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**RESUMO**

**Introdução:** O síndrome antifosfolipídico (SAF) é uma doença autoimune caracterizada por eventos tromboembólicos e/ou desfechos obstétricos adversos na presença de anticorpos antifosfolipídicos (aPL) circulantes persistentes. No entanto, vários doentes apresentam formas incompletas do mesmo, não preenchendo os critérios clínicos ou laboratoriais, denominadas por "SAF-*like*".

**Objetivos:** O objetivo deste estudo foi avaliar e comparar os desfechos obstétricos em mulheres com SAF e SAF-*like* e compará-los com um grupo controlo de grávidas saudáveis.

**Materiais e métodos:** Foi realizado um estudo de coorte retrospetivo, que analisou as gestações de mulheres com SAF e SAF-*like* seguidas no Centro Materno-Infantil do Norte entre 2000 e 2021. Os dados referentes à história passada, vigilância da gravidez, medicação, perfil imunológico materno e desfechos obstétricos foram obtidos. O teste do Qui-Quadrado, o teste Exato de Fisher e o Teste-T para Amostras Independentes foram usados para comparar os grupos. Um valor de $p$ <0.05 foi considerado estatisticamente significativo.

**Resultados:** No grupo de estudo, foram avaliadas 126 gestações (35 em mulheres com SAF e 91 em mulheres com SAF-*like*). O grupo de controlo foi composto por 194 grávidas saudáveis. O lúpus eritematoso sistémico foi a doença autoimune associada ao SAF mais prevalente (51.5% em SAF e 33.0% em SAF-*like*). Em relação aos antecedentes médicos, no grupo de estudo, a taxa de eventos trombóticos prévios foi significativamente superior nas mulheres com SAF, não tendo sido encontradas diferenças no que diz respeito à morbilidade obstétrica precedente, exceto para o aborto espontâneo (51.6% em SAF-*like* vs 28.6% em SAF, p=0.020). O tratamento combinado (aspirina em baixa dose e heparina de baixo peso molecular) foi oferecido a 90.9% das mulheres com SAF e a 66.3% das mulheres com SAF-*like* (p=0.007). A presença de aPL enquadráveis nos critérios de classificação foi significativamente superior nas mulheres com SAF (p<0.001). As categorias dos aPL também apresentaram diferenças significativas entre as mulheres com SAF e SAF-*like*: 94.3% vs 52.9% para a categoria I (p<0.001) e 5.7% vs 47.1% para a categoria II (p=0.002). A tripla positividade para os aPL foi associada ao desenvolvimento de desfechos obstétricos adversos e eventos trombóticos. A presença de aPL não enquadráveis nos critérios foi reportada em aproximadamente 13% das mulheres com SAF e SAF-*like*. Eventos trombóticos durante a gestação e/ou durante o puerpério foram raros e apenas reportados no grupo SAF (6.1%). Os desfechos obstétricos adversos, como desfecho composto, foram reportados de forma semelhante em 50.0% das mulheres com SAF e em 40.4% das mulheres com SAF-*like*, apesar da taxa de nados-mortos ter sido superior nas mulheres com SAF (14.3% em SAF vs 1.1% em SAF-*like*, p=0.006). A restrição de crescimento fetal foi o desfecho obstétrico adverso mais frequentemente reportado nos dois grupos (34.4% em SAF e 21.7% em SAF-*like*). O nascimento de um nado-vivo

foi conseguido na maioria das gestações, apesar desta taxa ter sido significativamente inferior nas mulheres com SAF (80.0% em SAF vs 93.3% em SAF-*like*, p=0.046). Não foram observadas diferenças significativas nos desfechos neonatais entre os grupos SAF e SAF-*like*. No grupo de controlo, a taxa de desfechos obstétricos adversos reportada foi de 13.4% (p<0.001).

**Conclusões:** Foram encontradas diferenças significativas nas categorias de aPL entre as mulheres com SAF e SAF-*like*. A tripla positividade para os aPL demonstrou associação com o desenvolvimento de desfechos obstétricos adversos e eventos trombóticos. As taxas de tratamento foram significativamente superiores nas mulheres com SAF. A gravidez com SAF e SAF-*like* apresenta um risco aumentado e semelhante de desfechos obstétricos adversos, pelo que a gestação destas doentes deve ser monitorizada de perto.

**Palavras-chave:** Síndrome antifosfolipídico; Anticorpos antifosfolipídicos; Síndrome antifosfolipídico seronegativo; Gravidez; Desfechos obstétricos; Restrição de crescimento fetal

**ABSTRACT**

**Introduction:** Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thromboembolic events and/or adverse pregnancy outcomes in the presence of persistent circulating antiphospholipid antibodies (aPL). However, several patients present with incomplete forms, neither meeting the clinical nor the laboratory criteria, referred to as "APS-*like*".

**Aims:** The aim of our study was to evaluate and compare pregnancy outcomes in women with APS and APS-*like* in addition to comparing them with a control group of healthy pregnant women.

**Materials and methods:** A retrospective cohort study was conducted, which analyzed the pregnancies of women with APS and APS-*like* followed at Centro Materno-Infantil do Norte between 2000 and 2021. Data regarding past history, pregnancy surveillance, medication, maternal immunological profile and pregnancy outcomes were recorded. Chi-Square test, Fisher's Exact test and Independent Samples T-Test were used to compare groups. A *p*-value of <0.05 was considered statistically significant.

**Results:** In the study group, a total of 126 pregnancies were evaluated (35 in women with APS and 91 in women with APS-*like*). The control group consisted of 194 healthy pregnant women. Systemic lupus erythematosus was the most prevalent autoimmune disease associated with APS (51.5% in APS and 33.0% in APS-*like*). Regarding past history, among the study group, the rate of previous thrombotic events was significantly higher in APS, while no differences were found regarding prior pregnancy morbidity, except for spontaneous miscarriage (51.6% in APS-*like* vs 28.6% in APS, p=0.020). Combined treatment (low-dose aspirin and low-molecular-weight heparin) was given to 90.9% of APS women and 66.3% of APS-*like* (p=0.007). The presence of criteria-aPL was significantly higher in APS (p<0.001). Overall, aPL categories in APS and APS-*like* showed significant differences: 94.3% vs 52.9% for category I (p<0.001) and 5.7% vs 47.1% for category II (p=0.002). Triple aPL positivity was found to be associated with adverse pregnancy outcomes and thrombotic events. Non-criteria aPL were reported in approximately 13% of both APS and APS-*like*. Thrombotic events during gestation and/or puerperium were rare and only reported in the APS group (6.1%). Adverse pregnancy outcomes as a composite outcome were similarly reported in 50.0% in APS and 40.4% in APS-*like*, although the rate of stillbirth was still higher in the APS group (14.3% in APS vs 1.1% in APS-*like*, p=0.006). Fetal growth restriction was the most reported adverse pregnancy outcome in both groups (34.4% in APS and 21.7% in APS-*like*). Live birth was achieved in most pregnancies, despite this rate being significantly lower in APS (80.0% in APS vs 93.3% in APS-*like*, p=0.046). No differences were observed in the neonatal outcomes between APS and APS-*like*. In the control group, a 13.4% rate of adverse pregnancy outcomes was reported (p<0.001).

**Conclusions:** Significant differences were found among aPL categories between APS and APS-*like*. Triple aPL positivity was found to be associated with the development of adverse pregnancy outcomes and thrombotic events. Treatment rates were higher in APS. Pregnancy in APS and APS-*like* is associated with an increased and similar risk of adverse pregnancy outcomes, and thus should be closely monitored.

**Keywords:** Antiphospholipid syndrome; Antiphospholipid antibodies; Seronegative antiphospholipid syndrome; Pregnancy; Pregnancy outcomes; Fetal growth restriction

**LIST OF ABBREVIATIONS**

aB2GPI: Anti-β2-glycoprotein-I
aCL: Anticardiolipin
ACOG: American College of Obstetricians and Gynecologists Committee
ANA: Antinuclear antibodies
anti-La/SSB: anti-Sjögren's syndrome-related antigen B
anti-Ro/SSA: anti-Sjögren's syndrome-related antigen A
aPL: Antiphospholipid antibodies
APO: Adverse pregnancy outcomes
APS: Antiphospholipid syndrome
ELISA: Enzyme immunoassay in solid phase
EULAR: European League Against Rheumatism
EUROAPS: European Registry on Obstetric Antiphospholipid Syndrome
G0: Control group
GAPSS: Global Anti-Phospholipid Syndrome Score
HELLP: Hemolysis, elevated liver enzymes, and low platelet count
LA: Lupus anticoagulant
LDA: Low-dose aspirin
LMWH: Low-molecular-weight heparin
SD: Standard deviation
SLE: Systemic lupus erythematosus

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**INTRODUCTION AND AIMS**

Antiphospholipid syndrome (APS) is a rare systemic autoimmune disorder clinically characterized by thromboembolic events and/or adverse pregnancy outcomes (APO) in the presence of persistent circulating antiphospholipid antibodies (aPL) (at least 12 weeks apart), namely lupus anticoagulant (LA), anticardiolipin (aCL) or anti-β2-glycoprotein-I (aB2GPI).[1]

The overall estimated prevalence of APS is around 40-50 cases per 100 000 individuals[1], with a female-to-male ratio of 5:1,[2] representing an important health burden for women of childbearing age.[3] APS is commonly associated with other autoimmune diseases, particularly systemic lupus erythematosus (SLE), which was previously referred to as 'secondary APS'.[4]

aPL are a heterogeneous group of autoantibodies directed against a wide variety of proteins with affinity for negatively charged phospholipids[5] and its presence in the general population ranges between 1 and 5%. They appear to play a central role in the pathogenesis of APS rather than just being a diagnostic marker, but the exact mechanisms underlying thrombotic events and pregnancy morbidity have not been yet fully elucidated.[1]

In addition to being acknowledged as a major acquired form of thrombophilia,[6] APS is also recognized as a unique prothrombotic condition, since it is capable of implicating any vascular bed, arterial or venous, regardless of its size.[3] Deep vein thrombosis of the lower limbs is the most frequent manifestation of the disease[7]. Arterial events are less common but more severe and involvement of the cerebral circulation might lead to transient ischemic attack and stroke.[7] Regarding obstetric morbidity, recurrent early pregnancy loss is the most frequent manifestation[8, 9], for which APS is known to be the most common treatable cause. [6] Other complications include fetal death, the most specific, and premature birth due to preeclampsia, eclampsia, fetal growth restriction or other consequences of placental insufficiency.[10] In less than 1%, APS can present as catastrophic APS, a life-threatening form of multiorgan thrombosis associated with a mortality of over 50%.[4, 6]

APS was first described in 1983[11] and its preliminary classification criteria were established in 1999, known as the Sapporo Criteria.[12] The latter were revised in Sydney, in 2006, leading to the Revised Classification Criteria for APS.[10] These currently guide diagnosis, which requires the presence of at least one of the clinical criteria and one of the laboratory criteria.[10] However, nowadays, it is widely recognized that there are non-criteria features associated with the presence of aPL, the most common being: neurologic manifestations, heart valve disease, livedo reticularis, thrombocytopenia, nephropathy, IgA aCL, IgA aB2GPI and antibodies against phosphatidylserine, phosphatidylethanolamine, prothrombin alone and to the phosphatidylserine–prothrombin complex.[10]

The aPL profile is an important risk stratification tool for aPL-associated adverse events.[13] Indeed, the presence of LA or triple positivity (simultaneous presence of LA, aCL and aB2GPI) seems to be associated with a higher risk of thrombosis and pregnancy morbidity.[1] Its combination with conventional cardiovascular risk factors has resulted in the development of the Global Anti-Phospholipid Syndrome Score (GAPSS), which has been validated in APS.[14]

Even though the ideal management of APS during pregnancy remains controversial, the current standard treatment consists of low-dose aspirin (LDA) and a heparin agent, usually low-molecular-weight heparin (LMWH).[13, 15] This combined regimen has improved pregnancy outcome to a live birth rate of over 70%[16], but pregnancy complications still occur in the remaining 30%.[6]

In clinical practice, patients may present with seronegative APS, defined as the presence of clinical manifestations of APS, but persistently negative conventional aPL[17] ; they may also present with positive aPL and prior obstetric morbidity not fulfilling APS classification criteria, usually referred to as non-criteria APS; in addition, they may present as asymptomatic carriers of aPL, subjects with positive aPL, but with no clinical features of APS. Management of these patients is still debated, but results from previous studies suggest they may benefit from treatment during pregnancy, as seronegative and non-criteria APS patients have shown similar pregnancy outcomes to seropositive[18] and criteria APS[19, 20], respectively, and asymptomatic carriers appear to have an increased risk of APO compared to the general population.[21]

In conclusion, some authors have claimed that the current classification criteria are too restrictive and of limited use for clinical purposes[22], as their stringency may give rise to missed diagnoses, with increased morbidity in women with APS-*like* manifestations. Presentation with these incomplete forms, neither meeting the clinical nor the laboratory criteria, represents a challenge for the clinician, and recognition of these entities is important to ensure adequate therapy. [23]

While several studies have addressed pregnancy outcomes in women with APS, only a few have addressed this issue in these incomplete entities. The purpose of the present study is to retrospectively evaluate and compare maternal, obstetric and neonatal outcomes in pregnant women with confirmed APS and APS-*like* and to assess whether the risk of APO is higher in these pregnancies when compared to pregnancies of healthy women.

**MATERIALS AND METHODS**

This retrospective cohort study was carried out at Centro Materno-Infantil do Norte, Centro Hospitalar Universitário do Porto, in Oporto, Portugal. The study's protocol was approved by the institutional Ethics Committee, the Department of Clinical Investigation and the Learning, Formation and Investigation Department – 2021.316 (261-DEFI/269-CE).

***Patients***

This study included pregnant women labelled as having APS, followed in our institution between 2000 and 2021. Each pregnancy was considered an event. Multiple gestations were excluded from the data analysis. Exclusion criteria also included pregnancy losses caused by other identifiable causes (such as infection, genetic, chromosomal, anatomic and hormonal factors) and lack of available data.

Patients were divided into two different groups, accordingly to the level of certainty of their diagnosis: pregnant women with APS (group 1) and pregnant women with APS-*like* (group 2). Definite APS was defined according to the Revised Classification Criteria for APS.[10] Women with no confirmation of the presence of aPL at least 12 weeks apart were also included in the APS group. The APS-*like* group consisted of three subgroups: seronegative APS, defined as meeting at least one clinical criteria and testing persistently negative for LA, aCL and aB2GPI or in the absence of aPL available data; non-criteria APS, defined as positive LA, aCL and/or aB2GPI in low or medium-high titers in women with prior obstetric morbidity not fulfilling clinical criteria (namely preterm delivery beyond the 34$^{th}$ week of gestation due to preeclampsia, eclampsia or recognized features of placental insufficiency and otherwise unexplained spontaneous miscarriages before the 10$^{th}$ week of gestation, with less than three consecutive events or three or more nonconsecutive events); and asymptomatic carriers of aPL, defined as positive LA, aCL and/or aB2GPI in low or medium-high titers in asymptomatic patients, detected during screening for inherited thrombophilia or autoimmune disorders.

Our sample comprised a total of 126 pregnancies from 82 women: 35 pregnancies from women with APS and 91 from women with APS-*like* (28 seronegative APS, 40 non-criteria APS and 23 asymptomatic carriers). The control group included 194 patients who were randomly selected from healthy women, with low-risk singleton pregnancies who were followed at our institution during the same period. The detailed patient selection protocol is represented in Figure 1.

***Data collection***

Data from the patients' electronic clinical files were retrieved, accessed through SClínico® and PCE® platforms. Information regarding the following parameters was collected: age at pregnancy, past medical and obstetric history, pregnancy surveillance and medication and maternal, obstetric and neonatal outcomes. Furthermore, in the study group, data regarding maternal immunological profile was also contemplated.

Concerning analytical profile during pregnancy, anemia was defined as hemoglobin or hematocrit levels below 11 g/dl and 33%, respectively, in the first and third trimester, and below 10.5g/dl and 32% in the second one. Thrombocytopenia was defined as a platelet count below 150x10$^{9}$/L.

Proteinuria was defined as urinary excretion of 300mg or more in a 24-hour urine collection or a protein/creatinine ratio of 0.3mg/dL or more or a dipstick reading of 2+. Prolonged partial thromboplastin time was defined according to the reference values protocoled by our institution.
Regarding aPL, LA was detected by coagulation assay according to the International Society on Thrombosis and Haemostasis, while aCL and aB2GPI were measured by a standardized enzyme immunoassay in the solid phase (Enzyme-Linked Immunosorbent Assay - ELISA), with a detection limit of 20UQ. Patients were classified into two profiles: high-risk profile, defined as the presence of LA or double (any combination of aPL) or triple (all three subtypes) aPL positivity or the presence of medium-high titers of aPL (aCL >40GPL or MPL or aCL/aB2GPI >99th percentile); low-risk profile, which included patients with isolated aCL or aB2GPI at low titers. Patients were also categorized into four categories as advised by the Revised Classification Criteria for APS[10]: category I (more than one laboratory criteria present); category IIa (LA present alone), category IIb (aCL present alone) and category IIc (aB2GPI present alone). Non-criteria aPL, anti-Sjögren's syndrome-related antigen A (anti-Ro/SSA), anti-Sjögren's syndrome-related antigen B (anti-La/SSB), antinuclear antibodies (ANA) and C3 and C4 complement components were detected as for clinical practice.

***Pregnancy outcomes***

APO as a composite outcome was defined as the occurrence of spontaneous miscarriage, stillbirth, preterm delivery, fetal growth restriction, placental abruption and/or development of hypertensive disorders of pregnancy (gestational hypertension, preeclampsia, eclampsia and/or hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome).
Spontaneous miscarriage was defined as the involuntary loss of a fetus before the 20$^{th}$ week of gestation and stillbirth as the death of the fetus beyond the 20$^{th}$ week of pregnancy. Preterm delivery was defined as a birth that occurs between 20 0/7 and 36 6/7 weeks of gestation.[24] Fetal growth restriction was defined as an estimated fetal weight less than the 10$^{th}$ percentile for gestational age, using the curves defined for the Portuguese population.[25] Placental abruption was defined as premature separation of the placenta before the end of the second stage of labor. Hypertensive disorders of pregnancy were defined according to the 2019 American College of Obstetricians and Gynecologists Committee (ACOG) criteria.[26] Gestational hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or both, on two occasions at least 4 hours apart after 20 weeks of gestation, in a woman with previously normal blood pressure in the absence of proteinuria and that returns to normal in the postpartum period.[26] Preeclampsia was defined as systolic blood pressure ≥140 mmHg or diastolic blood

pressure ≥90 mmHg on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure and proteinuria (defined as urinary excretion of 300mg or more in a 24-hour urine collection or protein/creatinine ratio of 0.3 or more or dipstick reading of 2+). In the absence of proteinuria, preeclampsia was defined as new-onset hypertension with new onset of target organ damage (platelet count less than 100x $10^9$/L; serum creatinine concentration greater than 1.1 mg/dL or doubling of the serum creatinine concentration in the absence of other renal disease; elevated blood concentrations of liver transaminases to twice the upper limit of normal concentration; severe persistent right upper quadrant or epigastric pain and not accounted for by alternative diagnoses; pulmonary edema or new-onset headache unresponsive to acetaminophen and not accounted for by alternative diagnoses; or visual disturbances).[26] Occurrence of new-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions established the diagnosis of eclampsia.[26] HELLP syndrome was defined as lactate dehydrogenase elevated to 600 IU/L or more, aspartate aminotransferase and alanine aminotransferase elevated more than twice the upper limit of normal and the platelet count less than 100x$10^9$/L.[26]

Regarding maternal outcomes, the occurrence of venous and/or arterial thrombosis during pregnancy and/or puerperium and maternal death was considered.

Neonatal outcomes included gestational age at delivery, birth weight, APGAR score at 5 minutes after birth, the need for admission to the neonatal intensive care unit and neonatal death (in the first 28 days of life).

***Statistical Analysis***

The statistical analysis was performed using the IBM SPSS Statistics® version 27.0.1 for Windows®. Descriptive data analysis was performed. Categorical variables were described in terms of frequency and percentage and continuous variables were expressed as mean and standard deviation (SD). Chi-Square and Fisher's Exact tests were used to compare categorical data, whereas Independent Samples T-test was used to compare quantitative data. Correlational tests were also performed. A *p*-value of <0.05 was considered statistically significant.

**RESULTS**

The study group included 126 pregnancies, 35 from women with APS and 91 from women with APS-*like* (28 seronegative APS, 40 non-criteria APS and 23 asymptomatic carriers), while the control group (G0) was composed of 194 healthy women pregnancies. Two comparison tables were designed: Table I, between APS and APS-*like* groups; Table II, between the control group and APS and APS-*like* groups.

***Demographic and Clinical Characteristics – comparison among groups***

The average age at conception was 30.26 years in APS, 32.02 in APS-*like* and 32.55 in G0. A significant difference was found between APS and the control group (p=0.030).

SLE was the most prevalent autoimmune disease, equally present in 51.5% of APS and 33.0% of APS-*like* women. No cases of SLE were reported in the control group (p<0.001). The prevalence of Behçet's disease was 5.7% in APS, 1.1% in APS-*like* and 0.5% in G0, similar between the three groups. Sjögren's syndrome was only found in two women with APS-*like* (2.2%). The presence of other autoimmune diseases was reported in 25.7% in APS, 14.3% in APS-*like* and 1.0% in G0, which was significantly higher in the study group (p<0.001).

Previous deep vein thrombosis was reported in 34.3% of women with APS, whereas arterial thrombosis was reported in 28.6%. In APS-*like*, thrombosis was found in 3.3% and 2.2%, respectively. There were no reported cases in the control group. These events were significantly more frequent in APS compared to the other two groups (p<0.001). The rate of venous events was also higher in APS-*like* compared to controls (p=0.032).

With respect to the presence of other clinical manifestations associated with APS, migraine was reported in 8.3% in APS and 7.7% in APS-*like*, livedo reticularis in 8.3% and 2.2% and chronic renal disease in 5.7% and 3.3%, respectively. There were no reported cases of heart valve disease. In the control group, none of these manifestations were reported. These results were similar between APS and APS-*like*, while showing a significant difference compared to the control group (except for livedo reticularis in APS-*like* vs G0).

Regarding cardiovascular risk factors, the rate of preexisting arterial hypertension was 31.4% in APS, 8.8% in APS-like and 1.1% in G0, being significantly higher in APS compared to the other two groups (p=0.001 for APS-*like* and p<0.001 for controls). The prevalence of smokers was 30.0% in APS, 17.6% in APS-*like* and 1.0% in G0, with a significant difference between the study group and the control group (p<0.001). Dyslipidemia was reported in 11.4% in APS, 4.4% in APS-*like* and 1.0% in G0; a significant difference was only found between APS and controls (p=0.006). The incidence of obesity was 28.6% in APS, 18.7% in APS-*like* and 22.8% in G0, which was similar between groups. No significant difference was found in the rate of APO and thrombotic events based on the presence of these cardiovascular risk factors among the study group (Table III).

The rate of primigravida was 37.1% in APS, 22.0% in APS-*like* and 39.1% in G0, different between APS-*like* and controls (p=0.005).

Assisted reproductive technologies pregnancy incidence was similar between the three groups: 2.9% in APS, 4.4% in APS-*like* and 2.6% in G0.

With regard to past obstetric history, in the APS group, previous spontaneous miscarriage was reported in 28.6%, stillbirth in 17.1%, preterm delivery in 5.7%, preeclampsia in 2.9%, fetal growth

restriction in 11.4% and 14.3% of the pregnancies were voluntarily interrupted. In the APS-*like* group, the respective rates were 51.6%, 11.0%, 12.1%, 4.4%, 6.6% and 5.5%. From the available data in the control group, previous spontaneous miscarriage was reported in 22.3%, preeclampsia in 0.5% and fetal growth restriction in 0.5%. When comparing the three groups, a higher incidence of previous spontaneous miscarriage was found in APS-*like* compared to APS (p=0.020); the study group showed higher rates of prior fetal growth restriction compared to the control group (p=0.002 for APS and p=0.005 for APS-*like*); preeclampsia incidence was higher in APS-*like* compared to controls (p=0.037); no other significant difference was found.

Concerning therapeutic regimens, among APS patients, 97.0% were treated with LDA, 90.9% with LMHW, 48.5% with hydroxychloroquine and 18.2% with corticosteroids. In the APS-*like* group, LDA was used in 82.0%, LMHW in 68.5%, hydroxychloroquine in 28.9% and corticosteroids in 13.3%. Combined treatment (LDA plus LMHW) was given to 90.9% of women with APS and to 66.3% of women with APS-*like*. These treatment rates showed statistical significance within the study group, except regarding the use of corticosteroids (Table I). As for the control group, LDA was given to eight (4.8%) women and LMWH only to one (0.5%). None were prescribed with hydroxychloroquine, corticosteroids or combined treatment. These results were significantly different from those reported in the study group (p<0.001).

Regarding immunological profile, LA was positive in 69.6% of women with APS and in 23.9% of women with APS-*like* (p<0.001); positivity for aCL was reported in 94.3% in APS and 60.9% in APS-*like* (p<0.001); medium-high titers of aCL were respectively found in 51.5% and 21.8% (p=0.001); aB2GPI was positive in 94.3% in APS and 35.6% in APS-*like* (p<0.001). In both groups, IgG was the predominant form. Statistically significant differences were also found in laboratory categories (excluding seronegative APS patients): category I was found in 94.3% in APS and 52.9% in APS-*like* (p<0.001) and category II was found, respectively, in 5.7% and 47.1% (p<0.001). Within category II, category IIa was the only one found in APS. In the APS-*like* group, 9.8% belonged to category IIa, 31.4% to category IIb (p<0.001) and 5.9% to category IIc. Triple positivity was found in 56% in APS and 12.2% in APS-*like* (p<0.001). All patients with APS presented with a high-risk aPL profile, as opposed to 69.2% in APS-*like* (p<0.001) (excluding seronegative APS patients). Non-criteria aPL were reported in 12.9% in APS and 12.8% in APS-*like*, with no significant difference found between groups. Anti-Ro/SS-A and/or Anti-La/SS-B were positive in 24.3% in APS and similarly in 18.3% in APS-*like*. On the other hand, ANA were positive in 68.6% in APS and 40.7% in APS-*like* (p=0.005) and complement activation was found in 31.4% and 10.1% (p=0.007), respectively. When comparing positive with negative LA pregnancies within the study group, no significant difference was found in the rate of APO and thrombotic events (Table IV). On the other hand, the presence of triple aPL positivity showed statistical significance for the development of APO

(p=0.038) and thrombotic events (p=0.046) (Table V). To understand the impact of triple positivity on these outcomes, a correlation test was also performed, and a positive weak association was found for both APO (Φ= 0.204, p=0.038) and thrombotic events (Φ= 0.269, p=0.007).

Development of anemia during pregnancy was described in 15.2% in APS, 25.6% in APS-*like* and 4.0% in G0, which was similar within the study group, however different compared to the control group (p=0.040 for APS and p<0.001 for APS-*like*). Thrombocytopenia was reported in 9.1% in APS, 7.0% in APS-*like* and 0.5% in G0 (6.0%, 4.7% and none, respectively, if under anticoagulation), with a significant difference also being found between the study group and the control group (p=0.011 for APS and p=0.004 for APS-*like*). Within the study group, no significant difference was found in the development of APO and thrombotic events based on the presence of thrombocytopenia (Table VI). Prolonged partial thromboplastin time was found in 68.2% of APS women and 28.4% of APS-*like* (p<0.001). The rate of proteinuria was similar within the study group: 35.5% in APS and 28.4% in APS-*like*.

***Maternal Outcomes***

Thrombotic events during gestation and/or puerperium were rare and only reported in two women in the APS group (6.1%), one venous and the other in arterial territory. These results showed a statistically significant difference only when compared to the control group (p=0.021).

No significant difference was found in the development of thrombosis based on LDA plus LMWH treatment among the study group (Table VII). There were no reported cases of maternal death in any group.

***Obstetric Outcomes***

In the study group, APO as a composite outcome were similarly reported in 50.0% of APS and 40.4% of APS-*like* pregnancies. In the control group, the reported rate was 13.4% (p<0.001).

In women under combined treatment (LDA plus LMHW), among the study group, APO complicated 38.4% of pregnancies, which increased to 54.5% in women not receiving this regimen, although no significant difference was found between groups (Table VII). Regarding the development of hypertensive disorders of pregnancy, gestational hypertension was only reported in the APS-*like* group (4.7%), with a significant difference from the control group (p=0.009). The rates of preeclampsia were similar between the three groups: 6.3% in APS, 4.7% in APS-*like* and 2.1% in G0. No cases of eclampsia were reported in any group. One woman with APS developed HELLP syndrome (3.1%). Placental abruption complicated 3.5% of APS-*like* gestations. The incidence of fluxometric abnormalities was similar within the study group: 16.1% in APS and 6.0% in APS-*like*. Rates of lung maturation with corticotherapy were also approximate among the study

group: 21.9% in APS and 20.5% in APS-*like*. Fetal growth restriction was reported in 34.4% in APS, 21.7% in APS-*like* and 1.6% in G0, which was similar between APS and APS-*like* but significantly higher compared to controls (p<0.001). The rate of spontaneous miscarriage was 5.7% in APS, 5.5% in APS-like and 3.1% in G0, similar between groups. Stillbirth occurred in 14.3% of APS pregnancies and 1.1% of APS-*like*, with no reported cases in the control group, being significantly higher in the APS group (p=0.006 for APS-*like* and p<0.001 for controls). Inversely, live birth was achieved in 80.0% in APS, 93.3% in APS-like and 96.9% in G0, which was significantly lower in APS (p=0.046 for APS-like and p<0.001 for controls). Preterm delivery was reported in 25.0% of APS pregnancies, 23.8% in APS-*like* and 8.0% in G0, with a significant difference found between the study group and the control group (p=0.013 for APS and p<0.001 for APS-*like*). Labor was induced in 50.0% of APS pregnancies and similarly in 45.1% of APS-*like* pregnancies. A cesarean section was performed in 44.8% in APS, 48.2% in APS-like and 29.8% in G0, differing between APS-*like* and controls (p=0.003). There was no significant difference in the cesarean section APS-related rate within the study group (58.3% in APS and 43.6% in APS-*like*).

***Neonatal Outcomes***

Mean gestational age at delivery was 36.04 weeks in APS, 37.30 in APS-*like* and 38.40 in G0. Birth weight was 2567.69g in APS, 2829.52g in APS-*like* and 3120.77g in G0. These results were similar among the study group, but a significant difference was found in relation to the control group. The APGAR score at the 5$^{th}$ minute was similar between groups: 9.29 in APS, 9.40 in APS-*like* and 9.66 in G0. Admission to the neonatal intensive care unit was required in 26.1% in APS, 16.0% in APS-*like* and 0.5% in G0, which was similar within the study group, while different from the control group (p<0.001). There was one neonatal death of a newborn with sepsis in the APS-*like* group (1.2%).

**DISCUSSION**

The results of this study suggest that pregnancy in both APS and APS-*like* women is associated with an increased risk of adverse outcomes when compared to the general population. Moreover, our study shows similar pregnancy outcomes between APS and APS-*like*.

Women's average age at conception was within the fertile age and most pregnancies were achieved spontaneously. Interestingly, maternal age was significantly lower in the APS group than in the general population, suggesting that aPL, together with other risk factors, were able to elicit worse pregnancy outcomes at a younger age[27].

The presence of SLE and/or other concomitant autoimmune diseases has been identified as a risk factor for adverse pregnancy outcomes.[28, 29] In our cohort, concomitant autoimmune diseases

were globally more prevalent in the study group and SLE was the most frequently identified (51.4% in APS and 30.3% in APS-*like*), which is in accordance with previously published studies.[10, 30]

The presence of non-criteria clinical manifestations associated with the presence of aPL has been widely acknowledged.[10] Livedo reticularis is described as the most frequent dermatological feature and its presence has been associated with arterial thrombosis.[31] While it can occur in approximately 25.5% of APS patients[31], the incidence found in our study was significantly lower (8.6% in APS and 2.2% in APS-*like*). Also differing from the 30-50% previously reported in APS[4], no cases of heart valve disease were observed in our cohort, which may be related to the lack of information in some patients or the absence of routine cardiac studies at young ages. Migraine was equally present in both APS (8.6%) and APS-*like* (7.7%) women. Chronic renal disease was relatively infrequent (5.7% in APS and 3.3% in APS-*like*). In addition, to support the diagnosis of aPL-associated nephropathy, a kidney biopsy would be required[4], especially when considering that SLE was present in 3 out of the 5 women.

A higher prevalence of cardiovascular risk factors was identified in our cohort when compared to previous studies.[23, 30] Arterial hypertension, dyslipidemia and smoking were generally more reported in the study group, while similar rates of obesity were found in the three groups, even though the number of smokers appears to be underreported in the control group. The rate of preexisting arterial hypertension was significantly higher in APS (31.4%) compared to APS-*like* (8.8%). Despite being described as additional risk factors for clinical events in APS,[13] they were found not to be associated with a higher rate of APO and thrombotic events in our cohort, therefore excluding bias in the interpretation of results.

History of prior pregnancy morbidity and/or previous thromboembolic events have also been suggested as risk factors for APO.[29] Prior thrombotic events were more frequently reported in women with APS as vascular thrombosis is part of the clinical classification criteria. Inversely, no statistical-significant differences were found in most previous pregnancy morbidity within the study group. Other studies yielded similar results, despite different clinical inclusion criteria,[22] suggesting that women with APS-*like* experienced an obstetric course similar to women with APS. In our cohort, previous spontaneous miscarriage was the most prevalent obstetric complication in both groups (28.6% in APS and 51.6% in APS-*like*), followed by stillbirth in APS (17.1%) and preterm delivery in APS-*like* (12.1%). A significant difference was only found regarding previous spontaneous miscarriage (p=0.020) and the higher incidence in APS-*like* may be related to the different management and therapeutic approaches between the two groups. When comparing to the general population, our results suggest that APS-*like* women experience more venous thromboembolic events and higher rates of obstetric morbidity. Surprisingly, not all obstetric

complications showed a significant difference between APS and controls, which may be related to improved pregnancy outcomes in APS women under treatment.

Regarding therapeutic aspects, the combination of LDA plus a heparin agent is currently considered the standard treatment for pregnant women with APS.[13, 15] In the present study, 90.9% of women with APS were treated with LDA plus LMHW. Although this combination was given to most APS-*like* women (66.3%), the treatment rate was significantly lower in this group, suggesting that clinicians are more prone to prescribe a full treatment if in the context of complete APS criteria. This is in accordance with findings from the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS) cohort, in which non-criteria APS patients less frequently received treatment during pregnancy when compared to criteria APS, despite experiencing a similar rate of complications.[22] However, it is important to acknowledge that the current guidelines are not consensual regarding the prescription of LDA plus LMWH in pregnant women with APS-*like*. [13, 15] Still, our treatment rates were higher than reported in certain studies.[20, 21]

This combined treatment has resulted in a live birth rate of over 70%[16], although some trials have shown no significant improvement in pregnancy outcomes in patients treated with LMWH plus LDA with respect to those treated with LDA alone.[32, 33] In our cohort, women under combined treatment displayed reduced, although not significantly, incidence of APO in comparison to those without treatment. Because this combination fails in about 30% of pregnant APS women, additional treatments may be required. Some studies suggest that hydroxychloroquine, an antimalarial drug widely used in the treatment of SLE, is safe and reduces the rate of aPL-related pregnancy morbidity, in particular fetal loss and placenta-mediated complications.[34] The HYPATIA study, a prospective randomized controlled trial of hydroxychloroquine versus placebo in addition to standard treatment in pregnant women with aPL, is now in progress.[35] Addition of prednisolone seems to improve the rate of live births in refractory aPL-related first trimester pregnancy losses, but it is associated with important complications.[36] Treatment with these two agents was considered in our cohort, regardless of the medical indication, and hydroxychloroquine was found to be given to a significant percentage of patients (48.5% of women with APS and 28.9% with APS-*like*). Other additional therapies include intravenous immunoglobulins, plasma exchange and pravastatin.[29, 37]

In our study, live birth was achieved in 80.0% of APS pregnancies and higher rates were found in APS-*like*, reaching up to 93.3%. Differences in clinical inclusion criteria difficult comparison with previously published results. While the EUROAPS preliminary first year report observed similar rates as ours (79.4% in criteria APS and 93.7% in non-criteria APS),[38] another study based on the EUROAPS cohort found comparable live birth rates between APS and non-criteria APS (72.8% and

72.43%, respectively).[20] The PREGNANTS study reported an overall live birth of only 54.3% in patients with primary APS, which decreased to 30% in triple-positive women.[39]

Regarding immunological profile, as anticipated, detection of criteria-aPL was significantly higher in women with APS when compared to APS-*like*, as seronegative APS was included in the second group. In APS, aCL and aB2GPI were the most frequently detected, present in 94.3%, whereas LA was present in 69.6%. Other studies have also identified aCL as the most prevalent antibody.[9, 30, 39.] Almost 95% of women diagnosed with APS belonged to category I. Opposite results were reported in the EUROAPS registry, in which category IIa was the most prevalent.[23] In the APS-*like* group, the most common aPL was aCL (60.9%) and category I (52.9%) was also more prevalent over category II (47.1%). When comparing both groups, category I was more frequent in APS and category II in APS-*like*, which is in line with data from the EUROAPS cohort,[22] although a latter study also found category IIa to be more frequent in the APS group.[20] Triple positivity was identified in 56.0% of women with APS, which is significantly higher than the 2.7% reported in the PREGNANTS study [39] or the 11% reported in the EUROAPS registry [23]. A lower percentage of triple positivity was reported in APS-*like* women, as predicted. However, almost 70% were classified as having a high-risk aPL profile.

The risk of obstetric complications according to the aPL profile is still subject of debate. In the multicenter PREGNANTS study, aB2GPI was associated with the lowest live birth rate and the highest incidence of preeclampsia, fetal growth restriction and stillbirth in primary APS, compared to the presence of aCL or LA alone.[39] A prospective study identified aCL as the main independent risk factor for fetal growth restriction in aPL carriers[40]. In addition, data from the PROMISSE study indicates that LA is the one that correlates better with APO (present in approximately 40% of LA-positive women).[41] Also, LA was identified as the only aPL strongly associated with late fetal loss in APS in a recent meta-analysis.[42] Conversely, several studies have identified triple aPL positivity as a major risk factor for adverse pregnancy outcomes in both APS and non-criteria patients.[27, 43] As for thrombotic events, LA and triple aPL positivity have been identified as the main risk factors[9, 44-46] and IgG-type antibodies seems to be more strongly associated than the IgM isotype.[47] In our cohort, triple aPL positivity and not LA positivity was found to be associated with the development of APO and thrombotic events. Interpretation of these results should be cautious due to the small number of women included in the cohort and since information on the presence of the LA and, consequently, triple positivity, was not available in all cases.

Many authors have described a wide variety of non-criteria aPL related to thrombosis and obstetric morbidity, including antibodies anti-B2GPI domain I and anti-phosphatidylserine/prothrombin.[48-50] Alijotas-Reig et al. reported twice the positivity of non-criteria aPL in patients with non-criteria APS when compared to criteria APS (11.2% vs 5.1%,

respectively).[20] Different results were observed in the present study, in which almost 13% of both APS and APS-*like* women tested positive for some of the non-criteria aPL. This rate may underestimate the real incidence, as they are not routinely assessed in current practice and not all are performed. However, they could be useful for patients classified as seronegative APS and non-criteria APS[20, 51].

Maternal anti-Ro/SS-A and/or anti-La/SS-B were identified in a significant number of patients (24.3% in APS and 18.3% in APS-*like*). In their presence, serial fetal echocardiography is usually recommended from 16-18 weeks of gestation, as positivity for these antibodies is associated with a 2% risk for development of irreversible congenital heart block (16% in women with a previously affected child), which can lead to death to in utero or in the first year of life and to a pacemaker need in more than half of live-born children.[15, 52]

ANA were significantly more prevalent in APS women (68.6%) despite similar rates of SLE in both groups. These results diverge from others previously published, as they report lower rates of ANA positivity and a higher incidence of these antibodies in SLE patients. [9, 23, 30, 45]

Several authors have studied the complement role in the pathogenesis of APS and complement activation has been proposed as an early predictor of APO in APS patients.[53] In our cohort, 31.4% of APS women presented with low levels of C3 and/or C4 *versus* 10.1% of APS-*like*, which is located within the range reported by other studies.[20, 23] This rate may be underestimated, as complement levels were not systematically assessed. On the other hand, these low levels may be associated with lupus activity.[9]

Concerning the analytic profile, the incidence of anemia, thrombocytopenia and proteinuria was comparable among APS and APS-*like* pregnancies and higher than those observed in the general population for the first two. Although thrombocytopenia can occur in at least 30% of APS patients and its presence has been associated with obstetric morbidity and thrombosis,[4] a lower incidence was found in our study in comparison to the literature and a decreased platelet level was not found to be associated with a higher devolvement of these complications. Our main concern regarding low hemoglobin and platelet levels was the development of autoimmune hemolysis, which is rare even in the presence of a positive Coombs test (occurring in 10% of APS individuals).[(8)] Indeed, autoimmune hemolysis was not observed in our cohort, despite a previous diagnosis of autoimmune hemolytic anemia in two women (included in other autoimmune diseases). Prolonged partial thromboplastin time was more frequent in women with APS, which can be related to the highest prevalence of LA, as this antibody is known to cause a prolonged clotting time in vitro.[5]

Incidence of thrombotic events during pregnancy and/or puerperium is highly variable in literature[23, 51] and reaches close to 8% in some studies[38]. Within the European multicentre cohort,

no major differences between criteria and non-criteria APS were observed in thrombotic complications.[20] In our cohort, these events were rare and only reported in two women in the APS group (6.1%). This preference for women with definite APS may be explained by the higher rates of triple positivity in this group, as previously mentioned, which was present in both cases. However, asymptomatic aPL carriers and women with purely obstetric APS are also at high risk for developing a thrombotic event over a long-term period.[46, 54, 55] These findings highlight the importance of close monitoring of APS-*like* patients, as some of these women may evolve to definite APS after developing a thrombotic event. There were no cases reported of maternal death.

There is a relatively small number of published studies comparing pregnancy outcomes among definite APS and incomplete forms of APS and differences in both clinical and laboratory inclusion criteria difficult comparison to our results. In our cohort, APO as a composite outcome were identified in 50.0% of the APS and in 40.4% of the APS-*like* pregnancies. Rates reported in previous studies are highly variable and range from approximately 20% to 70%[9, 20, 22, 23, 56]. No significant differences were found between the two groups, which emphasizes the idea that pregnancies in women with APS-*like* may have the same risk as those with definite diagnosis of APS and thus deserve similar management. These results are in line with previous studies, including a multicenter retrospective study that used analogous groups to ours and reported similar rates of APO in women with criteria APS and non-criteria APS plus asymptomatic carriers[56]. In two large retrospective uncontrolled studies, both criteria and non-criteria APS experienced similarly successful obstetric outcomes when treated.[20, 22] Another prospective study suggested that all the categories of women with aPL antibodies positivity have an increased incidence of APO, even asymptomatic carriers, although complete APS is associated with a higher risk and a higher fraction of adverse obstetric events.[21] When considered individually, stillbirth was the main difference found, as it complicated 14.3% of APS pregnancies when compared to 1.1% of APS-*like*.

The prevalence of clinical manifestations and obstetric outcomes in women with APS differs in the published literature and there is great variability in the definitions used. In the EUROAPS registry, miscarriage was reported in 38.6%, fetal loss in 25.3% and stillbirth in 23%.[23] In a multicenter prospective study of 1000 patients, prematurity and fetal growth restriction were the most prevalent complications, being reported in 48.2% and 26.3% of APS pregnancies, respectively.[30] In non-criteria APS, prematurity and miscarriage have been identified as the most prevalent APO. [20, 22] In our cohort, fetal growth restriction was the most prevalent obstetric complication in both groups (34.4% in APS and 21.7% in APS-*like*), followed by preterm delivery (25.0% in APS and 23.8% in APS-*like*). These results may be related to the high rates of instituted treatment with a consequent increase in the rates of successful pregnancies. The low rates of spontaneous

miscarriage, stillbirth, placental abruption and hypertensive disorders of pregnancy may also be a reflex of the improvement in the management and monitoring of pregnancies in women diagnosed with APS. When comparing to the general population, the study group developed a significantly higher rate of APO as a composite outcome, although the previously mentioned low incidences make it difficult to value the results obtained in the individual variables. Still, fetal growth restriction and preterm delivery were significantly higher in both women with APS and APS-*like* when compared to controls, as well as stillbirth, which was more prevalent in APS.

Fluxometric abnormalities (from the umbilical artery, middle cerebral artery and/or ductus venosus) were identified in 16.1% of APS pregnancies and 6.0% of APS-*like*. However, the use of uterine artery Doppler ultrasound in pregnancy monitoring is now recommended by the European League Against Rheumatism (EULAR)[52], as a reduced blood flow in these arteries is an indirect indicator for the development of placental insufficiency and/or preeclampsia.[57]

Regarding labor in the APS group, 50% were induced and a cesarian delivery occurred in 44.8%. The major indications for induction of elective cesarean section were disease related. These findings are similar to those found in APS-*like*. The mode of delivery showed statistical significance when comparing APS-*like* to controls: higher rates of cesarean delivery were reported in the APS-*like* group, which can be related to the higher rate of APO.

No differences were found regarding neonatal outcomes in APS and APS-*like*. Lower gestational age at delivery and birth weight and higher rates of admission in the neonatal intensive care unit were reported in the study group when compared to controls, which is in line with the results of a recent meta-analysis.[58] The APGAR score at the 5$^{th}$ minute was similar in the three groups. Only one neonatal death was reported in the APS-*like* group.

The main differences of the present study compared to previous similar ones include the presence of a control group consisting of healthy women and the inclusion of seronegative APS and asymptomatic carriers in the APS-*like* group in addition to non-criteria APS, which may difficult comparison to previously published studies. A major limitation is the retrospective nature and the lack of data in some variables, since the information reported in medical records is sometimes insufficient. Also, it is a single-center study in a tertiary hospital with a relatively small sample size, which may not be representative of the national population. The inclusion of women with no confirmatory testing of aPL positivity increases the risk of misdiagnosing APS in patients. Inversely, the fact that not all laboratory category subsets were available can lead to false-negative diagnoses.[23] In addition, we cannot exclude the presence of aPL in the control group, as we do not perform these laboratory tests on healthy pregnant women.

Therefore, a larger multicenter prospective study should be conducted in order to increase the validity of our results and consequently improve medical practice regarding APS and APS-*like*.

**CONCLUSIONS**

Our study found similar obstetric and neonatal outcomes among pregnant women with confirmed APS and APS-*like*, with fetal growth restriction being the most reported APO in both groups. Still, higher rates of stillbirth and consequently lower rates of live birth were observed in APS, despite being more intensively treated. Significant differences were found among aPL categories between the study group, with category I being more frequent in the APS group and category II in the APS-*like* group. Triple aPL positivity was found to be associated with the development of APO and thrombotic events. Although pregnancy in both APS and APS-*like* women is associated with an increased risk of adverse pregnancy outcomes and should be closely monitored, successful outcomes and a high rate of live births can still be achieved. Future investigation is needed to further understand the extent of APS-*like* implications on pregnancy and to define its proper management and treatment.

**APPENDIX**

Table I – Comparison between APS and APS-*like* groups

| **Variable** | **APS group** (n=35) | **APS-*like group*** (n=91) | ***P*-value** |
|---|---|---|---|
| **Age (years, mean ± SD)** | 30.26±5.74 | 32.02±4.71 | NS |
| **Medical history (n, %)** | | | |
| Deep vein thrombosis | 12(34.3) | 3(3.3) | <0.001* |
| Arterial thrombosis | 10(28.6) | 2(2.2) | <0.001* |
| Systemic lupus erythematosus | 18(51.4) | 30(33.0) | NS |
| Behçet's disease | 2(5.7) | 1(1.1) | NS* |
| Sjögren's syndrome | 0(0) | 2(2.2) | NS* |
| Other autoimmune diseases | 9(25.7) | 13(14.3) | NS |
| Heart valve disease | 0(0) | 0(0) | |
| Migraine | 3(8.6) | 7(7.7) | NS* |
| Livedo reticularis | 3(8.6) | 2(2.2) | NS* |
| Chronic renal disease | 2(5.7) | 3(3.3) | NS* |
| Chronic hypertension | 11(31.4) | 8(8.8) | 0.001 |
| Dyslipidemia | 4(11.4) | 4(4.4) | NS* |
| Obesity | 10(28.6) | 17(18.7) | NS |
| Smoking | 7(30.0) | 16(17.6) | NS |
| **Obstetric history (n, %)** | | | |
| Primigravida | 13(37.1) | 20(22.0) | NS |
| ART pregnancy | 1(2.9) | 4(4.4) | NS* |
| Previous spontaneous miscarriage | 10(28.6) | 47(51.6) | 0.020 |
| Previous VIP | 5(14.3) | 5(5.5) | NS* |
| Previous stillbirth | 6(17.1) | 10(11.0) | NS* |
| Previous pre-term delivery | 2(5.7) | 11(12.1) | NS* |
| Previous preeclampsia | 1(2.9) | 4(4.4) | NS* |
| Previous fetal growth restriction | 4(11.4) | 6(6.6) | NS* |
| **Medical therapy (n, %)** | | | |
| Low-dose aspirin | 32(97.0) | 73(82.0) | 0.039* |
| Low molecular weight heparin | 30(90.9) | 61(68.5) | 0.012 |
| LDA + LMWH | 30(90.9) | 59(66.3) | 0.007 |
| Hydroxychloroquine | 16(48.5) | 26(28.9) | 0.042 |
| Corticosteroids | 6(18.2) | 12(13.3) | NS* |
| **Immunological profile (n, %)** | | | |
| Lupus anticoagulant | 16(69.6) | 16(23.9) | <0.001 |
| Anti-cardiolipin | 33(94.3) | 53(60.9) | <0.001 |
| *aCL IgM* | 16(45.7) | 23(26.4) | 0.039 |
| *aCL IgG* | 26(74.3) | 40(46.0) | 0.005 |
| *aCL in medium-high titers*[1] | 18(51.4) | 19(21.8) | 0.001 |
| Anti-β2 glycoprotein | 33(94.3) | 21(35.6) | <0.001 |
| *aB2GPI IgM* | 17(48.6) | 14(16.1) | <0.001 |
| *aB2GPI IgG* | 21(60.0) | 26(29.9) | 0.002 |
| Category I | 33(94.3) | 27(52.9) | <0.001 |
| Category II | 2(5.7) | 24(47.1) | 0.002 |
| Category IIa | 2(5.7) | 5(9.8) | NS* |
| Category IIb | 0(0) | 16(31.4) | <0.001 |
| Category IIc | 0(0) | 3(5.9) | NS* |
| Triple positive | 14(56.0) | 10(12.2) | <0.001 |

| **Variable** | **APS group** (n=35) | **APS-*like group*** (n=91) | ***P*-value** |
|---|---|---|---|
| High-risk aPL profile | 35(100) | 36(69.2) | <0.001 |
| Non-criteria aPL[2] | 4(12.9) | 10(12.8) | NS* |
| Anti-Ro/SS-A and/or Anti-La/SS-B | 8(24.2) | 15(18.3) | NS |
| ANA | 24(68.6) | 37(40.7) | 0.005 |
| C3 and/or C4 consumption | 11(31.4) | 7(10.1) | 0.007 |
| **Analytic profile (n, %)** | | | |
| Anemia | 5(15.2) | 22(25.6) | NS |
| Thrombocytopenia | 3(9.1) | 6(7.0) | NS* |
| Prolonged partial thromboplastin time | 15(68.2) | 19(28.4) | <0.001 |
| Proteinuria | 11(35.5) | 21(28.4) | NS |
| **Maternal outcomes (n, %)** | | | |
| Thrombotic events | 2(6.1) | 0(0) | NS* |
| Venous | 1(3.0) | 0(0) | NS* |
| Arterial | 1(3.0) | 0(0) | NS* |
| Maternal death | 0(0) | 0(0) | |
| **Obstetric outcomes (n, %)** | | | |
| Adverse pregnancy outcomes[3] | 17(50.0) | 36(40.4) | NS |
| Gestational hypertension | 0(0) | 4(4.7) | NS* |
| Preeclampsia | 2(6.3) | 4(4.7) | NS* |
| Eclampsia | 0(0) | 0(0) | |
| HELLP syndrome | 1(3.1) | 0(0) | NS* |
| Placental abruption | 0(0) | 3(3.5) | NS* |
| Fetal growth restriction | 11(34.4) | 18(21.7) | NS |
| Fluxometric abnormalities | 5(16.1) | 5(6.0) | NS* |
| Lung maturation with corticotherapy | 7(21.9) | 17(20.5) | NS |
| Spontaneous miscarriage | 2(5.7) | 5(5.5) | NS* |
| Stillbirth | 5(14.3) | 1(1.1) | 0.006 |
| Live birth rate | 28(80.0) | 84(93.3) | 0.046* |
| Preterm delivery | 7(25.0) | 20(23.8) | NS |
| **Labor (n, %)** | | | |
| Induced labor | 14(50.0) | 37(45.1) | NS |
| Vaginal birth | 16(55.2) | 44(51.8) | NS |
| Cesarean delivery | 13(44.8) | 41(48.2) | NS |
| APS related cesarean[4] | 7(58.3) | 17(43.6) | NS |
| **Neonatal outcomes** | | | |
| Gestational age (weeks, mean ± SD) | 36.04±3.50 | 37.30±2.38 | NS |
| Birth weight (g, mean ± SD) | 2567.69±836.10 | 2829.52±688.27 | NS |
| Apgar score at 5 minutes (mean ± SD) | 9.29±2.12 | 9.40±1.80 | NS |
| Admission to the neonatal ICU (n, %) | 6(26.1) | 13(16.0) | NS* |
| Neonatal death (n, %) | 0(0) | 1(1.2) | NS* |

*APS,* antiphospholipid syndrome*. NS,* not significant. *NA,* not available*. ART,* assisted reproductive technology. *VIP,* voluntary interruption of pregnancy. *LDA,* low-dose aspirin. *LMWH,* low molecular weight heparin. *aCL,* anti-cardiolipin. *aB2GPI,* anti-β2 glycoprotein. *aPL,* antiphospolipid antibodies. *ICU,* intensive care unit. **P*-value calculated with Fisher's Exact Test. [1]aCL >40GPL or MPL, according to laboratory criteria of APS. [2]IgA aCL, IgA aB2GPI, antibodies against phosphatidylserine, phosphatidylethanolamine, prothrombin alone and to the phosphatidylserine–prothrombin complex. [3]Includes spontaneous miscarriage, stillbirth, preterm delivery, fetal growth restriction, placental abruption, gestational hypertension, preeclampsia eclampsia and HELLP syndrome. [4]Includes preeclampsia, fetal growth restriction, abnormal or non-reassuring fetal surveillance tests, abnormal Doppler flow suggestive of fetal hypoxemia, oligohydramnios.

Table II – Comparison between the control group and APS and APS-*like* groups

| **Variable** | **Control group** (n=194) | **APS group** (n=35) | ***P*-value** | **APS-*like* group** (n=91) | ***P*-value** |
|---|---|---|---|---|---|
| **Age (years, mean ± SD)** | 32.55±5.70 | 30.26±5.74 | 0.030 | 32.02±4.71 | NS |
| **Medical history (n, %)** | | | | | |
| Deep vein thrombosis | 0(0) | 12(34.3) | <0.001* | 3(3.3) | 0.032* |
| Arterial thrombosis | 0(0) | 10(28.6) | <0.001* | 2(2.2) | NS* |
| Systemic lupus erythematosus | 0(0) | 18(51.5) | <0.001* | 30(33.0) | <0.001 |
| Behçet's disease | 1(0.5) | 2(5.7) | NS* | 1(1.1) | NS* |
| Sjögren's syndrome | 0(0) | 0(0) | - | 2(2.2) | NS* |
| Other autoimmune diseases | 2(1.0) | 9(25.7) | <0.001* | 13(14.3) | <0.001* |
| Heart valve disease | 0(0) | 0(0) | - | 0(0) | - |
| Migraine | 0(0) | 3(8.6) | 0.003* | 7(7.7) | <0.001* |
| Livedo reticularis | 0(0) | 3(8.6) | 0.003* | 2(2.2) | NS* |
| Chronic renal disease | 0(0) | 2(5.7) | 0.023* | 3(3.3) | 0.032* |
| Chronic hypertension | 2(1.1) | 11(31.4) | <0.001* | 8(8.8) | 0.002 |
| Dyslipidemia | 2(1.0) | 4(11.4) | 0.006* | 4(4.4) | NS* |
| Obesity | 34(22.8) | 10(28.6) | NS | 17(18.7) | NS |
| Smoking | 2(1.0) | 7(20.0) | <0.001* | 16(17.6) | <0.001 |
| **Obstetric history (n, %)** | | | | | |
| Primigravida | 72(39.1) | 13(37.1) | NS | 20(22.0) | 0.005 |
| ART pregnancy | 5(2.6) | 1(2.9) | NS* | 4(4.4) | NS* |
| Previous spontaneous miscarriage | 41(22.3) | 10(28.6) | NS | 47(51.6) | <0.001 |
| Previous VIP | NA | 5(14.3) | - | 5(5.5) | - |
| Previous stillbirth | NA | 6(17.1) | - | 10(11.0) | - |
| Previous pre-term delivery | NA | 2(5.7) | - | 11(12.1) | - |
| Previous preeclampsia | 1(0.5) | 1(2.9) | NS* | 4(4.4) | 0.037 |
| Previous fetal growth restriction | 1(0.5) | 4(11.4) | 0.002* | 6(6.6) | 0.005* |
| **Medical therapy (n, %)** | | | | | |
| Low-dose aspirin | 8(4.8) | 32(97.0) | <0.001 | 73(82.0) | <0.001 |
| Low molecular weight heparin | 1(0.5) | 30(90.9) | <0.001* | 61(68.5) | <0.001 |
| LDA + LMHW | 0(0) | 30(90.9) | <0.001* | 59(66.3) | <0.001 |
| Hydroxychloroquine | 0(0) | 16(48.5) | <0.001* | 26(28.9) | <0.001 |
| Corticosteroids | 0(0) | 6(18.2) | <0.001* | 12(13.3) | <0.001* |
| **Analytic profile (n, %)** | | | | | |
| Anemia | 9(4.8) | 5(15.2) | 0.040* | 22(25.6) | <0.001 |
| Thrombocytopenia | 1(0.5) | 3(9.1) | 0.011* | 6(7.0) | 0.004* |
| **Maternal outcomes (n, %)** | | | | | |
| Thrombotic events | 0(0) | 2(6.1) | 0.021* | 0(0) | - |
| Venous | 0(0) | 1(3.0) | NS* | 0(0) | - |
| Arterial | 0(0) | 1(3.0) | NS* | 0(0) | - |
| Maternal death | 0(0) | 0(0) | - | 0(0) | - |

| Variable | Control group (n=194) | APS group (n=35) | *P*-value | APS-*like* group (n=91) | *P*-value |
|---|---|---|---|---|---|
| **Obstetric outcomes (n, %)** | | | | | |
| Adverse pregnancy outcomes[1] | 26(13.4) | 17(50.0) | <0.001 | 36(40.4) | <0.001 |
| Gestational hypertension | 0(0) | 0(0) | - | 4(4.7) | 0.009* |
| Preeclampsia | 4(2.1) | 2(6.3) | NS* | 4(4.7) | NS* |
| Eclampsia | 0(0) | 0(0) | - | 0(0) | - |
| HELLP syndrome | 0(0) | 1(3.1) | NS* | 0(0) | - |
| Placental abruption | 0(0) | 0(0) | - | 3(3.5) | 0.028* |
| Fetal growth restriction | 3(1.6) | 11(34.4) | <0.001* | 18(21.7) | <0.001 |
| Spontaneous miscarriage | 6(3.1) | 2(5.7) | NS* | 5(5.5) | NS* |
| Stillbirth | 0(0) | 5(14.3) | <0.001* | 1(1.1) | NS* |
| Live birth rate | 188(96.9) | 28(80.0) | <0.001* | 84(93.3) | NS* |
| Preterm delivery | 15(8.0) | 7(25.0) | 0.013* | 20(23.8) | <0.001 |
| **Labor (n, %)** | | | | | |
| Induced labor | NA | 14(50.0) | - | 37(45.1) | - |
| Vaginal birth | 132(70.2) | 16(55.2) | NS | 44(51.8) | 0.003 |
| Cesarean delivery | 56(29.8) | 13(44.8) | NS | 41(48.2) | 0.003 |
| APS-related cesarean[2] | NA | 7(58.3) | - | 17(43.6) | - |
| **Neonatal outcomes** | | | | | |
| Gestational age (weeks, mean ± SD) | 38.49±2.03 | 36.04±3.50 | 0.001 | 37.30±2.38 | <0.001 |
| Birth weight (g, mean ± SD) | 3120.77 ±524.09 | 2567.69 ±836.10 | 0.002 | 2829.52 ±688.27 | <0.001 |
| Apgar score at 5 minutes (mean ± SD) | 9.66±1.06 | 9.29±2.12 | NS | 9.40±1.80 | NS |
| Admission to the neonatal ICU (n, %) | 1(0.5) | 6(26.1) | <0.001* | 13(16.0) | <0.001* |
| Neonatal death (n, %) | 0(0) | 0(0) | - | 1(1.2) | NS* |

*APS,* antiphospholipid syndrome*. NS,* not significant. *NA,* not available*. ART,* assisted reproductive technology. *VIP,* voluntary interruption of pregnancy. *LDA,* low-dose aspirin. *LMWH,* low molecular weight heparin. *ICU,* intensive care unit. **P*-value calculated with Fisher's Exact Test. [1]Includes spontaneous miscarriage, stillbirth, preterm delivery, fetal growth restriction, placental abruption, gestational hypertension, preeclampsia eclampsia and HELLP syndrome. [2]Includes preeclampsia, fetal growth restriction, abnormal or non-reassuring fetal surveillance tests, abnormal Doppler flow suggestive of fetal hypoxemia, oligohydramnios.

Table III – Association between cardiovascular risk factors and pregnancy outcomes

| **Variable** | **Cardiovascular risk factors** (n=58) | **No cardiovascular risk factors** (n=65) | ***P*-value** |
|---|---|---|---|
| Thrombotic events | 1(50.0) | 1(50.0) | NS |
| Adverse pregnancy outcomes[1] | 23(39.7) | 30(46.2) | NS |

*NS,* not significant. [1]Includes spontaneous miscarriage, stillbirth, preterm delivery, fetal growth restriction, placental abruption, gestational hypertension, preeclampsia eclampsia and HELLP syndrome.

Table IV – Association between LA and pregnancy outcomes

| **Variable** | **Positive LA** (n=32) | **Negative LA** (n=58) | ***P*-value** |
|---|---|---|---|
| Thrombotic events | 2(6.7) | 0(0) | NS* |
| Adverse pregnancy outcomes[1] | 17(54.8) | 22(39.3) | NS |

*LA,* lupus anticoagulant. *NS,* not significant. **P*-value calculated with Fisher's Exact Test. [1]Includes spontaneous miscarriage, stillbirth, preterm delivery, fetal growth restriction, placental abruption, gestational hypertension, preeclampsia eclampsia and HELLP syndrome.

Table V – Association between triple aPL positivity and pregnancy outcomes

| **Variable** | **Triple aPL positivity** (n=24) | **No triple aPL positivity** (n=83) | ***P*-value** |
|---|---|---|---|
| Thrombotic events | 2(9.1) | 0(0) | 0.046* |
| Adverse pregnancy outcomes[1] | 15(65.2) | 33(40.7) | 0.038 |

*aPL,* antiphospholipid antibodies. *NS,* not significant. **P*-value calculated with Fisher's Exact Test. [1]Includes spontaneous miscarriage, stillbirth, preterm delivery, fetal growth restriction, placental abruption, gestational hypertension, preeclampsia eclampsia and HELLP syndrome.

Table VI – Association between thrombocytopenia and pregnancy outcomes

| **Variable** | **Thrombocytopenia** (n=9) | **No thrombocytopenia** (n=107) | ***P*-value** |
|---|---|---|---|
| Thrombotic events | 1(50.0) | 1(50.0) | NS |
| Adverse pregnancy outcomes[1] | 5(10.2) | 44(89.8) | NS |

*NS,* not significant. [1]Includes spontaneous miscarriage, stillbirth, preterm delivery, fetal growth restriction, placental abruption, gestational hypertension, preeclampsia eclampsia and HELLP syndrome.

Table VII – Association between LDA plus LMWH treatment and pregnancy outcomes

| **Variable** | **LDA plus LMWH** (n=89) | **Not treated with LDA plus LMWH** (n=33) | ***P*-value** |
|---|---|---|---|
| Thrombotic events | 2(2.4) | 0(0) | NS* |
| Adverse pregnancy outcomes[1] | 33(38.4) | 18(54.5) | NS |

*NS,* not significant. *LDA,* low-dose aspirin. *LMWH,* low molecular weight heparin. **P*-value calculated with Fisher's Exact Test. [1]Includes spontaneous miscarriage, stillbirth, preterm delivery, fetal growth restriction, placental abruption, gestational hypertension, preeclampsia eclampsia and HELLP syndrome.

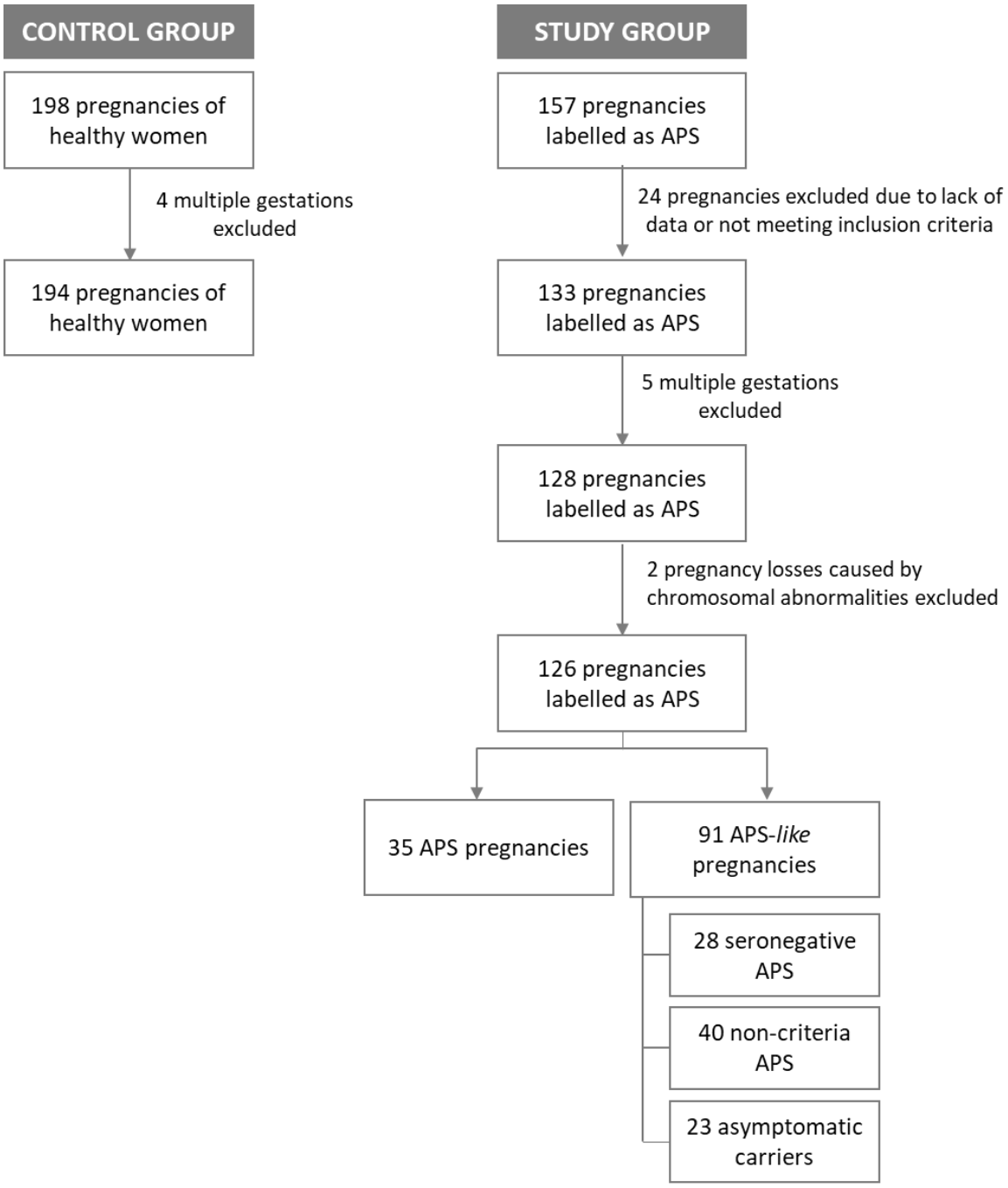


Figure 1 – Patient selection protocol
*APS*, Antiphospholipid Syndrome.

**REFERENCES**


1. Arslan E, Branch DW. Antiphospholipid syndrome: Diagnosis and management in the obstetric patient. Best Pract Res Clin Obstet Gynaecol. 2020;64:31-40.
2. Cohen H, Cuadrado MJ, Erkan D, et al. 16th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends. Lupus. 2020;29(12):1571-93.
3. Antovic A, Sennström M, Bremme K, Svenungsson E. Obstetric antiphospholipid syndrome. Lupus Sci Med. 2018;5(1):e000197.
4. Schreiber K, Sciascia S, de Groot PG, et al. Antiphospholipid syndrome. Nat Rev Dis Primers. 2018;4:18005.
5. Molhoek JE, de Groot PG, Urbanus RT. The Lupus Anticoagulant Paradox. Semin Thromb Hemost. 2018;44(5):445-52.
6. Schreiber K, Hunt BJ. Managing antiphospholipid syndrome in pregnancy. Thromb Res. 2019;181 Suppl 1:S41-s6.
7. Cervera R, Piette JC, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum. 2002;46(4):1019-27.
8. Alijotas-Reig J, Ferrer-Oliveras R, Ruffatti A, et al. The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): A survey of 247 consecutive cases. Autoimmun Rev. 2015;14(5):387-95.
9. Muñoz-Rodriguez FJ, Font J, Cervera R, et al. Clinical study and follow-up of 100 patients with the antiphospholipid syndrome. Semin Arthritis Rheum. 1999;29(3):182-90.
10. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4(2):295-306.
11. Hughes GR. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. Br Med J (Clin Res Ed). 1983;287(6399):1088-9.
12. Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum. 1999;42(7):1309-11.
13. Tektonidou MG, Andreoli L, Limper M, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis. 2019;78(10):1296-304.
14. Sciascia S, Sanna G, Murru V, et al. The global anti-phospholipid syndrome score in primary APS. Rheumatology (Oxford). 2015;54(1):134-8.
15. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. Arthritis Rheumatol. 2020;72(4):529-56.
16. Mak A, Cheung MW, Cheak AA, Ho RC. Combination of heparin and aspirin is superior to aspirin alone in enhancing live births in patients with recurrent pregnancy loss and positive anti-phospholipid antibodies: a meta-analysis of randomized controlled trials and meta-regression. Rheumatology (Oxford). 2010;49(2):281-8.
17. Nayfe R, Uthman I, Aoun J, et al. Seronegative antiphospholipid syndrome. Rheumatology (Oxford). 2013;52(8):1358-67.
18. Rodriguez-Garcia JL, Bertolaccini ML, Cuadrado MJ, et al. Clinical manifestations of antiphospholipid syndrome (APS) with and without antiphospholipid antibodies (the so-called 'seronegative APS'). Ann Rheum Dis. 2012;71(2):242-4.
19. Li X, Deng X, Duan H, et al. Clinical features associated with pregnancy outcomes in women with positive antiphospholipid antibodies and previous adverse pregnancy outcomes: a real-world prospective study. Clin Rheumatol. 2021;40(1):193-204.

20. Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R, et al. Comparative study of obstetric antiphospholipid syndrome (OAPS) and non-criteria obstetric APS (NC-OAPS): report of 1640 cases from the EUROAPS registry. Rheumatology (Oxford). 2020;59(6):1306-14.
21. Spinillo A, Bellingeri C, De Maggio I, et al. The impact of various entities of antiphospholipid antibodies positivity on adverse pregnancy outcome. An epidemiological perspective. J Reprod Immunol. 2021;145:103304.
22. Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R, et al. Comparative study between obstetric antiphospholipid syndrome and obstetric morbidity related with antiphospholipid antibodies. Med Clin (Barc). 2018;151(6):215-22.
23. Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R, et al. The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): A survey of 1000 consecutive cases. Autoimmun Rev. 2019;18(4):406-14.
24. ACOG. Practice Bulletin No. 171: Management of Preterm Labor. Obstet Gynecol. 2016;128(4):e155-64.
25. Sousa-Santos RF, Miguelote RF, Cruz-Correia RJ, Santos CC, Bernardes JF. Development of a birthweight standard and comparison with currently used standards. What is a 10th centile? Eur J Obstet Gynecol Reprod Biol. 2016;206:184-93.
26. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020;135(6):e237-e60.
27. Lazzaroni MG, Fredi M, Andreoli L, et al. Triple Antiphospholipid (aPL) Antibodies Positivity Is Associated With Pregnancy Complications in aPL Carriers: A Multicenter Study on 62 Pregnancies. Front Immunol. 2019;10:1948.
28. Ruffatti A, Tonello M, Visentin MS, et al. Risk factors for pregnancy failure in patients with anti-phospholipid syndrome treated with conventional therapies: a multicentre, case-control study. Rheumatology (Oxford). 2011;50(9):1684-9.
29. De Carolis S, Tabacco S, Rizzo F, et al. Antiphospholipid syndrome: An update on risk factors for pregnancy outcome. Autoimmun Rev. 2018;17(10):956-66.
30. Cervera R, Serrano R, Pons-Estel GJ, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis. 2015;74(6):1011-8.
31. Francès C, Niang S, Laffitte E, et al. Dermatologic manifestations of the antiphospholipid syndrome: two hundred consecutive cases. Arthritis Rheum. 2005;52(6):1785-93.
32. Laskin CA, Spitzer KA, Clark CA, et al. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA Trial. J Rheumatol. 2009;36(2):279-87.
33. Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. Obstet Gynecol. 2002;100(3):408-13.
34. Sciascia S, Hunt BJ, Talavera-Garcia E, et al. The impact of hydroxychloroquine treatment on pregnancy outcome in women with antiphospholipid antibodies. Am J Obstet Gynecol. 2016;214(2):273.e1-.e8.
35. Schreiber K, Breen K, Cohen H, et al. HYdroxychloroquine to Improve Pregnancy Outcome in Women with AnTIphospholipid Antibodies (HYPATIA) Protocol: A Multinational Randomized Controlled Trial of Hydroxychloroquine versus Placebo in Addition to Standard Treatment in Pregnant Women with Antiphospholipid Syndrome or Antibodies. Semin Thromb Hemost. 2017;43(6):562-71.
36. Bramham K, Thomas M, Nelson-Piercy C, Khamashta M, Hunt BJ. First-trimester low-dose prednisolone in refractory antiphospholipid antibody-related pregnancy loss. Blood. 2011;117(25):6948-51.
37. Lefkou E, Mamopoulos A, Dagklis T, et al. Pravastatin improves pregnancy outcomes in obstetric antiphospholipid syndrome refractory to antithrombotic therapy. J Clin Invest. 2016;126(8):2933-40.

38. Alijotas-Reig J, Ferrer-Oliveras R. The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): a preliminary first year report. Lupus. 2012;21(7):766-8.
39. Saccone G, Berghella V, Maruotti GM, et al. Antiphospholipid antibody profile based obstetric outcomes of primary antiphospholipid syndrome: the PREGNANTS study. Am J Obstet Gynecol. 2017;216(5):525.e1-.e12.
40. Xi F, Cai Y, Lv M, et al. Anticardiolipin Positivity Is Highly Associated With Intrauterine Growth Restriction in Women With Antiphospholipid Syndrome. Clin Appl Thromb Hemost. 2020;26:1076029620974455.
41. Lockshin MD, Kim M, Laskin CA, et al. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. Arthritis Rheum. 2012;64(7):2311-8.
42. Xu J, Chen D, Duan X, et al. The association between antiphospholipid antibodies and late fetal loss: A systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2019;98(12):1523-33.
43. Högdén A, Antovic A, Berg E, Bremme K, Chaireti R. Obstetric outcomes in patients with primary thrombotic and obstetric antiphospholipid syndrome and its relation to the antiphospholipid antibody profile. Lupus. 2019;28(7):868-77.
44. Ruffatti A, Del Ross T, Ciprian M, et al. Risk factors for a first thrombotic event in antiphospholipid antibody carriers: a prospective multicentre follow-up study. Ann Rheum Dis. 2011;70(6):1083-6.
45. Pengo V, Ruffatti A, Legnani C, et al. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. J Thromb Haemost. 2010;8(2):237-42.
46. Pengo V, Ruffatti A, Legnani C, et al. Incidence of a first thromboembolic event in asymptomatic carriers of high-risk antiphospholipid antibody profile: a multicenter prospective study. Blood. 2011;118(17):4714-8.
47. Kelchtermans H, Pelkmans L, de Laat B, Devreese KM. IgG/IgM antiphospholipid antibodies present in the classification criteria for the antiphospholipid syndrome: a critical review of their association with thrombosis. J Thromb Haemost. 2016;14(8):1530-48.
48. Sciascia S, Sanna G, Murru V, et al. Anti-prothrombin (aPT) and anti-phosphatidylserine/prothrombin (aPS/PT) antibodies and the risk of thrombosis in the antiphospholipid syndrome. A systematic review. Thromb Haemost. 2014;111(2):354-64.
49. Žigon P, Perdan Pirkmajer K, Tomšič M, et al. Anti-Phosphatidylserine/Prothrombin Antibodies Are Associated with Adverse Pregnancy Outcomes. J Immunol Res. 2015;2015:975704.
50. Chighizola CB, Pregnolato F, Andreoli L, et al. Beyond thrombosis: Anti-β2GPI domain 1 antibodies identify late pregnancy morbidity in anti-phospholipid syndrome. J Autoimmun. 2018;90:76-83.
51. Litvinova E, Darnige L, Kirilovsky A, et al. Prevalence and Significance of Non-conventional Antiphospholipid Antibodies in Patients With Clinical APS Criteria. Front Immunol. 2018;9:2971.
52. Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis. 2017;76(3):476-85.
53. Tabacco S, Giannini A, Garufi C, et al. Complementemia in pregnancies with antiphospholipid syndrome. Lupus. 2019;28(13):1503-9.
54. Tonello M, Calligaro A, Favaro M, et al. The first thrombotic event in purely obstetric antiphospholipid syndrome patients and in antiphospholipid antibody carriers: comparison of incidence and characteristics. Arch Gynecol Obstet. 2021;303(2):455-61.
55. Drozdinsky G, Hadar E, Shmueli A, Gabbay-Benziv R, Shiber S. Obstetric antiphospholipid syndrome and long term arterial thrombosis risk. J Thromb Thrombolysis. 2017;44(3):371-5.
56. Fredi M, Andreoli L, Aggogeri E, et al. Risk Factors for Adverse Maternal and Fetal Outcomes in Women With Confirmed aPL Positivity: Results From a Multicenter Study of 283 Pregnancies. Front Immunol. 2018;9:864.

57. Carbillon L, Uzan M, Uzan S. Pregnancy, vascular tone, and maternal hemodynamics: a crucial adaptation. Obstet Gynecol Surv. 2000;55(9):574-81.
58. Liu L, Sun D. Pregnancy outcomes in patients with primary antiphospholipid syndrome: A systematic review and meta-analysis. Medicine (Baltimore). 2019;98(20):e15733.

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