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Low Molecular Weight Heparin Treatment in Pregnant Women with a Mechanical Heart Valve Prosthesis

No definitive recommendation is available concerning optimal antithrombotic therapy in pregnant women with a mechanical heart valve. The purpose of the current study was to evaluate the clinical results of nadroparin treatment with respect to pregnancy outcome and maternal complications. From 1997 to 2005, 31 pregnancies were reviewed in 25 women. Nadroparin (7,500 U, twice daily) was used in 23 pregnancies between 6 and 12 weeks of gestation and close-to-term only, and coumarin derivatives were used with aspirin at other times. Eight pregnant women treated with coumarin derivatives throughout pregnancy were compared to evaluate the safety and efficacy of nadroparin. No maternal death or bleeding complication occurred in either of the two groups, and frequencies of maternal thromboembolism including valve thrombosis (8.7% vs. 12.5%, $p>0.05$) were similar. However, the frequencies of live born (91.3% vs. 50%, $p=0.01$) and healthy babies (90.4% vs. 25%, $p<0.01$) were significantly higher, and the fetal loss rate was significantly lower (8.7% vs. 50%, $p=0.01$) in the nadroparin-treated group. Regarding the efficacy and safety of antithrombotic treatment in pregnant women with prosthetic heart valves, nadroparin treatment during the first trimester is an acceptable regimen and produces better results than coumarin derivatives.

Key Words : *Low Molecular Weight Heparin; Heart Valve Prosthesis; Pregnant Women*

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INTRODUCTION

In pregnant women with mechanical heart valves, the frequency of valve thrombosis increases due to pregnancy-related hypercoagulability. Therefore, effective anticoagulation is critical in pregnant patients with mechanical heart valves but remains problematic because both oral anticoagulation and heparins have been associated with important fetal and maternal side effects (1).

Coumarin derivatives are anticoagulants of choice for mechanical heart valves, but they cross the placenta and are associated with coumarin-induced fetal loss or embryopathy (1-3). Unfractionated heparin (UFH) provides an alternative therapy that avoids fetal side effects, however, the use of UFH is associated with increased maternal thromboembolic and bleeding complications (1, 4, 5). Low molecular weight heparin (LMWH) may be more advantageous than UFH (6), and appears a good alternative. However, little clinical information and no reliable data are available regarding its efficacy and safety.

No consensus has been reached about optimal antithrombotic therapy in pregnant patients with a mechanical heart valve. Coumarins are contraindicated in pregnancy in North America due to fetal concerns, but European experts have recommended low dose coumarins (less than 5 mg daily) throughout pregnancy given a very low frequency of fetal anomalies (2, 3). Reports of LMWH use began to appear, and many physicians now use LMWH because of its good safety profile for both mother and baby (7-10). However, treatment failures have been reported (11, 12), and no LMWH has been licensed for use in pregnant patients with mechanical heart valves. Thus, physicians and patients face dilemmas when making decisions on anticoagulation therapy.

Available published data regarding the efficacy and safety of LMWH in this clinical setting have been derived from small case series, and usually enoxaparin has been used. Here, we report our experience of nadroparin treatment, and its associated pregnancy outcomes and maternal complications.

MATERIALS AND METHODS

Between 1997 and 2005, 31 pregnancies were analyzed retrospectively in 25 women with mechanical heart valves. Basic characteristics and previous operative data are listed in Table 1. In 23 of these 31 pregnancies, nadroparin was used as an anticoagulant during the first trimester with given informed

consent, concerning the risks and benefits of LMWH. Others were anticoagulated with coumarin derivatives (CMD) with or without aspirin due to unawareness of pregnancy until the first trimester, or because of refusal or poor compliance on self-injected LMWH.

In the LMWH-treated group, our anticoagulation protocol was as follows. When pregnancy was confirmed, coumarins were stopped and changed to subcutaneous nadroparin (7,500 U, twice daily), from 6 weeks to 12 weeks of gestation. Subsequently, nadroparin was changed to coumarins until the middle of the third trimester. Aspirin, at 100 mg/day, was also administrated throughout the pregnancy. At gestation week 38, women were scheduled for labor induction and changed to nadroparin to avoid the delivery of an anticoagulated fetus. After establishing labor, we carefully checked for hemorrhages and other complications, and babies were examined for congenital anomalies and weight.

In the CMD-treated group, coumarins and aspirin were continued throughout the pregnancy and the target International Normalized Ratio (INR) was maintained between 2.5 to 3.5. Coumarins were changed to nadroparin before 2 weeks prior to the expected delivery date to avoid fetal bleeding complications during delivery.

Pregnancy outcomes, namely, numbers of healthy babies, fetal anomalies, fetal losses, and maternal complications, including thromboembolism or bleeding, were analyzed. To evaluate the efficacy and safety of LMWH, eight pregnancies, maintained using coumarins throughout pregnancy, were compared.

Data were analyzed using SPSS for windows version 10.0 software and compared using the Student's t-test, at a level of significance of $p<0.05$.

Table 1. Baseline characteristics of pregnancies (n=31)

	LMWH (n=23)	CMD (n=8)
Age (mean)	26.3 yr	24.3 yr
Previous operation		
MVR	15	6
AVR	3	1
DVR	4	1
Valve types		
Carbomedics	10	5
St. Jude Medical	6	2
Edward-Tekna	3	0
Duromedics	2	1
ATS	2	0

LMWH, low molecular weight heparin; CMD, coumarin derivatives; MVR, mitral valve replacement; AVR, aortic valve replacement; DVR, double valve replacement.

Table 2. Incidence of materal thromboembolism

	LMWH (n=23)	CMD (n=8)
TIA*	1 (4.3%)	1 (12.5%)
Valve thrombosis*	2 (8.7%)	1 (12.5%)
Mitral	2	1
Aortic	0	0

LMWH, low molecular weight heparin; CMD, coumarin derivatives; TIA, transient ischemic attack. *$p>0.05$.

RESULTS

No maternal death or bleeding complication occurred in either the LMWH-treated group or the CMD-treated group. Frequencies of maternal thromboembolism were not different between the two groups (Table 2). A maternal transient ischemic attack (TIA) occurred in one case in each group, and both patients had previously undergone mitral valve replacement. Prosthetic mitral valve thrombosis occurred in three pregnancies, two in the LMWH group and one in the CMD group (Table 3). The two of these three patients underwent redo surgery, and other patient was managed on thrombolytic therapy. All three patients recovered without complications; however, their fetal outcomes were unfavorable.

Numbers of live born and healthy babies were higher in the LMWH group (Table 4). In both groups, two babies had low birth weights of 2.1 kg and 2.4 kg, but were otherwise healthy. In the CMD group, one baby had hydrocephalus. However, the frequency of fetal loss including therapeutic abortion and stillbirth were significantly higher in the CMD group. Two fetal losses occurred in the LMWH group, both occurred in cases of maternal valve thrombosis. Four fetal losses occurred in the CMD group, and one of these involved maternal valve thrombosis.

DISCUSSION

This study demonstrates that LMWH-based therapy is

Table 3. Valve thrombosis

Age	Group	Time	Fetus	Treatment
37	CMD	18 wk	stillbirth	Redo MVR
28	LMWH	16 wk	abortion	Thrombolysis
32	LMWH	16 wk	abortion	Redo MVR

LMWH, low molecular weight heparin; CMD, coumarin derivatives; MVR, mitral valve replacement.

Table 4. Summary of fetal outcomes

	LMWH (n=23)	CMD (n=8)	*p*
Live born baby	21	4	0.011
Healthy baby	19	1	0.000
Hydrocephalus	0	1	NS
Low birth weight*	2	2	NS
Fetal loss	2	4	0.011

*Low birth weight, ≤2,500 gm.
LMWH, low molecular weight heparin; CMD, coumarin derivatives.

superior to coumarin therapy in pregnant women with a prosthetic heart valve, and that the use of nadroparin during the first trimester with 100 mg of aspirin throughout pregnancy could be a safe and effective protocol for thromboprophylaxis in these women.

Recent recommendations, published in 2004 as part of the 7th American College of Chest Physicians (ACCP) consensus on antithrombotic therapy (12), included the following three regimens: 1) aggressive adjusted-dose LMWH throughout pregnancy; 2) adjusted-dose UFH, throughout pregnancy; or 3) either LMWH or UFH between 6 and 12 weeks and close-to-term only and the use of CMD at other times. In particular, the use of CMD during the first trimester was not recommended. Our protocol was similar to the third regimen, but we also administered aspirin (100 mg daily) throughout pregnancy to reduce coumarin dosages and the risk of thromboembolism. The overall frequencies of maternal thromboembolism, including valve thrombosis, were similar in both groups, but the frequencies of live and healthy baby births were higher in the LMWH group. These results demonstrate that LMWH-based therapy is a good alternative to coumarins, because it has similar anticoagulation effects with lower fetal side effects.

Exposure to coumarins during the second part of the first trimester is associated with fetal loss, primarily due to spontaneous abortion or coumarin-induced embryopathy. The reported frequencies of coumarins-related embryopathy vary for debatable reasons (14, 15), a recent study suggested that coumarin risk is dose related and that adverse effects occur mainly in women taking >5 mg daily. However, this finding was not confirmed by another study. In our series, the target INR was maintained with less than 5 mg of coumarins in all patients in the CMD group; however, a half of these lost their babies due to abortion or stillbirth. Our results represent only observational data, and the effect of dose-related embryopathy remains uncertain. Furthermore, the use of coumarins in pregnant women still poses medicolegal problems.

LMWH does not cross the placental barrier and offers potential advantages compared with UFH in terms of better safety profile with less thrombocytopenia, less bleeding, less osteoporosis with prolonged treatment, a more predictable and rapidly reached anticoagulant effect, and the possibility of self-administration of anticoagulant therapy without laboratory monitoring. However, treatment failures have been reported, and the use of LMWH for pregnant women with mechanical heart valves has become controversial due to small numbers of patients and a lack of accurate postmarketing data (16). A recent review of 81 pregnancies in 75 women treated with LMWH reported an 8.6% rate of valve thrombosis (17), and found that appropriate dose adjustments could reduce the frequency of thromboembolism. The 7th ACCP recommendations call for the use of LMWH at levels that achieve peak anti-factor Xa values of around 1.0 U/mL (12). A recent prospective study with deltaparin reported that dosages based on body weight were inadequate to maintain a therapeutic level of LMWH in pregnancy (18). Our data demonstrate that valve thrombosis occurred in 2 patients treated with nadroparin; a prevalence of 8.7%. Unfortunately, we did not monitor anti-Xa levels during nadroparin administration, and thus, we cannot conclude that valve thrombosis is associated with an inadequate nadroparin dose. Further studies, with sufficient statistical power, are required to clarify the clinical significance of anti-Xa levels.

In conclusion, despite the retrospective design of the present study, it might be worth to mention that LMWH appears a safe and effective substitute for any other anticoagulants in pregnant women with mechanical heart valves. We have experienced that pregnancy outcomes are acceptable with LMWH, but that its efficacy for preventing valve thrombosis remains uncertain. Further studies are needed in order to establish appropriate management protocols for pregnant women with mechanical heart valves.

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