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ORIGINAL ARTICLE

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

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Abstract

Objective This study was carried out to determine the maternal (including thromboembolic and hemorrhagic complications) and fetal outcomes (including miscarriage, stillbirth, baby death, and live birth) in women with mechanical heart valves managed with therapeutic doses of unfractionated heparin (UFH) versus enoxaparin during pregnancy.

Methods This is a prospective comparative, nonrandomized study. Pregnant women with mechanical heart valves presenting to high-risk pregnancy unit of Benha University Hospital, Egypt were treated with UFH 15,000 U/12 h versus enoxaparin (Clexane) 1 mg/kg SC/12 h during pregnancy and the results were analyzed.

Results 40 pregnant women were included in the study. In 20 pregnant women, anticoagulation was with UFH, and 20 pregnant women received enoxaparin. One (3 %) thrombotic complication occurred with enoxaparin treatment. Noncompliance or subtherapeutic levels contributed to this outcome in this case. Antenatal hemorrhage occurred in 4 (10 %) and postpartum hemorrhagic complications in 5 (12.5 %) pregnancies. Of the 32 pregnant women who continued after 20 weeks' gestation, 100 % (17/17) of the women taking predominantly UFH had a surviving infant compared with 93 % (14/15) of the women taking primarily enoxaparin ($p = 0.25$). One intrauterine fetal death occurred in the enoxaparin group. There was no significant difference in the live birth rates between the two groups ($p = 0.31$).

Conclusions Compliance with therapeutic dose of 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.

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Introduction

Mechanical heart valves have high risks of thrombosis and thromboembolism without concomitant anticoagulation. The risks are 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 risk of thromboembolic disease as well as the risk of anticoagulation for mother and fetus in patients with mechanical valves [1].

The main risks 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, and maternal bleeding from anticoagulation during (i) gestation, (ii) labor, and especially (iii) during delivery [2].

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 [3]. Warfarin is the mainstay of anticoagulation in the nonpregnant population, and pregnant patients with prosthetic valves have the lowest risks of valve thrombosis and thromboembolic events when appropriately anticoagulated. For the fetus, warfarin (coumadin) is relatively contraindicated due to its association with fetal warfarin syndrome during the weeks 6–9, and its relationship to fetal intracranial hemorrhage and secondary scarring at later stages [4, 5]. The attractiveness of both UFH and low-molecular-weight heparin (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 activated partial thromboplastin time (aPTT).

Heparin

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 aPTT at two to three times the normal in patients with valvular prostheses. 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, 4–6 h after delivery [6].

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 [7, 8]. LMWH should be monitored and dose-adjusted to achieve an anti-factor Xa level of a minimum of 0.7–1.2 unit/ml 4–6 h after injection to reduce the possibility of valve thrombosis [1, 9].

Recommendations from an American consensus conference on antithrombotic therapy for patients with mechanical heart valves stipulated three anticoagulation management choices [10]:

(1) High dose (e.g., 17,500–20,000 units) subcutaneous UFH throughout pregnancy given twice daily, with monitoring to guide dosing (aiming for a 6-hour post-dose of aPTT of twice the control level, or anti-factor Xa level maintained at 0.35–0.70 IU/ml).
(2) LMWH (e.g., dalteparin 100 units/kg) subcutaneously given throughout pregnancy with anti-factor Xa monitoring to guide dosing (aiming for a 4-hour post dosing to achieve an anti-factor Xa level of about 1.0 IU/ml).
(3) UFH or LMWH therapy as above until the 13th week of gestation, followed by warfarin until the middle of the third trimester, and then restarting with UFH or LMWH therapy until delivery.

Materials and Methods

This prospective comparative, nonrandomized study was conducted at the Department of Obstetrics and Gynecology, Benha University Hospital, and private centers, during the period from May 2012 till March 2014. After the approval of the study protocol by the Local Ethical Committee, fully informed patients' written consents were obtained. 40 pregnant women presenting with prosthetic heart valves were attended in the high-risk pregnancy unit—Benha University Hospital and were interviewed about their medical, personal, family, obstetrical, and thrombosis history.

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 during the decision-making process of anticoagulation.

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

(A) Replacement of warfarin with therapeutic dose of UFH (15.000 IU/12 h) before 6 weeks of gestation, continued throughout pregnancy but stopped 12 h

before delivery is anticipated and can be restarted, in the absence of hemorrhagic problems, 4–6 h after delivery.

(B) Replacement of warfarin with therapeutic dose of enoxaparin (1 mg/kg bid) before 6 weeks of gestation, continued until the 36th week of gestation, then switched to UFH (15.000 IU/12 h) until delivery. In the intrapartum setting, heparin injection should be stopped 12 h before delivery is anticipated and can be restarted, in the absence of hemorrhagic problems, 4–6 h after 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 2 weeks of pregnancy; both groups received heparin at the time of delivery.

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

For women in the enoxaparin group, monitoring of anti-factor Xa levels was recommended every month; our aim for target levels of anti-factor Xa was 0.7–1.2 IU/ml/4 h post dose [8]. Anti-factor Xa levels were first checked 3–7 days after starting treatment or following dose modification and the monitoring was repeated monthly at routine prenatal visits, for adjusting the level upward or downward as necessary.

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

Pediatricians examined all the 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, intrauterine fetal death (IUFD), IUGR preterm labor, and mode of delivery, while maternal outcomes included bleeding, valvular thrombosis, and maternal death.

Results were expressed as mean ± SD, range, numbers, and percentages. Intra-Group data were statistically analyzed using t test, and the inter-Group analysis was examined using Chisquare test (χ^2 test). Statistical analysis was conducted using SPSS statistical program, (Version 12). P value <0.05 was considered statistically significant.

Outcome Evaluation

The primary outcome measure was the rate of live births. Secondary outcomes included rates of miscarriage, IUFD, and obstetrical complications. Such complications included small size for gestational age, placental abruption, postpartum hemorrhage, premature delivery, maternal thrombotic complications, and maternal death.

Sample size calculation was according to the following formula:

$$N = 2\,\text{Standard deviation} \times K/E2,$$

where Standard deviation is the population of the previous literature; K is the constant (7.8) from statistical table; and $E2$ is the minimal change in mean that would be clinical.

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.

Overall, 77.5 % of pregnancies resulted in live births, while 20 % resulted in abortions and 2.5 % in 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 %) (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 % vs. 12 %).

There was one case of valve-related thrombosis in Group B (enoxaparin group), which occurred at 29 weeks of gestation in a 25-year old patient who had undergone mitral-valve replacement at the age of 10 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 of gestation 1 year before while on warfarin treatment. She switched to therapeutic dose of LMWH, enoxaparin 1 mg/kg/12 hourly (weight 50 kg) at 8 weeks of gestation. By

Table 1 Maternal characteristics at booking

Variables	Group A (UFH) ($n = 20$)	Group B (LMWH) ($n = 20$)	Test of significance	p value
Maternal age (years)	26.85 ± 4.65	26 ± 3.16	$T = -0.68$	=0.5
Weight(kg)	72.4 ± 6.68	71.25 ± 5.71	$T = -0.59$	=0.56
Total pregnancies	2.05 ± 1.28	2.25 ± 1.16	$T = 0.52$	=0.61
MVR	12 (60 %)	14 (70 %)		
AVR	5 (25 %)	4 (20 %)		
MVR and AVR	3 (15 %)	2 (10 %)		

Data presented by mean ± standard deviation or number or percentage

MVR Mitral valve replacement, *AVR* aortic valve replacement

Table 2 Pregnancy outcomes

Variables	Group A (UFH) ($n = 20$)	Group B (LMWH) ($n = 20$)	Test of significance	p value
Abortion	3 (15 %)	5 (25 %)	$Z = 0.35$	=0.58
Spontaneous	2 (10 %)	3 (15 %)		
Therapeutic	1 (5 %)	2 (10 %)		
EGA at loss (weeks)	11.67 ± 3.79	12.6 ± 3.78	$T = 0.34$	=0.75
IUFD	–	1 (5 %)	$Z = -1.01$	=0.31
Live births	17 (85 %)	14 (70 %)	$Z = 1.14$	=0.25
Preterm	2 (12 %)	2 (14 %)	$\chi^2 = 0.43$	=0.81
IUGR	4 (23 %)	2 (14 %)		
Full term	11 (65 %)	10 (72 %)		
EGA at birth	38.2 ± 2.05	38.1 ± 1.35	T = −0.15	=0.89
Birth weight (g)	3306 ± 463	3361 ± 451	T = 0.33	=0.74
Mode of delivery of live birth	($n = 17$)	($n = 14$)	$\chi^2 = 1.29$	=0.26
Vaginal delivery	10 (59 %)	9 (43 %)		
Cesarean Section	7 (41 %)	5 (57 %)		
Antepartum bleeding	2 (10 %)	2 (10 %)	Z = 0	=1
Postpartum bleeding	2 (10 %)	3 (15 %)	Z = −0.48	=0.63
Thrombotic complications	–	1 (5 %)	Z = −1.01	=0.31
Maternal death	–	–	–	–

Data presented by mean ± standard deviation or number or percentage

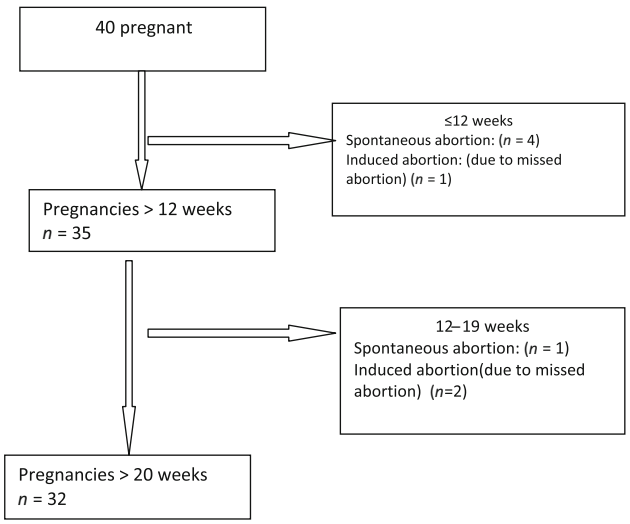

Fig. 1 Flow chart of pregnant women in the study

week 29, her enoxaparin dose was 60 mg/12 hourly (peak dose during pregnancy) and she developed progressive dyspnea. Pulmonary edema secondary to mitral valve thrombosis was diagnosed. She underwent emergency cesarean section (CS) with delivery of a female infant weighing 1.4 kg followed by emergency mitral valve replacement. Importantly, anti-factor Xa levels at 18 and 24 weeks of gestation were subtherapeutic (0.6 and 0.64 IU/mL, respectively).

Discussion

The combination of heart disease and pregnancy can present a challenge to the physician caring for both the mother and fetus [11]. Pregnancy after mechanical heart valve replacement requires strict control of coagulation. Special attention should be paid to the occurrence of complications during anticoagulation therapy [12]. The risks of thromboembolism, miscarriage, and premature birth seem to be higher in patients with prosthetic heart valves that require anticoagulation [13]. In order to prevent abortions and possible teratogenic effects, it was suggested that heparin should be substituted in place of warfarin in favor of the fetus before the most vulnerable period—embryogenesis [14].

It is important to consider women's preference in decisions about anticoagulation, and this is emphasized in the recent American College of Chest Physicians guidelines. Compliance with frequent blood tests for anti-factor Xa levels and twice-daily injections throughout pregnancy is important to provide safe management of these women. With good compliance, a low rate of valve thrombosis can be achieved, together with a high rate of live births [2].

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 $\geq 2 \times$ control levels. Strict and frequent monitoring is essential [15].

On the basis of small studies demonstrating the need for increased LMWH to maintain anti-factor Xa levels in the 0.6–1.0 U/mL range, some advocate the performance of periodic (every 1–3 months) anti-factor Xa levels 4–6 h after injection, but other studies have shown that few women actually require increased doses when LMWH 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 by monitoring monthly at routine prenatal visits, for adjusting the level upward or downward as necessary. When patients are converted to UFH in the last month of pregnancy, we check an 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 [16].

In the present study, the overall abortion rate was 20 % (15 % in the UFH group and 25 % in LMWH group).The UFH group had more spontaneous abortions (10 %) compared with the LMWH (low molecular weight heparin) group (15 %), although this difference was not significant. This finding disagreed with studies by Nassar et al. 2004 [17], Geelani et al. 2005 [18], Cotrufo et al. 2002 [19], and Al-lawati et al. 2002 [20] who noted fewer abortions in the LMWH group.

Our result also disagreed with a study by Akhtar et al. (2007) [21] who found 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 [22], while Ben et al. 1986 [14] 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 [20] 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-factor Xa levels were well maintained. Bleeding episodes occurred in nine (22.5 %) patients; however, there were good maternal and fetal outcomes in all cases. In their review, James et al. 2006 [23] had reported a 10.9 % rate of hemorrhage including one fatal, whereas Rowan et al. 2001 [24] in their study reported a rate of 14.3 %.

The importance of meticulous anti-factor Xa level 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 where the anti-factor Xa level was subtherapeutic 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 delivered by these mothers was 57.9 % in group A and 63.6 % in group B, which is similar to the results reported by Nassar et al. 2004 [17] and Kim et al. 2007 [25].

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

Conclusions

Compliance with therapeutic dose 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.

Compliance with ethical requirements and Conflict of interest The authors declare that they have no conflict of interest.

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