PRIMARY ANTIPHOSPHOLIPID SYNDROME: PREGNANCY OUTCOME IN A PORTUGUESE POPULATION

Fatima Serrano,[*,***] Isabel Nogueira,[*] Augusta Borges,[**] Jorge Branco[***]

Abstract

Introduction: Women with antiphospholipid syndrome (APS) may suffer from recurrent miscarriage, fetal death, fetal growth restriction (FGR), pre-eclampsia, placental abruption, premature delivery and thrombosis. Treatment with aspirin and low molecular weight heparin (LMWH) combined with close maternal-fetal surveillance can change these outcomes.

Objective: To assess maternal and perinatal outcome in a cohort of Portuguese women with primary APS.

Patients and Methods: A retrospective analysis of 51 women with primary APS followed in our institution (January 1994 to December 2007). Forty one (80.4%) had past pregnancy morbidity and 35.3% (n=18) suffered previous thrombotic events. In their past they had a total of 116 pregnancies of which only 13.79 % resulted in live births. Forty four patients had positive anticardiolipin antibodies and 33 lupus anticoagulant. All women received treatment with low dose aspirin and LMWH.

Results: There were a total of 67 gestations (66 single and one multiple). The live birth rate was 85.1% (57/67) with 10 pregnancy failures: seven in the first and second trimesters, one late fetal death and two medical terminations of pregnancy (one APS related). Mean (± SD) birth weight was 2837 ± 812 g and mean gestational age 37 ± 3.3 weeks. There were nine cases of FGR and 13 hypertensive complications (4 HELLP syndromes). 54.4% of the patients delivered by caesarean section.

Conclusions: In our cohort, early treatment with aspirin and LMWH combined with close maternal-fetal surveillance was associated with a very high chance of a live newborn.

Keywords: Primary Antiphospholipid Syndrome; Aspirin; Low Molecular Weight Heparin; Pregnancy; Outcome.

Resumo

Introdução: A Síndrome de Anticorpos Antifosfolípidos (SAAF) associa-se a aborto recorrente, morte fetal, restrição de crescimento fetal (RCF), pre-eclampsia, *abruptio placentae*, parto pretermo e trombose materna. O tratamento com aspirina e heparina de baixo peso molecular (HBPM) e uma vigilância obstétrica apertada podem mudar estes resultados.

Objectivo: Avaliar os resultados maternos e perinatais numa coorte de grávidas Portuguesas com SAAF primária.

Materiais e Métodos: Análise retrospectiva de 51 grávidas com SAAF primária vigiadas na nossa instituição (Janeiro 1994 a Dezembro 2007). Quarenta e uma (80,4%) apresentavam história de perdas gestacionais, com uma taxa de filhos vivos de apenas 13,79 % (16/116). Dezoito (35,3%) tinham antecedentes de trombose venosa ou arterial. Quarenta e quatro grávidas tinham anticorpos anticardiolipina e 33 anticoagulante lúpico positivos. Todas as grávidas foram medicadas com aspirina de baixa dosagem (100 mg) e HBPM.

Resultados: Houve 67 gestações (66 simples e uma gemelar). A taxa de filhos vivos foi de 85,1% (57/67) com 10 perdas de gravidez: sete abortos, uma perda fetal tardia e duas interrupções médicas da gravidez (uma das quais relacionada com o SAAF). O peso médio (± SD) dos recém-nascidos foi de 2.837 ± 812 gr com uma idade gestacional média de 37 semanas ± 3,3. Houve nove restrições de crescimento fetal e 13 complicações hipertensivas (4 síndromes HELLP). 54,4% das gestações termi-

*Recurrent miscarriage Clinic, Department of Maternal and Fetal Medicine, Maternidade Dr. Alfredo da Costa
**Department of Medicine, Maternidade Dr. Alfredo da Costa
***Faculdade Ciências Médicas, Universidade Nova de Lisboa

nou em cesariana.
Conclusões: Na nossa população, o tratamento precoce com aspirina e HBPM e uma vigilância multidisciplinar associaram-se a um aumento significativo da percentagem de filhos vivos.

Palavras-Chave: Síndrome Anticorpos Antifosfolípido Primária; Gravidez; Aspirina; Heparina de Baixo Peso Molecular.

Introduction

Antiphospholipid syndrome (APS) is an acquired thrombophilia characterized by the persistent presence of circulating antiphospholipid antibodies (aPLA), associated with thromboembolic events, pregnancy loss or both.[1-4]

In 1963 Bowie reported thrombosis in systemic lupus erythematosus (SLE) patients with circulating anticoagulants.[5,6] Two decades later, and since the first description by Nilsson in 1975 of a circulating lupus-like anticoagulant in the plasma of women with a history of recurrent miscarriage,[7] other reports enhanced this possible relationship between pregnancy loss and antiphospholipid antibodies.[8,9]

But it was only in 1987 that Harris and Hughes first formalized the concept of primary Antiphospholipid syndrome (PAPS) as a distinct clinical entity that occurs also in individuals in absence of underlying SLE or other autoimmune diseases.[10]

APS is clearly related to maternal morbidity. The main obstetric-related characteristic is pregnancy loss, namely early recurrent miscarriage and late fetal death; however, several other complications have been reported including placental insufficiency leading to fetal growth restriction (FGR), preeclampsia and HELLP syndrome, placental abruption, premature delivery and maternal thrombosis.[11] The pathogenesis of pregnancy failure and thrombosis in APS is multifactorial, and includes perturbations of vascular endothelium, coagulation and fibrinolytic mechanisms and activation of complement.[5,12]

The goal of pharmacological treatment is to protect the mother from thrombosis and reduce the risk of fetal loss. When no specific therapy is given during pregnancy, the rate of pregnancy loss may be as high as 50% to 90%.[13-15] In last decades several therapeutic options including corticosteroids, low dose aspirin, heparin and immunoglobulin have been used either as single agents or in combination in an attempt to improve the rate of live births in these women.[4,15-18] Since 1994, LMWH was introduced in our institution, and combined with low dose aspirin was the therapeutic option to treat APS in pregnancy.

The aim of this study was to evaluate the outcome of PAPS pregnancies managed in our recurrent miscarriage clinic.

Patients and Methods

To assess maternal and perinatal outcome of women with PAPS we performed a retrospective analysis of 51 pregnant women (mean age 31.3, SD 4.6; min 20 max 42) surveilled in our recurrent miscarriage clinic (January 1994 to December 2007).

APS was diagnosed in the great majority of cases 41/51 (80.4%) during the investigation of pregnancy loss. All women met the accepted clinical criteria for APS and tested positive for lupus anticoagulant (LA) and/or medium to high titres anticardiolipin antibodies (aCL) measured on two occasions at least 6 weeks apart.[1,2]

Eighteen women (35.3%) had a history of thrombosis. Deep venous thrombosis (DVT) was the most frequent thrombotic event (n=16). Two patients had suffered previous arterial cerebrovascular accidents, and five past pulmonary thromboembolism. Seven of these women were on warfarin before pregnancy. First thrombotic episode was related to estrogen containing oral contraceptives use in 8 patients, to pregnancy in two, and plane travel in one.

Forty one (80.4%) of these women had past pregnancy morbidity, with a total of 116 past pregnancies of which only 13.79% (n=16) resulted in live births. Ten were nulligests. Twenty one patients (42%) had a history of three or more previous pregnancy losses. Embryonic and fetal losses were the most frequent type of pregnancy failure (Table I).

Anticardiolipin antibodies (IgG and IgM) were identified with an enzyme-linked immunosorbent assay (ELISA) and LA was detected with a standard activated partial thromboplastin time (aPTT) followed by dilute Russell's viper venom time (dRVVT). Forty four patients (86.3%) had positive aCL and 33 (64.7%) lupus anticoagulant. 27 tested positive for both tests. β2 glycoprotein I antibodies were not routinely measured until 2002. Since that year 22 women tested positive for anti-β2 glycopro-

Table I. Previous obstetric history

Pregnancy loss	Pre-embryonic	Embryonic	Fetal	Stillbirth
Gestational age	< 6 w	6-9 w	10-22 w	>22 w
N° losses	6	44	34	16

tein I (all positive for either aCL or LA).

Women with systemic lupus erythematosus or other autoimmune diseases were excluded.

All patients were managed by a multidisciplinary support team, which included an obstetrician and an internist. Most of the patients 43/51 (84.3 %) had a preconcepcional consultation. One woman carried already a 2nd trimester pregnancy in the first visit to our clinic. Although the frequency of the surveillance was individualized, women attended for antenatal care as having high-risk pregnancies and, both the mother and the fetus, were closely monitored at least monthly until 32th week and weekly thereafter.

All patients except that one presenting with an ongoing 2nd trimester pregnancy started low dose aspirin (100 mg daily) as soon as they had a positive urinary pregnancy test. Vaginal ultrasound scans were performed from 6 weeks of amenorrhoea. When fetal heart activity was seen on ultrasonography, low molecular weight heparin (LMWH) was added. Treatment with aspirin was stopped one week before delivery, to allow for epidural analgesy. LMWH was continued until onset of labor or the day before a planned delivery and resumed for 4 to 6 weeks. Women with previous venous thrombotic events, and on oral anticoagulation, started LMWH when an urinary pregnancy tested positive and restarted postpartum warfarin as soon as possible. Anti-Xa activity was not measured routinely.

Uterine artery Doppler waveform studies were perform at 22 - 24 weeks' gestation in 30 gestations; serial growth scans were accomplished in all pregnancies from 24 week´s until delivery, with increased fetal surveillance if FGR was suspected.

The timing of delivery was assessed individually. In uncomplicated cases, induction of labor was not recommended until 40 weeks' gestation. Cesarean sections were performed for obstetric reasons.

After delivery, patients were counseled about the important risk of developing thrombotic complications associated with APS and were referred to our family planning clinic. Estrogen containing oral contraceptives use was contraindicated.

Obstetric outcomes included: pregnancy loss, the presence or absence of gestational hypertensive disorders, fetal growth restriction (estimated fetal weight below the 10th centile for gestational age), premature delivery (before 37 weeks of gestation), caesarean delivery, neonatal intensive care unit admission, birth weight and maternal thromboembolism.

Results are presented as frequencies and mean ± SD as appropriate. Fisher's exact test was used to compare categorical variables. For comparison between two means an independent student's t test was performed. Statistical significance was defined as $p<0.05$ (SPSS version 15, Chicago IL, USA).

Results

There were a total of 67 gestations (66 singleton and one twin gestation). Fourteen women had more than one subsequent pregnancy. The live birth rate was 85.1% (57/67) with 10 pregnancies failures: seven in the first and second trimesters, one late fetal death and two medical terminations of pregnancy (one APS related and one due to fetal cardiac malformation). The only patient, who started late pregnancy surveillance and carried already a 12th week gestation in the first visit to the clinic, resulted in a 2nd trimester miscarriage (Table II).

The group of patients who were positive for both LA and aCL had the worst pregnancy outcome with a success rate of 75.7% against 96.71% if only one antibody was present ($p<0.05$). A past thrombotic event was also a strong risk factor for pregnancy failure, odds ratio 5.98 95% CI (1.17 – 33.98).

In pregnancies that progressed beyond 20 weeks there were 13 hypertensive complications: two pregnancy induced hypertensions, 4 superimposed preeclampsia, 2 mild and two severe preeclampsia and 3 HELLP syndromes. The most serious situations (2 severe preeclampsias and three

Table II. Pregnancy outcome

	Pregnancy losses				Living children (weeks)				
Loss Type	1st trim	2nd trim	Stillbirth	TOP*	24 - 27	28 - 31	32 - 33	34-36	>37
n	3	4	1	2*	1	4	3	5§	45
Total	10				58				

*Two Terminations of Pregnancy: One severe hypoplastic left heart syndrome (HLHS) diagnosed at 20th week. One severe FGR diagnosed at 22th week
§One twin pregnancy

HELLP) occurred before 34 weeks of gestation. One woman developed HELLP syndrome at 18' weeks of gestation with a prolonged stay in an intensive care unit.

There were 9 cases of fetal growth restriction (FGR) with four fetal deaths: three before 24 weeks' gestation and one 31 weeks` stillbirth. Two of these FGR gestations were complicated by placental abruption at 28 and 32 weeks' (one HELLP syndrome), both with living children.

46.7 % (14/30) of women had Doppler uterine artery protodiastolic notches. This finding was associated with prematurity ($p< 0.01$) and FGR ($p<0.05$). Patients with FGR were 2.6 times more likely to have an abnormal uterine artery Doppler profile than patients without FGR (likelihood ratio of 2.6). The small number of cases does not permit the 95% CI calculation.

54.4% of the patients delivered by caesarean section. The major indication was fetal distress (35.5 %), followed by failed induction of labor (21.6%).

There were 58 live newborns (one twin gestation)**.** The probability of having a live baby was 85.1%, a figure significantly greater than that (13.79%) observed before therapy ($p<0.001$). Mean (± SD) birthweight was 2837 ± 812 g (min 460 max 4050) at mean gestational age 37 ± 3.3 weeks (min 24 max 40). Mean birthweight percentile was 42.8 ± 23.5.

Twelve of the successful pregnancies (21 %) resulted in a preterm delivery. This was due to spontaneous labour in four cases (one twin pregnancy). Fetal growth restriction was the indication for termination of pregnancy in 4 patients, HELLP syndrome in two and placental abruption in another two cases. One third (4/12) of these mothers had history of previous late fetal deaths and eight (67%), of previous thrombotic events. Most of them (83%) had pathological uterine Doppler at 22-24 weeks.

All babies were examined by a paediatrician shortly after delivery. Ten were admitted to the neonatal intensive care unit (NICU). Only one neonate weighed 460 g, who was delivered by caesarian section at 24 week' gestation for HELLP syndrome, required a more aggressive management due to bronchopulmonar dysplasia and retinopathy of prematurity grade II. This neonate responded well in the NICU and was discharged 154 days after. The other 9 babies were admitted to the unit with mild prematurity complications. Four of them required a short time of ventilatory support. There were no cases of neonatal thrombosis, intraventricular hemorrhage or neonatal deaths.

No woman developed a thromboembolic complication during pregnancy or puerperium. There were no maternal deaths (Table III).

Discussion

In the last three decades many efforts have been made to identify the best way to monitor and to manage pregnancies associated to APS. Nowadays, with an appropriate treatment, a close obstetric monitoring and careful delivery timing, APS patients can reach live birth rates higher than 70%.[18]

Table III. Outcome data (67 pregnancies)

Live births (n)	58 *	(85.1%)
Mean Gestational age at birth	37.05	± 3.3 W
Mean Birth weight	2837	± 812 g
Pregnancy loss (n)	10	(14.9 %)
Preterm birth (n)	12	(21%)
FGR (n)	9	(15.5%)
Pregnancy-related hypertension (n)	13	(21.3%)
Caesarean section (n)	31	(54.4%)

*One twin pregnancy

Success, defined as fetal survival, was reached in 85.1% of our patients, similar to reported by others in treated women with PAPS.[19-21]

Positivity for both LA and aCL and a previous thrombotic history were the two main predictors for bad outcome.

The association between severe preeclampsia and APS has long been described in several studies. Since the statement of the clinical criteria for antiphospholipid syndrome in 1999,[1] several publications emerged supporting or refuting an association between these antibodies and preeclampsia.[14,23-25] In a recent study including 406 women with severe preeclampsia, the prevalence of antiphospholipid antibodies (13%) was significantly higher than in controls (3.7%).[26] In our cohort, 21.3% of pregnancies (13/61) that progressed beyond 20 weeks were complicated by hypertensive disorders (pre-eclampsia, superimposed preeclampsia or HELLP syndrome). This was a very high prevalence compared to the overall hospital rate (6%).[27] Elevated preeclampsia prevalence (18%) was also found by Lima et al, in sixty patients with primary and secondary APS,[20] and by Tincani et al (11.6%) in 58 patients with PAPS.[22]

APS patients seem to be more susceptible to early-onset HELLP syndrome. This complication can occur as early as 15–20 weeks' gestation and might progress rapidly, often necessitating termination of the pregnancy.[28,29] In our series, all the four cases of HELLP syndrome occurred before the 32th week of gestation. In one case it developed at 18th weeks, and was a life-threatening condition. In a recent study, HELLP developed in 44% of the cases during the second trimester and 12.5% at 18–20 weeks.[28]

Fetal growth restriction complicated five (10.6%) of our successful pregnancies (5/47), similar to those found by Stone et al (13.3%)[21] and Cervera & Balasch (12.8%).[19]

Uterine artery Doppler blood flow analysis provides a noninvasive indirect method of screening women with risk for uteroplacental insufficiency.[30-32] Various studies have been performed to validate the predictive value of uterine artery Doppler waveform pattern in relation to pregnancy outcome in APS patients.[21,31,33] In our data, the existence of protodiastolic uterine artery notches was also associated with fetal growth restriction and preterm delivery.

The cesarean section rate in this cohort was very high (54.4%), compared to the overall rate of our hospital (30%). However, high cesarean section rates were described as well by other authors, probably related to women's past obstetric history. Stone et al in a prospective study with 33 PAPS gestations reported a 59% C-section rate.[21] In the study by Backos et al, 46% of the women also delivered by caesarean.[34]

In most studies, a significant number of APS pregnancies were associated with premature delivery. In a controlled evaluation of 69 gestations in 58 PAPS patients, Tincani et al found an 18.8% overall prevalence of prematurity.[22] Cervera & Balasch in a series of 77 treated pregnancies in 56 women with primary or secondary APS, found a similar rate of premature deliveries (21.4%).[19] Rai et al reported a 24% preterm rate.[4] In our population, the main problem was also prematurity which occurred in up to 21 % of the successful pregnancies.

Conclusions

Antiphospholipid syndrome is frequently associated with complications during pregnancy. Despite a high incidence of obstetric complications, such as preeclampsia, FGR and prematurity, early treatment with aspirin and LMWH combined with careful maternal-fetal monitoring was, in our population, associated with a high chance of a live newborn. An accurate preconceptional counseling and a close collaboration between obstetricians and other specialities was essential for this outcome.

Correspondence to
Fátima Serrano
Rua Joaquim Paço D'Arcos, nº 2, 3º F;
1500-366 Lisboa
Tel.: +351 213 184 000
E-mail: fatima_serrano@hotmail.com

Acknowledgments
We are especially grateful to Israel Macedo for his valuable revision of the manuscript and to Paulo Onofre for his support with a "computer crash".

References

1. Wilson W, Gharavi A et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: Report of an International Workshop. Arthritis Rheum 1999; 42:1309-1311.
2. Miyakis S, Lockshin T, Branch D et al. International consensus statment on an update of the classification criteria for definite antiphospholipid syndrome. J Thromb Haemost 2006; 4: 297.
3. Branch D, Eller A. Antiphospholipid syndrome and

thrombosis. Clin Obstet and Gynecol 2006; 49: 861--874.
4. Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with antiphospholipid antibodies. BMJ 1997; 314: 253-257.
5. Bowie E, Thompson J, Pascuzzi C. Thrombosis in systemic lupus erythematosus despite circulating anticoagulants. J Lab Clin Med 1963; 62: 416-430.
6. Greaves M. Pathogenesis and management of antiphospholip syndrome. Thromb Res 2009; 123: 4-9.
7. Nilsson I, Asted B, Hedner U. Intrauterine death and circulating anticoagulant. Acta Med Scand 1975; 197: 153-159.
8. Firkin B, Howard M, Radford N. Possible relationship between lupus inhibitor and recurrent abortion in young women. Lancet 1980; 2: 366.
9. Carreras L, Defreyn G, Machin S et al. Arterial thrombosis, intrauterine death and "lupus" anticoagulant: detection of immunoglobulin interfering with prostacyclin formation. Lancet 1981; 1: 244- 246.
10. Harris E. Syndrome of the black swan. Br J Rheumatol 1987; 26: 324-326.
11. Derksen RH, Khamashta MA, Branch DW. Obstetric antiphospholipid syndrome. Arthritis Rheum 2004; 50: 1028- 1039.
12. MackmanN, Girardi G. Tissue factor in antiphospholipid antibody-induced pregnancy loss: a pro-inflamatory molecule. Lupus 2008; 17: 931-936.
13. Rai L, Clifford K, Cohen H, Regan L. High prospective fetal loss rate in untreated pregnancies of women with recurrent miscarriage and antiphospholipid antibodies. Hum Reprod 1995; 10: 3301-3304.
14. Geis W, Branch W. Obstetric implications of antiphospholipid antibodies: pregnancy loss and other complications. Clin Obstet and Gynecol 2001; 44: 2--10.
15. Branch D. Antiphospholipid antibodies and pregnancy maternal implications. Semin Perinatal 1990; 14: 139-146.
16. Esplin M. Management of antiphospholipid syndrome during pregnancy. Clin Obstet Gynecol 2001; 44: 20-28.
17. Branch D, Peacemen A et al. A multicenter, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. Am J Obst and Gynec 2000; 182: 122-127.
18. Branch DW, Khamashta MA. Antiphospholipid syndrome: obstetric diagnosis, management and controversies. Obstet Gynecol 2003; 101: 1333-1344.
19. Cervera R and Balasch J. The management of pregnant patients with antiphospholipid syndrome. Lupus 2004; 13: 683-687
20. Lima F, Khamashta M, Buchanan N, Kerslake S, Hunt B, Hughes G. A study of sixty pregnancies in patients with the antiphospholipid syndrome. Clin Exp Rheumat 1996; 14: 131-136.
21. Stone S, Hunt BJ, Khamashta MA, Bewley SJ, Nelson-Piercy C. Primary antiphospholipid syndrome in pregnancy: an analysis of outcome in a cohort of 33 women treated with a rigorous protocol. J Thromb Haemost 2005; 3: 243-245.
22. Tincani A, Lojacono A, Taglietti M et al. Pregnancy and neonatal outcome in primary antiphospholipid syndrome. Lupus 2002; 11: 649.
23. Branch DW, Andres R, Digre KB, Rote NS, Scott Jr. The association of antiphospholipid antibodies with severe preeclampsia. Obstet Gynecol 1989; 73: 541--545.
24. Dreyfus M, Hedelin G, Kutnahorsky R et al. Antiphospholipid antibodies and preeclampsia: a case-control study. Obstet Gynecol 2001; 97: 29-34.
25. Lee R, Brown M, Branch D, Ward K, Silver R. Anticardiolipin and anti B2 glicoprotein I antibodies in preeclampsia. Obstet Gynecol 2003; 102: 294-300.
26. Mello G, Parretti E, Marozio L et al. Thrombophilia is significantly associated with severe preeclampsia: results of a large-scale, case-controlled study. Hypertension 2005; 46: 1270-1274.
27. Lermann R, Ribeiro F, Dias E, Campos A. Complicações hipertensivas na gravidez na Maternidade Dr. Alfredo da Costa. Arquivos Mat. Alfredo da Costa 2006; 6: 9 -11.
28. Le Thi Thuong et al. The HELLP syndrome in the antiphospholipid syndrome: retrospective study of 16 cases in 15 women. Ann Rheum Dis 2005; 64: 273--278.
29. Salmon JE, Girardi G, Lockshin MD. The antiphospholipid syndrome as a disorder initiated by inflammation: implications for the therapy of pregnant patients. Nat Clin Pract Rheumatol 2007; 3:140-147.
30. Harrington K, Cooper D, Lees C, Hecher K, Campbell S. Doppler ultrasound of the uterine arteries: the importance of bilateral notching in the prediction of pre-eclampsia, placental abruption or delivery of a small-for-gestational-age baby. Ultrasound Obstet Gynecol 1996; 7: 182- 188.
31. De Carolis S, Botta A, Garofalo S et al. Uterine artery velocity waveforms as predictors of pregnancy outcome in patients with antiphospholipid syndrome: a review. Ann N Y Acad Sci. Jun 2007; 1108: 530-539.
32. Ruiz-Irastorza G, Khamashta MA. Antiphospholipid syndrome in pregnancy. Rheum Dis Clin North Am 2007; 33: 287-297.
33. Le Thi Thuong D, Wechsler B, Vauthier-Brouzes D et al. The second trimester Doppler ultrasound examination is the best predictor of late pregnancy outcome in systemic lupus erythematosus and/or the antiphospholipid syndrome. Rheumatology 2006; 45: 332-338.
34. Backos M, Rai R, Baxter N, Chilcott I, Cohen H, Regan L. Pregnancy complications in women with recurrent miscarriage associated with antiphospholipid antibodies treated with low dose aspirin and heparin. BJOG 2005; 106: 102 - 107.