Pregnancy Outcome in Women with Mechanical Prosthetic Heart Valves Treated with Unfractionated Heparin (UFH) or Enoxaparin

Khalid Abd Aziz Mohamed
Egypt

ABSTRACT
The objective of this study was to determine maternal (included thromboembolic and haemorrhagic complications) and fetal outcomes (included miscarriage, stillbirth, baby death and live birth) in women with mechanical heart valves managed with therapeutic dose unfractionated Heparin (UFH) versus enoxaparin during pregnancy. This is a prospective comparative, non-randomized study. Pregnant women with mechanical heart valves attending high-risk pregnancy unit high-Benha university hospital, treated with Unfractionated Heparin (UFH) 15,000 U/12 h versus enoxaparin (Clexane) 1 mg kg⁻¹ SC/12 h during pregnancy. Forty pregnant. In 20 pregnancies anticoagulation was with Unfractionated Heparin (UFH) and 20 pregnancies women received enoxaparin. One (3%) thrombotic complications occurred with enoxaparin treatment. Non-compliance or sub-therapeutic levels contributed in this case. Antenatal hemorrhage occurred in 4 (10%) and postpartum haemorrhagic complications in 5 (12.5%) pregnancies. Of 32 pregnancies continued after 20 weeks’ gestation, 100% (17/17) of women taking predominantly Unfractionated Heparin (UFH) had a surviving infant compared with 93% (14/15) in women taking primarily enoxaparin (p = 0.25). One intrauterine fetal death (IUFD) occurred in enoxaparin group. There was no significant difference in live birth rate between the two groups (p = 0.31). Compliance with therapeutic dose Unfractionated Heparin (UFH) during pregnancy in women with mechanical heart valves is associated with a low risk of valve thrombosis and good fetal outcomes but meticulous monitoring is essential.

Key words: Enoxaparin, prosthetic heart valves, UFH, pregnancy, thromboembolism

INTRODUCTION
Mechanical heart valves have a high risk of thrombosis and thromboemboli without concomitant anticoagulation. The risk is further increased if there is atrial fibrillation or if the valve is one of the older models, particularly in the mitral position. Pregnancy increases the risks of thromboembolic disease as well as the risks of anticoagulation for mother and fetus in patients with mechanical valves (Elkayam and Bitar, 2005).

The main risks are associated with anticoagulation include maternal thromboembolic events due to insufficient anticoagulation, maternal valve thrombosis, fetal complications due to the effects of the anticoagulant used and the timing of administration, maternal bleeding from anticoagulation during (1) Gestation, (2) Labor and especially (3) During delivery (Chan et al., 2000).

Anticoagulation in the patient with an artificial heart valve and/or atrial fibrillation during pregnancy remains controversial because of the lack of an ideal agent for anticoagulation during pregnancy (Ginsberg and Barron, 1994). Warfarin is the mainstay of anticoagulation in the non-pregnant population and pregnant patients with prosthetic valves have the lowest risk of valve
thrombosis and thromboembolic events when appropriately anticoagulated. For the fetus, warfarin (coumadin) is relatively contraindicated at all stages of gestation due to its association with fetal warfarin syndrome in 6-9 weeks and its relationship to fetal intracranial hemorrhage and secondary scarring at later stages (Hall et al., 1980; Briggs et al., 1994). The attractiveness of UFH and LMWH is that they do not cross the placenta and the risk to the fetus is less. The maternal effects of long-term administration of UFH include thrombocytopenia, bone loss and uneven therapeutic attainment of aPTT.

Heparin has a long track record of use in pregnancy, is safe for the fetus and can be used either subcutaneously in the antepartum period or intravenously in the peripartum period. Unfractionated heparin (UFH) should be dosed to achieve the activated partial thromboplastin time (aPTT) at two to three times the normal in patients with valvular prostheses. In the third trimester, women have increased heparin-carrying proteins and may require a dose increase. Other considerations with heparin include the risk for thrombocytopenia and osteoporosis with long term administration. In the intrapartum setting, heparin infusion should be stopped 12 h before delivery is anticipated and can be restarted, in the absence of hemorrhagic problems, 4 to 6 h after delivery (Rowan et al., 2003).

Low-molecular-weight heparin (LMWH): LMWH is more expensive than heparin or warfarin and is injected subcutaneously. Recent clinical trials demonstrate safety and efficacy in pregnancy but this LMWH is not approved by the FDA for use with prosthetic heart valves (Huxtable et al., 2005; Oran et al., 2004). LMWH should be monitored and dose-adjusted to achieve an anti-factor Xa level of a minimum of 0.7 to 1.2 unit mL\(^{-1}\) 4-6 h after injection to reduce the possibility of valve thrombosis (Oran et al., 2004). Elkayam and Bitar (2005) also recommend measuring peak levels of anti-Xa (<1.5 U mL\(^{-1}\)) to avoid excessive anticoagulation. It can be stopped 12 h before delivery without an increase in hemorrhagic complications (Maslojitz et al., 2005).

Recommendations from an American consensus conference on antithrombotic therapy for patients with mechanical heart valves recommended three anticoagulation management choices (Bates et al., 2004):

- High dose (e.g., 17500 to 20000 units) subcutaneous UFH throughout pregnancy given twice daily with monitoring to guide dosing (aiming for a 6 h post-dose Activated Partial Thromboplastin Time (APTT) of twice the control level, or anti-Xa level maintained at 0.35-0.70 IU mL\(^{-1}\))
- LMWH (e.g., dalteparin 100 units kg\(^{-1}\)) subcutaneously given throughout pregnancy with anti-Xa monitoring to guide dosing (aiming for a 4 h post dosing anti-Xa level of about 1.0 IU mL\(^{-1}\))
- UFH or LMWH therapy as above until the 13th week of gestation, followed by warfarin until the middle of the third trimester, then restart UFH or LMWH therapy until delivery

MATERIALS AND METHODS

This prospective comparative, non-randomized study was conducted at Department of Obstetrics and Gynecology, Benha University Hospital and private centers, since May 2012 till October 2013. After approval of the study protocol by the Local Ethical Committee a written fully informed patients' consents was obtained. Forty pregnant women with prosthetic heart valves were followed in the high-risk pregnancy unit- Benha university hospital and were interviewed about their medical, personal, family, obstetrical and thrombosis history.
J. Name

Women were reviewed urgently upon confirmation of pregnancy (at booking) to discuss with them treatment options and the risks of continuing the pregnancy. Women were informed of both the maternal and fetal risks associated with anticoagulant regimen choices and fully participated in the decision process of anticoagulation.

After her choice of one of the following treatment options each pregnant woman completed written informed consent:

- Replacement of warfarin with therapeutic dose UFH (15,000 IU/12 h) before 6 weeks’ gestation, continued until delivery
- Replacement of warfarin with therapeutic dose enoxaparin (1 mg kg⁻¹ bid) before 6 weeks’ gestation, continued until 36th week gestation then shift to UFH until delivery

Thus, we had two study groups according to the anticoagulation regimen. A total of 20 patients were on UFH throughout their pregnancy (group A). The remaining 20 patients (group B) had enoxaparin till the 36th week of gestation followed by heparin for the last two weeks of pregnancy; both groups received heparin at the time of delivery.

During heparin treatment, the Activated Partial Thromboplastin Time (aPTT) was maintained at twice the control level. All patients underwent periodic transthoracic echocardiography (TTE) when needed during the follow up period.

For women in enoxaparin group, monitoring of anti-Xa levels was recommended every month, our aim for target levels of Anti-Xa was 0.7 to 1.2 IU mL⁻¹ 4 h post dose (Oran et al., 2004). Anti-Xa levels were first checked 3-7 days after starting treatment or following dose modification and then repeated monthly at routine prenatal visits, adjusting the level upward or downward as necessary. The enoxaparin dose was changed according to the level of anti-Xa. While for women with UFH we checked an activated partial thromboplastin time (aPTT) once or twice a week and adjust their dose of heparin to maintain the mid-dose aPTT at the lower end of the therapeutic range (Rowan et al., 2003).

Foetal growth was monitored by fundal height measurement and serial ultrasounds. Doppler umbilical wave flow velocity was studied for foetuses with suspected intrauterine growth retardation.

Pediatricians examined all new-borns. Spontaneous abortion was defined as fetal loss before 20 weeks of gestation. Fetal and maternal outcomes were evaluated. Fetal outcomes included abortion, live birth, Intra Uterine Fetal Death (IUFD), IUGR preterm labor and mode of delivery while maternal outcomes included bleeding, valvular thrombosis and maternal death.

Outcome evaluation: The primary outcome measure was the rate of live births. Secondary outcomes included rates of miscarriage, intrauterine fetal death (fetal death after 20 weeks of gestation) and obstetrical complications. Such complications included small size for gestational age (birth weight below the 10th percentile for gestational age and sex), placental abruption, postpartum hemorrhage, premature delivery, maternal thrombotic complications and maternal death.

RESULTS

Table 1 shows the demographic details of the women. There were no significant differences in the patient’s age at entry, weight and prior pregnancies. There were 26 pregnancies in women with mitral valve replacement, 9 in women with aortic valve replacement and 5 in those with both aortic and mitral valve replacement.
### 3. Name

Table 1: Maternal characteristics at booking

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups (n = 20)</th>
<th></th>
<th>Test of significance</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A (UPH)</td>
<td>B (LMWH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>26.80±4.05</td>
<td>26±3.16</td>
<td>T = -0.68</td>
<td>0.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.4±6.68</td>
<td>71.25±5.71</td>
<td>T = -0.59</td>
<td>0.66</td>
</tr>
<tr>
<td>Total pregnancies</td>
<td>2.05±1.28</td>
<td>2.25±1.16</td>
<td>T = 0.52</td>
<td>0.61</td>
</tr>
<tr>
<td>MVR</td>
<td>12 (60%)</td>
<td>14 (70%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVR</td>
<td>5 (25%)</td>
<td>4 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVR and AVR</td>
<td>3 (15%)</td>
<td>2 (10%)</td>
<td></td>
<td></td>
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</tbody>
</table>

Table 2: Pregnancy outcome

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups (n = 20)</th>
<th></th>
<th>Test of significance</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A (UPH)</td>
<td>B (LMWH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abortion</td>
<td>3 (10%)</td>
<td>5 (25%)</td>
<td>Z = -0.79</td>
<td>0.43</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>2 (10%)</td>
<td>3 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic</td>
<td>1 (5%)</td>
<td>2 (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGA at loss (weeks)</td>
<td>11.67±3.79</td>
<td>12.6±3.78</td>
<td>T = 0.34</td>
<td>0.75</td>
</tr>
<tr>
<td>IUFD</td>
<td>-</td>
<td>1 (5%)</td>
<td>Z = -1.01</td>
<td>0.31</td>
</tr>
<tr>
<td>live births</td>
<td>17 (85%)</td>
<td>14 (70%)</td>
<td>Z = 1.14</td>
<td>0.25</td>
</tr>
<tr>
<td>Preterm</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IUGR</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full term</td>
<td>11</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGA at birth</td>
<td>38.2±2.05</td>
<td>38.1±1.35</td>
<td>T = -0.15</td>
<td>0.89</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>3306±463</td>
<td>3361±451</td>
<td>T = 0.33</td>
<td>0.74</td>
</tr>
<tr>
<td>Mode of delivery of live birth</td>
<td>(n = 17)</td>
<td>(n = 14)</td>
<td>X² = 1.29</td>
<td>0.26</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>10 (59%)</td>
<td>9 (43%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caesarean section</td>
<td>7 (41%)</td>
<td>5 (57%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antepartum bleeding</td>
<td>2 (10%)</td>
<td>2 (10%)</td>
<td>Z = 0</td>
<td>1</td>
</tr>
<tr>
<td>Postpartum bleeding</td>
<td>2 (10%)</td>
<td>3 (15%)</td>
<td>Z = -0.48</td>
<td>0.63</td>
</tr>
<tr>
<td>Thrombotic complications</td>
<td>-</td>
<td>1 (5%)</td>
<td>Z = -1.01</td>
<td>0.31</td>
</tr>
<tr>
<td>Maternal death</td>
<td>-</td>
<td>-</td>
<td></td>
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</tbody>
</table>

Data presented by Means Standard deviation or number or percentage

Overall, 77.5% of pregnancies resulted in live births while 20% aborted and 2.5% IUFD. As shown in Table 2, group A had 17 live births (85%) and 3 abortions (15%). Abortion rates were similar between the two study groups (p = 0.729). In group B, there were 14 live births (70%), 5 abortions (25%) and 1 IUFD (5%). The flow chart of pregnant women in study in shown in Fig. 1.

Four infants were born prematurely, two in group A and two in group B. Overall the low birth weight rate was 19% in our study (6/31 cases, 2 in group A and 4 in group B). Thus the rate was higher in group B (29% versus 12%).

There was one valve-related thrombosis in Group B (enoxaparin group), which occurred at 29 weeks gestation in a 25-year old patient who had undergone mitral-valve replacement at the age of ten years for left atrio-ventricular valve regurgitation. This was her third pregnancy, the first ending in an early spontaneous miscarriage while her second ended by IUFD at 30 weeks gestation one year previously whilst on warfarin treatment. She switched to therapeutic dose LMWH, enoxaparin 1 mg kg⁻¹ 12 hourly (weight 50 kg) at eight weeks gestation. By week 29, her enoxaparin dose was 60 mg kg⁻¹ 12 hourly (peak dose during pregnancy) and she developed progressive dyspnea. Pulmonary edema secondary to mitral valve thrombosis was diagnosed. She
underwent emergency CS with delivery of a female infant weighing 1.4 kg followed by emergency mitral valve replacement. Importantly, anti-Xa levels at 18 and 24 weeks gestation were subtherapeutic (0.6 and 0.64 IU mL⁻¹, respectively).

**DISCUSSION**

The combination of heart disease and pregnancy can present a challenge to the physician caring for both the mother and fetus (Danik and Fuster, 2004). Pregnancy after mechanical heart valve replacement requires strict control of coagulation. Special attention should be paid to the occurrence of complications during anticoagulation therapy (Kawamata et al., 2007). The risk of thromboembolism, miscarriage and premature birth seems to be higher in patients with prosthetic heart valves that require anticoagulation (Born et al., 1992). In order to prevent abortions and possible teratogenic effects, it was suggested that heparin should be substituted for warfarin in favor of the fetus before the most vulnerable period, embryogenesis (Ismail et al., 1986).

The importance of considering women's preference in decisions about anticoagulation is emphasized in the recent American College of Chest Physicians guidelines. Compliance with twice daily injections and frequent blood tests for anti-Xa levels throughout pregnancy is critical to provide safe management of these women. In women who are compliant, a low rate of valve thrombosis can be achieved that is acceptable to clinicians, together with a high rate of baby survival (Chan et al., 2000).

Aggressive dose-adjusted subcutaneous heparin can also be used. The aPTT response to heparin is diminished during pregnancy due to increased levels of factor VIII and fibrinogen. Heparin is given every 12 h subcutaneously with a mid-interval (6 h after dosing) aPTT = 2×control levels. Strict and frequent monitoring is essential (Bonow et al., 2006).

On the basis of small studies demonstrating the need for increased low-molecular-weight heparin to maintain anti-factor Xa levels in the 0.3 to 1.0 U mL⁻¹ range, some advocate the performance of periodic (every 1 to 3 months) anti-factor Xa levels 4 to 6 h after injection but other studies have shown that few women actually require increased doses when low-molecular-weight heparin is used. It is our practice to obtain an anti-factor Xa level approximately 4 h after injection within the first week of starting therapy and then repeat the level monthly at routine prenatal
visits, adjusting the level upward or downward as necessary. When patients are converted to unfractionated heparin in the last month of pregnancy, we check an Activated Partial Thromboplastin Time (aPTT) once or twice a week and adjust their dose of heparin to maintain the mid-dose aPTT at the lower end of the therapeutic range (Hung and Rahimtoola, 2003).

In the present study, the overall abortion rate was 20% (15% in the UFH group and 25% in the LMWH group). The UFH group had more spontaneous abortions (10%) compared to the IMWH group (15%), although this difference was not significant. This finding disagreed with studies by Nassar et al. (2004), Geelani et al. (2005), Cotrufo et al. (2002) and Al-Lawati et al. (2002) who noted fewer abortions in the LMWH group.

Our result also disagreed with a study by Akhtar et al. (2007) who showed a significantly higher spontaneous abortion rate in the heparin group.

Salazar and colleagues have reported a 37.5% incidence of spontaneous abortions in a series of patients treated with subcutaneous heparin during the first trimester of pregnancy. These high abortion rates could be explained by placental hemorrhage, which may occur during effective anticoagulation with UFH (Salazar et al., 1996), while Ismail et al. (1986) have reported a 23.8% (5/21) incidence of spontaneous abortion in 21 of patients treated with subcutaneous heparin throughout pregnancy.

The number of thrombotic complications in this study (2.5%) is lower than that documented by James et al. (2006) in their review, where they reported 17 thrombotic complications in 72 pregnancies (22%). It is notable that we observed no thrombotic complications in those patients whose anti-Xa levels were well maintained. Bleeding episodes occurred in 9 (22.5%) patients; however, there was a good maternal and fetal outcome in all cases. In their review, James et al. (2006) reported a 10.9% rate of haemorrhage including one fatal, whereas Rowan et al. (2001) in their study reported a rate of 14.3%.

This experience has demonstrated that an adjusted-dose high intensity LMWH regimen in pregnant women with prosthetic heart valves provides effective anticoagulation provided anti-Xa levels are kept within a tight therapeutic range of 0.7-1.2 IU mL⁻¹. The importance of meticulous anti-Xa monitoring with appropriate LMWH dose adjustment is underlined by the occurrence of a mitral valve thrombosis in one patient whose monitoring was not well maintained and the anti-Xa level was sub-therapeutic albeit transiently, although there were other contributory factors. There were live births in 14/20 pregnancies and no maternal mortality. Large increases in the doses of LMWH were required to achieve effective anticoagulation during pregnancy.

The rate of healthy babies born by these mothers was 57.9% in group A and 63.6% in group B, which is similar to results reported by Nassar et al. (2004) and Kim et al. (2007).

The main limitation of this study that it was non randomized study which can be explained by the need of active participation of the patients in buying the medication (cost implication).

REFERENCES


