INTRODUCTION

Expectant women with mechanical heart valves need to undergo an event-free period of gestation with a successful outcome for both mother and child. Unfortunately, pregnancy in these patients does not follow its usual benign course and is associated with high maternal and foetal risks.

The incidence of rheumatic heart disease has declined dramatically in the industrialised nations. However, in India it has not shown a similar decline, with hospital admissions ranging from 16.5–50.6% of all cardiac in-patients. As rheumatic heart disease primarily affects younger patients, most women undergoing a heart valve replacement belong to the child-bearing age group and this potentially magnifies this problem in the developing countries.

During pregnancy there is a 50% increase in blood volume, an increase in cardiac output and a decrease in systemic vascular resistance (from uterine circulation and hormonal changes). During labour and delivery, cardiac output increases abruptly followed by a sudden increase in preload (due to autotransfusion of uterine blood and caval decompression). This increased haemodynamic burden, which is well tolerated by most women, may lead to cardiac decompensation in patients with prosthetic valves, especially those with left ventricular (LV)
dysfunction or a relatively small-sized valve prosthesis.

For patients with mechanical heart valve, lifelong anticoagulation is mandatory. However in pregnant women, anticoagulation management is a complex issue. Pregnancy is a hypercoagulable state, due to increase in fibrinogen, factors VII, VIII and X, von Willebrand factor; and relative decrease in protein S activity; stasis and venous hypertension. This further increases the already existing risk of thrombo-embolic complications (TEC) in these patients. This state of hypercoagulability extends into the postpartum period too and requires a persistently higher maintenance dose of warfarin. Similarly, increase in total blood volume affects the distribution of heparin and low molecular weight heparin (LMWH). The presence of placental heparinase further contributes to unpredictable changes in the quantum of medication required. Thus, optimal anticoagulation therapy is considered essential, but the appropriate choice of agent among the options available (warfarin, heparin or LMWH) is highly debatable.

**RISK ASSESSMENT**

**PATIENT FACTORS**

There is an increased haemodynamic load during pregnancy, labour and delivery. The published experience indicates that most patients that were asymptomatic or only mildly symptomatic before conception, tolerate this haemodynamic burden well. However, cardiac de-compensation may occur, especially in patients with impaired LV function and/or possible patient-prosthesis mismatch. In addition, an increased incidence of arrhythmia is reported during pregnancy17 and may add to patient discomfort. Thus it is not surprising that decreased functional capacity, pulmonary oedema and death are not uncommon in pregnant women with mechanical valves. Patients with prosthetic heart valves and markedly impaired LV function that are moderately or severely symptomatic (New York Heart Association, class III and IV) are best advised against pregnancy.

Residual tricuspid incompetence often co-exists in patients with prosthetic heart valves. The reported incidence of foetal loss in mothers suffering from tricuspid incompetence severe enough to require diuretics is around 73%. This risk is significantly higher when compared with foetal loss in pregnancies in which the mother did not exhibit tricuspid incompetence.

**PROSTHESIS RELATED FACTORS**

The commonest cause of maternal death in patients with mechanical heart valves is the device thrombosis. In addition, there is also a high incidence of thromboembolic events in these patients, ranging from 7% to 23%.

**DRUG THERAPY**

Foetal complications related to maternal anticoagulant therapy are teratogenicity and foetal loss. The incidence of abortion or foetal wastage (resulting from retroplacental haemorrhage, congenital malformations, etc) in these patients is
high, with reported rates ranging between 23% and 50%.
Maternal risk of haemorrhage while on anticoagulation is estimated at around 2.5%, with majority of such episodes (almost 80%) occurring in association with delivery.

Moreover, in addition to anticoagulants, the use of other cardiovascular drugs during pregnancy may also adversely affect the foetal outcome. Cardiac drugs that are relatively safe during pregnancy include heparin, propranolol (and other beta blockers), verapamil, digoxin and few antihypertensives such as labetolol, methyldopa, hydralazine, nifedipine and prazosin. Amiodarone is associated with foetal hypothyroidism and intrauterine growth retardation. It should be reserved only for cases with refractory arrhythmias.

In these patients, a planned pregnancy is preferred to an unplanned one. Evaluation of pregnant women with prosthetic heart valves should include information about her pre-pregnancy functional capacity, ongoing drug treatment, a full clinical assessment, details of valvular prosthesis, an ECG, as well as an echo-Doppler study to evaluate cardiac status. A fairly good estimate of maternal and foetal risk can then be made. Patient should also be advised on the potential complications that may occur during pregnancy: symptomatic worsening, higher incidence of thromboembolism, and potential harmful effects to the foetus.

ANTI-COAGULANTS AND PREGNANCY
Choice of anticoagulant is limited to warfarin, heparin or LMWH. The advantage of warfarin lies in its ease of administration, dependability and low cost. However, the associated risk of embryopathy has limited its use in pregnant women, particularly in the first trimester. Heparins need to be administered parenterally and produce less dependable anticoagulation, but are not teratogenic.

WARFARIN
Oral anticoagulants interfere with the cyclic inter-conversion of vitamin K and its epoxide, thus inhibiting the production of vitamin K dependant clotting factors. Dosage is adjusted to attain a desired international normalized ratio (INR) level (Table 2), which is calculated by the formula:

\[
\text{INR} = \frac{\text{patient PT}}{\text{mean normal PT}} \times \text{ISI}
\]

(PT stands for prothrombin time and ISI denotes International Sensitivity Index of thromboplastin used at the laboratory).

UN-FRACTIONATED HEPARIN
Measuring activated partial thromboplastin time (aPTT) remains the most frequently used method for monitoring the anticoagulant response of unfractionated heparin (UFH) and should be measured about 6 hours after the bolus dose, the continuous intravenous dose is adjusted accordingly. Long-term heparin therapy may cause osteoporosis.

LOW MOLECULAR WEIGHT HEPARIN
LMWH has a better bioavailability than unfractionated heparin, and may also have a lower risk of bleeding, thrombocytopaenia and osteoporosis. These advantages, however, are partly offset by its longer half life (making it more difficult to handle during premature labour), and its unpredictable reversal with protamine. As already mentioned, because of an increased volume of distribution of LMWH in pregnancy and placental heparinase, dose adjustments based on plasma anti-Xa levels 4 hours after the morning dose are essential. The target is to achieve an anti-Xa level of 1.0 to 1.2 units per ml.

**ASPIRIN**
Small-doses of aspirin are safe during the 2nd and 3rd trimesters of pregnancy. Aspirin reduces the incidence of systemic embolization or death when added to oral anticoagulation in the non-pregnant population with mechanical heart valve. Thus, based on current data, 80-100 mg of aspirin during the second and third trimesters may be added to improve antithrombotic effects.

**EMBRYOPATHY**
Heparin (both UFH and LMWH) does not cross the placenta, and does not cause teratogenicity. On the contrary, warfarin readily crosses the placenta. Vitamin K acts as a co-factor for carboxylation of glutamic acid residues of osteocalcin and matrix Gla protein, which modulate calcium deposition. Oral anticoagulants when used during the first trimester, may thus cause a failure in the synthesis of osteocalcin and Gla matrix protein resulting in nasal hypoplasia and stippling seen on X-ray of proximal epiphyseal growth areas (Chondroplasia punctata). Exposure during the second and third trimesters may lead to central nervous system and eye abnormalities (optic atrophy, cataract, blindness, microphthalmia, intraventricular haemorrhage, microcephaly, hydrocephalus, seizures, and growth/mental retardation).

Warfarin when used in the post-partum period does not cause an anticoagulant effect on the breast fed infant. Likewise neither UFH nor LMWHs are secreted into breast milk.

**FOETAL LOSS**
Spontaneous abortion is by far the most frequent foetal complication, associated with pregnancy in women with mechanical heart valves. Both oral anticoagulants and heparin carry this risk. Inhibition of the immature liver enzyme system of the foetus by warfarin may result into an increased risk of haemorrhagic complications and stillbirth. Although heparin will not cross the placenta, bleeding at the utero-placental junction is still possible. Replacing warfarin with heparin during the first trimester prevents the occurrence of malformations, but this does not translate into an improved pregnancy outcome.

**MODE OF DELIVERY**
Several studies suggest that heparin therapy is safe for the foetus particularly at the time of delivery, when trans-placental transfer of oral anticoagulants may lead to bleeding in the neonate. Caesarean section is indicated, if labour starts while the
mother is still on oral anticoagulants; rapid reversal of the mother's anticoagulation is attempted with liberal use of fresh frozen plasma. Avoiding vaginal delivery decreases birth trauma to the anticoagulated baby.

Recommendations on the management of elective deliveries, however, are more controversial. There are suggestions that continuing warfarin till 38 weeks of pregnancy, followed by a 2-day interruption of anticoagulant therapy and cesarean section may improve outcome and decrease the time for which the mother remains unprotected. This represents a non-obstetrical indication for cesarean section, which is itself known to increase venous thromboembolic risk over that of natural childbirth. Also, anticoagulated preterm infants are at in risk for intracranial haemorrhage during both vaginal and caesarean delivery. Therefore, stopping warfarin at the 36th week, replacing it with adequate heparin and planned induction of labour at 38th week is a more appealing alternative, and is recommended by most authorities on this subject.

Available Recommendations
As in most areas of medicine, management of pregnant patients with mechanical heart valves is now covered by guidelines. Yet, this controversial issue remains unabated, partly from the need of well-designed prospective studies and partly due to the lack of consensus among various study groups. In this regard, the Task Force of the European Society of Cardiology, (ESC) On the Management of Cardiovascular Diseases during Pregnancy in its expert consensus statement2 avers: “In pregnant patients with mechanical prosthesis, the choice of anticoagulant therapy during the first trimester should take into account the greater thromboembolic risk with heparin and the risk of embryopathy with vitamin K antagonist. The use of vitamin K antagonist during the first trimester is the safest regimen for the mother.”

References
1. American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease); Society of Cardiovascular Anesthesiologists;
As LMWH is not approved for use in prosthetic valve patients in pregnancy due to the high risk of thrombosis, and as subcutaneous unfractionated heparin throughout pregnancy carries a similar high risk, strategies which should be discussed with patients are:

(a) Heparin during the 1st trimester (to avoid warfarin embryopathy), followed by oral anticoagulation up to the 36th week with subsequent replacement by heparin until delivery.

(b) Oral anticoagulation throughout pregnancy, until the 36th week, followed by heparin until delivery.

Because of high rate of maternal complications with heparin therapy, particularly when given throughout the pregnancy, the committee strongly recommends strategy (b).

LMWH : Low Molecular Weight Heparin

Table 4. Acc/aha 2006 Guidelines For The Management Of Patients With Valvular Heart Disease. Selection Of Anticoagulation Regimen In Pregnant Patients With Mechanical Prosthetic Valves 1

Class I
1. All pregnant patients with mechanical prosthetic valves must receive continuous therapeutic anticoagulation with frequent monitoring. (Level of Evidence : B)
2. For women requiring long-term warfarin therapy who are attempting pregnancy, pregnancy tests should be monitored with discussions about subsequent anticoagulation therapy, so that anticoagulation can be continued uninterrupted when pregnancy is achieved. (Level of Evidence : C)
3. Pregnant patients with mechanical prosthetic valves who elect to stop warfarin between weeks 6 and 12 of gestation should receive continuous intravenous UFH, dose-adjusted UFH, or dose-adjusted subcutaneous LMWH. (Level of Evidence : C)
4. For pregnant patients with mechanical prosthetic valves, up to 36 weeks of gestation, the therapeutic choice of continuous intravenous or dose adjusted subcutaneous UFH, dose-adjusted LMWH, or warfarin should be discussed fully. If continuous intravenous UFH is used, the foetal risk is lower, but the maternal risks of prosthetic valve thrombosis, systemic embolization, infection, osteoporosis, and heparin-induced thrombocytopenia are relatively higher. (Level of Evidence : C)
5. In pregnant patients with mechanical prosthetic valves who receive dose adjusted LMWH, the LMWH should be administered twice daily subcutaneously to maintain the anti-Xa level between 0.7 and 1.2 U per ml 4 hr. after administration. (Level of Evidence : C)
6. In pregnant patients with mechanical prosthetic valves who receive dose adjusted UFH, the aPTT should be at least twice the control. (Level of Evidence : C)
7. In pregnant patients with mechanical prosthetic valves who receive warfarin, the INR goal should be 3.0 (range 2.5 to 3.5). (Level of Evidence : C)
8. In pregnant patients with mechanical prosthetic valves, warfarin should be discontinued and continuous intravenous UFH given starting 2 to 3 weeks before planned delivery. (Level of Evidence : C)

Class IIa
1. In patients with mechanical prosthetic valves, it is reasonable to avoid warfarin between weeks 6 and 12 of gestation showing to the high risk of foetal defects. (Level of Evidence : C)
2. In patients with mechanical prosthetic valves, it is reasonable to resume UFH 4 to 6 h after delivery and begin oral warfarin in the absence of significant bleeding. (Level of Evidence : C)
3. In patients with mechanical prosthetic valves, it is reasonable to give low-dose aspirin (75 to 100 mg per day) in the second and third trimesters of pregnancy in addition to anticoagulation with warfarin or heparin. (Level of Evidence : C)

Class III
1. LMWH should not be administered to pregnant patients with mechanical prosthetic valves unless anti-Xa levels are monitored 4 to 6 h after administration. (Level of Evidence : C)
2. Dipyridamole should not be used instead of aspirin as an alternative antiplatelet agent in pregnant patients with mechanical prosthetic valves because of its harmful effects on the foetus. (Level of Evidence : B)

Class I : Conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective. Class II : Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. Class IIa : Weight of evidence / opinion is in favor of usefulness/efficacy. Class III : Usefulness/efficacy is less well established by evidence/opinion. Class III : Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/efficacious and in some cases may be harmful. Weight of evidence in support of the recommendation is listed as follows: Level of Evidence A : Data derived from multiple randomized clinical trials. Level of Evidence B : Data derived from a single randomized trial or nonrandomized studies. Level of Evidence C : Only consensus opinion of experts, case studies, or standard-of-care. ACC : American College of Cardiology, AHA : American Heart Association, UFH : unfractionated heparin, LMWH : low molecular weight heparin, aPTT : activated partial thromboplastin time, INR : international normalized ratio.