfarin exposure in the second and third trimesters[21]. Central nervous system abnormalities include an increased risk of a low intelligence quotient (below 80) with a relative risk quoted as 7.6[28]. Eye abnormalities such as micropthalmia optic atrophy and blindness have been reported[21]. Despite its teratogenic effects, and primarily due to its proven efficacy in prevention of maternal valvular thrombosis, warfarin is still recommended by some authors as one of the options for prophylactic anticoagulation for higher risk pregnancies, such as those pregnant women with a first generation prosthetic heart valve in the mitral position[19]. The high risk of serious foetal abnormalities due to warfarin therapy highlights the need for alternative therapies to be sought for this patient group.

UFH is an alternative therapy in women who elect to avoid treatment with warfarin, especially during the first trimester. However two retrospective surveys conducted in Europe and a prospective study performed in Mexico reported a high incidence of valve thrombosis in pregnant women with old-generation mechanical prosthetic heart valves treated with fixed or adjusted dose subcutaneous UFH[12,29,30]. Although the clinical implications of these findings are questionable[31], owing to lack of information related to the level of anticoagulation and it's monitoring. Unfortunately, the efficacy of adjusted-dose subcutaneous heparin has not been definitively established[32]. The use of the APTT to determine UFH dosing is problematic for these patients for a number of reasons. Inherent limitations in using the APTT include the fact that the manufactured UFH polysaccharide chains consist of varying lengths hence introducing subtle variation between the effects of different vials used for the patient; there is nonspecific binding of UFH to plasma proteins in vivo with large inter-patient variability in the total protein

concentration; the normal range of the APTT is wide introducing a possible bias in the determination of a baseline control value required to adjust the patient's dose of UFH, and the ability of UFH to inactivate both factors IIa and Xa results in a less specific action of UFH[33,34]. These factors may have contributed to a less predictable anticoagulant response resulting in the treatment failures associated with UFH. Additional documented side effects of UFH include the serious complication of heparin induced thrombocytopaenia[35] and osteoporosis. It is estimated that approximately 30% of pregnant women receiving long term UFH therapy will lose 10% of their bone mass and 2% will have symptomatic vertebral fracture[36,37].

LMWHs are glycosaminoglycan molecules which exert their anticoagulant activity by binding to antithrombin and causing a conformational change that greatly enhances the ability of antithrombin to bind to and inhibit the action of the activated coagulation factor X (factor Xa). The LMWHs have generated a significant amount of interest in recent years; the reason for this is twofold. Firstly, the improved pharmacokinetics and side effect profile of the LMWHs compared to UFH and secondly, the potential benefits in pregnancy. LMWHs have been shown to cause less heparin induced thrombocytopaenia than UFH. As LMWH's have a smaller average molecular weight (of about 5 000) in comparison to UFH (average molecular weight of 12 000 to 15 000), LMWH's have a higher specificity for inhibition of activated factor X (factor Xa) via antithrombin, as opposed to the inhibition of activated factor II (factor IIa). Due to the higher molecular weight of UFH there is a greater frequency of sugar chains comprised of at least 13 sugars bound to the specific pentasaccharide sequences required to induce inactivation of factor IIa via antithrombin in comparison to LMWH. In addition a study performed in pregnancy showed that LMWH usage was associated with significantly less osteoporosis when compared to

UFH usage[38]. A study done in 44 pregnant women showed that the bone mineral density measured in the patients who received LMWH was significantly higher than those who received UFH[39]. A number of studies done on LMWH use in pregnancy show that the LMWHs are generally safe when administered for thromboprophylaxis in pregnancy[40]. Because the average molecular weight of LMWH is 5000 it has been shown not to cross the placenta, hence its use in pregnancy is safe for the foetus[41].

LMWH therapy monitoring is achieved by anti factor Xa (anti Xa) monitoring[42]. Two kinds of laboratory test are in use. These are the chromogenic and the clotting based anti Xa assays. Of the two assays consensus guidelines recommend the chromogenic assay for LMWH monitoring[43]. The principle of the chromogenic anti-Xa test is as follows. Factor X is initially activated in vitro by thromboplastin and calcium mediated activation of the coagulation cascade. A colour change is produced when factor Xa (a serine protease enzyme) cleaves a synthetic substrate as one of the products of cleavage emits colour at a particular wavelength. The degree of colour change is measured spectrophometrically using a light sensor. As LMWH inhibits factor-Xa, the degree of colour change is inversely proportional to the activity or concentration of LMWH. Peak anti-Xa activity in vivo, is measured 3-4 hours after subcutaneous LMWH injection and the half life is 12 hours. Routine clinical monitoring of anti Xa levels in general is not recommended. However the indications for routine monitoring include pregnancy complicated by the presence of mechanical prosthetic heart valves. This is because of the physiological hypercoagulable state of pregnancy and the pharmacokinetics of LMWH during pregnancy in addition to the increased thrombogenicity conferred by the prosthetic valve. The clinical applicability of the anti-Xa test is still however a subject of debate. This is because the

correlation between various commercial assays is poor[44]. Secondly a large study randomizing surgical patients to receive prophylactic LMWH or UFH showed that there was no correlation between the anti-Xa level and bleeding and little correlation between the anti-Xa and thrombosis[45]. This study is quoted in an authoritative review on the guidelines for monitoring of LMWH therapy[46].

Cases of valve thrombosis occurred in the absence of anti-Xa monitoring in the unpublished HIP-CAT study[23]. This raised questions regarding the safety of LMWH. Additionally concerns were highlighted about possible teratogenicity of LMWH exposure in pregnancy. This resulted in a "warning" being issued by a LMWH manufacturer regarding the use of LMWH in pregnant women with mechanical prosthetic heart valves[47]. As LMWH does not cross the placenta, it is implausible that it causes foetal morbidity or mortality[37]. Subsequent to the warnings release, a cardiology consensus statement regarding the use of LMWH in pregnancy was issued stating it "should more appropriately be considered an unproven and imperfectly studied alternative among a trio of suboptimal and potentially unfavourable options (warfarin, unfractionated heparin, low molecular weight heparins)" [48]. A number of reviews have stated that there are presently no good data documenting the use of LMWH in pregnant women with mechanical prosthetic heart valves and there have been calls for appropriately designed studies to investigate this therapeutic option. One review concluded that LMWH could be the best option out of the three treatment options available but that all three options have still been understudied[48]. More recently, the earlier warning by the LMWH manufacturer has been rephrased to "use of Lovonox (LMWH) for thromboprophylaxis in pregnant women with mechanical PHV (prosthetic heart valves) has not

been adequately studied"[49]. The 8th American College of Chest Physicians (ACCP) guidelines recommend the use of LMWH at a dose aiming to achieve peak anti-Xa levels of ~1.0 U/ml as one of the treatment options[50].

Bridging therapy refers to a temporary interruption of long term anticoagulation, usually by replacement with another anticoagulant, for a specific procedure such as surgery. Intrapartum bridging therapy, in this context, refers to altering the anticoagulant protocol to allow for safe delivery. As such delivery should be free of bleeding while still providing anticoagulant cover in order to prevent thrombosis. In addition to LMWH, unfractionated heparin (UFH) has also been recommended as a drug for bridging therapy during delivery for this group of women[51]. One of the main advantages of UFH is that can be reversed if necessary by protamine sulphate, whereas the effects of LMWH cannot be easily reversed. However the less predictable pharmacokinetics and pharmacodynamics of UFH noted above consequently result in some less desirable effects of UFH when compared to LMWH.

The use of LMWH in pregnancy may be affected by the specific pharmacokinetic profile in pregnancy. The pharmacokinetics of prophylactic fixed dose LMWH (enoxaparin) in pregnancy and post partum was assessed in a prospective study[52]. It was found that the volume of distribution of LMWH was lower in the post partum period compared to late pregnancy, the maximum concentration of LMWH was significantly higher post partum compared to late pregnancy and the renal clearance of LMWH was significantly decreased after delivery in compared to late pregnancy. The authors suggested that reducing the dose of LMWH may be required post delivery in order to prevent bleeding.

Due to the more predictable effects of LMWH, the indications for its use have continued to grow since its introduction. There are however still no guidelines on the use of LMWH for intrapartum bridging therapy in high risk pregnant women where the anti-Xa has been maintained at 1.0-1.2 U/ml throughout pregnancy. This is due to the paucity of clinical data in this area. Bridging therapy guidelines are however available for non pregnant patients undergoing surgery[53]. These have been applied to pregnant women at delivery but the unique physiology and altered pharmacokinetics of LMWH in pregnancy[52], especially for highly anticoagulated women, may ultimately expose these women to either bleeding or thrombosis. Studies are beginning to show that adjusted high dose LMWH therapy with monitoring may be efficacious for pregnant women at high risk of thrombosis, such as those with mechanical prosthetic heart valves[54]. As such a management protocol for the peripartum period should be designed to protect these maternal patients from both bleeding and thrombosis at this critical time.

In light of the above it was decided to investigate the safety of adjusted dose enoxaparin for thromboprophylaxis of pregnant women with mechanical prosthetic heart valves.

Objective:

To determine whether the use of the LMWH, enoxaparin, is safe for pregnant women with mechanical prosthetic heart valves during pregnancy when used with dosage adjustment in order to maintain a peak anti-Xa of 1.0-1.2 U/ml. Key outcomes measured were prosthetic valve thrombosis, bleeding and maternal mortality.

Materials & Methods:

This was a prospective observational study performed at Charlotte Maxeke Johannesburg Academic Hospital from 2007 to 2009. Our sample consisted of 15 consecutive pregnant women. Most of these women were either attending the anticoagulation clinic at Charlotte Maxeke Johannesburg Academic Hospital or Chris Hani Baragwanath Hospital for monitoring of warfarin therapy efficacy prior to conception.

Inclusion criteria included the following:

- Age between 18 and 49yrs
- Carrier of a mechanical prosthetic heart valve in either the mitral or aortic position (single or double)
- Written informed consent obtained prior to any protocol-specific procedures
- Cardiac assessment where possible to confirm clinical stability
- Ability to administer medication subcutaneously at home
- Normal platelet count for pregnancy (>100x19^9/L)

Exclusion criteria included the following:

- Obstetric indications- namely the anticipated need for delivery in 2 weeks
- Cardiac indications- namely infective endocarditis, very low ejection fraction
- Known thrombophilia or thrombocytopaenia
- Marked elevations of LDH level with clinical evidence of significant haemolysis
- Anaemia (defined by Hb <8g/dL)
- Active gastro-duodenal ulcer

- Patient involved in another clinical trial simultaneously
- Severe hypersensitivity to low molecular weight heparin, warfarin or unfractionated heparin
- Any condition that would make participation in the study impractical or is likely to be associated with non-compliance

Indications for removal of patients from therapy included the following:

- Non-compliance on treatment
- Inability to administer medication at home
- Development of thrombocytopaenia
- Patients who require administration of high molecular weight expanders such as dextran

The following concomitant medications were not administered:

- Any other anticoagulant drug
- Any antiplatelet drug e.g. non steroidal anti-inflammatory drugs, dipyridamole with the exception 75-150mg of aspirin
- Any medication which has interaction with LMWH or may interfere with evaluation of the clinical response (systemic glucocorticoids, ticlopidine, systemic salicylates, acetylsalicylic acid, thrombolytics and anticoagulants)

The experimental protocol observed was as follows. Women were admitted as soon as they discovered they were pregnant or whenever they presented to the hospital during pregnancy. All patients signed written consent to take part in the study.

Baseline information collected form the patients comprised the mother's age, demographics and previous medical history. The duration and type of anticoagulation in regard to the current pregnancy was recorded in addition to other medications being taken. Information pertaining to any previous clotting and bleeding was obtained. The women were asked about the underlying indication for valve replacement and problems relating to the mechanical heart valve since insertion. Patients were assessed in order to determine the New York Heart Association (NYHA) functional cardiac status. A full clinical examination followed including a haematological, cardiac and obstetric assessment. Baseline blood samples were taken for full blood count, differential blood count, renal function, liver function and blood type.

Women were started at a dose of enoxaparin calculated at 1mg/kg twice daily. The dose of enoxaparin was then adjusted to achieve a peak anti-Xa level (three hours post dose) of greater than 1.0 U/ml and less than 1.2 U/ml. The women were taught how to inject themselves in the hospital. A transthoracic echocardiogram was performed to assess baseline cardiac function. Patients were then discharged home where they injected themselves twice a day (12 hourly) with enoxaparin until just prior to delivery.

The women attended the ante-natal clinic weekly where they were asked about any overt bleeding, features of cardiac valve thrombosis such as chest pain and shortness of breath, as well

as symptoms of peripheral thromboembolic disease such as weakness. The mothers had a full clinical examination to assess for any bleeding, cardiac dysrythmias, congestive cardiac failure and neurological features of a cerebrovascular accident. Cardiac auscultation was performed to clinically assess valvular function.

Blood was taken weekly for peak anti Xa levels in a 3.2% sodium citrate tube (dilution 1:10 in whole blood). The blood was then transported directly to the laboratory within an hour of collection form the patient. The anti-Xa level was measured at the NHLS (National Health Laboratory Service) Haematology Coagulation Laboratory at Charlotte Maxeke Johannesburg Academic Hospital. At each visit the dose of enoxaparin given the corresponding anti-Xa level for each patient was recorded. The dose of enoxaparin was adjusted weekly in order to maintain the therapeutic peak anti-Xa level of 1.0-1.2 U/ml for the duration of pregnancy. Anti-Xa values outside the target range would result in an either upwards or downwards adjustment in the dose of enoxaparin by 10mg.

A transthoracic echocardiogram to exclude prosthetic valvular thrombosis was performed monthly. Valvular thrombosis was diagnosed by a suggestive history and clinical examination together with the following: observing a raised mean pressure gradient across the valve by transthoracic echocardiography; in the case of mitral valve thrombosis echocardiography may also detect a raised pulmonary artery pressure and right ventricular dysfunction; fluoroscopy would be performed to confirm valvular outflow obstruction by demonstrating reduced valvular leaflet movement.

All women were delivered while on LMWH therapy. Bleeding complications were noted using the standard bridging protocol for surgical procedures; the bridging regimen was subsequently adjusted to improve hemostasis as detailed below. The bleeding and thrombotic outcomes of the two LMWH bridging therapy regimens were then compared.

LMWH Bridging Regimen 1:

For the first seven consecutive women intrapartum bridging therapy was achieved by stopping the LMWH for at least 24 hours prior to delivery, unless the patient spontaneously went into labour. An intrapartum anti-Xa level was taken where possible, irrespective of mode of delivery. LMWH was restarted 12 hours post delivery. The initial postpartum dose was calculated as half the latest antepartum pre-delivery dose and the full antepartum dose was resumed thereafter. Anti-Xa levels were then monitored postpartum and the LMWH dose adjusted to achieve an Anti-Xa level of 0.8-1.0 U/ml. Bleeding was monitored clinically and by monitoring the patients' hemoglobin levels. Warfarin therapy was started approximately two days post delivery and LMWH was stopped once a therapeutic INR was achieved (2.5-3.5).

LMWH Bridging Regimen 2:

Subsequently for 8 consecutive women intrapartum bridging therapy was achieved initially by stopping the LMWH. Serial anti-Xa level monitoring was then initiated beginning 8-12 hours after the last dose of LMWH. Delivery by Caesarean section or normal vaginal delivery was only allowed to occur when the pre-delivery anti-Xa had dropped to less than 0.5 U/ml (wherever possible), irrespective of the amount of time that had lapsed from the last LMWH dose. LMWH was restarted 12 hours after delivery at half the pre-delivery antepartum dose. This dose was then

adjusted to achieve an anti-Xa level of 0.8-1.0 U/ml. Women were kept on LMWH alone till about 1 week post delivery when warfarin therapy was added if no bleeding was present. Bleeding was monitored clinically and by monitoring the patients' hemoglobin levels. LMWH was stopped once a therapeutic INR was achieved (2.5-3.5).

"Major" bleeding was defined as bleeding resulting in a drop in the haemoglobin concentration by greater than or equal to 2g/dL or as bleeding requiring transfusion of at least two units of packed red blood cells. Bleeding not fulfilling these criteria was defined as "minor".

At birth, the babies had their sex and birth weight recorded. The birth weight was charted to determine the percentile according to gestational age at birth as per Lubchenco et al[55]. The babies were examined by a clinical geneticist or paediatrician to observe for clinical evidence of warfarin embryopathy. A whole body X-ray of the baby was also performed to detect epiphyseal stippling. The presence of typical clinical features or the observation of the radiological findings was defined as warfarin embryopathy.

Maternal patients had a follow up transthoracic echocardiogram done post delivery and were discharged from the study on warfarin once the INR was therapeutic.

Statistical analysis involved obtaining the average anti-Xa levels of all the patients each month and calculating the 95% confidence intervals. The average corresponding dose of enoxaparin required each month was also calculated together with the 95% confidence intervals.

The data was periodically reviewed by a data review and safety committee.

A prospective control arm of pregnant women taking warfarin was not undertaken as we felt it was unethical to purposefully expose foetuses to a drug with known teratogenic potential.

Results:

A total of 18 consecutive women met the inclusion criteria and consented to be part of the study. Two of these women were not included in the write up of this study as they were treated with adjusted dose enoxaparin therapy for two weeks or less before delivery. A further patient was not included in the write up of this study due to insufficient data. Two of these patients did not develop any thrombotic or haemorrhagic complications during enoxaparin exposure in pregnancy. One patient developed haemorrhagic complications postpartum as outlined below. No patient who met the inclusion criteria declined to be part of the study. An additional patient with a mechanical prosthetic heart valve did not meet the inclusion criteria as she was less than 18 years of age.

Table 1 below illustrates baseline information of our patient group.

Table 1: Baseline Information

Patient Number	Mat age (yrs)	Parity	Other Medical Problems	NYHA Class
1	33	Multigravida	Epilepsy	1 to 2
2	18	Primigravida	Nil	1 to 2
3	24	Primigravida	Nil	1 to 2
4	32	Multigravida	Nil	1 to 2
5	20	Multigravida	Nil	1 to 2
6	40	Multigravida	Nil	1 to 2
7	28	Multigravida	Nil	1 to 2
8	22	Multigravida	Nil	1 to 2
9	23	Multigravida	Nil	1 to 2
10	32	Primigravida	Nil	1 to 2
11	27	Multigravida	Nil	1 to 2
12	21	Primigravida	Nil	1 to 2
13	31	Multigravida	HIV	1 to 2
14	23	Primigravida	Nil	1 to 2
15	21	Primigravida	Nil	1 to 2

The average age was 26.3 yrs (median 24 yrs); there were six primigravidas and nine multigravidas. One woman had epilepsy and was being treated with carbamazepine (patient 1); while another patient (patient 13) had HIV infection and was receiving antiretroviral therapy.

Table 2 below shows the indication for valve replacement, the type, size and location of the prosthetic heart valve and the type and duration of anticoagulation given in pregnancy.

Table 2: Indication for and Duration of Anticoagulation

Patient Number	Indication for LMWH	Type of Mechanical Prosthetic Valve	Prior Anticoagulation in Pregnancy	LMWH Duration (Adjusted Dose)
1	Mitral & Aortic MPHV 2° to RHD	MVR 27mm MIRA Edward, AVR 21mm MIRA Aortic	warfarin week 1 – 17	week 18 - 38
2	Mitral MPHV 2° to RHD	29 mm St Jude Medical	warfarin week 1 – 20	week 21 - 38
3	Mitral MPHV 2° to RHD	27mm St Jude Medical	warfarin week 1-4, fixed dose LMWH week 5-20	week 21 - 32
4	Mitral & Aortic MPHV 2° to RHD	MVR 27mm St Jude Medical, AVR 21mm St Jude Medical	warfarin week 1-12, no anticoagulation week 13-27	week 28-38
5	Mitral MPHV 2° to RHD	31mm MIRA	warfarin week 1 – 22	week 23 - 40
6	Mitral & Aortic MPHV 2° to RHD	MVR 27mm St Jude Medical, AVR 21mm St Jude Medical	warfarin week 1 – 23	week 24 - 37
7	Mitral & Aortic MPHV 2° to RHD & Pacemaker	MVR 29mm Mira, AVR 19mm St Judes Regent	no anticoagulation week 1 - 22	week 23 - 39
8	Mitral MPHV 2° to RHD	31mm Silzone St Judes Medical	warfarin week 1-27	week 28-38
9	Mitral MPHV 2° to RHD	29mm Carbomedics Orbis	warfarin week 1 – 10	week 11 – 38
10	Mitral MPHV 2° to RHD	27mm St Jude's Medical	warfarin week 1-5	week 6 - 39
11	Mitral MPHV 2° to RHD	33mm MIRA	warfarin week 1-9	week 10 - 38
12	Mitral & Aortic MPHV 2° to RHD	MVR 27mm Carbomedics Orbis, AVR 21mm Carbomedics	Warfarin week 1 - 5	Week 6 - 38
13	Mitral MPHV 2° to RHD	33mm St Judes Medical	Warfarin week 1-5	Week 6-38
14	Mitral & Aortic MPHV 2° to RHD	MVR 27mm MIRA, AVR 21mm MIRA	Warfarin week 1-5	Week 6-36
15	Mitral MPHV 2° to RHD	29mm Silzone St Judes Medical	Warfarin week 1-4	Week 5 - 38

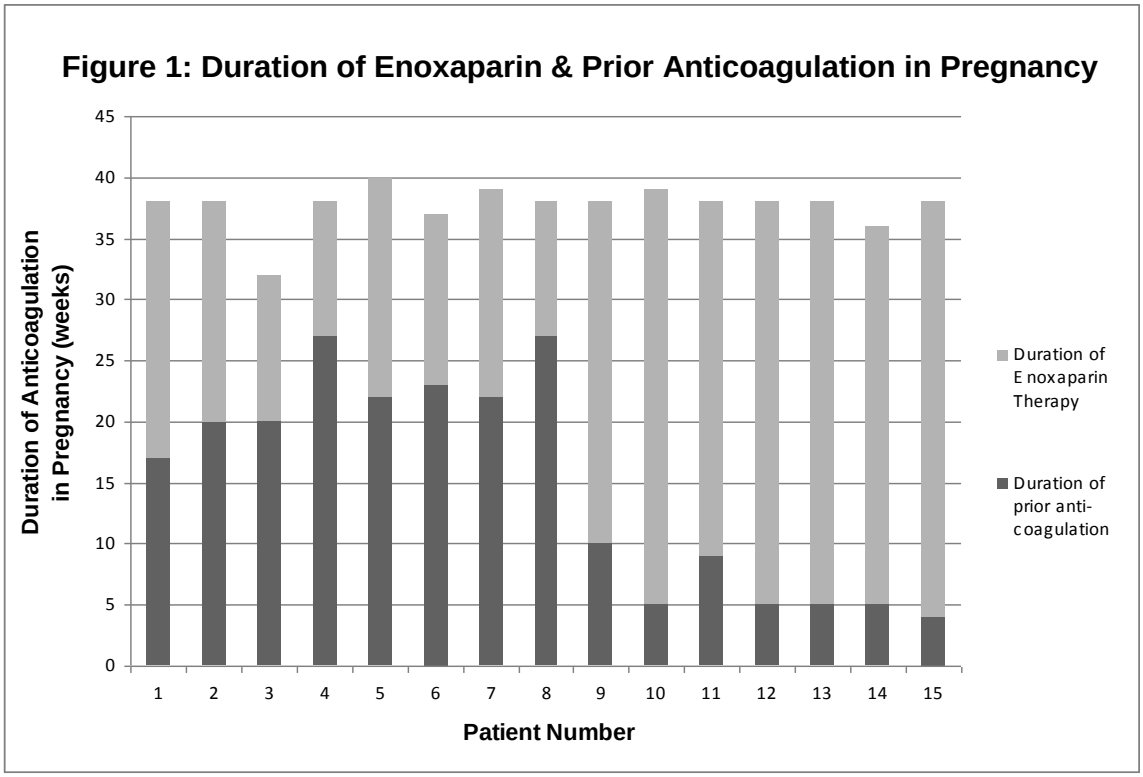
Key- MPHV = Mechanical Prosthetic Heart Valve
RHD = Rheumatic Heart Disease
MVR = Mitral Valve Replacement
AVR = Aortic Valve Replacement

Six of the fifteen women had double prosthetic valves with an aortic MPHV in addition to a mitral MPHV. All the women had bileaflet mechanical prosthetic heart valves (second generation valves).

Patient 4 previously had had one child and then had four previous miscarriages on warfarin therapy. Nine years prior to presentation she fell pregnant for the first time, while not on any anticoagulation and at eight months gestation developed valve thrombosis. She had an emergency valve replacement and caesarean section from which both she and her baby recovered well. Six years later she developed neurological features of thromboembolism (i.e. weakness) while not on any anticoagulation. She recovered from this with no overt long term sequelae. She did however develop a silent myocardial infarction which was discovered on enrolment into our study. Echocardiography revealed an old infarct on the anterior wall of the myocardium with a relatively good ejection fraction of 51%. She had no deterioration in cardiac function during her current pregnancy.

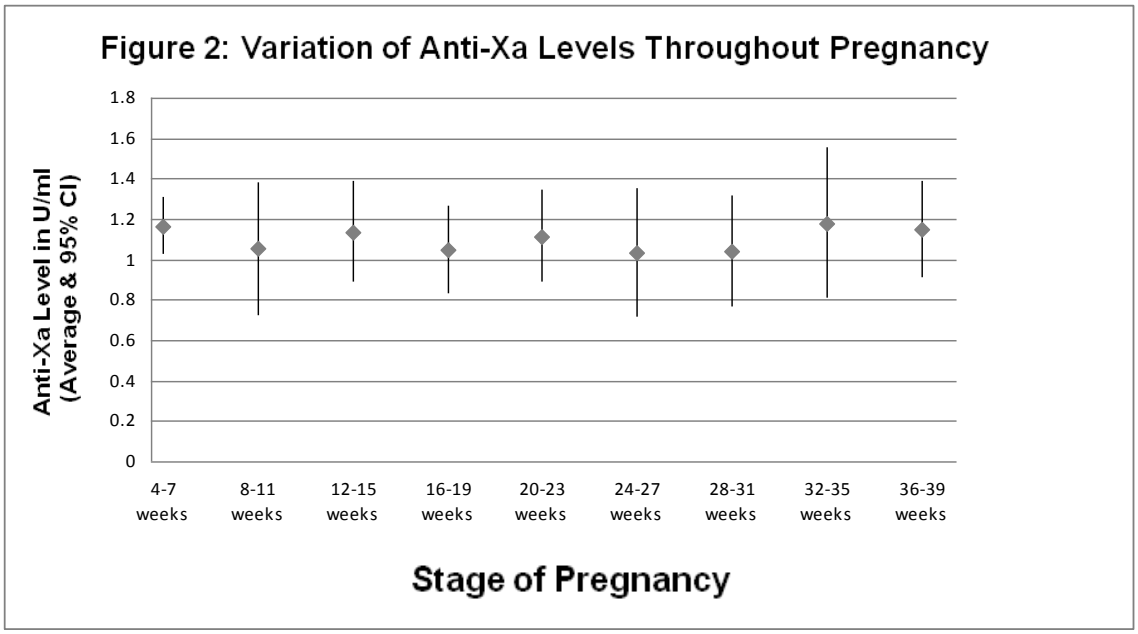
Two women were not on any anticoagulation during pregnancy prior to presentation for 15 weeks (patient four) and 23 weeks (patient seven).

Figure 1 below shows the duration of adjusted dose enoxaparin exposure relative to the duration of prior anticoagulation given in pregnancy.



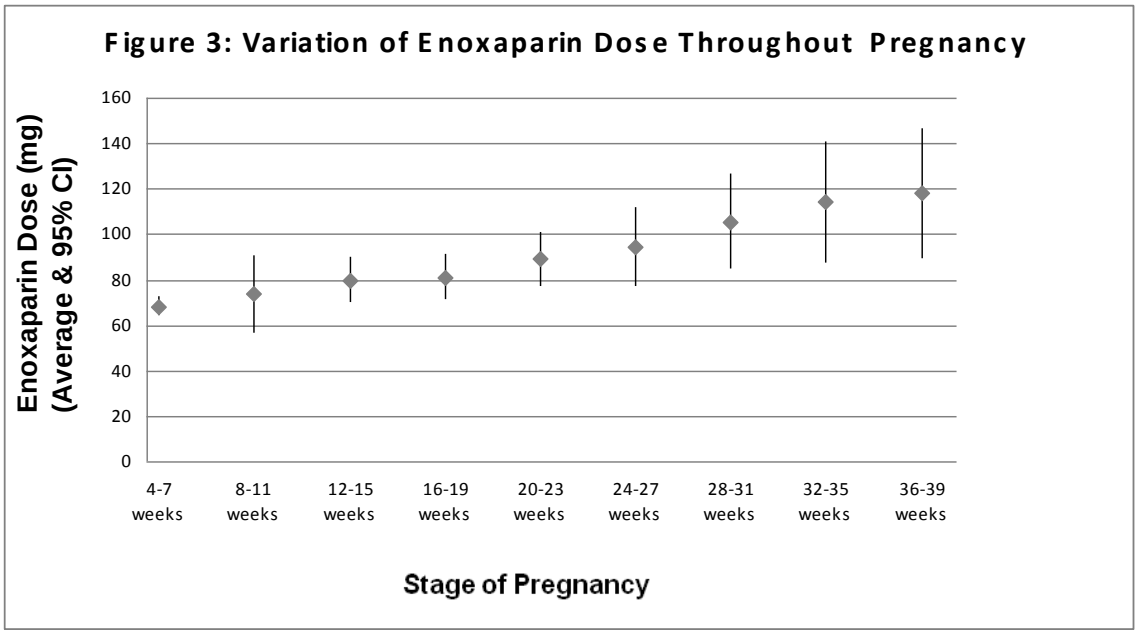
The average time to presentation to our unit and conversion to enoxaparin was 14.7 weeks (median 17 weeks). The total combined period of time that our women were exposed to adjusted dose enoxaparin during pregnancy was 344 weeks.

Figure 2 below shows the average anti-Xa readings recorded throughout pregnancy with the 95% confidence interval.



Maintenance of the average anti-Xa between 1-1.2 U/ml throughout pregnancy was achieved successfully for this patient group. A higher anti-Xa level tended to be recorded as delivery approached.

Figure 3 below shows the average enoxaparin doses in milligrams recorded throughout pregnancy with the 95% confidence interval.



This figure shows that the average dose of enoxaparin rose steadily throughout pregnancy. The total percentage increase in the average dose of enoxaparin given was 72.9%. The highest rate of change was noted just prior to and during the third trimester (after 27 weeks gestation). Of note, the range of the confidence intervals also grew throughout pregnancy, with the largest range recorded for 36-39 weeks.

Table 3 below demonstrates antepartum adverse maternal outcomes. Maternal morbidity was expressed as valve thrombosis, bleeding and cardiac, obstetric or other complications. Maternal mortality is also recorded.

Table 3: Antepartum Maternal Morbidity & Mortality

Patient Number	Maternal Morbidity			Maternal Mortality
	Valve Thrombosis	Bleeding	Cardiac/Obstetric/Other Complications	
1	Nil	1 Episode spotting per vagina	Nil	Nil
2	Nil	Nil	Nil	Nil
3	Nil	Nil	Nil	Nil
4	Nil	Nil	Nil	Nil
5	Nil	Nil	Nil	Nil
6	Nil	Nil	Nil	Nil
7	Nil	Nil	Nil	Nil
8	Nil	Nil	Nil	Nil
9	Nil	Nil	Nil	Nil
10	Nil	Nil	Nil	Nil
11	Nil	Epistaxis	Itchiness at enoxaparin injection site	Nil
12	Nil	Nil	Nil	Nil
13	Nil	Nil	Left Arm Numbness	Nil
14	Nil	Epistaxis	Nil	Nil
15	Nil	Nil	Nil	Nil

None of the women developed prosthetic valve thrombosis during pregnancy and there was no maternal mortality.

Patient 13 developed numbness and tingling of the left arm. This lasted about 6 hours and occurred at 19 weeks of gestation. On further enquiry it was revealed that she had suffered similar events since childhood prior to the insertion of the prosthetic valve. Echocardiography was carried out which revealed a normal functioning valve with no evidence of valvular thrombosis. A normal D-dimer level also confirmed the absence of thrombotic event. Her anti-Xa level at the time was 1.18 U/ml. This episode did not recur during her pregnancy.

Patient 11 had four episodes of epistaxis while on enoxaparin in this pregnancy. She presented with a history of epistaxis since childhood. Each episode of epistaxis in this pregnancy involved the left nostril (this was the same nostril from which she had had a long history of bleeding) and occurred when the ambient temperature was high. The severity of the bleeding varied from a few drops to an episode which required nasal packing with gauze soaked with zinc oxide paste in the casualty department. However the patient did not fulfil the criteria for major bleeding. A peak anti-Xa taken soon after presentation revealed an anti-Xa of 1.35 U/ml, mildly greater than the therapeutic range. She was subsequently treated with saline nasal drops and chloramphenicol ointment and her enoxaparin dose was adjusted downwards to return into the therapeutic range. This patient developed mild itching at the site of enoxaparin injection. This may have represented a mild allergy to the drug. This was treated with a topical antihistamine ointment with some improvement. Patient 15 had no previous history of epistaxis however developed an episode of epistaxis during her pregnancy. The bleeding was defined as minor, however she required nasal packing. A peak anti-Xa revealed a result of 1.79 U/ml at the time of bleeding. Her dose of enoxaparin was reduced in order to achieve the target anti-Xa level. She did not have any further epistaxis during her pregnancy. One woman developed spotting with a few drops of blood passed per vagina (patient 1). No other potential side effects of enoxaparin use were noted such as heparin induced thrombocytopaenia or alopecia and there was no clinical evidence of vertebral osteoporosis, however no bone mineral density studies were performed.

Tables 4 and 5 pertain to the intrapartum and postpartum obstetric outcome. All blood transfusions given are recorded below. No patient developed thrombocytopaenia in either the antepartum or post partum periods.

Table 4: Peripartum Obstetric Outcome LMWH Bridging Therapy Regimen 1

Patient No	Mode of delivery	Predelivery Dose of LMWH (mg, bid)	Intrapartum Anti Xa (U/ml)	Intrapartum Estimated Blood Loss	Postpartum Complications	Maternal Mortality
1	NVD - vacuum assisted & episiotomy	150	1.26	300ml	**major bleed** from episiotomy site	Nil
2	c/section for fetal distress	160	n/a	300ml	**minor bleed** into antecubital fossa post phlebotomy	Nil
3	elective c/section for IUGR & Oligohydramnios	90	0.8	+/-600ml	**minor bleed** from operation incision site	Nil
4	elective c/section for 1 prev c/section	150	0.41	800ml	**major bleed** into uterine broad ligament, hematoma measured +/- 10cm in diameter	Nil
5	NVD - BBA	100	>0.66*	n/a, on arrival bleeding per vagina	**major bleed** into perineum and vaginal wall at laceration site	Nil

Key- MPHV = Mechanical Prosthetic Heart Valve

The average antepartum dose of LMWH just prior to delivery was 130 mg bid. All the women in LMWH Bridging Regimen 1 bled. The average anti-Xa level at the time of delivery was 0.75 U/ml. The average estimated intrapartum blood loss was 500ml. Blood transfusions given are recorded below and no patient developed thrombocytopaenia in either the antepartum or post partum periods.

There were three major bleeds (60%) and two minor bleeds (40%). One patient who presented in the initial phase of the study but was excluded from the overall study, developed hemorrhagic complications postpartum. She was excluded from the study because she was converted to adjusted dose enoxaparin less than 2 weeks prior to delivery due to late presentation. She was a 23 yr old lady, P0 G2, with a mitral mechanical prosthetic heart valve. She had a cesarean section for failed induction. She was on 140mg bid of enoxaparin just prior to delivery and had an intrapartum anti-Xa level of 0.82 U/ml. The estimated blood loss during the cesarean section was 700ml. Haemostasis at the time of performing the Caesarean section was described as easy. She developed a non-fatal major bleed a few hours postpartum. 2.5L of serosanguinous fluid was drained from peritoneum on re-laparotomy 8 hours post delivery. She subsequently recovered after receiving a total of 6 units of pure red blood cells within 1 week.

Patient 5 went into spontaneous labour at home a few hours after having been seen at the clinic in hospital that morning. She had a precipitous labour and was not able to get to the hospital before delivery. On that morning, she visited the clinic, where her peak anti-Xa was 1.0 U/ml. She delivered 12 hours later and a further 12 hours after delivery her anti-Xa was still 0.66 U/ml, suggesting that her anti-Xa at time of delivery was in between these two values at delivery. On

arrival to hospital, she was bleeding from a vaginal laceration which was sutured. Three days after delivery while on LMWH therapy a perineal hematoma became clinically evident at the vaginal laceration site which extended up the posterior vaginal wall. On the day the perineal hematoma was first noted her peak anti-Xa was 1.38 U/ml. This hematoma was incised in theatre after which the patient recovered, however the patient had required 4 units of pure red blood cells.

Patient 4 had an anti-Xa of 0.41 U/ml at time of Caesarean section and showed no evidence of bleeding during the first 24 hours post delivery. However soon after resuming the pre-delivery doses of LMWH therapy, she developed a large hematoma in the broad ligament measuring 10cm in diameter. She required two re-look laparotomies which ended in a subtotal hysterectomy and required a total of 10 units of pure red blood cells, which were given within 1 week, prior to her recovery.

Patient 1 had an intrapartum anti-Xa of 1.26 U/ml. She developed recurrent bleeding from the site of an episiotomy which would occur two days after the addition of warfarin to LMWH therapy, for conversion to oral anticoagulation. The first bleeding episode began four days post delivery. Warfarin therapy would then be withheld and the bleeding would slowly subside, but two days after reintroduction of warfarin therapy the bleeding would resume. In the interim the patient would receive transfusions of pure red blood cells as needed. The timing of the bleeding appeared to coincide with the addition of warfarin therapy while the patient was already over anticoagulated as documented by anti-Xa levels of greater than 1.5U/ml (highest 1.75 U/ml).

INRs done at the time of bleeding were all normal. In total the patient received 16 units of pure red blood cells over a 3 week period before the bleeding subsided.

Table 5: Peripartum Obstetric Outcome LMWH Bridging Regimen 2

Patient No	Mode of delivery	Pre-delivery Dose of LMWH (mg, bid)	Pre-delivery Anti Xa (U/ml)	Intrapartum Estimated Blood Loss	Postpartum Complications	Maternal Mortality
6	NVD	90	0.46	250ml	**Minor Bleed** Passed clot PV during labour	Nil
7	c/section for failed induction	140	0.33	500ml	Nil	Nil
8	c/section for 1 prev c/section	120	0.06	800ml	Nil	Nil
9	c/section for 1 previous c/section	130	0.4	650ml	discovery of valvular pannus	Nil
10	c/section for failed induction	80	0.17	600ml	Nil	Nil
11	NVD with superficial laceration	90	0.3	300ml	Nil	Nil
12	NVD - vacuum assisted with episiotomy	100	0.22	300ml	**Minor Bleed** trace hematuria	Nil
13	c/section failed induction	70	0.17	650ml	Nil	Nil
14	nvd with episiotomy	130	0.11	350ml	**Major Bleed** episiotomy site	Nil
15	NVD	90	0.17	+/- 450ml	Nil	Nil

Key- MPHV = Mechanical Prosthetic Heart Valve

- mg = milligrams
- bid = twice daily
- PV = per vagina

The average antepartum dose of LMWH just prior to delivery was 104 mg bid. The average anti-Xa level prior to delivery was 0.24 U/ml. The estimated average blood at delivery loss was 485ml.

Three of the women in the LMWH Bridging Regimen 2 cohort (12.5%) developed bleeding. One major bleed was recorded in patient 14 who bled from an episiotomy site, this occurred 4 days post delivery. She recorded a drop in her hemoglobin from 13.2g/dL post partum to 10.4g/dL after the bleeding episode and did not require transfusion of pure red blood cells. Two minor bleeds were recorded. Patient 6 accidentally received a prophylactic dose of enoxaparin intrapartum, during prolonged labour, and subsequently passed a clot per vagina with no other clinical sequelae. Patient 12 developed a trace of blood in the urine post delivery, possibly due to a prolonged second stage of labour with foetus pressing on the bladder. The hematuria became microscopic within 24 hours and no further gross hematuria occurred despite continuation of anticoagulation. The microscopic hematuria resolved completely after a few days.

No valvular thromboses were found on final transthoracic echocardiography while on enoxaparin post delivery. Patient 9 developed asymptomatic pannus which was detected post delivery by echocardiography. She subsequently also developed valvular thrombosis on the same valve 4 weeks later, which was associated with significant dyspnoea. This occurred 2 days after the enoxaparin was stopped, despite the patient being therapeutic on warfarin therapy at the time (6 weeks post partum). She had an uneventful valve replacement.

There was no cardiac decompensation noted in either the antepartum or postpartum periods in any of the patients.

Table 6 below outlines the details pertaining to foetal outcome.

Table 6: Foetal Outcome

Patient No	Foetal Sex	Birth Weight	Birth-weight Percentile	Gestational age at birth	Congenital Malformations	Foetal Mortality
1	F	3182g	>10th	38	Nil	Nil
2	F	2590g	>10th	38	Nil	Nil
3	F	1750g	>10th	32	Nil	Nil
4	M	3150g	>10th	38	Nil	Nil
5	M	3450g	>10th	40	Nil	Nil
6	M	2600g	>10th	37	Nil	Nil
7	M	2700g	>10th	39	Nil	Nil
8	F	3060g	>10th	38	Hypoplastic toenails	Nil
9	M	2180g	<10th	38	Small convex toenails	Nil
10	M	3240g	>10th	39	Nil	Nil
11	M	2240g	<10th	38	Multiple Abnormalities*	Nil
12	M	2800g	>10th	38	Nil	Nil
13	F	2700g	>10th	38	Nil	Nil
14	M	2700g	>10th	36	Nil	Nil
15	F	2280g	<10th	38	Nil	Nil

* See text for details

There was no foetal mortality. The average foetal birth weight was 2708g. There were 3 babies born with intrauterine growth retardation (patients 9, 11, 15). The baby born to patient 11 was exposed to warfarin in utero until the 9^{th} week of gestation. He had a slightly flat nasal bridge and had respiratory distress after delivery, mild micrognathia, unusual ears with overfolded helices superiorly but unfolded helices posteriorly, low set and posteriorly rotated ears, diastasis recti, mild brachydactyly of his fingers with convex fingernails, absent 5th toenails with hypoplastic toenails on toes 1 to 4. None of the X-rays done on any of the babies showed any epiphyseal stippling.

Discussion

Pregnancy for a woman with a prosthetic heart valve poses risks to both her and her unborn child. It has appropriately been called a "double jeopardy" situation as these mothers are vulnerable to valve thrombosis due to treatment failure and the foetus may be exposed to potentially teratogenic anticoagulant therapy.

The use of LMWH in these women has been a subject of much controversy. This is because there are numerous cases and case series reporting valve thromboses in pregnant women with mechanical prosthetic heart valves treated with low molecular weight heparin. In the absence of randomized controlled trials, treatment decisions have been based on these anecdotal reports or on reviews of the literature. Two such reviews received acceptance. The first was a review of 81 pregnancies in 75 women with mechanical prosthetic heart valves treated with LMWH during pregnancy done by Oran et al[56]. This study reported an 8.6% rate (7/81) of valve thrombosis and a 12.35% rate (10/81) of thromboembolic complications. 51 of these pregnancies were associated with anti-Xa monitoring, and in only one of these monitored pregnancies was a thromboembolic phenomenon recorded. This nonfatal case of valve thrombosis was associated with a sub therapeutic peak anti-Xa level of 0.62 U/ml at the time (20 weeks gestation). It was however complicated by the fact that the patient had initially presented at 8 weeks pregnant with an atrial clot which had resolved two weeks after starting LMWH at 1mg/kg before the thrombotic reoccurrence[57]. The second review by James et al[58] similarly identified cases of low molecular weight heparin used for thromboprophylaxis for pregnant women with mechanical prosthetic heart valves. Of the 76 cases reviewed, 22% (17/76) were associated with thrombotic events.

Thirteen cases were valve thromboses, of which two were fatal from the HIP-CAT study[23]. The HIP-CAT study was a randomized controlled trial comparing enoxaparin (1mg/kg twice a day) throughout pregnancy to a regime consisting of UFH followed by warfarin. LMWH dosage adjustment was not performed.

It is possible that the rates of valve thrombosis quoted in the reviews above may represent an overestimate, given that cases are more likely to be written up and accepted for publication if a potentially catastrophic event took place. Despite the possible bias, the rates of valve thrombosis quoted are unacceptably high, especially as valve thrombosis in these women is often associated with maternal and foetal mortality. Careful review of the cases of valve thrombosis reported by both studies however indicated a consistent pattern; most, if not all of these cases were associated with an inadequate dose of LMWH, lack of monitoring, or sub therapeutic anti-Xa levels. These reports of valve thrombosis and deaths in the absence of monitoring of anti-Xa levels are a strong indication that monitoring is necessary for a good outcome of these patients. When the subset of patients reported by Oran et al[56] who were not monitored by anti-Xa levels is analysed, 30% (9/30) were associated with thromboembolic complications. Additionally a study done by Barbour et al has demonstrated that based on monitoring of the anti-Xa level, the requirements of LMWH increased during pregnancy in 85% of the women studied[59]. For these reasons, monitoring of anti-Xa levels was performed weekly in our study, and the dose of LMWH was subsequently adjusted in order to maintain the high level of anticoagulation required to keep the anti-Xa at 1.0-1.2 U/ml throughout pregnancy. Our results show that the average peak anti-Xa level was well maintained in the target range throughout pregnancy. Additionally

the confidence intervals appeared relatively well controlled showing that large variations in the anti-Xa levels were not a finding in this study.

Increasing doses of enoxaparin were required for our patients studied. The initial average dose progressively increased by 72% till the highest average dose was recorded at 36-39 weeks. The increased requirements of enoxaparin may be explained by a number of reasons. One possible reason could be that the increasing dosage mirrors the increasing thrombogenicity that occurs during pregnancy due to the documented increase in the concentration of coagulation factors and the suppression of anticoagulation and fibrinolysis[1, 3,4]. Another possibility could be that the rise in the average dose was a reflection of weight gain occurring in pregnancy. This would need to be verified by further studies. Higher confidence intervals of the average dose of enoxaparin were recorded in the final two average readings in the third trimester. This coincided with a higher average anti-Xa level recorded for the same period. These two observations may be explained by the drop in the glomerular filtration rate occurring towards the end of the third trimester. This could have resulted in reduced clearance of enoxaparin during this period hence higher concentrations and a greater predisposition to bleeding. This hypothesis has been proven by a study done by Casele et al[52]. This was a prospective study done to observe the pharmacokinetics of prophylactic fixed dose LMWH (enoxaparin) in early pregnancy (12-15 weeks), later in pregnancy (30-33 weeks) and postpartum. It was found that the renal clearance was significantly lower later in pregnancy compared to earlier in pregnancy and that the concentration of LMWH 12 hours post dose was significantly higher later in pregnancy compared to earlier in pregnancy.

Our data show that appropriate adjusted dose enoxaparin may be efficacious in the prevention of cardiac valve thrombosis in this high risk group of women. A similar finding has been shown by two other studies also performed in maternal patients with mechanical prosthetic heart valves in New Zealand[54], England[60] and Norway[61]. The New Zealand study used adjusted dose enoxaparin therapy to achieve a peak anti-Xa of 0.7-1.2 U/ml at four hours post dose. This was a large study (n=47) which showed a 10.6% rate of valve thrombosis related to enoxaparin therapy. The reasons outlined for valvular thrombosis were sub-therapeutic anti-Xa levels and poor compliance. The English study used adjusted dose dalteparin and enoxaparin in order to achieve a peak anti Xa of 1-1.2 U/ml throughout pregnancy 4 hours post dose. This study showed an 8.3% (1/12) rate of valve thrombosis. The reason stated for this was that the patient had a sub therapeutic anti-Xa level and frequent monitoring of the anti-Xa was not possible. A further complicating factor was that this patient also had an underlying thrombophilic state (heterozygous prothrombin G20210A gene mutation). It is not clear though how often patients had anti-Xa monitoring in this study.

The Norwegian study was a retrospective review of 12 patients with mechanical prosthetic heart valves treated with LMWH throughout pregnancy with dosage adjustment in order to achieve a target peak anti-Xa of 0.7-1.2 U/ml at 3-4 hours post dose (with the exception of the first two patients in whom the target peak anti-Xa was 0.4-0.8 U/ml). Patients were initially monitored fortnightly till a therapeutic anti-Xa was achieved, then monthly thereafter. One patient developed aortic valve thrombosis while another developed thromboembolism in the left leg. The reason given for thrombosis in these patients was a low dose of LMWH (dalteparin). It is not clear what the anti-Xa levels were at the time of thrombosis. A possible reason why the rate of

valvular thrombosis observed in our study was lower than that observed in these studies could be that there was a higher target range for the peak anti-Xa in our study in comparison to the New Zealand and Norwegian studies. This is especially so given the findings of Barbour et al who demonstrated that peak levels between 0.5-1.0U/ml were associated with trough levels of <0.5 U/ml in the great majority of cases[59]. Another possible reason for the lower rate of thromboembolism found in our study could be that more frequent anti-Xa monitoring was performed in our study (weekly as opposed to monthly). Both these factors could have reduced the likelihood of our patients developing sub therapeutic anti-Xa levels and subsequent valve thrombosis. Trough anti-Xa levels were however not measured in our study and there is currently no good data to show how frequently anti-Xa levels should be monitored for this patient group. More frequent antenatal visits may have also helped with patient compliance. The limitations of our study though are that there was no control group and it was not composed of a large sample size. The results of these studies would support the recommendation of the 7th ACCP guidelines[51] in which adjusted dose LMWH is recommended as treatment option for this patient group in order to achieve a peak anti-Xa of 1-1.2 U/ml. This is as no patients developed valvular thrombosis on enoxaparin while the anti-Xa was in this therapeutic range.

A few of our patients were at risk of thromboemboloic disease for inadequate therapy prior to presentation. Patient 3 was on fixed low dose LMWH from the fifth week of gestation till week 20, prior to presentation. This woman had a normal functioning valve when echocardiography was performed at presentation. Patients 4 and 7 were not on any anticoagulation for significant periods of time (15 and 23 weeks respectively). Patient 4 had a long term history of non compliance on warfarin which may have contributed to her decision to stop taking warfarin after

the 12th week of pregnancy. Patient 7 had not received enough education about her condition to understand the necessity of taking anticoagulation. These patients exposed themselves to the risk of developing serious thromboembolic complications. One study showed a 25% risk of developing thromboembolic complications if either no treatment was given or only antiplatelet therapy with aspirin was offered[23]. The compliance of both of these patients however once enrolled on the trial was excellent.

All the women on our study had second generation prosthetic valves. Despite still being high risk, they are at a lower risk than the group of women with older generation prosthetic valves in the mitral position[19]. The 8th ACCP guidelines recommend that these highest risk patients be treated with warfarin throughout pregnancy with replacement by adjusted dose UFH or LMWH closer to delivery[50]. Appropriate studies are therefore required to assess the efficacy of LMWH in pregnant women with first generation prosthetic valves. Due to their greater thrombogenicity however, these first generation prosthetic valves are no longer as commonly used as the second generation prosthetic valves in our centre.

Bleeding post delivery while on LMWH therapy is not a common problem reported in the literature. In one review of 41 pregnancies by Dulitzki et al, no significant bleeding problems were encountered at delivery for women taking prophylactic doses of LMWH or weight based treatment doses of LMWH[62]. This was confirmed by another study which showed that peripartum bleeding complications were not increased in 55 women taking prophylactic or treatment doses of LMWH compared to a matched control group not on any anticoagulation[63]. A possible explanation as to why significant peripartum bleeding was not encountered in the

women described in these studies is that most of these women were not as highly anticoagulated as those requiring maintenance of the anti-Xa between 1.0-1.2 U/ml. One study done in pregnant women with mechanical prosthetic heart valves treated with adjusted dose enoxaparin to achieve an anti-Xa level of 0.7-1.2 U/ml, showed a postpartum bleeding rate of 32%[9]. An issue further compounding the analysis of bleeding complications for patients on LMWH therapy is the controversy surrounding whether there is a correlation between the anti Xa level and clinical outcome. All the women on LMWH Regimen 1 bled around the time of delivery. This may have occurred as a result of a number of reasons, as outlined below.

A few hours post Caesarean section, the 23 yr old patient, excluded from the overall study, was discovered to have a significant bleed into the peritoneal cavity. Haemostasis at time of performing the Caesarean section was however described as easy and the blood loss during the procedure was within expected limits for non-anticoagulated women. This clinical picture of delayed bleeding is in keeping with a coagulation factor deficiency dependent type bleed. This is consistent with the mechanism of action of LMWH namely factor Xa inhibition via antithrombin. Hence the finding of an intrapartum anti-Xa of 0.82 U/ml in a patient who went on to bleed suggests, that for this woman, the anti-Xa was too high for delivery by Caesarean section and she may have fared better if anti-Xa was lower. Furthermore bleeding occurred despite the fact that surgery was performed 30 hours after the last dose of LMWH was administered; hence she was not protected from bleeding by waiting for 24 hours after receiving the last dose of LMWH.

In patient 5 the cause of the perineal hematoma appeared to be twofold. Firstly her anti-Xa may have been too high at time of delivery. Secondly, post delivery she seemed to develop a major bleed which was associated with a high peak anti-Xa of 1.38 U/ml on the day of the bleed. Her subsequent cause of bleeding appeared to be excessive anticoagulation post delivery despite aggressive anti-Xa monitoring and downward dosage adjustment. The same pattern of delayed onset major bleeding a few days post delivery, despite the same intensive monitoring and dose adjustment, was also noted for patient 4. Hence for patients 4 and 5 the resumption of pre-delivery doses of LMWH after delivery seemed to be associated with significant bleeding. Patient 1 however, who delivered vaginally, had no evident bleeding for the first 48hours despite having the highest anti-Xa at time of delivery of 1.26 U/ml. For this woman the timing of the bleeding seemed to coincide with the introduction of warfarin while highly anticoagulated on the enoxaparin.

None of the women in the Regimen 2 group developed major bleeding immediately post partum. Delivery at an average anti-Xa level of 0.75 U/ml in Regimen 1 was associated with a greater risk of developing bleeding immediately post partum. Due to the altered renal and cardiovascular changes in pregnancy, empirically waiting 24 hours from the last LMWH dose before delivery did not protect our women from bleeding. As shown in the Regimen 2 group, allowing the anti-Xa level to guide the time of delivery resulted in a favourable bleeding outcome. The average pre-delivery anti-Xa level found in this group was 0.24 U/ml. Hence attaining an appropriate anti-Xa level prior to delivery may allow for safer delivery of these women.

Upon resumption of pre-delivery doses 24 hours post delivery women had a tendency to bleed. We also found that it was very difficult to attain the target anti-Xa post delivery in the LMWH Bridging Regimen 1 group for about a week after delivery despite daily anti-Xa monitoring and aggressive subsequent dosage adjustment. These bleeding events are however, in keeping with the findings of Casele at al. They found that immediately post delivery the renal clearance of LMWH decreases sharply. This is also associated with a smaller volume of distribution for the drug. The factors combine to create comparatively greater peak concentrations of LMWH post delivery compared to pre-delivery[52]. If the same pre-delivery dose is given postpartum, greater LMWH peak concentrations result in over-anticoagulation followed by an increased propensity to bleed.

The lower rate of bleeding in LMWH Bridging Therapy Regimen 2 is encouraging, however the risk of thrombosis in these women should still be considered. None of the women displayed clinical features of valvular thromboembolic disease in the postpartum period prior to discharge on warfarin with therapeutic INR's. Despite its less predictable pharmacokinetics than LMWH, UFH has been used with success as intrapartum bridging therapy. A prospective trial comparing the use of UFH to an appropriate LMWH regimen for highly anticoagulated pregnancies may be of benefit in finding the safest mode of delivery for these women. When using intravenous UFH for bridging therapy, the practice of stopping this therapy 4-6 hours prior to surgery or immediate reversal with protamine sulphate may be used. On this regime the woman will be protected from bleeding but will not have any thromboprophylactic cover. This is contrasted to delivery on LMWH at an appropriate anti-Xa, possibly 0.5-0.2 U/ml, which would still provide a degree of

thromboprophylaxis until the next LMWH dose. The use of LMWH may thus be especially useful in these women in also protecting against the risk of thrombosis.

For a safe regimen for intrapartum bridging therapy using LMWH for women maintaining an anti-Xa of 1.0-1.2 U/ml the bridging protocol would need to strictly be adhered to, and may include the following aspects: women should be delivered when their anti-Xa is less than 0.5 U/ml as opposed to waiting for a prescribed 24 hour period; post delivery, half the pre-delivery dose should be given and that dose adjusted according to the anti-Xa level with the aim of maintaining a target anti-Xa value of 0.8-1.0 U/ml; warfarin therapy should be delayed for at least a week post delivery. These findings would need to be confirmed by a prospective study with a larger sample size.

Warfarin therapy for pregnant women with MPHVs is efficacious in the prevention of cardiac valve thrombosis with the reported overall maternal mortality reported as 2.9%[23]. In keeping with this, none of the women developed valvular thrombosis while on warfarin therapy. Until a randomized controlled study is done do compare the use of adjusted dose enoxaparin to warfarin it will be difficult to say that enoxaparin is at least as efficacious as warfarin in the prevention of maternal thromboembolic disease in this patient group. A prospective study such as this would be difficult to perform, and probably unethical, given the risk of warfarin embryopathy. Studies are however beginning to show that adjusted dose enoxaparin may have a significant role to play for these patients in both maternal thromboprophylaxis as well as the prevention of foetal morbidity and mortality related to oral anticoagulant use.

Maintenance of the anti-Xa at 1.0-1.2 U/ml throughout pregnancy results in a high degree of anticoagulation, thus a higher theoretical risk of bleeding. Using the anti-Xa as a predictor of bleeding has been disputed by some authors. The large studies that have found no correlation between anti-Xa levels and the risk of bleeding (or thrombosis), were either not based on pregnant patients[45], or actively excluded pregnancy[64]. This is especially so given the changes in the pharmacokinetics of LMWH occurring during pregnancy[52]. The patients in these studies were also either on prophylactic fixed dose LMWH[45] or had a lower target peak anti-Xa (0.3-0.9 U/ml)[64]. Contrastingly, our findings show that the two patients who developed epistaxis did so when their ant-Xa levels were greater than the therapeutic range. One of the two women with epistaxis already had a predisposition to nose bleeding which was exacerbated by the enoxaparin. None of the women in our study developed major bleeding requiring transfusion of as a complication of enoxaparin therapy during their pregnancy. The general lack of bleeding in the antepartum period is a positive finding which further supports the use of enoxaparin in the women studied. However as the use of adjusted dose enoxaparin for pregnancies at high thrombotic risk begins to gain favour, the risk of bleeding during the peripartum period should be highlighted. The clinical utility of the anti-Xa test, especially at high anti-Xa levels of 1-1.2U/ml, requires further investigation in pregnancy.

The overall foetal outcome was relatively good. The baby born to patient 1 had multiple congenital abnormalities. A paediatric geneticist with an interest in warfarin embryopathy examined the baby, and concluded that while the diagnosis of warfarin embryopathy was indeed possible, an underlying genetic abnormality could not be excluded. Interestingly, the mother also had a flat nasal bridge without being exposed to warfarin in utero herself. Two other babies (of

patients 8 and 9) had mild features which have previously been described as being due to intrauterine warfarin exposure. They did not have any other clinical features of warfarin embryopathy. The fact that the average time to presentation at our clinic was at least 2 weeks after the period of embryogenesis is concerning. Possibly, as the use of adjusted dose enoxaparin based on anti-Xa monitoring for this patient group becomes more publicised, this may increase the awareness of this alternative therapy among both physicians and patients. This may result in earlier referrals before the critical sixth week of gestation. Emphasis must be placed on frequent testing for pregnancy and on conversion to enoxaparin no later than upon earliest discovery of pregnancy.

The rate of improvement of the socioeconomic living conditions of the majority of people in developing countries, such as South Africa, is slow. Hence it is unlikely that the prevalence of rheumatic heart disease in such nations will drop significantly in the near future. More female adolescents and adults continue to require valve replacements due to rheumatic heart disease. Showing that enoxaparin may be administered safely to them when pregnant, without posing a significant risk to either mother or baby, would be of value to these patients. It would also serve to support the further use of the more durable mechanical prosthetic heart valves for this group of patients.

Conclusion

Our data show that enoxaparin may be administered safely in pregnant women with mechanical prosthetic heart valves when there is dosage adjustment throughout pregnancy in order to maintain an anti-Xa of 1.0-1.2 U/ml. Women with a significant bleeding tendency from prior to starting anticoagulation should be monitored closely to exclude bleeding as a complication of LMWH therapy.

References

1. Todd ME, Thompson JH, Jr., Bowie EJ, Owen CA, Jr. Changes in blood coagulation during pregnancy. Mayo Clin Proc. 1965; **40**: 370-83.

2. James AH. Pregnancy-associated thrombosis. Hematology Am Soc Hematol Educ Program. 2009: 277-85.

3. Brakman P. The fibrinolytic system in human blood during pregnancy. Am J Obstet Gynecol. 1966; **94**(1): 14-20.

4. Kurasawa G. Reduction in protein S activity during normal pregnancy. Aust N Z J Obstet Gynaecol. 2007; **47**(3): 213-5.

5. Carlin A, Alfirevic Z. Physiological changes of pregnancy and monitoring. Best Pract Res Clin Obstet Gynaecol. 2008; **22**(5): 801-23.

6. Baylis C, Davison J, editors. The urinary system. 3rd ed. Oxford: Blackwell Scientific Press; 1998.

7. Olivier C. Rheumatic fever--is it still a problem? J Antimicrob Chemother. 2000; **45 Suppl**: 13-21.

8. McLaren MJ, Hawkins DM, Koornhof HJ, Bloom KR, Bramwell-Jones DM, Cohen E, et al. Epidemiology of rheumatic heart disease in black shcoolchildren of Soweto, Johannesburg. Br Med J. 1975; **3**(5981): 474-8.

9. Soma-Pillay P, MacDonald AP, Mathivha TM, Bakker JL, Mackintosh MO. Cardiac disease in pregnancy: a 4-year audit at Pretoria Academic Hospital. S Afr Med J. 2008; **98**(7): 553-6.

10. Lee CN, Wu CC, Lin PY, Hsieh FJ, Chen HY. Pregnancy following cardiac prosthetic valve replacement. Obstet Gynecol. 1994; **83**(3): 353-6.

11. Yun KL, Miller DC, Moore KA, Mitchell RS, Oyer PE, Stinson EB, et al. Durability of the Hancock MO bioprosthesis compared with standard aortic valve bioprostheses. Ann Thorac Surg. 1995; **60**(2 Suppl): S221-8.

12. Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. Br Heart J. 1994; **71**(2): 196-201.

13. Sadler L, McCowan L, White H, Stewart A, Bracken M, North R. Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. BJOG. 2000; **107**(2): 245-53.

14. Hung L, Rahimtoola SH. Prosthetic heart valves and pregnancy. Circulation. 2003; **107**(9): 1240-6.

15. Jamieson WR, Miller DC, Akins CW, Munro AI, Glower DD, Moore KA, et al. Pregnancy and bioprostheses: influence on structural valve deterioration. Ann Thorac Surg. 1995; **60**(2 Suppl): S282-6; discussion S7.

16. Badduke BR, Jamieson WR, Miyagishima RT, Munro AI, Gerein AN, MacNab J, et al. Pregnancy and childbearing in a population with biologic valvular prostheses. J Thorac Cardiovasc Surg. 1991; **102**(2): 179-86.

17. Guidozzi F. Pregnancy in patients with prosthetic cardiac valves. S Afr Med J. 1984; **65**(24): 961-3.

18. Remadi JP, Baron O, Roussel C, Bizouarn P, Habasch A, Despins P, et al. Isolated mitral valve replacement with St. Jude medical prosthesis: long-term results: a follow-up of 19 years. Circulation. 2001; **103**(11): 1542-5.

19. Elkayam U, Bitar F. Valvular heart disease and pregnancy: part II: prosthetic valves. J Am Coll Cardiol. 2005; **46**(3): 403-10.

20. Copans H, Lakier JB, Kinsley RH, Colsen PR, Fritz VU, Barlow JB. Thrombosed Bjork-Shiley mitral prostheses. Circulation. 1980; **61**(1): 169-74.

21. Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med. 1980; **68**(1): 122-40.

22. Bonow R, E. B, editors. Valvular heart disease. 7th ed. Philadelphia,: Elsevier 2005.

23. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med. 2000; **160**(2): 191-6.

24. Frewin R, Chisholm M. Anticoagulation of women with prosthetic heart valves during pregnancy. Br J Obstet Gynaecol. 1998; **105**(7): 683-6.

25. Iturbe-Alessio I, Fonseca MC, Mutchinik O, Santos MA, Zajarias A, Salazar E. Risks of anticoagulant therapy in pregnant women with artificial heart valves. N Engl J Med. 1986; **315**(22): 1390-3.

26. Bonnar J, editor. Haemostasis and coagulation disorders in pregnancy. London: Churchill Livingstone; 1994.

27. Chen WW, Chan CS, Lee PK, Wang RY, Wong VC. Pregnancy in patients with prosthetic heart valves: an experience with 45 pregnancies. Q J Med. 1982; **51**(203): 358-65.

28. Wesseling J, Van Driel D, Heymans HS, Rosendaal FR, Geven-Boere LM, Smrkovsky M, et al. Coumarins during pregnancy: long-term effects on growth and development of school-age children. Thromb Haemost. 2001; **85**(4): 609-13.

29. Hanania G, Thomas D, Michel PL, Garbarz E, Age C, Millaire A, et al. [Pregnancy in patients with heart valve prosthesis. A French retrospective cooperative study (155 cases)]. Arch Mal Coeur Vaiss. 1994; **87**(4): 429-37.

30. Salazar E, Izaguirre R, Verdejo J, Mutchinick O. Failure of adjusted doses of subcutaneous heparin to prevent thromboembolic phenomena in pregnant patients with mechanical cardiac valve prostheses. J Am Coll Cardiol. 1996; **27**(7): 1698-703.

31. Elkayam UR. Anticoagulation in pregnant women with prosthetic heart valves: a double jeopardy. J Am Coll Cardiol. 1996; **27**(7): 1704-6.

32. ACC/AHA guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association. Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). J Am Coll Cardiol. 1998; **32**(5): 1486-588.

33. Weitz JI. Low-molecular-weight heparins. N Engl J Med. 1997; **337**(10): 688-98.

34. Heit JA. Low-molecular-weight heparin: biochemistry, pharmacology, and concurrent drug precautions. Reg Anesth Pain Med. 1998; **23**(6 Suppl 2): 135-9.

35. Greer IA. Exploring the role of low-molecular-weight heparins in pregnancy. Semin Thromb Hemost. 2002; **28 Suppl 3**: 25-31.

36. Douketis JD, Ginsberg JS, Burrows RF, Duku EK, Webber CE, Brill-Edwards P. The effects of long-term heparin therapy during pregnancy on bone density. A prospective matched cohort study. Thromb Haemost. 1996; **75**(2): 254-7.

37. Dahlman TC. Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. Am J Obstet Gynecol. 1993; **168**(4): 1265-70.

38. Barbour LA, Kick SD, Steiner JF, LoVerde ME, Heddleston LN, Lear JL, et al. A prospective study of heparin-induced osteoporosis in pregnancy using bone densitometry. Am J Obstet Gynecol. 1994; **170**(3): 862-9.

39. Pettila V, Leinonen P, Markkola A, Hiilesmaa V, Kaaja R. Postpartum bone mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMW heparin. Thromb Haemost. 2002; **87**(2): 182-6.

40. Ensom MH, Stephenson MD. Low-molecular-weight heparins in pregnancy. Pharmacotherapy. 1999; **19**(9): 1013-25.

41. Forestier F, Daffos F, Capella-Pavlovsky M. Low molecular weight heparin (PK 10169) does not cross the placenta during the second trimester of pregnancy study by direct fetal blood sampling under ultrasound. Thromb Res. 1984; **34**(6): 557-60.

42. Ozawa T, Mammen EF. LMW heparin (anti-Xa) assays for clinical monitoring and pharmacokinetic studies on the automated coagulation laboratory (ACL). Thromb Res. 1992; **66**(4): 287-98.

43. Laposata M, Green D, Van Cott EM, Barrowcliffe TW, Goodnight SH, Sosolik RC. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: the clinical use and laboratory monitoring of low-molecular-weight heparin, danaparoid, hirudin and related compounds, and argatroban. Arch Pathol Lab Med. 1998; **122**(9): 799-807.

44. Kitchen S, Iampietro R, Woolley AM, Preston FE. Anti Xa monitoring during treatment with low molecular weight heparin or danaparoid: inter-assay variability. Thromb Haemost. 1999; **82**(4): 1289-93.

45. Leizorovicz A, Bara L, Samama MM, Haugh MC. Factor Xa inhibition: correlation between the plasma levels of anti-Xa activity and occurrence of thrombosis and haemorrhage. Haemostasis. 1993; **23 Suppl 1**: 89-98.

46. Baglin T, Barrowcliffe TW, Cohen A, Greaves M. Guidelines on the use and monitoring of heparin. Br J Haematol. 2006; **133**(1): 19-34.

47. Lovenox injection (package insert). In: Pharmaceuticals A, editor. Bridgewater, NJ 2002.

48. Anticoagulation in Prosthetic Valves and Pregnancy Consensus Report Panel and Scientific Round Table Discussion. Anticoagulation and enox-aparin use in patients with prosthetic heart valves and/or pregnancy. Atlanta: American Health Consultants; 2002.

49. Lovenox Injection (packet insert). In: Pharmaceuticals A, editor. Bridgewater, NJ 2004.

50. Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008; **133**(6 Suppl): 844S-86S.

51. Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004; **126**(3 Suppl): 627S-44S.

52. Casele HL, Laifer SA, Woelkers DA, Venkataramanan R. Changes in the pharmacokinetics of the low-molecular-weight heparin enoxaparin sodium during pregnancy. Am J Obstet Gynecol. 1999; **181**(5 Pt 1): 1113-7.

53. Douketis JD, Berger PB, Dunn AS, Jaffer AK, Spyropoulos AC, Becker RC, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008; **133**(6 Suppl): 299S-339S.

54. McLintock C, McCowan LM, North RA. Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin. BJOG. 2009; **116**(12): 1585-92.

55. Lubchenco LO, Hansman C, Dressler M, Boyd E. Intrauterine growth as estimated from liveborn birth-weight data at 24 to 42 weeks gestation Pediatrics. 1963; **32**: 793-800.

56. Oran B, Lee-Parritz A, Ansell J. Low molecular weight heparin for the prophylaxis of thromboembolism in women with prosthetic mechanical heart valves during pregnancy. Thromb Haemost. 2004; **92**(4): 747-51.

57. Rowan J. Enoxaparin treatment in women with mechanical heart valves during pregnancy. Am J Obstet Gynecol. 2001; **185**(3): 633-7.

58. James AH, Brancazio LR, Gehrig TR, Wang A, Ortel TL. Low-molecular-weight heparin for thromboprophylaxis in pregnant women with mechanical heart valves. J Matern Fetal Neonatal Med. 2006; **19**(9): 543-9.

59. Barbour LA, Oja JL, Schultz LK. A prospective trial that demonstrates that dalteparin requirements increase in pregnancy to maintain therapeutic levels of anticoagulation. Am J Obstet Gynecol. 2004; **191**(3): 1024-9.

60. Quinn J, Von Klemperer K, Brooks R, Peebles D, Walker F, Cohen H. Use of high intensity adjusted dose low molecular weight heparin in women with mechanical heart valves during pregnancy: a single-center experience. Haematologica. 2009; **94**(11): 1608-12.

61. Abildgaard U, Sandset PM, Hammerstrom J, Gjestvang FT, Tveit A. Management of pregnant women with mechanical heart valve prosthesis: thromboprophylaxis with low molecular weight heparin. Thromb Res. 2009; **124**(3): 262-7.

62. Dulitzki M, Pauzner R, Langevitz P, Pras M, Many A, Schiff E. Low-molecular-weight heparin during pregnancy and delivery: preliminary experience with 41 pregnancies. Obstet Gynecol. 1996; **87**(3): 380-3.

63. Kominiarek MA, Angelopoulos SM, Shapiro NL, Studee L, Nutescu EA, Hibbard JU. Low-molecular-weight heparin in pregnancy: peripartum bleeding complications. J Perinatol. 2007; **27**(6): 329-34.

64. Nieuwenhuis HK, Albada J, Banga JD, Sixma JJ. Identification of risk factors for bleeding during treatment of acute venous thromboembolism with heparin or low molecular weight heparin. Blood. 1991; **78**(9): 2337-43.