

Low Molecular Weight Heparin and Warfarin in the Treatment of Patients with Antiphospholipid Syndrome during Pregnancy

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Keywords

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Summary

Fifty-seven pregnancies in women with antiphospholipid syndrome (APS) are presented. These were treated with s.c. enoxaparin and low dose aspirin. In fourteen pregnancies warfarin was prescribed between weeks 15-34 (warfarin group). The decision to switch to warfarin depended on a morbidity score, and the patient's consent. Neither teratogenicity nor significant maternal, fetal or neonatal hemorrhage was observed. Despite the higher pretreatment morbidity score of the warfarin group, the live birth rate was high in both groups: 86% in the warfarin group and 87% in the non-warfarin group. There was no significant difference in week of delivery, birth weight, or incidence of thrombosis between the groups. The study demonstrates the efficacy and safety of anticoagulants during pregnancy. The use of LMWH in pregnant women with APS not being moot, warfarin might be justified in selected patients.

Introduction

The antiphospholipid syndrome (APS) is characterized by the presence of antiphospholipid antibodies (APLA), associated with venous and/or arterial thrombosis, and/or pregnancy loss (1).

The adverse pregnancy outcomes associated with the presence of APLA include: recurrent fetal loss, intrauterine growth restriction (IUGR), and severe pre-eclampsia especially of early onset (2-8). Other complications such as HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets), DIC (Disseminated Intravascular Coagulopathy), and placental abruption may be additional manifestations of the same entity (9-11).

The pathophysiological mechanisms of fetal loss and other obstetrical complications include hypercoagulability and immunological reactions. Thrombosis of utero-placental vessels that leads to placental infarctions and hence to fetal loss is probably the major pathogenic factor (12-15). However, other mechanisms like vasculitis, immune complex deposition, direct antibody activity against endothelial cells, platelets and throphoblasts may also be involved (16, 17).

The thrombotic effect of APLA is of special interest during pregnancy, a situation in which hypercoagulability exists normally (18, 19).

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Several therapeutic approaches have been implied to improve the pregnancy outcome of these women. These include antiaggregating agents, and/or anticoagulants, prednisone, and high dose immunoglobulins (IVIg) (20-36).

The use of anticoagulants during pregnancy may cause complications both to the mother and the fetus. The anticoagulants commonly used are: unfractionated heparin, low molecular weight heparin (LMWH) and warfarin. Warfarin is teratogenic when given during the organogenetic stage of pregnancy: between 6 and 12 weeks of gestation. In addition, warfarin has a stronger anticoagulant effect in the fetus than in the mother due to low production of vitamin K dependent coagulation factors by the immature fetal liver. The risk of bleeding is increased especially during delivery (37). Even though, vitamin K antagonists have been used during pregnancy, hesitance to treat patients with warfarin even during the second trimester is still present (36, 38-43).

Unfractionated heparin, and LMWH can be used safely during pregnancy, as they do not cross the placenta. However, the use of unfractionated heparin during pregnancy is associated with increased risks for osteoporosis, maternal hemorrhage, heparin induced thromocytopenia and paradoxical thrombosis (44). The required dose rises during pregnancy, and b.i.d or t.i.d injections with frequent monitoring are needed to achieve the target aPTT (45).

LMWH seems to be safer than the unfractionated heparin with a lesser tendency to bleed due to its higher antithrombotic to anticoagulant ratio. The prolonged use of LMWH during pregnancy is however not without risk of osteoporosis and thrombocytopenia (36, 46-50).

Our own data as well as those of others encouraged us to embark on a therapeutic protocol that consists of a combined regimen of low dose aspirin and anticoagulants. In the past, we had patients treated with unfractionated heparin throughout the pregnancy that developed significant osteoporosis with compression fractures. This led to the idea of replacing heparin for warfarin during mid pregnancy. This switch was not associated with any teratogenicity or morbidity (26).

In the present study 57 pregnancies in 42 patients having the APS, either primary or secondary to SLE were treated with LMWH – s.c. enoxaparin during the pregnancy and the post partum period. In 14 pregnancies, enoxaparin was switched to warfarin during the mid-pregnancy Herein we present the results of the treatment with respect to efficacy and adverse effects to the mother and the fetus.

Patients and Methods

Fifty-seven pregnancies in 42 women with APS were followed.

APS was diagnosed whenever there was a history of previous fetal loss, and/or a previous thrombotic event, in the presence of lupus anticoagulant (LAC) and/or anticardiolipin (aCL) antibodies. LAC was determined by using KCT and the Rosner LAC index (51). IgG and IgM aCL antibodies were detected by an enzyme linked immunoabsorbent assay (ELISA) (Selisa, Cambridge Life Sciences, England).

Positive results were read as IgG aCL >8.4 IU/ml; IgM aCL >7 IU/ml.

	Warfarin group	Non-warfarin group	
No. of patients	11	31	
Age mean (range)	30.2 (24-39)	31.25 (20-42)	
Diagnosis			
SLE& APS	0	7	
Primary APS	11	24	
aCL IgG normal< 8.4 IU/ml			
negative:	0	8	
low positive: ≥8.4<12:	0	7	
medium positive: ≥12≤30:	5	7	P=0.057
high positive: ≥30:	6	10	
aCL IgM normal< 7 IU/ml			
negative:	1	7	
low positive: ≥7<10:	0	1	
medium positive: ≥10<20:	0	2	
high positive: ≥ 20:	1	2	
not assessed :	9	20	
LAC normal < 15%			
negative:	1	10	
low positive: ≤20:	0	7	
medium positive: ≥20≤30:	3	2	
high positive: ≥30:	7	11	P=0.042
Outcome of 120 previous pregnancies in 37 women			
Total no. of pregnancies	22 (1- twins)	84	
(artificial abortions)	(6)	(8)	
No. of live babies	**6/23 (26%)**	**40/84 (47.6%)**	P=0.043
Total no. of pregnancy loss	**17/23 (74%)**	**44/84 (52.4%)**	P=0.043
before 14 weeks	9	26	
between 14-24 weeks	1	15	
after 24 weeks	7	2	
neonatal death	0	1	
IUGR of live babies	1	5	
Pre-eclampsia	0	5	
Previous thrombotic events in 19 women			
Deep vein thrombosis	7	5	
Pulmonary emboli	0	3	
Neurological events (CVA-3,TIA's-4, chorea-2)	4	5	
Arterial events (non CVA)	1	4	
Morbidity score	**10.64**	**6.5**	**P=0.0066**

Table 1 Demographic data, LAC/ACL results, obstetrical and thrombotic history of the patients

Protocol of Treatment

Subcutaneous enoxaparin 0.7 mg/kg/d (the lowest initial dose was 40 mg/d) and tab. aspirin 0.1/d were given to patients with the following history: three or more early spontaneous abortions (<14 weeks of gestation), one or more late abortion (≥14 weeks of gestation), IUFD (≥24 weeks of gestation), IUGR, previous episode of pre-eclampsia or HELLP. Enoxaparin 1 mg/kg/d was given to patients with a previous episode of thrombotic event at any time. Therapy was started as early as possible after confirmation of the pregnancy by ultrasound and fetal heart beat. The dose of enoxaparin was boosted by 50% or more whenever body weight increased by more than 15 kg, in the presence of maternal thrombotic event, or when there was evidence for severe IUGR.

For the purpose of statistical analysis, the enoxaparin doses were divided to levels from 1-5: starting with a minimum dose of 40 mg/d (level 1) with increments of 20 mg/d up to a maximum dose of 120 mg/d (level 5).

Warfarin was offered to the patients between weeks 14 to 34 of pregnancy. The pregnancy was divided to 3 periods in relation to the anticoagulant therapy: period I – up to 14th week of gestation, period II – between the 14th and 34th week of gestation, period III – above the 34th week of gestation.

The patients were followed regularly by an obstetrician (DM), hematologist (MA), and by one of the rheumatologists (PR, LP, LA). This team evaluated the previous medical and obstetrical history of each case to determine the type of recommended therapy. A morbidity score as defined below reflects the decisions of the evaluating team. Each patient received a score according to the following index: Two early spontaneous abortions (SA): score = 1, SA ≥ 3: score = 2, late abortion: score = 2, IUFD: score = 3, IUGR: score = 3, eclampsia/pre-eclampsia or HELLP: score = 3, previous maternal thrombotic event related to pregnancy or contraceptive pills: score = 4, previous maternal thrombotic event not related to pregnancy or contraceptive pills: score = 5, failure of a previous treatment during pregnancy: score = 4, chronic warfarin therapy prior to current pregnancy: score = 5.

Warfarin was highly recommanded to pregnant women with high morbidity scores, to patients whose symptoms were not alleviated by increased doses of enoxaparin and to patients with osteoporosis. We explained the pros and cons regarding the use of different anticoagulants during pregnancy. The patients were party to the decision as to the type of anticoagulant. Some patients would not consider taking warfarin at all.

In this study we had 2 groups of patients: The warfarin group comprised of 14 pregnancies in 11 women that were treated with warfarin between weeks 14 and 34 of pregnancy. The non-warfarin group comprised of 43 pregnancies in 31 women treated with low dose aspirin and enoxaparin throughout the pregnancy.

The dose of warfarin was monitored by frequent measurements of INR aiming at INR between 2 and 2.5. The anticoagulant and anti-aggregating therapies were continued during the post partum period (6 weeks).

The demographic data, LAC/ACL results, obstetrical and thrombotic history of the patients are presented in Table 1.

Statistical Analysis

Standard Chi-square tests were applied to determine significance of differences in rate of occurrences of various events before and after treatment and between patient groups. P-values are given under the assumption of independence. Statistical distribution of morbidity scores and enoxaparin levels of the warfarin and non-warfarin groups are presented using box plots. The box boundaries are positioned at the lower and upper quartiles of the distribution. The box is split at the value of the median. The whiskers extend to the last observation in the three standard deviation range from the median. Observations beyond these limits are marked as stars. The large dot, within the box indicates the average value.

Results

The distribution of morbidity scores of the warfarin group and the non-warfarin group is presented in Fig. 1. The mean morbidity score of the warfarin group was 10.64, versus 6.5 for the non-warfarin group ($p = 0.0066$). The overall score distribution of the warfarin group was significantly higher reflecting the severity of the disease in this group. There was 25% overlap between the two groups reflecting the fact that treatment decisions were not only determined by the score.

Ten out of 14 pregnancies (71%) of the warfarin group had a morbidity score ≥7, while only 15/43 pregnancies (35%) of the non-warfarin group had such a score ($p = 0.053$).

Warfarin was given for a mean period of 13 weeks; range: 5-19 weeks.

The distribution of the sum of enoxaparin levels that were given during periods I, II and III were calculated and are demonstrated in Fig. 2. The difference in the spread of the enoxaparin levels in the two groups is apparent. The mean level for the warfarin group and the non-warfarin group was similar: 2.67 versus 2.26. However in the warfarin group more patients received higher levels of enoxaparin, in 25% of the cases the levels were between 4 and 7.

49 of 57 (86%) pregnancies ended successfully, with 52 live babies (3 pairs of twins), and 8 of 57 (14%) pregnancies failed. Three of the failures were between weeks 12 and 16 of gestation, while the other 5 were between weeks 20 and 31 of gestation. Of the 49 deliveries of the live babies 40 were vaginal deliveries (including 2 pairs of twins), whereas 9 pregnancies ended by cesarean section. The mean week of delivery was 37.8 (range 32-42); the mean delivery weight was 2812 g. (range: 1355-4380 g). There were 11 cases of IUGR, 6 of them are alive of whom 2 were born as severe IUGR (below 10th percentile).

There was no case of fetal or neonatal hemorrhage and no case of teratogenicity based on clinical evaluation.

Comparison of the obstetrical outcome between the warfarin group and the non-warfarin group did not show any significant difference regarding the live birth rate, week of delivery and birth weight (Table 2).

Maternal Complications

There was no case of significant maternal bleeding.

As shown in Table 2 complications were seen in both groups without significant difference ($p = 0.319$): There were 12 thorombotic events, 6 in each group. The details of the events and the timing of the events are of interest. In the warfarin group one pregnancy was complicated by DVT and PE in a non-compliant patient, and other 5 pregnancies of 3 women were complicated by minor thrombotic events. One thrombotic episode-nail infarct occurred while the patient was on warfarin with INR of only 1.34. The other thrombotic episodes included recurrent amaurosis fugax in 1 pregnancy, and black dots in the visual fields in 3 pregnancies. These minor neurological events occurred while the patients were being treated with enoxaparin, disappeared after the enoxaparin was substituted by warfarin, and recurred toward the end of the pregnancy, when the warfarin was replaced by enoxaparin.

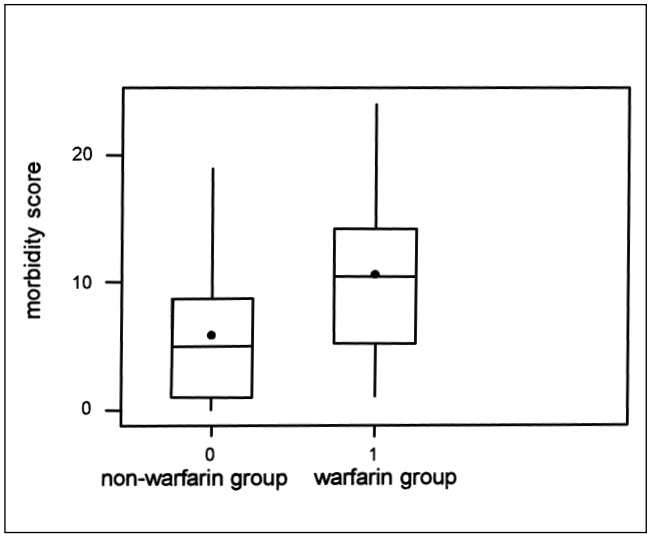

Fig. 1 Box plots of distributions of morbidity scores of the warfarin group and the non-warfarin group. The mean morbidity score of the warfarin group was 10.64, versus 6.5 for the non-warfarin group ($p = 0.0066$). The overall score distribution of the warfarin group was significantly higher reflecting the severity of the disease in this group. There was 25% overlap between the two groups reflecting the fact that treatment decisions were not only determined by the score

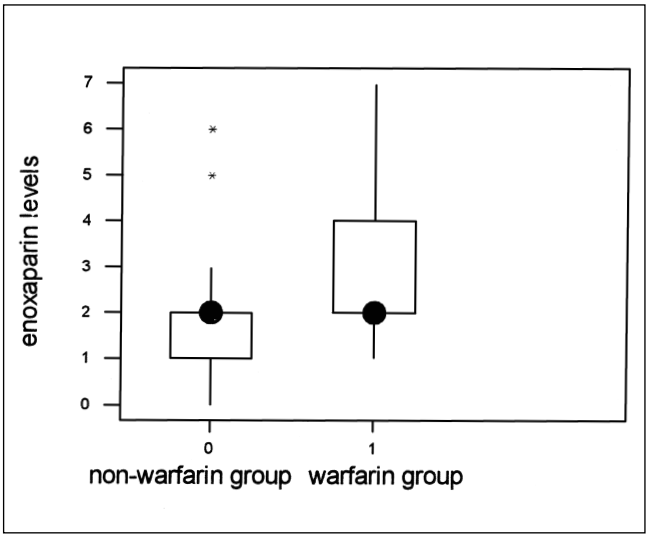

Fig. 2 Box plots of the distribution of the sum of enoxaparin levels that were given during periods I, II and III. The difference in the spread of the enoxaparin levels in the two groups is apparent. The mean level for the warfarin group and the non-warfarin group was similar: 2.67 versus 2.26. However in the warfarin group more patients received higher levels of enoxaparin, in 25% of the cases levels were between 4 and 7

Group	Warfarin group	Non-warfarin group	P value
pregnancies/ fetuses	14/14	43/46	
score (mean)	10.64	6.5	0.0066
successful pregnancies			
number	12/14	40/46fetuses (3 twins)	p=0.22
(%)	(85%)	(87%)	
birth weight gr.	2706	2833	P= 0.59
live IUGR	2/12	4/44	P=0.45
week of delivery	37.3	37	P= 0.7
Maternal complications			P= 0.319
no. of pregnancies with any event	8/14	18/43	
no. of thrombotic events	6·	6	
DIC	0	1	
pre-eclampsia	1	2	
HELLP	1	3	
other ··	5	15	

· 4 thrombotic events occurred in pregnancies of the warfarin group but while being on enoxaparin.
·· thrombocytopenia and/or abnormal liver function tests, hypertension

Table 2 Comparison of the pregnancy outcomes between the warfarin group and the non-warfarin group

In the non-warfarin group, there were 6 thrombotic events: 1-hepatic vein thrombosis and 5 minor transient neurological events.

Discussion

The results of the present study of 57 pregnancies (3 pairs of twins) in 42 women with APS are very encouraging. The patients were treated with low dose aspirin and s.c. enoxaparin throughout the pregnancy and the postpartum period. In 14 pregnancies warfarin was given during the mid-pregnancy. Fifty-two of the 60 fetuses were delivered successfully increasing the success rate of this group from 44% before the study to 86.6% (p = 0.0001). It should be noted that most of these women received some therapy in the past. Based on our historical data we know that without any therapy the prevalence of pregnancy loss was as high as 93% (26). The data is in accordance with reports in the literature that show pregnancy loss of 50-90% in untreated women with APS (4, 5).

The live birth rate of the pregnancies was high both in the warfarin group and the non-warfarin group. There was also no difference in the week of delivery, or birth weight between the 2 groups eventhough the warfarin group included more complicated patients with higher morbidity scores and higher levels of aCL and/or LAC (Table 1). We can speculate that the good results in the warfarin group were achieved because of the more intensive therapy that included warfarin and higher doses of enoxaparin.

In 2 of our patients enoxaparin was substituted by warfarin even though they had low scores. Both had recurrent SA and migraine headaches. We did not include migraine headaches in our score, but it is well known that it is one of the neurological manifestations of APS. TIAs occurred in 4 patients, even when they received high doses of enoxaparin, and disappeared during the warfarin period. We assume that this was the result of better anticoagulation during the warfarin treatment.

Maternal complications included a variety of disorders. Pre-eclampsia was seen in 3 pregnancies, which was not different from the number of events in the history of this group. However, 4 additional patients (3 in the non-warfarin group) had HELLP which was not reported in the history of our patients. Other 14 patients had either hypertension (3), thrombocytopenia (5), abnormal liver function tests (2), or different combinations of the above (4). Do these abnormalities represent incomplete forms of HELLP? We speculate that we had a significant number of complicated pregnancies because more pregnancies reached higher gestational age. Yet, again we raise the question of how aggressive should we be when using anticoagulant therapy?

It is still not clear what is the best management of pregnant women with APS. Anticoagulants are generally accepted by many groups as the main therapy. However, many points remain moot as to the indication for therapy, the type of anticoagulants, the doses and the duration of therapy, and the use of additional drugs such as prednisone and IVIG (20, 27-32, 34-36, 44, 46, 49, 50, 52-55).

Our study shows that the use of enoxaparin throughout the pregnancy and warfarin between the 14th and 34th week of gestation is safe. There was neither significant maternal or fetal bleeding, nor fetal teratogenicity.

It is not clear as yet in which patients warfarin is indicated. It appears that it may be used safely as an alternative therapy for patients with high morbidity scores. Support for the safety of the use of warfarin during the second trimester of pregnancy may be found in the 1998 recommendations of the ACCP Consensus Conference on Antithrombotic Therapy during pregnancy. Warfarin is also recommended to patients with mechanical heart valves during the second trimester of the pregnancy, similarly to our protocol (34).

There is no consensus as to the type, doses and duration of treatment with LMWH. Some use a very low dose of LMWH, and discontinue the anticoagulant treatment toward the end of the pregnancy (32).

Our study differs from others as it represents a group of patients with the same disease – APS either primary or secondary, treated with the same protocol. This is different from other studies that either describe different protocols for patients with APS seen in the same clinic (28), or the results of studies that combine different types of patients using the same protocol (54, 55).

The doses of enoxaparin were modified several times during the pregnancy. The initial dose was adjusted to the patient's weight, and was increased during the follow-up when body weight increased by more than 15 kg. The lowest initial dose was 40 mg/day. Higher initial doses were given to patients with high morbidity scores including women with previous thrombotic events related or not to pregnancy and/or oral contraceptives. The doses of enoxaparin were monitored during pregnancy by measuring the anti-Xa level, with the aim of anti-Xa of 0.05 to 0.1 at the nadir (data not shown).

So far, our results are encouraging. Women with APS, having a bad obstetrical history and even a major thrombotic event in the past, may embark on pregnancy, even though the risk is high. It is possible that the use of warfarin during the second trimester decreases the risk for thrombosis, and increases the live birth rate of the pregnancies. With a careful monitoring by an experienced team, there is a good chance for a safe delivery of a healthy baby.

Debatable issues still exist: should we increase the dose of LMWH throughout the pregnancy? Would it increase the success rate of the pregnancies and decrease the rate of complications that still occurs? Would it increase the rate of complications related to therapy? Should warfarin during the second trimester be recommended to more patients with APS? Addressing these issues requires a more extensive study with a larger group of patients. We hope that more studies from different centers using anticoagulants during pregnancy will help us answer some of these questions.

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