Clinical and Experimental Rheumatology 2011; 29: 551-554.

Adjusted prophylactic doses of nadroparin plus low dose aspirin therapy in obstetric antiphospholipid syndrome. A prospective cohort management study

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Reprints will not be available from the author.

Received on September 30, 2010; accepted in revised form on February 11, 2011.

Key words: nadroparin, neonatal outcome, obstetric antiphospholipid syndrome, pregnancy outcome

Competing interests: none declared.

ABSTRACT

Objective. *Current guidelines for the treatment of patients with obstetric antiphospholipid syndrome (APS) recommend low dose aspirin (LDA) and prophylactic doses of low molecular weight heparin (LMWH). Most clinicians use a fixed dosage of LMWH in pregnant APS women despite the fact that there are no clinical trials establishing that fixed doses are more efficacious than adjusted ones in preventing pregnancy complications. The efficacy and safety of adjusted single daily doses of LMWH (nadroparin) combined with LDA have thus been evaluated in 33 consecutive pregnancies in women with diagnosed obstetric APS.*

Methods. *LMWH doses were augmented as the pregnancies progressed and maternal/foetal weight increased. 70–80–90 U/Kg doses ranging between 3800 and 6650 U were administered daily during the first, second and third trimesters, respectively. LDA (100 mg/day) was also prescribed.*

Results. *Pregnancy outcome was successful in 97% of the patients studied, who delivered, between the 29th and 41st weeks of gestation (mean 37.4 ± 2.1 SD), 32 infants with a mean birth weight of 3084 g ± 514 SD. One woman (3%) experienced a spontaneous abortion at the 8th week of gestation.*

Conclusion. *The high live birth rate, the satisfactory mean gestational age and weight at birth and the absence of major pregnancy/neonatal-associated complications indicate that adjusted, once daily doses of LMWH together with LDA could be an efficacious treatment option for pregnant APS patients with no history of thrombosis.*

Introduction

Diagnosis of obstetric antiphospholipid syndrome (APS) is defined by pregnancy morbidity criteria consisting of late foetal loss, premature birth and recurrent early abortions and laboratory detection of antiphospholipid antibodies (aPL), such as lupus anticoagulant (LA), and/or anticardiolipin (aCL), and/or anti-$\beta_2$glycoprotein I (aβ_2GPI) antibodies (1, 2). Current guidelines for the treatment of pregnant APS patients with a history of pregnancy morbidity but no vascular thrombosis recommend low dose aspirin (LDA) and once-daily doses of low molecular weight heparin (LMWH) (3). Most clinicians (4-8) use a fixed dosage of LMWH in the treatment of pregnant APS women despite the fact that there are no clinical trials establishing that fixed doses are more efficacious than adjusted ones in preventing pregnancy complications. The following results were obtained in pregnant obstetric APS patients with no history of thrombosis treated with adjusted once-daily doses of LMWH (nadroparin) and LDA.

Materials and methods

Thirty-three women attending our Rheumatology Unit were enrolled in this study as they became pregnant between October 2002 and June 2008. In accordance with the International Consensus Statement for the classification of APS (1), clinical inclusion criteria consisted of a history of one or more of the following: a) one or more unexplained deaths of morphologically normal foetuses at or beyond the 10th week of gestation, b) one or more premature births of morphologically normal neonates before the 34th week of gestation because of severe preeclampsia-eclampsia or recognised symptoms of placental insufficiency, c) three or more unexplained consecutive spontaneous abortions before the 10th week of gestation. The laboratory criteria included LA and/or medium/high titres of aCL and/or aβ_2GPI antibodies detected on two or more occasions at least 12 weeks apart. The exclusion criteria were a prior history of thrombosis or the presence of a diagnosed autoimmune systemic disease.

The University's Research Ethics Committee approved the study protocol and, once informed consent was given, the patients were taught to self-administer once-daily subcutaneous injections of nadroparin from the time a pregnancy test resulted positive. Following a previous experience with adjusted LMWH doses (9), we increased the drug's dosage as the pregnancies progressed and foetal/maternal body weight augmented. The women were thus administered 70–80–90 U/kg dur-

Table I. Antiphospholipid antibody profiles and clinical characteristics of the 33 patients with obstetric antiphospholipid syndrome.

N.	Age (years)	Antibody profile	Pregnancy morbidity (weeks of gestation)	N.	Age (years)	Antibody profile	Pregnancy morbidity (weeks of gestation)
1	36	Medium IgG aCL, Medium IgG aβ_2GPI	*1 FL (10) + 2 EPL (6, 6)	18	40	Medium IgG aCL, Medium IgG aβ_2GPI, Medium IgM aβ_2GPI	^3 EPL (5, 6, 3)
2	27	Medium IgG aCL	*2 FL (12, 12) + 1 EPL (9)	19	40	High IgM aCL, high IgM aβ_2GPI	*1 FL (12)
3	41	Medium IgG aCL	*2 FL (11, 10)	20	38	High IgG aβ_2GP I	^4 EPL (5, 7, 4, 4)
4	41	Medium IgG aCL, Medium IgG aβ_2GPI	*1 FL (12) + 1 EPL (6)	21	34	LA	*2 FL (20, 16)
5	25	Medium IgG aCL	*1 FL (21)	22	34	Medium IgG aβ_2GPI, Medium IgM aβ_2GPI	*1 FL (16)
6	33	Medium IgG aCL, Medium IgM aCL, High IgG aβ_2GP	*1 FL (17) + 1 EPL (5)	23	36	Medium IgG aβ_2GPI, Medium IgM aβ_2GPI	*1 FL (27)
7	35	Medium IgG aCL, High IgG aβ_2GPI	¶1 FL (15) + 3 EPL (8, 6, 8)	24	40	Medium IgG aCL, Medium IgM aβ_2GPI	*1 FL (11) + 1 EPL (8)
8	32	Medium IgG aβ_2GPI	*1 FL (27)	25	37	Medium IgM aβ_2GPI	*1 FL (40)
9	33	Medium IgM aCL, Medium IgG aβ_2GPI	*1 FL (28)	26	30	Medium IgM aCL, Medium IgM aβ_2GPI	*1 FL (12) + 1 EPL (6)
10	33	Medium IgG aCL	*2 FL (11, 11) + 1 EPL (9)	27	40	Medium IgG aCL, High IgG aβ_2GPI	*1 FL (10) + 1 EPL (6)
11	36	Medium IgM β_2GPI	¶1 FL (21) + 3 EPL (7, 9, 8)	28	30	Medium IgG aCL,	*2 FL (12, 12) + 1 EPL (9)
12	35	Medium IgM β_2GPI	*3 FL (17, 10, 12)	29	33	Medium IgG aβ_2GPI	*1 FL (30)
13	28	Medium IgG aCL,	*1 FL (37)	30	38	Medium IgM aCL, Medium IgM aβ_2GPI	¶1 FL (13) +3 EPL (7, 8, 8)
14	37	LA	*1 FL (10) + 2 EPL (8, 8)	31	35	Medium IgM aβ_2GPI	*1 FL (16)
15	38	Medium IgG aCL	^3 EPL (7, 5, 7)	32	36	Medium IgG aβ_2GPI, Medium IgM aβ_2GPI	*1 FL (17) + 2 EPL (4, 8)
16	32	Medium IgG aβ_2GPI	*1 FL (31)	33	40	Medium IgM aβ_2GPI	1 FL (12) + 1 EPL (8)
17	30	Medium IgG, Medium IgM aβ_2GPI	^3 EPL (8, 8, 8)				

FL: foetal loss; EPL: early pregnancy loss; *Presence of FL criterion; ^Presence of EPL criterion; ¶Presence of both FL and EPL criteria.

ing the first, second and third trimesters, respectively. Patients with a body weight ranging from 54 to 64 kg (mean 61.5) received LMWH doses ranging between 3800 and 5700 U/daily, while those with a body weight ranging from 65 to 76 kg (mean 70.8) received doses ranging between 4750 and 6650 U/daily. A 475-950 U/daily LMWH supplement was, moreover, prescribed at the first signs of pregnancy complications and, in particular, whenever platelet counts began a progressive downward trend. A significant (>20% of the basal value) progressive platelet fall, in the absence of anti-platelet and anti-factor 4-heparin complex antibodies, has, in fact, been found to be an early sign of pregnancy complications (10, 11). In accordance with the manufacturer's recommendations, the once-daily dose never, in any case, exceeded the weight-adjusted dosage of 95 U/kg. The last injection of LMWH was administered 24 hours before a planned caesarean delivery or an epidural anaesthesia was given, while therapy was stopped at the beginning of labour when the pregnancy ended with a vaginal delivery. It was resumed 12 hours after delivery and was continued at a dosage of 3800 (weight ≤60 kg) - 4750 (weight >60 kg) U/daily for six weeks. The patients were also receiving LDA (100 mg/daily) which was stopped 10 days before the expected birth date.

Heparin-induced thrombocytopenia was monitored by checking platelet counts weekly during the first 2 weeks of treatment and monthly thereafter. The patients were advised to take one hour daily walks and to take 1000 mg/day calcium ion to prevent heparin-induced osteoporosis.

ACL and anti-β2GPI antibodies were determined using home-made ELISA assays. LA testing was carried out following internationally recognised recommendations (12).

Results

Thirty-three patients affected with primary obstetric APS (mean age 34.9 years ± 4.1 SD; range 25–41) were in-

Table II. Pregnancy and neonatal outcomes in the 33 patients with obstetric antiphospholipid syndrome.

N.	Pregnancy Complications	Gestational age at delivery (weeks)	Birth weight g percent.	Newborn complications	N.	Pregnancy Complications	Gestational age at delivery (weeks)	Birth weight g percent.	Newborn Complications
1	–	39	3000 25	–	18	–	37	2840 25	–
2	–	38	3255 50	–	19	–	37	3155 75	–
3	–	36	3020 50	–	20	–	36	2565 25	–
4	–	38	2745 25	–	21	–	36	3215 75	–
5	–	38	3000 25	–	22	–	39	3325 25	–
6	–	36	2700 50	–	23	–	39	4350 97	–
7	–	37	3340 75	*PNX	24	–	37	3070 50	–
8	–	40	3370 25	–	25	^TCP	38	3470 50	–
9	–	34	2038 25	–	26	–	37	2600 25	–
10	–	38	3010 25	–	27	§HYPT	38	3200 50	–
11	–	37	2835 25	–	28	¶EPL	–	–	–
12	–	29	1280 50	**RDS	29	–	39	3700 75	–
13	–	37	3270 75	–	30	–	40	3230 50	–
14	–	36	2840 50	–	31	–	40	3500 50	
15	^TCP	37	3095 50	–	32	–	38	3480 75	–
16	–	38	3360 50	–	33	–	39	3020 5	–
17	-	41	3300 25	–					

*PNX: pneumotorax; **RDS: respiratory distress syndrome; ^TCP. thrombocytopenia; §HYPT: hypothyroidism; ¶EPL: early pregnancy loss.

cluded in the study as their pregnancies were confirmed. Twenty-six (78.8%) had a history of foetal loss (type a), 4 (12.1%) had at least three consecutive early abortions (type c), and 3 (9.1%) presented more than one type of pregnancy morbidity (types a and c) (Table I). Fourteen of the patients (42.4%) were positive to IgG aCL, 5 (15.1%) to IgM aCL, 16 (48.5%) to IgG aβ_2GPI, 14 (42.4%) to IgM aβ_2GPI and 2 (6.1%) to LA, while 15 (45.4%) presented more than one type of aPL positivity. Isolated IgG aCL was found in 7 cases (21.2%), isolated IgG aβ_2GPI was found in 4 (12.1%), isolated IgM aβ_2GPI was found in 5 (15.1%), and isolated LA was found in 2 (6.1%). Isolated IgM aCL was not found in any of the patients and none were positive to all three aPL antibodies (Table I).

LMWH was begun at a mean gestational age of 8.5 weeks ± 3.8 SD (range 6–23). Platelet counts began to fall in two of the patients (6.1%) during the 11th and 10th weeks of pregnancy, respectively, but when nadroparin was increased by 950 U/daily they quickly returned to normal levels. No other complication requiring higher nadroparin dosages was noted.

None of the women suffered from thrombosis during pregnancy or puerperium. Minor side effects, such as bruising or rashes at the injection site, minor bleeding or higher eosinophil levels, were not serious enough to make it necessary to discontinue therapy.

Thirty-two of the women (97%) gave birth to 32 live infants between the 29th and 41st weeks of gestation (mean 37.4 ± 2.1 SD): 24 (75%) by caesarean delivery and 8 (25%) by vaginal birth. One (3.1%) infant was born prematurely at 29th week of gestation due to *placenta previa*. One woman (3.1%) had laboratory signs of hypothyrodism at the 20th week. No signs of foetal complications were registered during any of the pregnancies (Table II).

Pregnancy loss of an unknown origin occurred at the 8th week of gestation in a 30 year-old woman (3%) not suffering from other disorders but with a history of two late foetal losses and one early abortion as well as IgG aCL positivity (medium titer). The parents' karyotypes were normal, but the abortion material was not analysed.

When the different subsets of obstetric APS were examined, it was found that pregnancy loss occurred in only one of the patients with a history of foetal loss (3.8%) in none with histories of recurrent early abortions, and in none with both of these.

All 32 infants (16 females and 16 males, with a mean birth weight of 3084 g ± 514 SD; range 1280–4350) were above the 25th percentile. The mean Apgar score was 8.5±0.9 SD (range 6–9) at one minute and 9.6±0.8 SD (range 8–10) at 5 minutes. Two (6.2%) of the infants were transferred to the Neonatal Intensive Care Unit due to pneumothorax in one case and to respiratory distress in the other. Both responded to conventional therapies and their subsequent clinical course was normal. None of the infants suffered from thrombotic events or other antiphospholipid-related complications and no malformations were registered.

Discussion

The high rate of live births (97%), the satisfactory mean gestational age (37.4 weeks) and weight at birth (3084 g), and the absence of major pregnancy/neonatal complications found in the patients studied indicate that adjusted-dose once daily LMWH and LDA are an efficacious, safe therapy in the treatment of obstetric APS patients with no history of thrombosis. Employing fixed once-daily LMWH doses and LDA, some investigators have achieved as high as an 84% live birth rate in obstetric APS patients (4-8). Using higher, adjusted doses of LMWH as pregnancies progressed and maternal/foetal body weight increased probably explains the higher

birth rate noted in the patients studied. Sephton *et al*. (13), in fact, reported finding differences in LMWH pharmacokinetics and an overall reduction in anti-factor Xa levels as the pregnancies of the patients studied progressed. Reduced subcutaneous heparin bioavailability may be due to pregnancy associated physiological changes such as increases in heparin-binding proteins, in plasma volume, in renal clearance, and in heparin degradation by the placenta (14, 15). As LMWH activity seems to decrease during the course of pregnancies, a gradual, measured dose increase may be necessary. It must, in any case, be emphasised that the dose prescribed to our patients never exceeded the prophylactic weight-adjusted dosage recommended by the manufacturer and that no important side effects were observed in our patients.

This is the first prospective cohort study, to our knowledge, on the use of adjusted once daily LMWH doses in the treatment of pregnant APS patients affected with pregnancy morbidity alone. Its excellent results can be considered its strength while its limits are the modest number of patients who were not matched with controls treated with fixed LMWH once daily doses. Future large scale clinical trials on obstetric pregnant APS patients treated with adjusted or fixed LMWH are warranted to establish what therapy favours live birth rates and prevents maternal and foetal complications.

Acknowledgements

The authors are grateful to Mrs Linda Inverso Moretti for editing the English version of this manuscript.

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