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Complications of anticoagulation in pregnant women with mechanical heart valves.

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Declaration

I, Catherine Elliott, hereby declare that the work contained in this dissertation is my original work and work by others has been acknowledged as such. This study was carried out whilst a registrar in the Department of Obstetrics and Gynaecology at the University of Cape Town as required for the MMED degree.

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Abstract

Background

Pregnant patients with mechanical heart valves have a significant risk of thromboembolism which may be life threatening and continuous therapeutic anticoagulation is essential. Oral warfarin is the most effective anticoagulant; however, administration during pregnancy is associated with complications to both mother and fetus. Alternatives include low molecular weight heparin or unfractionated heparin. Low molecular weight heparin has a variable efficacy and is associated with life threatening thrombosis formation and unfractionated heparin requires administration via continuous intravenous infusion. The presence of differing opinions on the most effective regime with the least risk to mother and fetus highlights the difficulties confronting obstetricians when anticoagulation is required during pregnancy.

Objectives

Primary aim: 1) To describe the perinatal mortality rate in a group of pregnant women requiring anticoagulation therapy for the treatment of prosthetic heart valves and to compare it to the background rate for the population during the study period. 2) To describe the maternal mortality rate in the study group and to compare it to the background rate for the population during the study period. Secondary aims: To describe the specific fetal, neonatal and maternal complications attributable to the use of anticoagulation therapy in pregnancy and to make recommendations pertaining to counseling of pregnant women with prosthetic heart valves attending Groote Schuur Maternity Unit.

Methods

Cases were recruited from 2004 to 2008. Fifty one pregnancies in forty nine mothers with mechanical heart valves were studied in a retrospective review. Patients followed a standard protocol which applies to all pregnant women with mechanical heart valve prostheses managed at Groote Schuur Hospital.

Results

The perinatal mortality rate was 47.6 and was higher than the background rate of 31.52. There were 2 stillbirths and no neonatal deaths. There were 9 miscarriages with a total pregnancy loss rate of 21%. There were 6 cases of warfarin-associated embryopathy. There was 1 maternal death. The maternal case fatality rate was 1.9%. The maternal complication rate was 19%: 2 cases of valve thrombosis, 1 case of thrombophlebitis, 1 case of infective endocarditis and 3 cases of post partum haemorrhage.

Conclusion

Women with mechanical heart valves require therapeutic anticoagulation. There is a significant risk of a warfarin-associated embryopathy if warfarin is used between weeks 6 to 12 of pregnancy. The risk of fetal loss is greater in patients with mechanical heart valves. Intravenous unfractionated heparin is an effective anticoagulant and offers an alternative to warfarin. The anticoagulant regime adopted in this audit offers the best maternal protection with limited complications. Emphasis must be placed on adequate preconception counseling. Patients should be encouraged to book prior to 6 weeks gestation.

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Introduction

Valvular Heart Disease

Valvular heart disease represents a significant burden within our health care system. This condition remains an obstetric challenge, especially in developing countries such as South Africa. Pregnancy represents a state of physiological thrombophilia and it is therefore assumed that this time period is associated with an increased risk of thrombosis. The treatment of valvular heart disease may have an adverse effect on the pregnancy.

The incidence of cardiac disease among pregnant women is estimated at 1% of the total pregnant population¹. Pre-existing medical conditions constitute one of the five major causes of maternal mortality in South Africa². One of the ten key recommendations made in the document, *Saving Mothers: Fourth Report on Confidential Enquiries into Maternal Deaths in South Africa*, lists the need for protocols on the management of important medical conditions during pregnancy. One such condition is cardiac disease² and valvular heart disease is included in this high risk group.

In developing countries, rheumatic fever is the most common cause of cardiac valve lesions and the incidence of rheumatic heart disease remains high in these resource-poor settings.³ In South Africa the incidence is estimated at 23.5/100000/year and 68% of these patients are female⁴. Sixty three and a half percent of all pregnant women with cardiac disease suffer from rheumatic heart disease¹. Other causes of cardiac valve lesions include congenital abnormalities (9%), infection as in the case of bacterial endocarditis, or occasionally *de novo* in adult life⁵. Long-term complications associated with cardiac valve lesions often result in the need for one or more valve

replacements. Usually a prosthetic (metallic) valve is used.

Patients who have undergone a prosthetic heart valve replacement have a significant risk of thromboembolism which may be life threatening and life-long anticoagulation is essential^{6,7,8,9}. This will reduce the risk of thromboembolism by 75%¹⁰.

The risk of thrombus formation is even greater during pregnancy due to the manifestations of a physiological thrombophilia^{6,7}. This problem is of considerable interest to obstetricians and gynaecologists, as many female patients with replaced mechanical heart valves are of childbearing age, and prosthetic valve replacements complicate 38% of pregnancies¹.

Normal pregnancy maintains a physiological thrombophilia; the endogenous anticoagulant system is less effective and it is therefore assumed that the risk of prosthetic valve thrombosis is increased during this time period. The risk of maternal mortality from thromboembolism in a pregnant patient with a mechanical heart valve is estimated to be between 1 and 4%⁹. Replaced mechanical mitral valves have the greatest risk of thrombosis^{11,12,13}. For pregnant patients with mechanical heart valves anticoagulation is a necessity^{14,15,7}. However, all anticoagulation options available pose high risks to both the mother and fetus.

Patients with bioprosthetic valves have less risk of thrombosis, but a greater risk of decompensation and valve failure, especially during pregnancy. Premature valve failure is a well documented complication in young people with bioprostheses⁷ and it seems that pregnancy can accelerate this process. These valves are considered to be less durable^{14,16} and may only last 10 to 15 years. Generally it is not advised to place a bioprosthetic valve in young women who may plan to conceive. Mechanical valve replacement may be the only alternative and emphasis should be placed strongly on the judicious use of a well-controlled anticoagulant to prevent

thromboembolism of the replaced valve¹³.

Warfarin

Warfarin is a derivative of 4-hydroxycoumarin, and antagonises vitamin K-dependent gamma carboxylation of clotting factors II, VII, IX and X¹⁷. It causes a functional deficiency of Vitamin K¹². Due to its wide range of action it is a highly effective anticoagulant and offers the greatest maternal protection. It is taken as an oral dose and close monitoring is essential. This is achieved with a blood sample, measuring the prothrombin time, which is expressed as the internationalised normalised ratio (INR), and has now been accepted as the standardised method¹⁸. The target INR range in patients with mechanical heart valves is 2.5-3.5⁹. Keeping the INR within the therapeutic range is paramount to its safety and efficacy. If too low, a clot can form and if too high there is the risk of bleeding. It is important to be aware of the fact that when taking an anticoagulant, haemorrhage may still occur even in well-controlled cases, where the INR is less than 3¹⁰. Very few patients have completely stable INR's remaining within the therapeutic target range. Regulation of INR levels is a difficult challenge in non-pregnant patients and pregnancy only serves to exacerbate the problem. The efficacy of warfarin may be further reduced by the ingestion of other drugs, for example erythromycin, fluconazole, fluoxetine, and thyroid hormone as well as some foods rich in vitamin K such as garlic, ginseng and the natural remedy St John's Wart, although it is understood that substantial amounts are needed¹⁹.

Warfarin has a molecular weight of less than 1000 and crosses the placenta²⁰. The immature liver of the fetus cannot counteract the anticoagulant effect. In normal pregnancy the fetal liver has only a fraction (20%) of the adult amount of vitamin K and therefore has reduced vitamin

K-dependent clotting factors¹⁷. Warfarin binds to albumin and only the free fraction produces the anticoagulant effect. Bilirubin competes with warfarin on this albumin-binding site. The fetus has a high concentration of bilirubin and fetal albumin has a higher affinity for fetal bilirubin. More warfarin is therefore unbound and the result is a greater anticoagulant effect²⁰. Whilst the mother is within therapeutic range the fetus is essentially overdosed²¹.

The use of warfarin in pregnancy is associated with an embryopathy, characterised by nasal hypoplasia and epiphyseal stippling²², especially when used within the 6th -12th gestational week⁶. The embryopathy is an abnormality of cartilage formation, related to abnormal calcium deposition. Warfarin disrupts vitamin K regeneration, by inhibiting the enzyme epoxide reductase. Vitamin K is necessary in the synthesis and carboxylation of glutamic acid residues of osteocalcin in the osteoblasts Gla matrix protein^{20, 21}. Osteocalcin is found in embryonic and adult bone and is crucial in the early calcium deposition in bone in the developing embryo. The inhibition of osteocalcin results in chondrohypoplasia punctata (stippling) and nasal hypoplasia^{20, 23,15}. The critical period is thought to be between the 6th - 9th gestational week¹³. If exposure continues into the second and third trimester warfarin use can cause central nervous system abnormalities (thought mostly to be due to haemorrhage) and optic atrophy^{24,9,15,7}. The true incidence of the embryopathy is estimated to be low, less than 5%, (3.4% - 6.4%) and children born with the embryopathy associated with warfarin usage, in fact have low morbidity^{9, 15, 21}.

Additional documented complications associated with warfarin use during pregnancy are those of miscarriage (due to placental haemorrhage²⁴), stillbirth¹¹, preterm delivery and neonatal death (often related to prematurity or intracerebral haemorrhage), resulting in a higher percentage of fetal loss²⁵.

Warfarin may cause bleeding in the fetus and this anticoagulant effect is especially dangerous at the time of delivery when trauma caused by the delivery process may result in intracerebral haemorrhage^{24, 15, 9}. Fetal haemorrhage has been associated with both a vaginal delivery and caesarean section¹⁴. Some studies suggest that caesarean section would decrease this risk²⁴. The risk of bleeding to both mother and baby is greatest at delivery.

The risk of poor fetal outcome as well as the risk of warfarin-associated embryopathy is dose-dependent and 5mg a day or less has a lower risk of damage to the fetus^{22, 11}. Cortufo²⁰ documented poor outcome in 30 of the 70 pregnancies studied, and there were 2 embryopathies in full-term infants. Poor outcome (spontaneous abortion, still birth and embryopathy) was related to a warfarin dosage of more than 5mg per day. Warfarin dosage of less than 5mg per day had a good outcome. Vitale looked retrospectively at the effect of warfarin dosage on the fetus²¹. This audit documented 58 pregnancies requiring warfarin, which was used throughout pregnancy. This study showed a statistically significant relationship between warfarin dosage and fetal complications. As the dose increased so did the risk to the fetus. Included in this, is the risk of fetal loss due to spontaneous abortion (mostly in the first trimester)²¹. The warfarin embryopathies, of which there were two, occurred in babies born to mothers taking 6.5mg daily on one occasion and 7.5mg per day on the other. This view was not supported by a study done by Meschengieser⁶, where the relationship between warfarin dose and poor outcome with or without the embryopathy was not found to be present. This quoted relationship between dose and risk of embryopathy seems to decrease as the gestation increases and the liver of the fetus matures²⁰. The dosage of warfarin does not influence the rate of early pregnancy loss⁶. Warfarin does not anticoagulate the breast-fed infant and can be restarted safely after delivery¹⁵.

Heparin

The teratogenic effect of warfarin may be prevented if this agent is not used in the first trimester between weeks 6 to 12 of pregnancy^{6, 21}. Heparin is made from intestines of mammals and does not cross the placenta^{22, 9, 10, 15}. In an attempt to avoid the fetal complications, heparin has been used as a substitute for warfarin, either throughout pregnancy or only during the first trimester and towards the end of the third trimester. Administration of heparin in the first trimester of pregnancy eliminates the risk of the warfarin embryopathy²¹ and use towards the end of pregnancy reduces the risk of maternal and fetal haemorrhage^{22, 15}, however, bleeding at the uteroplacental bed may still occur¹⁵.

Unfractionated heparin

Unfractionated heparin binds to anti-thrombin III and thus inhibits thrombin and in addition inactivates clotting factor Xa. The anticoagulant effect is measured by the APTT ratio (activated partial thromboplastin time), aiming for 1.5-2.5 x the control at midpoint between doses⁹. Laboratories must be correctly calibrated when calculating the APTT⁷. Heparin may demonstrate a varied anticoagulant effect and also interacts with various proteins (platelet factor 4 and Von Willabrand Factor, which increase in pregnancy). The use of antiXa as a monitoring assay may be more useful. Aim for anti-factor Xa levels of at least 0.3-0.59.

Continuous intravenous unfractionated heparin infusion offers the most consistent level of anticoagulation¹⁴. This regime is inconvenient, as it requires admission to hospital and a prolonged in-patient hospital stay in the first trimester and again at the end of the third trimester⁹. It must be assumed that the effect of warfarin on the fetus can last for up to 10 days after the

warfarin has been discontinued^{8, 11, 24} and therefore it is important to admit the patient as near as possible to 36 weeks gestation and to replace the warfarin with heparin at this point because of the high incidence of preterm labour in patients with prosthetic heart valves¹⁴. If the mother goes into labour whilst still anticoagulated on warfarin she should be given fresh frozen plasma⁸ and Vitamin K, followed by an emergency caesarean section to decrease the risk of intracranial haemorrhage in the neonate. Elective caesarean section at 38 weeks has been considered. This would allow for a brief interruption of warfarin ingestion a few days before the scheduled delivery with no need for IVI heparin infusion^{24, 12}. Unfractionated heparin can be injected subcutaneously, but this regime is associated with a high risk of maternal thrombosis.

Low molecular weight heparin

Low molecular weight heparin (LMWH) is made from unfractionated heparin and also does not cross the placenta. It is administered subcutaneously. It does not bind to antithrombin III, but it does inactivate clotting factor Xa. It offers the potential for a once daily dose due to its longer plasma half life^{15, 9, 14}. LMWH has a better bioavailability and absorption from subcutaneous administration than unfractionated heparin¹⁴ and may offer a more consistent protection⁶. It has been used successfully in pregnant patients in the treatments of coagulopathies such as antiphospholipid syndrome, factor V Leiden mutation and deep vein thrombosis²⁶. LMWH is also associated with a lower rate of spontaneous abortions¹⁴.

However, the fact remains that LMWH has been associated with thrombosis of mechanical heart valves if used for thromboprophylaxis in pregnancy and its use in this situation has not been unequivocally recommended^{22, 9, 11}. There is limited data, but some authors would suggest that LMWH may be a suitable anticoagulant option for pregnant patients with mechanical heart

valves provided treatment is aggressive and along an adjusted-dosage regime^{9,25}. LMWH must be monitored using the anti-Xa levels and dosages adjusted accordingly. This regime of aggressively adjusted dosage of LMWH throughout pregnancy is one of three suggested by the American College of Chest Physicians 2004.

Many authors remain hesitant regarding the efficacy of unfractionated heparin or low molecular weight heparin in preventing thromboembolism and suggest the efficacy is much lower than that of warfarin. It is clear that the efficacy has not yet been fully established^{14, 24, 7, 9}. The concern is that an effective dosage regime and accurate monitoring of the anticoagulant effect during pregnancy remains unclear⁶ and is further complicated by the fact that the pharmacokinetics of heparin are altered in pregnancy. The increased plasma volume and increased renal clearance in pregnancy influence the volume of distribution^{9, 27}. Lower doses of heparin carry the risk of thrombosis and higher doses, the risk of haemorrhage⁷.

Side Effects

The known side effects of heparin include two types of thrombocytopenia. Early onset thrombocytopenia (occurring within 3-5 days) usually resolves spontaneously and may go unnoticed by the patient. Late onset, (after about 6 days) results in a drastic drop in platelet level, marked symptoms and in most cases necessitates the discontinuation of heparin¹². Long-term heparin use is associated with osteoporosis, which is mostly asymptomatic and vertebral fractures occur in approximately 3% of the patient population⁹, while 30% may be left with decreased bone mineral densities¹⁵. Three percent of non-pregnant patients on long-term heparin develop immune IgG-mediated thrombocytopenia¹⁵. LMWH has been associated with less thrombocytopenia and a decreased chance of developing osteoporosis^{28, 21, 15}.

When using heparin, the risk of haemorrhage is always present. In a systematic review by Chan the use of any anticoagulant resulted in bleeding in 2.5% of patients and haemorrhage usually occurred during delivery²⁵. Bates¹⁵ quotes a similar rate: The risk of bleeding is 2.5% during any pregnancy requiring anticoagulation and the risk of bleeding in patients using unfractionated heparin is equivalent at 2%⁹.

It is important to note that there is no benefit to using heparin in the first trimester to prevent early pregnancy loss, as the rate is the same when using heparin or warfarin^{6, 12, 25}. Vitale²¹ found a spontaneous abortion rate of 37.9% on warfarin throughout pregnancy, similar to that quoted by Salazar (37.5%) using subcutaneous heparin²⁴. The miscarriage is thought to be due to placental haemorrhage in the case of both anticoagulants^{24, 6}.

Anticoagulation Regimes

In general, clinicians worldwide are in strong agreement that all patients with mechanical heart valves must be anticoagulated, including during pregnancy. The debate revolves around the choice of anticoagulant and the timing of the prescription. Differing opinions only serve to highlight the difficulties confronting obstetricians when faced with the dilemma of required anticoagulation during pregnancy.

Unfractionated heparin has been used subcutaneously in a number of studies and in most cases carried a high rate of adverse outcome in the mother - thromboembolism being one of the most common and dangerous. The incidence of thromboembolism in pregnant patients with mechanical heart valves using subcutaneous heparin ranges from 5% - 33%^{17, 24, 15, 7}. Frewin¹⁷ suggested a dose of unfractionated heparin of 17500IU - 20000IU 12-hourly to achieve a mid-

interval APTT of 2.0 - 2.55 x the control. The APTT was checked daily until the anticoagulant effect had been established and weekly thereafter. The study done by Salazar²⁴ used a lower dosage of subcutaneous heparin according to a dose-adjusted regime, aiming for an APTT level of 1.5 - 2.5 x the control. During this study there were two maternal deaths due to thromboembolism and the study was prematurely terminated and it was concluded that administration of subcutaneous heparin was not effective in preventing thromboembolism during pregnancy. Oakley⁷ found 13 valve thromboses in 151 pregnancies in patients with mechanical heart valves, 6 of which were fatal, and 10 occurred with the use of subcutaneous heparin administration (2 with warfarin and 1 whilst no anticoagulant was given). Complications were higher in women with mechanical heart valves and mostly in those using heparin. There was no difference in fetal outcome between the patients on heparin throughout pregnancy or those on warfarin throughout pregnancy. However, women taking heparin and then warfarin were more likely to have a healthy baby than those taking either heparin or warfarin throughout. This study concluded that, "heparin was neither effective nor safe for long-term use in pregnancy bringing an increased risk of both thromboembolism and bleeding and a hazard to mother and fetus". Chan agreed: In this systematic review of the literature²⁵ it was reported that when heparin was used in the first trimester the risks of maternal thromboembolism, and therefore death, more than doubled. This large literature review quoted a 3.9% thromboembolism complication rate in women taking warfarin compared to a rate of 9.2% in women taking unfractionated heparin (UFH) in the first trimester followed by warfarin and a massive 33% in women taking UFH throughout pregnancy²⁵. Meschengieser⁶ documented a rate of 4.92% for embolic events in pregnancies where oral anticoagulation was replaced with subcutaneous heparin, compared to 0.33% in pregnancies where the oral anticoagulation was continued throughout pregnancy and

only discontinued 15 days before delivery. Early fetal loss was much the same between the two groups. This study concluded that fixed or adjusted-dosage of subcutaneous heparin was not sufficient to prevent thromboembolism and the protection given was not constant. Mohamed¹³ documented 3 valve thromboses (1 fatal) and 3 instances of uterine haemorrhage in 71 pregnancies in patients requiring anticoagulation. The complications were ascribed to the use of heparin as an anticoagulant. This study concluded that heparin was less effective than oral anticoagulants in preventing thrombosis. Bates¹⁵ suggested a risk of 9.2% for valve thrombosis when using unfractionated heparin from week 6 to 12. The regime least associated with complications was that of warfarin throughout pregnancy. However, to minimize the risk of the warfarin-associated embryopathy, the authors suggest stopping warfarin between 6-12 weeks gestation and close to term and substituting the warfarin for unfractionated or low molecular weight heparin subcutaneously¹⁵.

This view that heparin is not effective as an anticoagulant in pregnant patients was not supported by a small number study published in the Journal of the American College of Cardiology in 1986, where adjusted-dose subcutaneous heparin was used in 18 pregnancies in 16 women with mechanical heart valves. There were no instances of thromboembolism in the mothers and no congenital abnormalities reported in the babies²⁹.

Administering UFH as a continuous intravenous infusion to offer a more consistent anticoagulation has been suggested in a number of trials^{22, 7}. Hung²² suggests substituting IVI unfractionated heparin for warfarin from week 6 to 12 and then again in the last two weeks of pregnancy. Oakley⁷ recommends heparin only be used in the last two weeks of pregnancy while the patient is an in-patient and the heparin is to be administered intravenously.

The use of LMWH has been explored in an attempt to find a regime that is convenient, effective and safe, whilst providing an anticoagulant medication that does not cross the placenta. Yinon²⁷ discusses the option of adjusted doses of subcutaneous LMWH in pregnancy for women with mechanical heart valves. This study looked at 23 pregnancies over a 10-year period. The heparin was administered subcutaneously twice a day. Anti-Xa levels were taken every two weeks, 4 hours post administration and the dose adjusted accordingly. This regime continued until delivery. The authors reported 1 maternal death from a valve thrombus, which developed on a replaced aortic valve. They concluded that warfarin was still considered the best anticoagulant, but suggested adjusted-dose subcutaneous LMWH as an alternative option.

McLintok and North³⁰ agree that warfarin is the safest option in pregnancy for the mother. However, in pursuit of a more acceptable regime, their retrospective audit looked at women using enoxeparin (LMWH). They reported 5 cases of thromboembolism related to enoxeparin (10.6%) and noted that sub-therapeutic anti-Xa levels were a documented problem. There were no cases of thrombosis related to warfarin usage. However there was a much higher rate of fetal loss in the group using warfarin. The authors were happy to recommend enoxeparin together with low dose aspirin as an acceptable treatment regime³⁰.

The discrepancies between centers on management protocols for pregnant patients with mechanical heart valves, highlights the difficulties facing the clinician as he or she takes into account the intricate balance between the risks facing the mother and those affecting the fetus. From a review of the literature it is clear that there is both consensus and concern regarding the embryopathy associated with the administration of warfarin, especially in doses greater than 5mg, during the first trimester. Most clinicians would suggest discontinuing warfarin from week 6 to 12 of pregnancy. In general, most would agree that the use of subcutaneous heparin, even in

the setting of an aggressive, dose-adjusted regime, does not offer sufficient anticoagulant cover to the mother. Admitting the patient for IVI unfractionated heparin administration will offer a more consistent anticoagulant cover as well as allow for close monitoring of the mother and fetus, and would be the ideal choice if it did not require a long in-patient hospital stay and expose the patient to the associated risks of intravenous administration, namely those of thrombophlebitis and infective endocarditis. A question still remains regarding the use of low molecular weight heparin as an anticoagulant in pregnant women with mechanical heart valves.

Pregnancy in a patient with a mechanical heart valve is fraught with danger. Each patient should be fully informed of the risks associated with each anticoagulant available and counseled correctly on the possible maternal and fetal complications. In order to advise patients in our clinical setting we require documented information pertaining to the complication rates associated with the current treatment regime.

Objective

Primary Aim

1. To describe the perinatal mortality rate in a group of pregnant women requiring anticoagulant therapy for the treatment of prosthetic heart valves and to compare it to the background rate for the population during the study period.
2. To describe the maternal mortality rate in the study group and compare it to the background rate for the population during the study period.

Secondary Aim

1. To describe the specific fetal and neonatal complications attributable to the use of anticoagulant therapy in pregnancy.
2. To describe the specific maternal complications attributable to the use of anticoagulant therapy in pregnancy.
3. To make recommendations pertaining to counselling pregnant women with prosthetic heart valves attending the Groote Schuur maternity unit

Methods

Fifty one pregnancies in forty nine mothers with mechanical valve prostheses were studied in a retrospective review.

Ethics approval

The study was approved by the University of Cape Town Ethics Committee.

Participants

Cases were recruited from February 2004 to November 2008.

In the case of the mothers, the patients were identified when they booked their pregnancy at the Groote Schuur Hospital antenatal clinic.

Folders of the mothers and the neonates were reviewed retrospectively.

All of the patients attended the Groote Schuur Hospital antenatal clinic in Cape Town, South Africa. All of the patients had metallic, mechanical valve replacements and because of this were automatically referred to this unit from outlying primary or secondary units once pregnancy was confirmed.

All patients required life-long anticoagulation and all were treated with the coumarin derivative oral anticoagulant known as warfarin. All patients were treated within either the Groote Schuur Hospital Gynaecology Unit or were delivered within the Groote Schuur Hospital Maternity Unit.

The Management Protocol

Antenatal

Patients followed a standard protocol which applies to all pregnant patients with mechanical valve prostheses managed at Groote Schuur Hospital. Once pregnancy was confirmed, the gestational age was calculated using a baseline ultrasound. If the patient attended the clinic (booked the pregnancy) within the first trimester she was admitted to the ward from week 6 until the end of week 12. If the first contact with the clinic was after 6 weeks, but before the end of the 12th week she was admitted immediately. As an inpatient she received intravenous (IVI) unfractionated heparin. This was administered as a continuous rate-controlled infusion, aiming to keep the APTT within the therapeutic range of 1.5 to 2.5 x the control. The APTT was monitored daily via a venous blood sample and the heparin infusion rate adjusted accordingly. If adjustment was required the change was made within one hour of the blood sample and the APTT checked again 6 hours after the adjustment. The cannula was changed every three days to avoid thrombophlebitis. The patient was attended to daily (and more often if necessary) by the registrar in charge of the ward.

At the end of the 12th week, the patient was restarted on warfarin under cover of heparin until the international normalised ratio (INR) was within the therapeutic range of 2.5-3.5. Once this was achieved, the patient was discharged on warfarin, to continue as an outpatient. The INR was checked weekly at a designated clinic. The patient's warfarin dose was adjusted if necessary on the same day.

If the INR was sub-therapeutic at any point during the pregnancy, the patient was again admitted to the ward for intravenous unfractionated heparin infusion until the INR reached a therapeutic level.

All patients who attended the clinic before 22 weeks had a routine 22-week fetal anomaly scan in the Fetal Medicine Unit. This scan routinely screened for fetal anomalies and also specifically documented any evidence of a warfarin-associated embryopathy.

Patients were again admitted to the ward at 36 weeks to receive IVI unfractionated heparin as before. The warfarin was stopped and the APTT monitored as described previously.

Labour and Delivery

Patients awaited spontaneous labour unless there was a clear indication for operative delivery or induction of labour. At the onset of labour, the heparin was stopped immediately, to be restarted no sooner than 6 hours after delivery. Patients delivered in the Labour Ward at the Groote Schuur Hospital Maternity Unit. Indications for delivery by caesarean section were the same as those applied to the general population and included fetal hypoxia (documented as fetal distress), previous caesarean section, failed induction of labour and failure to progress.

IVI antibiotics were given pre and post-delivery to prevent infective endocarditis.

Postnatal Care

The patient was transferred to the High Care area of the Labour Ward for 24 hours for observation. Heparin was restarted 6 hours postpartum as a continuous infusion monitored as previously via the APTT taken as a venous blood sample.

If the patient remained stable she was transferred to the Postnatal Ward and restarted on warfarin under cover of heparin until the INR reached a therapeutic level.

All patients were encouraged to breastfeed unless there was an indication for formula, as in the case of an HIV-positive mother choosing to formula feed.

Folder review

Folders were reviewed on the hospital premises. INR results were obtained from the patients' records or from the computer laboratory system. Data was captured on a spreadsheet.

Recorded Information

Preterm delivery was documented if the baby was delivered before 37 completed weeks gestation.

INR was considered therapeutic if the value was between 2.5 and 3.5.

APTT was considered therapeutic if the value was between 1.5 and 2.5 x the control.

The site of the mechanical valve was recorded but not the type, as in most cases this was not known. The patient's usual dosage of warfarin was recorded as well as the dosage with which they continued in the pregnancy. It was noted if the patient developed a complication or had to be admitted out of the normal routine for INR stabilisation.

Miscarriages were documented if the pregnancy was lost before 28 weeks gestation. Stillbirth was documented if the pregnancy was lost at or after 28 weeks gestation.

A paediatric medical officer examined the neonates routinely. The examining doctor recorded warfarin-associated embryopathy as positive if the baby was noted to have a flat nasal bridge. Any other abnormalities were recorded and noted. The miscarriages were not examined for embryopathy or abnormality, however the stillbirths were examined.

Results

The analysis of the 51 pregnancies in 49 patients revealed the following:

Demographics

Table 1: Demographics

	(n)
<i>Average age (years)</i>	28
<i>Replaced valve: Mitral only</i>	27
<i>Aortic only</i>	6
<i>Aortic and mitral</i>	14
<i>Pulmonary only</i>	1
<i>Mitral Aortic Tricuspid</i>	1
<i>Replacement pre-pregnancy (yrs)</i>	9.8

The ages of the patients ranged from the youngest of 14 years to the oldest of 42 years. The average number of years from the valve replacement to the current pregnancy was 9.4 years, the shortest being 2 years and the longest being 25 years.

The majority of the patients (27) had replaced mitral valves. The type of valve prosthesis used was not recorded, as this information could not be extracted. The average age at which the valve had been replaced was 18 years, the youngest being 5 years of age and the oldest 36 years. The average number of years prior to the pregnancy at which the valve had been replaced was 10 years. The smallest interval between the valve replacement and the current pregnancy was 2 years and the longest interval was 25 years. Only 14 of the 49 patients were in their first pregnancy.

All patients met the criteria for life-long anticoagulant therapy. Warfarin was the therapy of choice and the prescribed medication in all cases. In 14 of the 51 pregnancies patients had discontinued (defaulted) their treatment and were not on warfarin at first antenatal clinic attendance (booking visit). This was noted and the patients were included in the analysis. One patient had a miscarriage at 6 weeks, it was not noted if she was on warfarin at the time of miscarriage.

Table 2: Obstetric data and outcome

<i>Mean gestational age at booking (months)</i>	<i>17.2 (weeks)</i>
<i>Mean gestational age at delivery</i>	<i>32.7(weeks)</i>
<i>Primigravid</i>	<i>14 (n)</i>
<i>Stillbirths</i>	<i>2 (n)</i>
<i>Neonatal deaths</i>	<i>0 (n)</i>
<i>Miscarriages</i>	<i>9 (n)</i>
<i>Embryopathy</i>	<i>6 (n)</i>
<i>Caesarean Sections</i>	<i>17(n)</i>
<i>Normal vaginal deliveries</i>	<i>19(n)</i>
<i>Assisted deliveries</i>	<i>2(n)</i>
<i>Perinatal mortality rate</i>	<i>47.6</i>
<i>Caesarean section rate</i>	<i>33%</i>

Table 3: Indications for caesarean section: CTG= cardiotocograph

Indications for caesarean:	(n)
<i>Pathological CTG</i>	9
<i>Previous caesarean</i>	4
<i>Labour not progressing</i>	2
<i>Failed induction of labour</i>	2

The protocol at Groote Schuur Hospital is to allow for vaginal birth in all patients unless there is a medical indication for operative delivery. The caesarean section rate was 33% in this group of patients.

Outcome

Perinatal mortality rate

(Number of fetal deaths + neonatal deaths) / (live births + Stillbirths) x 1000

$$(2 + 0) / (40 + 2) \times 1000 = 47.6$$

The background perinatal mortality rate for the peninsula maternal and neonatal service = 31.52

Maternal mortality rate

Number of maternal deaths / number of deliveries x 100 000 live births

$1/39000 \times 100\,000 = 2.5$ per 100 000 live births. (39000 births in the peninsula maternal neonatal service)

Maternal Mortality Rate for the peninsula maternal and neonatal service for the time period 2005-2007, is 67.7 per 100 000 live births.

Case fatality rate $1/51 = 1.9\%$

Fetal Complications

Warfarin-associated Embryopathy

There were 6 cases of documented warfarin-associated embryopathy.

Rate of 11.7%

All 6 were identified as nasal hypoplasia. All 6 cases were warfarin-exposed during the first trimester. Five of the 6 patients were taking more than 5mg of warfarin a day and 1 patient was on an unknown dose but had conceived whilst taking warfarin. Four of the 6 cases first attended (booked) at an advanced gestational age, which was too late to be admitted for intravenous heparin (IVI) infusion in the first trimester. One patient (taking 7.5mg daily) booked at 10 weeks, subsequently only receiving unfractionated heparin from 10 weeks to 12 weeks gestation. One patient (taking 7.5mg and 10mg on alternate days), 2 patients (taking 7.5mg and 5mg on alternate days) and 1 patient (taking 7.5mg daily) completely missed the opportunity for first trimester heparin by only booking (first attendance) at 12 weeks, 24 weeks, 15 weeks and 20 weeks respectively. In the case where the exact dosage of warfarin was not known, it was clear that the pregnancy had been conceived whilst the patient was taking warfarin. This patient's first attendance (booking visit) was within the first trimester, at 7 weeks and she was admitted until 12 weeks for heparin administration. Four of the 6 cases were identified on the routine antenatal 22-week fetal anomaly (FA) ultrasound. One of the 6 cases booked at 24 weeks, which was too

late for a detailed FA scan, and 1 baby born with nasal hypoplasia, had a normal FA ultrasound. Only 1 infant with a warfarin-associated embryopathy was referred to the Red Cross War Memorial Children's Hospital for follow up. One was born with bilateral talipes equinus which was not considered to be associated with warfarin ingestion. This patient's sister had two children with the same abnormality. The infant was referred to the orthopaedic clubfoot clinic for bilateral posterior release, which was successful.

Table 4: Indicating the relationship between warfarin dose and the associated embryopathy: T1 = first trimester

Warfarin embryopathy	Dosage of warfarin	Warfarin at conception	Heparin during T1
Nasal hypoplasia	7.5mg	Yes	Yes: weeks 10-12
Nasal hypoplasia	7.5mg	Yes	No
Nasal hypoplasia	7.5mg/10mg	Yes	No
Nasal hypoplasia	5mg/7.5mg	Yes	No
Nasal hypoplasia	Not known	Yes	Yes: weeks 7-12
Nasal hypoplasia	5mg/7.5mg	Yes	No

Of the babies born without signs of the warfarin-associated embryopathy, 21 of the mothers were on more than 5mg of warfarin per day and of these 21, only 6 received heparin in the first trimester.

Detailed patient information: Appendix 1

Neonatal deaths

There were no neonatal deaths

Stillbirths and Early Pregnancy Loss

The total fetal wastage was 21%

Stillbirths

Two pregnancies ended with the delivery of a stillborn infant. One occurred at 28 weeks and one at 34 weeks gestation. One patient with a MVR (mitral valve replacement) had defaulted warfarin for over 10 years. She was on no other medication. She attended the clinic for the first visit at 27 weeks. During the second trimester, she was prescribed 7.5mg daily, but required admission at 31 weeks for a sub-therapeutic INR. She was screened for syphilis as part of the routine antenatal screening tests and was found to have a positive result: (VDRL positive) with a titre 1:16. She had only received 1 bicillin injection and was not fully treated. She went into spontaneous labour at 34 weeks and delivered a macerated stillborn baby. There were no signs of warfarin embryopathy and the placental histology did not reveal any further information.

The second patient delivered a stillborn infant at 28 weeks, with signs of a warfarin-associated embryopathy. Her warfarin dosage was 7.5mg and 10mg on alternate days for mechanical aortic valve prosthesis. Her first attendance at the clinic (booking visit) was at 12 weeks. She continued on warfarin at doses of 7.5mg and 10mg on alternate days. The 22-week scan showed nasal hypoplasia and at 28 weeks an intrauterine fetal demise (IUCD) was diagnosed. She underwent an induction of labour and delivered a 945g stillborn infant with features of a warfarin-associated embryopathy.

Table 5: Stillbirths

Gestation	Warfarin dose	Heparin in T1	Warfarin embryopathy	Cause
28 weeks	7.5mg/10mg	No	Yes	Unknown
34 weeks	Defaulted	No	No	Unknown

Detailed patient information: Appendix II

Miscarriages

There were 9 miscarriages: 17.6% of the total 51 pregnancies.

Six of the 9 occurred in the second trimester and 3 in the first trimester.

Two out of the total 9 patients who miscarried presented with spontaneous vaginal bleeding. Early pregnancy ultrasound identified 6 of the remaining 7 by indicating an absent fetal heart and 1 case was an anembryonic pregnancy. Seven of the 9 miscarriages were warfarin-exposed at the time of the miscarriage. One patient had discontinued (defaulted) her medication. This fetus had an identified anomaly, that of multiple pterigium syndrome. In the case of the other patient, the documentation of her warfarin regime was omitted. It was unclear whether or not she was compliant at the time of the miscarriage at 6 weeks.

Four of the total 9 patients were taking additional medication such as a diuretic, digoxin or an antihypertensive. Two of the 9 patients had additional co-morbidities namely a previous cerebral

vascular accident and there was 1 case of documented Human Immunodeficiency Virus (HIV) (CD4 count of 182). This patient was not on anti-retroviral therapy.

The gestational ages at the first clinic attendance (booking visit) ranged from 6 weeks to 21 weeks with a mean of 14 weeks. Four of the patients booked in the first trimester and 5 in the second trimester.

Five patients were taking more than 5mg of warfarin daily and all 5 conceived whilst taking warfarin. Only 2 of these 5 patients booked the pregnancy at an early enough gestational age to receive IVI heparin during the first trimester. One patient was on exactly 5mg per day and also attended (booked) too late to receive heparin in the first trimester. One patient was on 2.5mg and 5mg on alternate days. This patient had a fetal abnormality (multiple pterigium syndrome) and had discontinued (defaulted) her treatment. Two patients (both first trimester miscarriages) were on an unknown dose of warfarin. One had conceived whilst taking warfarin - the dose was not documented - and she presented at 7 weeks. She was commenced on IVI heparin, but miscarried 6 days later. The other presented for the first time at 6 weeks with an incomplete miscarriage.

Five of the 6 second trimester miscarriages occurred in patients who had booked too late for first trimester heparin administration.

There was 1 documented fetal abnormality (multiple pterigium syndrome). The remaining 8 fetuses were not examined for abnormalities and the cause of the miscarriage was not explored.

Table 6: Number of miscarriages in each trimester

T1	3
T2	6

Figure 1

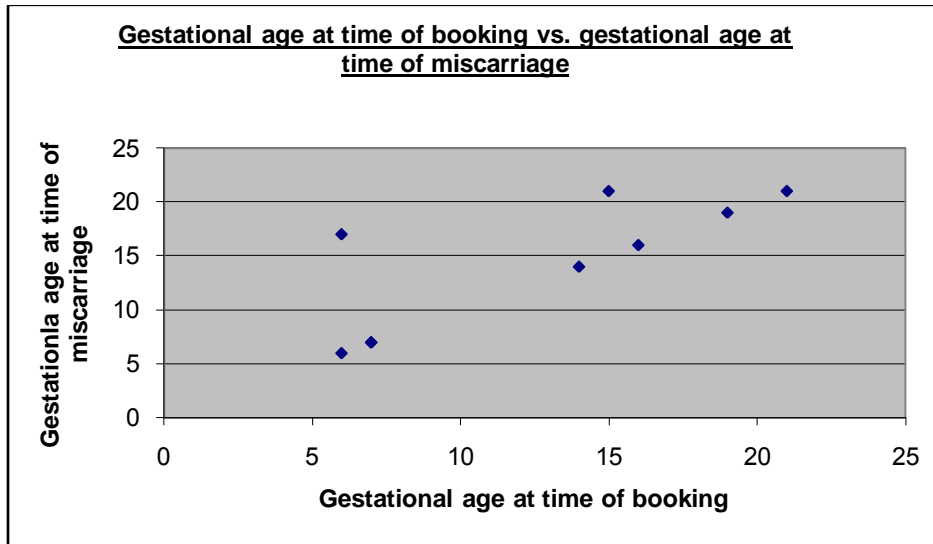


Figure 2

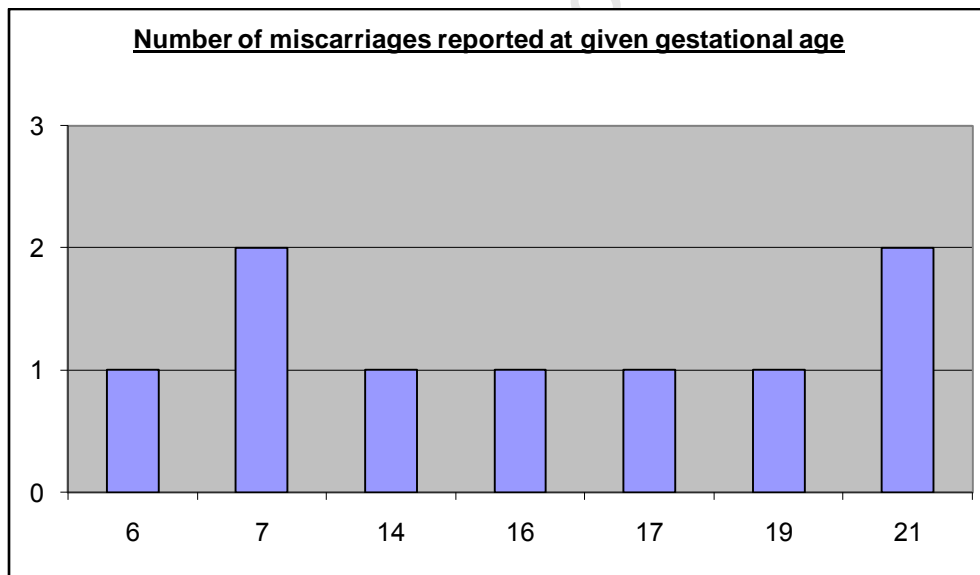


Table 7: Miscarriages:

D=diuretic, dig= digoxin, ACE-I=ace-inhibitor, CVA=cerebral vascular accident, FA=fetal anomaly (in this case multiple pterigium syndrome)

Miscarriage	Warfarin at conception	Gestational age at booking	Heparin in first trimester	Additional factors and medications
6 weeks	Unknown	6 weeks	No	D, ACE-I
7 weeks	Unknown dose	7 weeks	No	ACE-I
7 weeks +6d	5mg/10mg	7 weeks	Yes: from week 7	None
14 weeks	Defaulted	14 weeks	No	FA
16 weeks	5mg	Unbooked	No	D, Dig
17 weeks	10mg	6 weeks	Yes: from week 6 – 12	None
19 weeks	5mg /7.5mg	19 weeks	No	D
21 weeks	7.5mg	21 weeks	No	CVA
21 weeks	5mg/7.5mg	15 weeks	No	HIV CD4=182

Detailed patient information: Appendix III

Preterm delivery

There were four instances of preterm delivery.

Of these 4 cases, one was due to an unrelated cause, that of pre-labour preterm rupture of membranes at 32 weeks, the patient went into spontaneous labour and delivered a 1635g baby. The remaining 3 were due to maternal complications related to the underlying cardiac condition and the cause of the preterm delivery was iatrogenic. These 3 mothers had additional co-morbidities such as atrial fibrillation (2 of the 3) and the development of valve thromboses (2 of the 3). All 3 were on additional medications such as an anti-hypertensive, digoxin, diuretics and β -blockers. All 3 of these patients delivered prematurely due to maternal complications related to the underlying maternal co-morbidity, and all 3 were delivered by emergency caesarean section. One patient delivered at 35 weeks and the baby weighed 1965g, the second delivered a 2115g baby at 32 weeks, and the third delivered a 2145g baby at 34 weeks.

Table 8: Gestational age, precipitating factor and infant weight in preterm deliveries in patients taking Warfarin in pregnancy:

PPROM= pre-labour preterm rupture of membranes. MVR= mitral valve replacement.

AVR = aortic valve replacement. AF= atrial fibrillation.

Gestational age	Precipitating factor	Valve replaced / Additional complications	Warfarin dose	Infant weight
32 weeks	PPROM	MVR	10mg Mon-Sat 15mg Sun	1635g
35 weeks	Maternal valve thrombosis	AVR MVR	5mg	1965g
32 weeks	Maternal valve thrombosis	MVR AF	5mg /7.5mg alternate days	2115g
34 weeks	Worsening maternal condition	AVR MVR AF	Defaulted, then 5mg/7.5mg alternate days	2145g

Detailed patient information: Appendix IV

Additional fetal complications

Two babies were considered to be growth restricted, which equated to 5% of the total live births.

Both were delivered by emergency caesarean section after an attempted induction of labour. The first at 37 weeks, the infant weighed 2390g, and the second at 38 weeks and the infant weighed 2435g. Both fetuses were warfarin–exposed in the first trimester, although the first patient attended at 8 weeks and had the benefit of 4 weeks of intravenous heparin infusion during the first trimester. Both babies progressed well and were discharged to the mother on day 2 and 8 respectively.

One neonate developed a cephalohaematoma. The most likely cause of this complication was the assisted vacuum delivery. This patient had a MVR and was on a warfarin dose of 5mg and 7.5mg on alternate days. She was fully heparinised for 4 weeks prior to delivery; from 36 weeks to 40 weeks, when she went into spontaneous labour. A 2580g baby was delivered by vacuum extraction and sustained a cephalohaematoma. The infant progressed well and was discharged from the nursery to the mother on day 1.

Detailed patient information: Appendix V

Maternal Complications

The maternal complication rate was 13%.

Maternal Death

There was 1 maternal death. This is a case fatality rate of 1.9%.

This patient had a MVR. She was carrying a twin pregnancy. She was taking warfarin in doses of 5mg and 7.5mg on alternating days, having conceived on warfarin. She was also taking a diuretic. She booked at 9 weeks, and was admitted for continuous unfractionated heparin infusion until the end of the first trimester. She was discharged on 5mg warfarin daily at 12 weeks. She died at 14 weeks gestation. She was an outpatient at the time of death. No post mortem was requested and the cause of death is unknown.

Valve Thrombosis

There were 2 cases of maternal valve thrombosis: which equates to 3.9 % of the total 51 pregnancies.

Both cases occurred in patients with mitral valve prostheses. One patient had a metallic mitral valve prosthesis and the other had a metallic aortic and mitral valve replacement, as well as a fistula between the aorta and right atrium. Valve thromboses occurred in both patients whilst on warfarin at 35 weeks and 32 weeks respectively. Both had therapeutic anticoagulation levels. The valve thromboses occurred close to the time of delivery. Both delivered by emergency caesarean section (the indications for operative delivery were fetal distress and maternal

pulmonary edema). Both patients survived and one went on to have an emergency valve replacement 3 days postpartum.

Thrombophlebitis

There was 1 case of thrombophlebitis: which equates to 1.9% of the total 51 pregnancies.

This occurred whilst the patient was receiving continuous intravenous unfractionated heparin infusion. She had a total of 30 days of IVI heparin. She went into spontaneous labour at term and delivered a 2870g healthy baby. The patient recovered well and was discharged 9 days post partum.

Infective Endocarditis

There was 1 case of infective endocarditis: which equates to 1.9% of the total 51 pregnancies.

This patient was 28 years old. She had conceived on warfarin and was admitted during the first trimester until 12 weeks for IVI heparin. She had a total of 38 days in the first trimester on IVI heparin and was discharged on warfarin 5mg and 7.5mg on alternating days. She was admitted at 37 weeks for IVI heparin and had a total of 28 days of IVI administration. She developed an endocarditis, with no associated thrombophlebitis, but did have a documented lower urinary tract infection. She went into spontaneous labour at term and delivered a 3450g baby by caesarean section for fetal distress. Baby and mother were discharged 8 days post delivery.

Postpartum Haemorrhage

There were 3 cases of postpartum haemorrhage: which equates to 5.8% of the total 51 pregnancies. Two of the 3 cases were patients who had delivered vaginally and 1 case was after a delivery by caesarean section. All 3 patients were on heparin at the time.

Detailed patient information: Appendix VI

Table 9: Summary: Outcome

<i>Caesarean section</i>	<i>17</i>	<i>33%</i>
<i>Preterm Delivery</i>	<i>4</i>	<i>7.8%</i>
<i>Warfarin associated embryopathy</i>	<i>6</i>	<i>11.7%</i>
<i>Neonatal death</i>	<i>0</i>	<i>0%</i>
<i>Perinatal mortality</i>	<i>2</i>	<i>47.6</i>
<i>Miscarriages</i>	<i>9</i>	<i>17.6%</i>
<i>Growth restriction</i>	<i>2</i>	<i>5%</i>
<i>Maternal Death</i>	<i>1</i>	<i>2%</i>
<i>Valve thrombus</i>	<i>2</i>	<i>4%</i>
<i>Endocarditis</i>	<i>1</i>	<i>2%</i>
<i>Thrombophlebitis</i>	<i>1</i>	<i>2%</i>
<i>Post partum haemorrhage</i>	<i>3</i>	<i>5.8%</i>

Additional co-morbidities documented in the 51 pregnancies are listed in Table 10 and include immune thrombocytopenia pupura (1 patient), previous cerebral vascular accidents (2 patients),

epilepsy (1 patient), and HIV infection (4 patients). One patient had undergone an embolectomy previously and 3 had undergone repeat valve replacements prior to the current pregnancy. Three patients were in chronic atrial fibrillation (AF). Of these 3 patients; 1 had an uncomplicated pregnancy and went into spontaneous labour at term. She delivered by caesarean section for fetal distress and not for a maternal indication. The other 2 patients developed complications related to the underlying maternal condition. One booked late at 23 weeks, having defaulted treatment for 6 months. She was admitted at 32 weeks in fast AF and was induced at 34 weeks. She had a caesarean section for fetal distress. Fast (uncontrolled) AF, congestive cardiac failure and sepsis complicated the post partum period.

Thirteen patients were on diuretics, 6 on an antihypertensive, 2 patients were on a β -blocker and 2 on digoxin.

Table 10: Additional co-morbidities

<i>ITP</i>	<i>1</i>
<i>CVA previously</i>	<i>2</i>
<i>Epilepsy</i>	<i>1</i>
<i>HIV</i>	<i>4</i>
<i>Embolectomy previously</i>	<i>1</i>
<i>Redo valve replacements</i>	<i>3</i>
<i>AF</i>	<i>3</i>

Table 11: Additional medication

<i>Diuretics</i>	13
<i>Anti-hypertensive</i>	6
<i>B blockers</i>	2
<i>Digoxin</i>	2

Of the 51 pregnancies, 36 patients were on warfarin at their first clinic visit (booking visit). The deduction made from this information was that they had conceived whilst taking warfarin. In 1 case it had not been recorded if the patient was taking warfarin at the time of her first presentation. This patient had a miscarriage at 6 weeks; her first recorded INR was not therapeutic. Of the 36 patients on warfarin at booking, 13 of them booked early enough (i.e. before 12 weeks) to be admitted within the first trimester for unfractionated heparin infusion to avoid the warfarin-associated embryopathy.

No miscarriages occurred during the period when the patient was receiving IVI unfractionated heparin.

Fourteen of the total of 51 were not compliant and were not taking warfarin at first clinic attendance (booking). One patient had defaulted for 4 months and 1 patient for more than 10 years. There were no miscarriages or stillbirths in this group.

Thirty seven of the 51 patients were not admitted within the first trimester for heparin. Of these 37, 23 were taking warfarin at booking but booked after 12 weeks and were too late to be admitted for heparin infusion. One patient had a miscarriage at 6 weeks and was not counted in

this group. Fourteen patients were not on warfarin at booking and not admitted during the first trimester as they booked too late (after 12 weeks).

Of the 37 patients who were not admitted for first trimester heparin administration, all booked too late to receive intravenous heparin (i.e. after 12 weeks) except for the patient who presented and miscarried at 6 weeks. Of these 37, 2 pregnancies ended in second trimester miscarriages, and there was 1 termination of pregnancy at 17 weeks for medical reasons, which has been documented as a miscarriage.

All of the patients, bar 2, were prescribed warfarin during the second trimester. One patient booked very late at 36 weeks and was admitted immediately for IVI heparin. One patient was lost to follow up during the second trimester. She went into spontaneous labour at term and delivered in the unit.

Discussion

Pregnant women with mechanical heart valves have a significant risk of both thromboembolism and cardiac decompensation during pregnancy. Effective and safe management throughout the pregnancy requires careful consideration of the effects of treatment on both the mother and fetus. This consideration should be applied to the choice of anticoagulant prescribed during the pregnancy.

The number of patients included in this audit is comparable to current literature relating to anticoagulation therapy in pregnant patients with mechanical valves. There was a wide range of ages in this group of patients and only 14 were primigravid patients indicating that women may choose to conceive more than once within their lifetime even with the high risk nature of their underlying cardiac condition. The average age of the valve replacement surgery was 18 years, near the beginning of the reproductive period. This emphasizes the need for a multidisciplinary approach in the management of these patients involving cardiologists, obstetricians and anaesthetists^{28, 11} as well as effective and timeous preconception counseling.

All patients in this group met the criteria for life long anticoagulant therapy. Warfarin was the therapy of choice and the prescribed medication in all cases. Warfarin remains the anticoagulant of choice as it has the widest range of action by antagonizing clotting factors II, VII, IX and X. Normal haemostasis is achieved through the clotting system, which is a cascade of reactions in which coagulation factors activate each other. Clotting factor X is central to the common pathway, whilst clotting factors II, VII and IX are activated in the preceding pathways. Tissue

factor (factor III) initiates haemostasis by forming an active complex with factor VII. This complex may then directly activate factor X or follow the route via activated factors XII, XI and IX to activate factor X. The final part of the cascade is a common pathway in which activated factor Xa together with factor V convert prothrombin to thrombin. Thrombin activates factor XIII (cleaving fibrinogen to fibrin), which stabilizes the fibrin threads to form a clot. Platelets aggregate and adhere to the clot^{10, 33}.

If unchecked the clotting system would continue to build clot on top of clot. Thrombin has two positive feedback mechanisms. It activates factors V, VII and XIII as well as activating platelets, reinforcing their aggregation. To regulate the coagulation cascade and to prevent continued clot formation there is an endogenous anticoagulant system. Firstly, thrombin itself is regulated by fibrin, which has the ability to absorb and inactivate up to 90% of the thrombin formed. Secondly, there is endogenous heparin cofactor II and antithrombin to which thrombin binds and is subsequently inactivated. The third mechanism to control clot formation is proteins C and S. Thrombin binds to thrombomodulin and thus activates protein C, which binds to protein S and inactivates factors VIIIa and Va. Fourthly, plasmin (cleaved from plasminogen by tissue type plasminogen activator, tPA) breaks down fibrin. tPA is in itself inactivated by PAI-1 and PAI-2, produced by the placenta and the decidua.^{10, 33}

Normal pregnancy maintains a physiological thrombophilia. The endogenous anticoagulant mechanism is less effective and there is an increased concentration of clotting factors VII, VIII, IX and X. There is also an increase in fibrinogen and prothrombin (resulting in an increase in thrombin) as well as a decrease in the level of protein S and resistance to protein C. Platelet consumption is quicker and clot breakdown less efficient, due to the production of PAI-1 and PAI-2 by the placenta and decidua. Virchow's triad (stasis, hypercoagulability and vascular

trauma) all exist as normal physiology in pregnancy and these physiological changes lead to an even greater risk of thromboembolism^{6, 9, 28, 7, 10}. For patients with mechanical prosthetic heart valves pregnancy represents a period of extreme risk and anticoagulation is essential. All patients recruited in this audit required life-long anticoagulation therapy including for the duration of pregnancy. The anticoagulant of choice is warfarin, which is substituted by unfractionated intravenous heparin from week 6 to 12 and from week 36 to delivery. This substitution is done in an attempt to limit complications in the fetus, namely miscarriage, stillbirth, warfarin-associated embryopathy, and intracerebral haemorrhage during delivery.

In addition to these changes in the clotting system there are also changes within the cardiovascular system during normal pregnancy, namely adjustments to the blood volume, cardiac output and peripheral vascular resistance. These necessary adjustments are important to note as they may lead to decompensation during pregnancy even in patients who have previously tolerated the heart lesion well²⁸.

The physiological changes in pregnancy result in an increased cardiac output (mainly due to increased blood volume) and decreased peripheral vascular resistance. There is a 50% increase in blood volume, which begins in the first trimester and peaks at 20-24 weeks^{16, 28}. The increase in pulse rate and stroke volume lead to an increase in cardiac output of 40%, peaking in the 25th week of pregnancy. Labour leads to an increase in cardiac output of 15% in the first stage and 50% during the second stage. As the uterus contracts, blood shifts from the myometrium into the general circulation. This is called auto-transfusion¹¹. Postpartum, the patient remains at risk of decompensation as the cardiac output increases by 60-80% due to the blood shift from the empty uterus and placental bed into the general circulation and the relief of pressure on the inferior vena cava which occurs once the baby is delivered. The changes in blood volume, pulse

rate and cardiac output that occur in normal pregnancy may lead to congestive cardiac failure in women with valvular heart disease¹⁰. However, it has been found that the pregnancy may be well-tolerated if ventricular function is adequate and the replaced valve is functioning well¹³.

Pregnancies in women with a poor baseline function, classified as New York Heart Association (NYHA) grade 3 (breathlessness on minimal exertion) or NYHA 4 (breathlessness at rest), are associated with a higher incidence of maternal, fetal and neonatal morbidity and mortality^{3, 14, 10, 16}. The maternal outcome depends largely on the state in which the woman enters the pregnancy and in general the overall tolerance to pregnancy depends on her general health and reserve^{3, 8}. Sawhney quoted a death rate of 2% in this group of high risk patients³. Adverse effects are more likely with an ejection fraction of less than 40%, aortic stenosis with an area under the valve of less than 1.5cm², mitral stenosis with an area under the valve of less than 2 cm², a NYHA class of 3 or 4 and a history of a previous cardiac event¹⁶. A reliable predictor of poor fetal outcome is left ventricular dysfunction and a poor baseline function¹⁶. Information on the type of replaced valve and the underlying cardiac condition and baseline functional level of the patients in the group studied was not available and could not be included in this audit. However there were significant co-morbidities documented: Twenty three of 49 women were on additional cardiac medication, 3 patients were in chronic atrial fibrillation, 3 had undergone repeat cardiac valve surgery and 1 had had a previous embolectomy. Three out of the 4 documented preterm deliveries were iatrogenic on the background of the deteriorating cardiac and medical condition of the mothers.

The site of the replaced valve plays a role in reducing or increasing the risk to the pregnancy¹⁴. Replaced mechanical mitral valves have the greatest risk of thrombosis^{11, 12, 13}. All of the patients in this cohort had metallic replaced cardiac valves and the majority of patients (55%) had

replaced mitral valves.

The mode of delivery of choice in patients with mechanical heart valves is vaginal delivery with a short second stage³². In this group the caesarean section rate of 33% is acceptable, noting that the operative deliveries were done for obstetric indications which would apply to all pregnant patients.

Overall, the risk of fetal loss is greater in patients with mechanical valves³¹. The percentage of 21% fetal wastage (stillbirths and miscarriages) is marginally higher than that quoted in the literature. There were 2 stillborn infants in 51 pregnancies and no neonatal deaths. The perinatal mortality rate was significantly higher in this group of patients compared to the rate for the general patient population. This can be accounted for in two ways: This patient group was a small number study and this group of patients is identified as a high risk group. The perinatal mortality rate of 31.52 is quoted for the perinatal maternal and neonatal service which has a higher number of pregnancies and births and would include both low and high-risk pregnancies.

The use of warfarin in pregnancy is associated with an embryopathy, characterized by nasal hypoplasia and epiphyseal stippling²², especially when used within weeks 6-12 of pregnancy⁶. The rate of warfarin embryopathy of 11.7% in this group is higher than that quoted in the literature (3.4% - 6.4%). Bates estimated a 6.4% rate of embryopathy in live births when warfarin was used throughout pregnancy¹⁵. Cotrufo estimated an incidence of warfarin-associated embryopathy to be 5.5%²⁰. Vitale quoted a rate of 3.4%²¹ and Jeffrey quoted a rate below 5%⁹ when the fetus had been exposed to warfarin between weeks 6-12. The most notable fact in this group is that 4 out of the 6 patients with a documented embryopathy presented after the first trimester, having exposed the fetus to warfarin throughout the first trimester, and that the 2 who were eligible for heparin during the first trimester did not fully comply with the protocol

as they presented after the 6th week, at 7 and 10 weeks respectively. This indicates a significant problem within our patient population: the patient's first attendance at the antenatal clinic is at an advanced gestational age, despite the high-risk nature of their pregnancy. The mean gestational age at the first clinic visit (booking visit) for all 51 pregnancies was 17.2 weeks, well into the second trimester, and dangerously late in the pregnancy for this high-risk group. Five of the 6 cases of warfarin-associated embryopathies occurred in patients taking more than 5mg of warfarin per day. In 1 case the dose is unknown. Cortufo and Vitale describe an association between warfarin dosage and the risk of a fetal embryopathy, reporting that 5mg a day or less has a lower risk of damage to the fetus^{22, 11}. In the study by Cortufo²⁰, 30 out of 71 pregnancies had a poor outcome and there were 2 embryopathies in term infants. This was specifically related to dose, with 27 patients out of the 30 receiving more than 5mg of warfarin daily. Warfarin dosage of less than 5mg per day had a good fetal outcome. Vitale²¹ documented 58 pregnancies in 43 patients, aiming for INR of 2.5 to 3.5. The patients were kept on warfarin throughout the pregnancy, and there was a statistically significant relationship between warfarin dosage and fetal complications. Based on the outcome of this study the authors suggested that those patients usually taking more than 5mg of warfarin per day, should decrease their dose to 5mg or less per day and aim for INR of 2 to 2.5 to limit the risk to the fetus. The specific dosage of warfarin does not influence the rate of early pregnancy loss⁶. On the basis of these findings, some authors suggest that women on warfarin dosage of 5mg or less should continue warfarin use throughout pregnancy stopping only close to delivery. If the patient desires normal vaginal delivery then intravenous heparin should be used in an in-patient setting for the last two weeks of the pregnancy. If the patient declines warfarin then the suggestion is for IVI heparin in the first trimester between week 6 and 12 and then again two weeks before delivery²¹.

An association between warfarin dosages and the associated embryopathy cannot be drawn from this audit as there were 36 babies born without documented signs of the embryopathy and 21 of these were exposed to more than 5mg per day. Of these 21, only 6 presented early enough to receive first trimester heparin infusion.

Intravenous use of unfractionated heparin in the first trimester of pregnancy eliminates the risk of the warfarin embryopathy²². Of the 51 pregnancies in this audit, 36 patients were on warfarin at the time of their first presentation and of these 36, only 13 presented early enough (before 12 weeks) to receive heparin to avoid the warfarin-associated embryopathy.

Of great concern is the fact that 14 patients presenting in the total 51 pregnancies were not taking warfarin at the time of their first clinic attendance. This is a poor compliance rate. And of the 36 patients compliant on warfarin only 13 attended early enough to be eligible for heparin in the first trimester. The remainder (23) presented after 12 weeks.

The figure quoted in this audit for the rate of early pregnancy loss (17.6%) is smaller than that quoted in the literature (>20%). Of the 9 documented miscarriages, 7 occurred at the time of warfarin exposure. One miscarriage occurred in a patient who had discontinued (defaulted) treatment. This fetus had a documented anomaly and it is assumed that this, rather than the underlying maternal cardiac condition, was the cause of the fetal wastage. There was no early fetal loss in patients receiving IVI heparin during the first trimester. It has been found that if warfarin is used throughout pregnancy there is a higher percentage of fetal loss through stillbirth and spontaneous miscarriage as well as neonatal death²⁵. In those patients who conceived on warfarin and did not receive heparin during the first trimester, the miscarriage rate was 26%. This finding indicates that in this audited group, warfarin exposure is associated with a higher

rate of pregnancy loss and replacing warfarin with unfractionated intravenous heparin may protect against early pregnancy loss. This finding is in contradiction to recent literature, where authors found no difference in early pregnancy loss when using heparin in the first trimester^{6, 12, 25, 21, 24}.

Noting that 37 of the 51 pregnancies were not treated with heparin during the first trimester, this smaller percentage of fetal wastage (17.6%) is unexpected. This may be explained by taking into account that in 14 of the 51 pregnancies, patients were non-compliant which raises the question of the true compliance rate of the 23 patients who were documented to be taking warfarin, but who presented after the first trimester. In fact, the lower rate of fetal wastage may be due to erratic compliance within this group of patients; if this assumption is true it puts these patients at an even greater risk and gives rise to grave concern with respect to maternal anticoagulant protection.

The cause of the maternal death was unknown. It occurred whilst the patient was taking warfarin within the second trimester and her anticoagulation levels were therapeutic at the time. In the absence of a postmortem investigation no conclusive deduction can be made.

The maternal complication rate of 13% is not higher than figures quoted in similar audits. There were 2 cases of maternal valve thrombosis: 3.9 % of the total 51 pregnancies. Both cases occurred in patients with mitral valve prostheses. One patient had a metallic mitral valve prosthesis and the other had a metallic aortic and mitral valve replacement. This rate is lower than that described in the literature, and there were no cases of thromboembolism whilst the patients were receiving intravenous unfractionated heparin.

The fact that there was only 1 case of thrombophlebitis and 1 case of infective endocarditis can possibly be ascribed to the protocol of changing the venous access site every three days whilst the patients are receiving heparin. This is necessary to maintain sterility and limit the risk of infection.

The continuous intravenous heparin infusion offers a consistent level of maternal anticoagulation¹⁴, but requires prolonged in-patient hospitalisation. Whilst this carries a cost both financially for the medical service provider and socially for the patient, it offers adequate and effective anticoagulation to the mothers and reduces the risk to the fetus and neonate. The efficacy of low molecular weight heparin in pregnant patients with mechanical heart valves at this stage remains uncertain and its use in this setting is not advised.

Limitations of this audit are noted as the inability to determine the cause of the maternal death and of the stillbirths. Postmortems were not carried out in all three of these cases. It would be preferred if the cause of the stillbirths and maternal death could have been determined as this would have value to the outcome of this audit. Deaths ascribed directly to the use of anticoagulation would influence the findings and recommendations of this study.

Conclusion

The regime adopted for the management of pregnant patients with mechanical heart valve prostheses described in this audit, offers the best maternal protection with limited complications. Replacing warfarin with unfractionated heparin as a continuous intravenous infusion from week 6 to 12 provides adequate anticoagulation for the mother whilst protecting the fetus from complications associated with warfarin ingestion and reducing the risk of early pregnancy loss. Replacing warfarin with unfractionated heparin infusion from 36 weeks until delivery provides adequate anticoagulation protection for the mother and protects the baby from warfarin-associated complications such as intracerebral haemorrhage. The concern pertaining to this group of patients is the fact that a significant number do not comply with treatment and a significant number present for the first time in the pregnancy after 12 weeks gestation, thereby eliminating the opportunity to protect the fetus against the potentially harmful effects of warfarin exposure during the first trimester. This audit indicates that the maternal complication rate was not higher than that reported in other studies and there was no early pregnancy loss associated with the use of heparin and no neonatal haemorrhage associated with the regime. However the regime requires a long in-patient hospital stay with associated costs and inconvenience to the patient.

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Appendices

Patient Information

Appendix I

1: Warfarin associated Embryopathy

- 1) The first patient had a mechanical aortic valve replacement (AVR) and mitral valve replacement (MVR). She was taking 7.5mg warfarin daily and conceived whilst taking warfarin. Her first attendance (booking visit) was at 10 weeks gestation and she was admitted for the remainder of the first trimester for unfractionated heparin (UFH) via continuous intravenous infusion. She was on no additional medication. The 22-week fetal ultrasound documented nasal hypoplasia in the fetus. The patient continued through the second trimester on warfarin 5mg and 7.5mg on alternate days. She required one additional admission to correct a sub-therapeutic anticoagulation (sub-therapeutic INR) level. At 36 weeks she was admitted for continuous intravenous heparin infusion. She delivered by caesarean section (C/S) at term for failure to progress in labour and a healthy baby of 3860g was born. The infant was noted to have a flat nasal bridge and was

referred to the local tertiary children's hospital (Red Cross Children's War Memorial Hospital) for further management.

- 2) This patient had a MVR and was taking 7.5mg warfarin daily. She was on no additional medication. Her first attendance (booking visit) was at 20 weeks gestation. She was taking warfarin at conception. The 22-week fetal anomaly scan of the fetus identified a mid-facial defect with possible nasal hypoplasia. The patient was admitted at 37 weeks for intravenous heparin infusion and went into spontaneous labour at 41 weeks. A 3420g baby was born, with nasal hypoplasia, however the infant was not referred for further management or follow up.
- 3) The third patient is also included and discussed in the stillbirth group. She had an AVR and was on warfarin 7.5mg and 10mg alternate days. She was also taking an antihypertensive (ACE-inhibitor) and a diuretic. Her first attendance (booking visit) was at 12 weeks having conceived on warfarin and at this gestation it was too late to receive continuous heparin infusion. She continued during the second trimester on warfarin at doses of 7.5mg and 10mg on alternate days. The 22-week detailed fetal ultrasound showed nasal hypoplasia and at 28 weeks an intrauterine fetal demise (IUID) was diagnosed. She was induced and delivered a 945g stillbirth which had features of a warfarin embryopathy.
- 4) The next patient had a mechanical MVR and was also in chronic atrial fibrillation (AF). She was taking warfarin at doses of 5mg and 7.5mg on alternate days and was also

prescribed spironolactone, atenolol, an ACE-inhibitor and digoxin. Her first attendance (booking) was at an advanced gestation (late) at 24 weeks and she was taking warfarin at the time of conception. She was not adequately anticoagulated at her first attendance. This gestation was too late for heparin administration and also too late for a detailed fetal anomaly scan. She was admitted at 31 weeks complaining of difficulty in breathing, was in respiratory distress and atrial fibrillation and developed a valve thrombus. She had an emergency caesarean section (C/S) at 32 weeks and a baby of 2115g was delivered. The neonate developed HMD. The baby had dysmorphic features and this was considered to be due to warfarin ingestion. The infant was discharged on day 19. The patient went on to have an emergency valve replacement 3 days after delivery

- 5) The fifth patient had a MVR and AVR. At first attendance (booking visit) her dose of warfarin was not known, although she had conceived on warfarin. She booked at 7 weeks and was admitted until 12 weeks for continuous heparin infusion. She then continued taking 5mg and 7.5mg warfarin on alternate days. The 22-week fetal ultrasound showed bilateral talipes equinovarus and a flat nasal bridge. The bilateral club feet were thought to be of possible familial origin, as the patient's sister had two children with the same abnormality. The rest of the scan revealed no spina bifida and a normal central nervous system. She had two additional admissions for chest pain and antepartum haemorrhage. She was admitted at 36 weeks for continuous IVI UFH infusion and went into spontaneous labour at 39 weeks. She delivered a baby of 3105g by vacuum extraction. The infant was thought to have features of a warfarin-associated embryopathy; the talipes

was thought not to be associated with warfarin ingestion. The infant was referred to the orthopaedics clubfoot clinic for bilateral posterior release, which was successful.

- 6) The last patient had an AVR. She was on warfarin 5mg and 7.5mg on alternate days. She first attended (booked) at 15 weeks having conceived whilst taking warfarin and at this gestational age it was too late for first trimester heparin infusion. She had a normal fetal anomaly scan. During the second trimester and into the third, she continued on 7.5mg and 10mg on alternate days. She had two extra admissions for high INR levels and a urinary tract infection. She was admitted at 36 weeks for heparin and delivered a 2537g baby by elective caesarean section.

Appendix II

Stillbirths

2 pregnancies ended in the birth of a stillborn infant. One occurred at 28 weeks gestation and the other at 34 weeks.

- 1) One patient had a MVR. She had discontinued her warfarin and had not taken it for over 10 years. She was on no other medication. Her first attendance (booking visit) was at an advanced gestation (late) at 27 weeks, which was too late in the pregnancy to receive IVI UFH and too late for a detailed fetal anomaly scan. During the second trimester, she was prescribed warfarin at a dose of 7.5mg daily and required admission at 31 weeks to correct a sub-therapeutic INR. She was screened for syphilis as part of the routine

antenatal screening and was found to have a positive test result: (VDRL positive) with a titre 1:16. She received only 1 bicillin injection and was not fully treated. She went into spontaneous labour at 34 weeks and delivered a macerated stillbirth there were no signs of warfarin-associated embryopathy and the placental histology did not reveal any further information.

- 2) The second patient has been discussed as a warfarin embryopathy case. She was taking warfarin 7.5mg and 10mg alternate days for mechanical aortic valve prosthesis (AVR). She was also taking an antihypertensive (ACE-inhibitor) and a diuretic. Her first attendance (booking) was at 12 weeks having conceived on warfarin and this was too late to be admitted for the continuous UFH infusion. She continued taking warfarin at doses of 7.5mg and 10mg on alternate days. The 22-week fetal ultrasound showed nasal hypoplasia and at 28 weeks an intrauterine fetal demise (IUFD) was diagnosed. She was induced and delivered a 945g stillbirth, which had features of a warfarin embryopathy.

Appendix III

Miscarriages

The 6 second-trimester miscarriages are described as follows:

- 1) This patient had a MVR and was taking warfarin in doses of 2.5mg and 5mg on alternate days. She had discontinued (defaulted) her medication and had only taken the warfarin for a total of 2 days during the first trimester. Her first attendance (booked) was at a

gestational age of 14 weeks and a fetal ultrasound indicated there was no fetal heart activity. Labour was induced. The post mortem investigation showed multiple pterigium syndrome.

- 2) This patient had a metallic MVR and AVR and a bioprosthetic (tissue) tricuspid valve replacement (TVR). She was on warfarin 5mg daily and also taking a diuretic and digoxin. She presented at 16 weeks gestation with vaginal bleeding and had not yet registered for antenatal care. The pregnancy ended in a miscarriage, and the patient required an evacuation of the uterus. The fetus was not examined for any abnormalities.
- 3) This patient miscarried at 19 weeks. She had a MVR and was taking warfarin 5mg and 7.5mg on alternate days, having conceived whilst taking warfarin. She was also taking a diuretic. She continued taking warfarin during the second trimester at dosages of 5mg and 7.5mg on alternate days. She registered and first attended (booked) at 19 weeks gestation and the absence of fetal heart activity was diagnosed on the routine ultrasound. The labour was induced and she delivered a 480g fetus. It was not examined for abnormalities.
- 4) This patient miscarried at 21 weeks. She had a MVR and AVR and the medical comorbidities included a CVA (cerebral vascular accident). She was taking warfarin 7.5mg daily. She conceived whilst taking warfarin and attended (booked) too late in the pregnancy, at 21 weeks, for heparin during first trimester. The 21-week fetal ultrasound

showed absent fetal heart activity. The INR was 4.0. The labour was induced and she delivered a 320g fetus that was not examined for and abnormalities.

- 5) This pregnancy ended in a miscarriage at 21 weeks. The patient had a MVR and was taking 5mg and 7.5mg warfarin on alternate days. She tested positive for Human Immunodeficiency Virus (HIV) and had a low CD4 count of 182. She was not on antiretroviral therapy. She booked at 15 weeks, too late in the pregnancy for first trimester heparin. The patient was admitted at 17 weeks for sub-therapeutic INR. The fetal ultrasound at 21 weeks showed absent fetal heart activity and the labour was induced. She delivered a 340g fetus and placental histology revealed mild ischemia. No definitive cause for the miscarriage was found.
- 6) This patient had a MVR. She was on 10mg of warfarin daily. She booked the pregnancy at 6 weeks gestation and was admitted for heparin until the end of the first trimester. She was subsequently put onto 5mg and 7.5mg warfarin on alternate days. At 17 weeks a fetal ultrasound showed absent fetal heart activity. She had an induction of labour and delivered a 100g fetus. The fetus was not examined for abnormalities.

The first trimester miscarriages occurred as follows:

- 1) This patient was on warfarin 7.5mg and 10mg alternate days for an AVR. She booked at 7 weeks and was admitted for heparin infusion until the end of the first trimester. The first dating fetal ultrasound showed a 7-week gestational sac, but no fetal pole. She had a

spontaneous miscarriage 6 days after the scan and required an evacuation of the uterus. The miscarriage was not investigated and no placental histological analysis was requested.

- 2) This patient had a particularly poor obstetric history. She had a replaced aortic valve and mitral valve. Repeat surgery had been done on the aortic valve in 1996. The 4 preceding pregnancies had ended in miscarriages: 3 first trimester miscarriages and 1 second trimester miscarriage. It is unclear whether or not she was taking warfarin at this time. She was however on an antihypertensive and a diuretic. She was diagnosed with an anembryonic pregnancy at 6 weeks. She had an evacuation of the uterus.
- 3) This patient had an AVR and MVR. Her usual dose of warfarin had not been documented. She had conceived whilst taking warfarin. She was also taking an ACE-inhibitor. She was admitted during the first trimester for heparin. An ultrasound at 7 weeks showed absent fetal heart activity. She had an evacuation of the uterus. The placental tissue was not sent for histological analysis.

Appendix IV

Preterm Deliveries

- 1) The first patient had a mitral valve replacement (MVR) and was taking 10 mg of warfarin daily with the exception of Sunday when she took 15 mg. She was also taking digoxin and a diuretic. She booked (first attendance at the antenatal clinic) at an advanced

gestation (late), at 28 weeks, having conceived on warfarin. The pregnancy was complicated by preterm pre-labour rupture of membranes and she went into spontaneous labour at 32 weeks and delivered a 1635g infant. The infant was treated for pneumonia and recovered well and was discharged at approximately one month old.

- 2) The second patient delivered at 35 weeks. She had an aortic valve replacement (AVR) and a MVR having undergone a *redo* (repeat surgery) MVR in 1995. She was taking 5mg and 10mg of warfarin on alternate days, which was decreased to 5mg daily during the pregnancy. She was adequately anticoagulated. She was also taking digoxin, an ACE-inhibitor and spironolactone. She booked at an advanced gestation, at 24 weeks, having conceived on warfarin. She was admitted at 32 weeks and induced at 35 weeks and delivered a 1965g baby by emergency caesarean section (C/S) for fetal hypoxemia made evident on a pathological cardiotocograph tracing (also termed fetal distress). The patient was transferred to the Intensive Care Unit after delivery for a valvular thrombosis. The baby was thought to be growth restricted but progressed well and was discharged on day 8 in a healthy condition.
- 3) The third patient had an emergency caesarean section at 32 weeks. She had a MVR and was also in atrial fibrillation (AF) she was on warfarin 5mg and 7.5mg on alternate days and was also on spironolactone, atenolol, an ACE-inhibitor and digoxin. She booked at an advanced gestational age (late), at 24 weeks having conceived on warfarin. She was not adequately anticoagulated at this first attendance. She was admitted at 31 weeks with the complaint of shortness of breath, was in AF and developed a valve thrombosis. She had an emergency C/S at 32 weeks and delivered a baby of 2115g. The baby developed

Hyaline Membrane Disease (HMD), but progressed well and was discharged day 19. The patient went on to have an emergency valve replacement on the third day after delivery.

- 4) Patient number 4 was induced at 34 weeks. She had MVR and AVR was also in atrial fibrillation. She was taking atenolol and furosemide (lasix), but had defaulted warfarin therapy for 6 months. The patient was not taking warfarin at the time of conception. She booked (first attendance) late (at an advanced gestational age) at 23 weeks. She was not adequately anticoagulated at booking. She was put onto 5mg and 7.5mg warfarin on alternate days. The pregnancy was complicated by three extra admissions for sub-therapeutic anticoagulation levels (low INR) and fast AF. She was induced at 34 weeks and delivered a 2145g infant by emergency caesarean section for fetal distress. Post delivery she went into cardiac failure, was in fast AF with sepsis caused by MRSA. The baby was discharged well on day 17.

Appendix V

Additional fetal complications

Two babies were considered to be growth restricted, which equated to 5% of total live births.

Of these, 1 patient had a MVR. She was taking 2.5mg and 5mg warfarin on alternate days. She was also on a β -blocker and a diuretic. She booked at 8 weeks having conceived on warfarin and was admitted for continuous heparin infusion through the first trimester until 12 weeks. She had a normal 22-week scan and continued on warfarin 2.5mg and 5mg alternate days. She was admitted at 36 weeks for heparin and was induced at 37 weeks. She delivered a 2390g baby by caesarean section for fetal distress, the baby was considered to be growth restricted, but was

discharged from the nursery 2 days after delivery and discharged home with the mother on day 10.

The second patient was 40 years old. She had a mechanical aortic valve. She was on warfarin 2.5mg and 5mg alternating days. She booked at 16 weeks, too late for first trimester heparin infusion. The first INR reading was sub-therapeutic and was corrected. She continued on 2.5mg and 5mg alternate days. She was admitted at 36 weeks according to the protocol and was induced at 38 weeks. A 2435g baby was delivered by Caesarean section for fetal distress and was thought to be growth restricted. The baby progressed well and was discharged from the nursery to the mother on day 8.

One baby developed a cephalohaematoma. The most probable cause of this complication was the assisted vacuum delivery. This patient had a MVR and was on warfarin 5mg and 7.5mg alternate days. She was fully heparinised from 36 weeks according to our protocol and went into spontaneous labour at 40 weeks. She had an assisted delivery, vacuum extraction and delivered a 2580g baby. The baby sustained a cephalohaematoma, but did well, did not develop jaundice and was discharged from the nursery to mother on day 1.

Appendix VI

Maternal Complications

There were 2 cases of maternal valve thrombosis: 3.9 % of the total 51 pregnancies.

The first patient was 35 years old and in her second pregnancy. She had a mechanical aortic valve and mechanical mitral valve (the mitral valve had been replaced for the second time in 1995, 12 years prior to the current pregnancy) and a fistula between the aorta and right atrium. In addition to warfarin, she was taking a diuretic, digoxin, spironolactone and an ACE-inhibitor. The warfarin dosage was 5mg and 10mg on alternate days. She booked at 24 weeks and had been on warfarin throughout the first trimester. She continued on 5mg daily and was well anticoagulated with therapeutic INR levels throughout the pregnancy. She was admitted at 32 weeks and labour was induced at 35 weeks. She delivered by emergency caesarean section at 35 weeks for fetal distress. She was transferred to the cardiac ward post-delivery for a valve clot.

The second patient was 30 years old. She was a gravida 4 para 3. She had had a MVR 2 years prior to the current pregnancy. In addition, she was in chronic atrial fibrillation (AF) and was taking digoxin, spironolactone, atenolol and an ACE-inhibitor. Her warfarin dosage was 5mg and 7.5mg alternate days. She booked late at 24 weeks and had been on warfarin during the first trimester. The first INR recorded was sub-therapeutic. She was put on 5mg and 7.5mg alternate days. She was admitted at 31 weeks complaining of shortness of breath. She was in AF

and went on to have an emergency caesarean section for pulmonary edema at 32 weeks. A 2115g baby was delivered. The patient had an emergency valve replacement day 3 post partum. The baby had features consistent with warfarin embryopathy.

There was 1 case of thrombophlebitis. This equates to 2% of patients

This patient was 25 years old. She was in her third pregnancy, and had had a MVR 15 years prior to the current pregnancy. She was on warfarin 5mg daily, but had defaulted and was not on warfarin when she booked at 26 weeks. The warfarin was restarted and she continued on 5mg and 7.5mg alternate days. She was admitted at 36 weeks as per the protocol for continuous heparin infusion. She developed a thrombophlebitis. She had a total of 30 days of IVI heparin. She went into spontaneous labour at term and delivered a 2870g healthy baby. The patient recovered well and was discharged 9 days post partum.

There was 1 case of infective endocarditis: This equates to 2%

This patient was 28 years old. She was in her third pregnancy and had had a MVR 6 year prior to the current pregnancy. Her dosage of warfarin was not known at booking at 7 weeks. The first INR reading was sub-therapeutic. She had conceived on warfarin and was admitted until 12 weeks for IVI heparin. She had a total of 38 days in the first trimester on IVI heparin and was discharged on warfarin 5mg and 7.5mg alternating days. She was admitted at 37 weeks for IVI heparin and had a total of 28 days of IVI administration. She developed an endocarditis, no associated thrombophlebitis, but did have a documented lower urinary tract infection. She went

into spontaneous labour at term and delivered a 3450g baby by caesarean section for fetal distress. Baby and mother were discharged 8 days post-delivery.