A Study of 75 Pregnancies in Patients with Antiphospholipid Syndrome

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ABSTRACT. ***Objective***. To describe a French tertiary referral center experience in the treatment of pregnancies in patients with the antiphospholipid syndrome (APS).

Methods. Retrospective review of the data of 75 consecutive pregnancies in 47 women.

Results. After exclusion of induced abortions and pregnancies occurring before APS onset, the prior live birth rate was 7.9%. Forty-nine pregnancies occurred in women with history of vascular thrombosis, 17 with history of thrombocytopenia. Heparin was prescribed in 39 pregnancies, associated with aspirin in 35 cases, and aspirin alone was used in 36 as first-line therapy. Corticosteroids were prescribed in 38 pregnancies. Three pregnancies by *in vitro* fertilization led to one embryonic loss, one full term birth, and one premature birth. Six pregnancies treated with immunoglobulin ended in one fetal death, 2 premature and 3 full term deliveries. The outcome of the other 66 pregnancies was one embryonic loss, 8 fetal deaths, 16 prematurates, and 38 full term births. Use of corticosteroids correlated with severe prematurity ($p = 0.005$), preeclampsia ($p = 0.014$), intrauterine growth retardation ($p = 0.005$), and presence of disease associated to APS ($p = 0.009$). After exclusion of one fetal death associated with congenital anomaly, live birth rate was 72.9%. There was a trend for higher rate of fetal survival in patients without history of vascular thrombosis (84.6 vs 66.4%; $p = 0.11$).

Conclusion. Obstetrical prognosis in APS was improved by antithrombotic therapy. Studies are needed to define individual risk and specific significance of the various antiphospholipid antibodies, in order to improve the respective indications for aspirin alone or with heparin in women without thrombotic events. (J Rheumatol 2001;28:2025–30)

Key Indexing Terms:
ANTIPHOSPHOLIPID SYNDROME SYSTEMIC LUPUS ERYTHEMATOSUS PREGNANCY

The antiphospholipid syndrome (APS) is a cause of pregnancy loss that can explain recurrent miscarriages in up to 25% of the cases[1]. In pregnant women with history of unsuccessful pregnancies, spontaneous rate of live birth is below 10%[2]. The other obstetrical complications are intrauterine growth retardation (IUGR), preterm delivery, preeclampsia, hemolysis, liver, low platelets syndrome (HELLP), and vascular thrombosis. The pathogenesis of obstetrical complications remains unclear although multiple placental infarcts are generally present when fetal death occurs[3]. Several treatments have been proposed including corticosteroids, aspirin, heparin, high dose intravenous immunoglobulin, and azathioprine. Although incompletely standardized, therapy has improved pregnancy outcome, with live birth rate above 70%, irrespective of the prescribed protocol[4]. We describe our experience in the treatment of APS pregnancies followed in our department of internal medicine during the period 1984 to 1998.

MATERIALS AND METHODS

Patients. We retrospectively reviewed the data of 75 consecutive pregnancies in 47 women with APS. Diagnosis of APS was based on one or more of the following criteria at some point in the disease course[5]: (1) vascular thrombosis; (2) pregnancy morbidity, i.e., (a) one or more unexplained fetal deaths; (b) one or more premature births of a morphologically normal neonate at/or before 34 weeks of gestation because of severe preeclampsia or eclampsia, or because of severe placental insufficiency; or (c) 3 or more unexplained consecutive spontaneous abortions before the 10th week of gestation; (3) persistent medium or high anticardiolipin antibodies of IgG and/or IgM isotype or lupus anticoagulant (LAC).

LAC was usually detected by activated partial thromboplastin time (PTT), diluted thromboplastin time, or kaolin clotting time. Abnormal coagulation times were confirmed by a 1:1 mixture of patient and control plasma to exclude clotting factor deficiencies. aCL antibodies were measured by ELISA for IgG and IgM aCL. Results were reported as negative when < 15 U/ml, low positive between 16 and 25 U/ml, medium positive between 26 and 80 U/ml, and high positive when > 80 U/ml. Besides one woman who had history of recurrent thrombophlebitis, fetal death with

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Table 1. Number of pregnancies according to type of antiphospholipid syndrome.

Diagnosis	No. of Women	No of Pregnancies 1	2	3	4
Primary APS, n = 40	24	13	6	5	0
Secondary APS, n = 35					
SLE	21	13	6	1	1
Mixed connective tissue disease	1	0	1	0	0
Ulcerous colitis	1	1	0	0	0

false positive test for syphilis, and low aCL (16 GPL), all patients had LAC or medium IgG aCL, or both.

Mean age at pregnancy was 30 ± 4 years (range 21–39). APS was found to be primary in 27 women and secondary in 20 (Table 1). Mean duration from date of diagnosis was 4.94 ± 3.9 years (maximum 18). APS was revealed by vascular occlusion in 31 women (thrombophlebitis, n = 24, arterial thrombosis, n = 5, both arterial and venous thrombosis, n = 2); by obstetrical complications in 21 cases, of which 5 had both vascular and obstetrical complications. Out of 13 women with history of thrombocytopenia, one had had splenectomy. Before pregnancy diagnosis, 7 women, all with history of thrombophlebitis, were treated with vitamin K antagonists and 32 with low dose aspirin. Nineteen women with secondary APS were treated with corticosteroids, at a mean dosage of 10 mg/day (range 5–25). Pregnancy was monitored from pregnancy diagnosis up to 12 weeks postpartum, by at least a monthly consultation (more frequently after 30 weeks' gestation depending on disease activity and fetal status) by medical and obstetrical physicians. At each visit, weight and blood pressure were measured; fetal growth was assessed by abdominal palpation, by evaluation of symphysis-fundal height, and by ultrasound; and urinalysis was performed using Multistix. Monthly routine laboratory assessment consisted of total blood count, liver enzyme determination, uric acid, serum creatinine, aCL determination, and 24 h proteinuria. For secondary APS, specific laboratory assessments were carried out for systemic lupus erythematosus (SLE), antinuclear antibodies, anti-dsDNA, anti-ENA, total complement, C3, and C4. A fetal ultrasound was done at least every 3 months; evaluation of uteroplacental perfusion by artery Doppler was performed starting in 1993. Upon pregnancy diagnosis, therapy included low dose aspirin, heparin, corticosteroids, high dose immunoglobulin, and plasma exchanges depending on obstetric and vascular history. The aim of corticosteroid therapy was to prevent and/or treat pregnancy induced SLE flare, during the whole study period; and to reduce antiphospholipid antibody (aPL) titer in primary APS, from 1984 to the early 1990s. During the 1983–93 period, regimens of low dose aspirin alone or associated with prednisone were predominantly used. Heparin was generally prescribed when fetal loss had occurred earlier despite low dose aspirin, or in patients with a history of thrombotic events. During this period, we followed 27 pregnancies, of which 9 were treated with heparin, 2 secondarily. A femoral thrombophlebitis occurred at 28 weeks' gestation in a woman taking aspirin. Heparin was then added until cesarean section 2 weeks later indicated because of acute fetal distress; the woman delivered a growth retarded baby. Heparin was added secondarily in one other case. After 1993, heparin with low dose aspirin became the favored treatment: among 48 pregnancies, 35 were treated with heparin and aspirin. However, heparin was prescribed as first-line therapy in 31 women only. It was added secondarily to aspirin in 4 pregnancies when growth rate decreased or elevated uteroplacental resistance appeared on fetal Doppler ultrasound. Thus, 39 pregnancies were treated as first-line therapy with self-administered subcutaneous heparin: calcium heparin twice daily in 4 cases at a daily dose varying between 5,000 and 12,000 units, low molecular weight heparin (LMWH) once (12 pregnancies) or twice daily (23 pregnancies) at a daily dose ranging between 3,000 and 16,000 units. Except for 4 pregnancies, heparin was associated with 100 mg daily aspirin. Thirty-six pregnancies were initially treated with low dose aspirin without heparin. Low dose aspirin was prescribed from pregnancy diagnosis to 36 weeks' gestation. Then it was converted to calcium heparin 3,000 units twice daily until delivery. In the postpartum period, heparin was continued for 4–6 weeks. Then anticoagulation was maintained in 24 women by vitamin K antagonists and the others were switched to low dose aspirin. Six pregnancies were treated with high dose immunoglobulins: 70–80 g during 2 successive days every 3–4 weeks associated with low dose aspirin and heparin in 5 cases, after failure of low dose aspirin, alone or associated with heparin. Plasma exchanges were added in 2 cases. Corticosteroids, mean dose 22 mg/day (range 7–60), were prescribed in 38 pregnancies, i.e., in 29/35 secondary APS pregnancies and in 9 primary APS pregnancies (2 with autoimmune thrombocytopenia). In case of secondary APS, prednisone dose could be increased during the pregnancy according to disease activity, but it was never decreased up to the postpartum period. Seven of 24 pregnancies followed after 1995 in women with SLE or mixed connective tissue disease were treated with 400 mg/day hydroxychloroquine.

Definitions. The following definitions were used:

Duration of gestation was measured from the first day of the last normal menstrual period or, if not available, on the ultrasound estimate.

Embryonic loss: spontaneous termination of pregnancy prior to 10 weeks' gestation[5]

Fetal death: according to Branch's definition[4], death of a fetus shown to be alive at or beyond 10 weeks' gestation

Premature birth: termination of pregnancy with a live birth before 37 weeks' gestation

Full term birth: termination of pregnancy with a live birth between 38 and 40 weeks

Intrauterine growth retardation (IUGR): birth weight below the 10th percentile for the stated gestation

Hypertension: diastolic pressure > 90 mm Hg

Preeclampsia: hypertension complicated with 0.5 g/24 h proteinuria or edema or both

Eclampsia: preeclampsia complicated with seizures.

Adverse pregnancy outcome: at least 3 embryonic losses, fetal or neonatal death, or premature birth of a morphologically normal neonate at or before 34 weeks' gestation because of severe preeclampsia or eclampsia, or severe placental insufficiency.

Statistical methods. Statistical analyses were by Fisher's exact test.

RESULTS

The 47 women had a total of 75 treated pregnancies (Table

Table 2. Pregnancy outcome in 46 women with APS: 71 prior untreated pregnancies and 75 treated pregnancies.

No. of Pregnancies	Induced Abortion for Unwanted Pregnancy	Therapeutic Abortion	Embryonic Loss	Fetal Death and Stillbirth	Premature Birth	Full Term Birth
Prior untreated, n = 71	5	3*	25	26**	3	9
Treated, n = 75	0	0	2	19***	16	38

* Including 1 SLE; ** Including 5 cases of preeclampsia; *** Including 2 cases of preeclampsia.

1). Fourteen women were initially nulliparous. Sixteen who were multiparous had history of thrombophlebitis.

Previous pregnancies. Thirty-three women had a total of 71 prior untreated pregnancies (Table 2). Two multiparous women had had only one induced abortion for unwanted pregnancy. Out of 12 live births, 7 were borne by 5 women before the first clinical or laboratory evidence for APS. All these 7 babies were born at full term, but one pregnancy had been complicated by HELLP syndrome and IUGR. In the 5 other live births, one mother had had asymptomatic false positive syphilis test, one had prior thrombophlebitis, and 3 had prior complicated pregnancy (embryonic loss with thrombocytopenia, n = 2, fetal death with preeclampsia, n = 1). Two babies were born at full term without complication and 3 prematurely. Two pregnancies were complicated by HELLP syndrome, prematurity, and IUGR. One prematurate presented neonatal hemiplegia and seizures and is now mentally retarded. Thus, after exclusion of induced abortions and pregnancies occurring before APS onset, only 5 out of 63 pregnancies (7.9%) ended in live births.

All 14 initially nulliparous women had history of vascular thrombosis: lower limb thrombophlebitis in 9 cases, arterial thrombosis in 4 cases (lower limb in 2 cases, stroke in 2), and both thrombophlebitis and stroke in one case.

Induced pregnancies. Pregnancy was induced in 3 cases. Infertility was secondary in all cases, with a history of fetal death in all women. It was related to salpingitis in one case, and remained unexplained, except for presence of aPL, in the others. Induced ovulation therapy was performed under aspirin, prescribed solely in 2 cases, and associated with low molecular weight heparin (LMWH) in one. It was associated in one case with embryo transfer in a woman with SLE related APS. A previous cycle of *in vitro* fertilization had failed under aspirin, hydroxychloroquine, and prednisone. Premature delivery was undertaken by cesarean section because of preeclampsia with features of HELLP syndrome and fetal distress at 27 weeks' gestation. The growth retarded baby (birth weight 500 g) had respiratory distress syndrome and staphylococcus sepsis and is still growth retarded at present. Induced ovulation employed clomifene in 2 cases. Three cycles failed under aspirin and prednisone in one case, leading to addition of LMWH. Spontaneous abortion occurred at 5 weeks' gestation. The last pregnancy, following one year of clomifene and aspirin therapy, ended in full term vaginal delivery of a healthy girl of 3100 g birth weight.

Fetal outcome in spontaneous pregnancies. One embryonic loss and 19 fetal deaths occurred. Hygroma was present in one fetal death. One fetal death was complicated by HELLP syndrome, and another case was preceded by superfical thrombophlebitis. Doppler ultrasound examination was performed in 6 cases at 20–22 weeks. It showed elevated resistance to blood flow in the umbilical artery without IUGR in one case, with IUGR in 3 cases, with lower impedance to blood flow in the uterine artery in one case, and sudden polyhydramnios in the last case. Pathological examination discovered multiple placental infarcts in the 3 studied cases, one of which was associated with congenital anomalies.

Fifteen babies were premature. Mean duration of these pregnancies was 33 ± 2 weeks (range 30–36). Delivery was induced in 8 cases because of preeclampsia or fetal distress. Mean birth weight was 1764 ± 649 g (range 1000–2980). Two out of 4 growth retarded prematurates were born from mothers having preeclampsia. Eight cesarean sections were carried out. Indications were fetal distress in 7 cases and retroplacental hematoma in one case. One severely growth retarded prematurate died at 6 weeks. Six other prematurates developed neonatal complications: streptococcus beta hemolytic sepsis, n = 2, respiratory distress, n = 3, hypoglycemia, n = 1, gastroesophageal reflux, n = 2 and jaundice, n = 3. One baby had congenital pulmonary stenosis that required neonatal percutaneous balloon valvuloplasty.

Thirty-seven pregnancies ended in full term delivery after a mean duration of pregnancy of 39 ± 1 weeks (range 37–40). Delivery was induced in 4 cases because of hypertension in 2 cases, premature membrane rupture in one case and for personal reasons in the other. Mean birth weight was 3016 g (range 2000–4040). Fourteen cesarean sections were carried out. Indications were fetal distress in 4 cases, history of cesarean section in 3, and failure to progress in 3. One neonatal death occurred in a eutrophic fetus that suffered cardiac rhythm disturbances not related to maternal anti-SSA/SSB. One growth retarded baby had hypospadias. Another baby developed neuroblastoma, which was cured by chemotherapy.

Pregnancies treated with high dose immunoglobulins. Six women were treated by high dose immunoglobulins with aspirin, associated with plasma exchanges in 2 cases and with heparin in 4 cases. Pregnancies ended in one preeclampsia complicated by fetal death at 30 weeks, 3 premature deliveries (at 29, 33, 36 weeks), and 2 full term deliveries.

Maternal outcome. Five women developed flare of an associated disorder during pregnancy: 4 had SLE and had one ulcerative colitis. Among the former, flare occurred at the end of first trimester in 2 cases and in the postpartum period in 3. It consisted of arthralgias and/or cutaneous manifestations. Severe digestive flare occurred during the first trimester in the patient with ulcerative colitis. All patients remitted with increased corticosteroid dosage (mean dosage increase 20 mg daily). Preeclampsia occurred in 10 patients between 25 and 36 weeks: 6 had preeclampsia, 2 preeclampsia associated with features of HELLP syndrome, and 2 had HELLP syndrome. All but one were treated with steroids, of which one had a history of SLE diffuse proliferative glomerulonephritis. Seven women were treated with heparin and aspirin and 3 with aspirin only. For one woman

who developed preeclampsia at 25 weeks, use of labetalol therapy and increased LMWH dosage from 5000 to 8000 units twice daily allowed delay of a cesarean section for 3 weeks. Seven pregnancies ended in preterm deliveries and 3 in fetal deaths. Two babies were growth retarded. Delivery was induced by cesarean section in 6 cases at between 27 and 34 weeks. Vaginal delivery was performed in one case at 36 weeks.

Maternal complications were intraperitoneal hemorrhage after cesarean section needing surgery (n = 1), delivery hemorrhage (n = 4), transient autoimmune (non-toxemia related) thrombocytopenia (n = 2), infection (n = 2: acute pyelonephritis, herpes zoster infection), and postpartum pulmonary embolism after having stopped aspirin mistakenly without switching to heparin. Diabetes occurred in 1/38 steroid treated pregnancies. All 14 women with history of adverse pregnancy outcome who were followed for at least 2 treated pregnancies had at least one successful pregnancy. At longterm followup, 2/16 women presenting with obstetrical APS developed vascular complications during the subsequent 3–4 years.

Indicators of fetal prognosis. After exclusion of one fetal death associated with congenital anomaly, the live birth rate was 54/74 (72.9%). We analyzed the following indicators of live birth rate: maternal age; date of pregnancy; duration from APS diagnosis; primary versus secondary APS; nulliparity; history of normal pregnancy; history of adverse pregnancy outcome; history of thrombophlebitis, of arterial thrombosis, or of either venous or arterial thrombosis, and of thrombocytopenia; LAC positivity; aCL levels; and use of steroids and of heparin as first-line therapy. We found no significant indicator of prognosis. However, a trend for lower live birth rate was associated with history of vascular thrombosis (66.4% vs 84.6%; p = 0.11). Severe premature delivery was associated with steroid therapy. Twenty-four of 35 premature (35 weeks or before) and 5/19 babies born at 36 weeks or after occurred in steroid treated women (p = 0.005). Preeclampsia (p = 0.014) and IUGR (p = 0.005) also correlated with corticosteroid use. Of 26 babies from mothers with secondary APS, 20 were prematurates versus 15/28 from mothers having primary APS (p = 0.009) (Table 3).

DISCUSSION

In our study, the live birth rate increased from 12/63 (19%, but no more than 7.9% if only pregnancies occurring after APS onset were taken into account) to 54/75 (72%). The finding is similar to other series, varying between 63%[6] and 100%[7,8], even if the definition of APS varied: at least one[7,9] or 2 spontaneous abortions[8,10-13] or thrombocytopenia[6,10], or low aCL[14,15] were sufficient in some series that might have selected less severe types of APS. A count of at least 3 consecutive spontaneous abortions is now required in the consensus criteria for definite APS[5]. Only 5 series met these criteria, of which 4 excluded women with secondary APS[11,14-16], with history of thrombosis[14-16], and with LAC[16]; and 2 might have included women with only low aCL, but in a maximum proportion of 8.9%[15] to 33%[14] (Table 4). Kutteh, *et al*[16] included women with medium or high aCL or antiphosphatidylserine, this latter not being routinely tested. Hence, only the study of Branch, *et al*[6] is similar to ours. The study by Lima, *et al*[10] might also be compared to our study, although only at least 2 spontaneous abortions were required for inclusion, because it has the same practical approach.

Incidence of fetal death fell from 41.2% to 25.3% while incidence of embryonic loss fell from 36.7% to 2.6%. Most fetal losses occurring during the first trimester are considered to be associated with morphological and chromosomal anomalies. This fact led Branch[4] to distinguish embryonic loss and fetal death (i.e., after 10 weeks' gestation), the latter being more specific for APS. Hence, after exclusion of embryonic losses and fetal death associated with congenital anomaly, we observed that fetal survival increased from 31.5% to 75% under therapy. However, prior fetal deaths might be underestimated, since duration of pregnancies was

Table 3. Outcome of 75 pregnancies in 47 women with APS according to first-line therapy.

First-line Treatment	Embryonic Loss	Fetal Death	Preterm Delivery	Full Term Delivery	IUGR	Neonatal Death	Preeclampsia
Aspirin, n = 17	0	5	2	10	0	1	0
Heparin with or without aspirin, n = 17	0	6	0	11	0	0	1
Aspirin plus prednisone, n = 18	1	5	5	7	2	1	3
Heparin with or without aspirin plus prednisone, n = 17	1	2	7	7	6	0	5
Other, n = 6	0	1	2	3	0	0	1

IUGR: intrauterine growth retardation.

Table 4. Comparison of pregnancy outcome in APS according to treatment.

Author	APS Type	Therapy	Number of Pregnancies	Miscarriages and Neonatal Deaths (%)	Live Births (%)
Rai[2]	Primary	None	20	18 (90)	2 (10)
Kutteh[16]	Primary	Aspirin	25	14 (56)	11 (44)
		Heparin plus aspirin	25	5 (20)	20 (80)
Balasch[11]	Primary	Aspirin	12	1 (8%)	11 (92)
Branch[6]	Primary and secondary	Aspirin plus prednisone	39	18 (46)	21 (54)
		Heparin plus aspirin	19	5 (26)	14 (74)
		Heparin plus aspirin plus prednisone	12	2 (17)	10 (83)
		Other	12	5 (42)	7 (58)
Rai[15]	Primary	Aspirin	45	26 (58)	13 (29)
		Heparin plus aspirin	45	19 (42)	32 (71)
Backos[14]	Primary	Heparin plus aspirin	150	43 (29)	107 (71)
Lima[10]	Primary and secondary	Aspirin	27*	7 (26)	20 (74)
		Aspirin plus prednisone	9	2 (22)	7 (78)
		Heparin plus aspirin	7	1 (14)	6 (86)
		Heparin plus aspirin plus prednisone	16	7 (44)	9 (56)
Our series	Primary and secondary	Aspirin	17	6 (35)	12 (65)
		Aspirin plus prednisone	18	7 (39)	11 (61)
		Heparin with or without aspirin	17	6 (35)	11 (65)
		Heparin with or without aspirin plus prednisone	17	3 (18)	14 (82)
		Other	6	1 (17)	5 (83)

* After exclusion of 1 induced abortion.

difficult to determine because of data missing from medical reports. We found no strong indicator for fetal prognosis. The influence of maternal history of thrombocytopenia[10] and prior pregnancy loss[6,10] were not confirmed in our study. We did not find that heparin was better than aspirin, but our study was retrospective and not controlled. We confirmed that steroid therapy correlated with preterm delivery.

Interventions such as drug therapies and monitored pregnancy have increased fetal survival, but no gold standard has been determined. Therapeutic regimens tried in APS pregnancies include various combinations of low dose aspirin, heparin, steroids, high dose immunoglobulin, and plasma exchanges. Steroids were initially prescribed in the hope of lowering antibody levels, until Lockshin's determination[17] of the inefficiency of prednisone. Two randomized trials testing corticosteroids were conducted. One compared heparin (20,000 U/day) versus prednisone (40 mg/day) plus aspirin[12], the other prednisone (20 mg/day) plus aspirin or aspirin alone[18], with a similar live birth rate but higher incidence of premature rupture of the membranes[12,18], preeclampsia[12], and abruptio placenta[18]. The live birth rate was also similar in a randomized trial in women with a history of at least 2 fetal losses associated with various autoimmune anomalies[19] comparing prednisone (0.5–0.8 mg/kg daily) plus aspirin to placebo. From these studies, it is clear that steroids should not be used as the first-line regimen in primary APS pregnancies.

In 1990, Rosove, *et al*[9] observed that under heparin (mean dose 24,700 U/day), 14/15 pregnancies ended in live births in 14 women with aPL and history of 28/29 miscarriages. Ruffatti, *et al*[8] obtained 53/53 live births under heparin (initial dose 15,000 U/day) in women with aPL and history of 119/132 miscarriages. Balash, *et al*[11] noted 19/21 live births under aspirin alone in 18 women with primary APS. The question of choice between heparin alone or with aspirin versus aspirin alone remains debated. Branch, *et al*[6] compared results of 4 regimens consisting of prednisone and aspirin; heparin and aspirin; prednisone, heparin and aspirin; and other combinations of these medications or immunoglobulins. They found no significant difference among the first 3 treatments. Lima, *et al*[10] found no considerable difference in terms of fetal outcome between pregnancies treated with only aspirin and those with heparin and aspirin, whether associated with prednisolone or not. However, therapy was not randomized and heparin was generally preferred to aspirin in cases of vascular history[6,10], and several thrombotic events occurred under aspirin[6,10]. In addition, Silver, *et al*[18] noted that out of 32 thrombotic events occurring during pregnancy or the postpartum period, 3 took place despite 10,000 U/day heparin. Hence, it seems clear that heparin should be preferred to aspirin in

patients with vascular history. Two recent trials have proved the benefit of adding heparin to aspirin in women with primary APS with no history of thrombophlebitis. Kutteh, *et al*[16] alternately assigned aspirin or aspirin plus 10,000 U/day heparin in 50 women with aCL without LAC. The live birth rate was 80% versus 44% in women treated with aspirin alone. Rai, *et al*[15] conducted a randomized controlled trial comparing aspirin with heparin 10,000 U/day plus aspirin in 90 women. The live birth rate was 71% versus 42% with aspirin alone. Rates of prematurity, IUGR, preeclampsia, and bleeding were similar. No case of thrombocytopenia or thrombosis occurred, although heparin was stopped at 34 weeks in Rai's series[15]. Nevertheless, we think that heparin should be stopped during labor and restarted soon after delivery because pregnancy is itself a prothrombotic state[20]. LMWH has recently been used as thromboprophylaxis in high risk pregnancies. It offers advantages over unfractionated heparin because of better bioavailability and longer half-life, allowing administration once daily, and an increased anti-Xa/anti-IIa ratio and a decreased risk of thrombocytopenia and perhaps of osteoporosis[21,22]. Enoxaparin instead of heparin plus aspirin was prescribed in 53 women with recurrent spontaneous abortions and aCL[14]. No significant difference in bone density was observed between women treated with LMWH and those with unfractionated heparin.

The obstetric prognosis of APS has been improved by antithrombotic therapy. Studies are needed to determine the individual risks and the specific significance of the various antiphospholipid antibodies, in order to improve the respective indications for aspirin alone or associated with heparin in women without thrombotic events.

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