TREATMENT WITH LOW-DOSE PREDNISONE IN REFRACTORY OBSTETRIC ANTIPHOSPHOLIPID SYNDROME: A RETROSPECTIVE COHORT STUDY AND META-ANALYSIS

Short title: Prednisone in refractory obstetric antiphospholipid syndrome

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ABSTRACT

Background: Glucocorticoids have been suggested as a potential therapy in refractory obstetric antiphospholipid syndrome (oAPS). Our aims were to describe a cohort of patients with oAPS treated with low-dose glucocorticoids and to perform a systematic review and meta-analysis evaluating the effects of additional glucocorticoids on the pregnancy outcomes in oAPS patients.

Methods: Retrospective study that included 11 women diagnosed with primary APS. The meta-analysis was conducted by fitting random effects models and was checked for heterogeneity.

Results: All women had suffered from early pregnancy losses and two also had a history of fetal deaths. We studied 47 pregnancies that resulted in 32 abortions (68.1%) and 3 fetal deaths (6.4%). Twenty-six pregnancies were under treatment, mainly LDA and LMWH. Low-dose glucocorticoids were indicated in 13 pregnancies (always in association with LDA and LMWH). There was a decrease in pregnancy loss in those patients treated with LDA and LMWH. Treatment with glucocorticoids significantly increased the rate of successful pregnancy (38.5% abortions in treated *vs* 85.3% abortions in non-treated pregnancies; p=0.003). After multivariate GEE analysis, only glucocorticoids remained inversely associated with pregnancy loss [OR=0.157, (CI 0.025-0.968, p=0.046)]. The meta-analysis showed that glucocorticoids tended to improve the frequency of successful pregnancy [OR= 0.509 (0.252-1.028), p=0.06]. Three cases of gestational diabetes and one of preeclampsia were observed in our cohort. The meta-analysis, which mostly included studies using high-dose steroids, showed that glucocorticoids increased not only the frequency of preeclampsia and gestational diabetes, but also the rate of pre-term birth.

Conclusions: The efficacy of low-dose glucocorticoids in addition to the standard therapy in patients with refractory oAPS should be confirmed in well-designed clinical trials. However, high doses of steroids significantly increase the frequency of maternal and fetal morbidities, making their use strongly inadvisable.

Keywords: obstetric antiphospholipid syndrome, recurrent pregnancy loss, glucocorticoids, treatment

INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies (aPL) and at least one clinical event defined as thrombosis or pregnancy morbidity. Pregnancy morbidities compounding the Sydney classification criteria include three or more spontaneous abortions 10 weeks before gestational age, one or more deaths of morphologically normal fetuses over 10 weeks or premature birth before 34 weeks due to preeclampsia, eclampsia or placental insufficiency [1]. Recurrent pregnancy losses (RPL) or recurrent spontaneous abortions are the most common obstetric manifestation, although APS only explains between 7-25% of such cases [2]. Current management of RPL in APS includes low-dose aspirin (LDA) and low molecular weight heparin (LMWH) combination therapy [3]. However, despite adequate treatment, the rate of pregnancy morbidities remains high. Other treatments - including hydroxychloroquine (HCQ) [4], intravenous immunoglobulins (IvIg) [5] or statins [6] - are recommended in refractory cases [7]. Glucocorticoids seem promising as they have been successfully reported in some, mostly uncontrolled, studies [8-18]. Nonetheless, the results are conflicting [19-22].

The aims of the present study were: 1) To analyze a cohort of patients with refractory obstetric APS treated with low-dose glucocorticoids and compare the rates of successful pregnancy outcome with versus without treatment; 2) To describe potential adverse events related to the use of low-dose glucocorticoids; and 3) To perform a meta-analysis evaluating the effects of additional glucocorticoids on the pregnancy outcome in patients with obstetric APS.

MATERIALS AND METHODS

Study population

We conducted a retrospective study which included 11 women diagnosed with APS according to classification criteria [1] who had an obstetric history of at least two spontaneous abortions. Medium-high aCL and aB2GPI antibodies titers were considered those >99th percentile. We established time 0 as the first evaluation in the obstetric autoimmune pathology clinic.

Data collection

Information including demographic data, traditional cardiovascular risk factors, concomitant autoimmune diseases, other thrombophilias, genetic alterations and uterine morphologic abnormalities was collected. Regarding APS, thrombotic events and pregnancy morbidities included in the classification criteria were evaluated. We also analyzed other manifestations not included in the Sydney criteria that could be related to APS such as thrombocytopenia, livedo reticularis and other pregnancy morbidities such as HELLP syndrome, preeclampsia or eclampsia (after 34 weeks), abruptio placentae, premature birth (<37 weeks), early neonatal death (<1 week), intrauterine growth restriction (IUGR) and oligohydramnios. Moreover, data on delivery, birth weight and Apgar tests were collected. Data on treatment-related adverse events such as gestational diabetes, preeclampsia, eclampsia among others were specifically collected.

Treatment protocol

Patients refractory to LDA and LMWH were treated with glucocorticoids (methylprednisolone 4 mg bid orally until the 12th week of gestation followed by tapering 2 mg per week until discontinuation) or intravenous immunoglobulins (Iv Ig) (0.5 gr/Kg monthly for 6 months). Corticosteroids were used when the number of NK cells were within the normal range. IvIg were chosen if NK cells were expanded.

In certain patients with NK cells expansion if treatment with IvIG failed, corticosteroids were used as a second line.

Meta-analysis

A comprehensive search of PubMed was completed and supplemented by hand searching of the references of all selected articles. Terms used included "Recurrent pregnancy loss AND antiphospholipid syndrome AND corticosteroids ", "obstetric antiphospholipid syndrome AND corticosteroids" and "antiphospholipid syndrome AND corticosteroids" without restriction on language or date. This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23].

Articles were reviewed as shown in **Supplementary figure 1.** Information was collected on study design and sample, characteristics of the study population, treatment protocols, obstetric outcomes and corticosteroid-related adverse events. For the meta-analysis purpose, corticosteroid doses were considered high if they exceeded 20 mg/day prednisone or the equivalent; otherwise they were regarded as low-moderate doses.

Statistical analysis

Statistical analysis was performed using IBM SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Median and ranges or mean values and standard deviations were calculated for the continuous variables. Between-group differences were analyzed using the Student t-test, ANOVA or the chi-square test. A 2-tailed $p< 0.05$ was considered statistically significant.

In order to account for the lack of outcome independence for pregnancies involving the same woman and the confounding effects of other variables, we used generalized linear

models (generalized estimating equations), with a binomial distribution and an exchangeable correlation matrix structure, adjusted by age and parity.

Meta-analysis were conducted by fitting random effects models and were checked for publication bias by funnel plots as shown in **Supplementary Figure 2** [24]. I^2 statistic was calculated to quantify the proportion of the total variation stemming from any heterogeneity [25]. Statistical analysis were performed using Comprehensive Meta-analysis software, version 2.2.064 (Biostat, Englewood, NJ, USA) [29].

RESULTS

Demographic and clinical baseline characteristics

We included 11 women diagnosed with primary APS. The main characteristics of the study population are summarized in **Table 1**. Regarding traditional cardiovascular risk factors, 2 patients were smokers and 2 others reported previous tobacco use. Two patients were obese and one had high blood pressure. In terms of concomitant diseases, 3 patients suffered thyroid disease, while 2 others were positive for antithyroid antibodies with no diagnosed disease.

Regarding APS features, only one woman had a history of thrombosis while the remaining 10 had purely obstetric manifestations. All of them suffered from early pregnancy losses and two of them also had a history of fetal death. Interestingly, one woman suffered from thrombocytopenia and livedo reticularis as clinical manifestations related to APS. In line with their immunological profiles, 2 patients were positive for lupus anticoagulant, 5 for anticardiolipin antibodies and 7 for antiB2glycoprotein antibodies (**Table 1).** The patient with a history of thrombosis presented triple positivity. Two patients were positive for hereditary thrombophilias (One patient was homozygous

for 677 C>T in the MTHFR gen, another patient was also homozygous for 677 C>7 in the MTHFR gen and also heterozygous for 1619G>A in the V factor of Leyden).

Fetal outcomes

As shown in **Table 2**, we studied a total of 47 pregnancies in 11 women with primary APS. Most of the pregnancies (57.4%) were spontaneous, although 42.6% followed assisted reproduction techniques (23.4% in vitro fertilization with autologous oocytes and 17% involved oocyte donors). The number of pregnancies for each women ranged from 2 to 6 (4.3±1.1). Maternal age was 34.1 ± 4.8 years (range 25-45 years). Overall, there were 32 abortions (68.1%) and 3 fetal deaths (6.4%). Only 12 pregnancies were successful in these patients (including among them one premature birth before 34 weeks). Regarding obstetric morbidities during the second half of the pregnancy, gestational diabetes was reported in 3 pregnancies, preeclampsia in 1 pregnancy and premature membrane rupture (PRM) in another. Among the successful pregnancies, the mean gestation was 37.8±3.1 (range 28-40); 9 ended in cesarean section (75%), 2 in induced labor and 1 in natural labor. Mean birth weight was 3106 ± 422 (range 2460-3800gr). No malformations nor cases of neonatal death occurred.

The effects of the different therapeutic schemes

Fifty-five percent of the pregnancies (n=26) were undergoing some type of treatment: LDA (n=25), LMWH (n=24), and Iv Ig (n=4). Low-dose glucocorticoids were indicated in 13 pregnancies. As expected, in all cases corticosteroid treatment was used in combination with LDA and LMWH. **(Table 3).**

When analyzing the overall effects of each treatment, we found that the use of either LDA or LMWH tended to be protective against pregnancy loss (LDA: 60 *vs* 86.4%, p

=0.056; LMWH: 58.3 *vs* 87%,p=0.049). Regarding glucocorticoids, only 38.5% of pregnancies receiving this treatment resulted in abortions compared with 85.3% of the non-treated pregnancies (p=0.003).

In keeping with the univariate analysis, a generalized linear model confirmed the beneficial effects of those treatments. Thus, both LDA [OR=0.282, (CI 0.087-0.912, p=0.035)] and LMWH [OR=0.259, (CI 0.105-0.643, p=0.004)] showed a protective effect. Similarly, glucocorticoids markedly reduced the risk of pregnancy loss [OR=0.196, (CI =0.072-0.529, p=0.001)]. However, neither maternal age nor Iv Ig were associated with pregnancy success (p=0.379).

After multivariate analysis, including LDA, LMWH and glucocorticoids, only treatment with the latter remained independently associated with a diminished risk of pregnancy loss [OR=0.157, (CI 0.025-0.968, p=0.046)]. Due to the frequency distribution of therapies and the fact that many patients received combined therapies prevented us from fitting models with interaction terms. Thus potential drug-drug interactions could not be explored.

Fetal adverse events

No cases of intrauterine growth restriction, oligohydramnios, abruption placentae or PRM were reported in pregnancies treated with glucocorticoids. One case of PRM was reported in the non-treated group. When non-treated and corticosteroid-treated pregnancies were compared, we found no differences in the gestational age at birth (35.7 ± 5 vs 38.9 ± 0.9 weeks), birth weight (3208 ± 414 g in the non-treated vs 3055 ± 455 g in the treated group) or in the 1 and 5 minutes Apgar scores.

Maternal adverse events

Among the pregnancies treated with glucocorticoids, gestational diabetes and preeclampsia were observed in 3 and 1 pregnancies, respectively. Only 4 pregnancies were successful among those not treated with glucocorticoids. In these 4 pregnancies, no cases of gestational diabetes or preeclampsia were reported (p=NS).

Meta-analysis

Efficacy of glucocorticoid treatment

Fourteen studies including ours [12;18-22;27-34] evaluated the effect of glucocorticoids on pregnancy outcomes. However, the dosage used and the duration of the corticosteroid treatment varied widely among the different studies, as shown in **Table 4.** Glucocorticoids were added to other treatments, mainly ASA and/or LMWH; however, concomitant treatments varied among studies. Our meta-analysis of these studies showed that glucocorticoids tended to increase the frequency of a successful pregnancy [OR= 0.509 (0.252-1.028), p=0.06], although the difference was not statistically significant. (**Figure 1a).** Only four studies, including ours, [18;22;34] evaluated the effects of low or medium doses of steroids (≤20 mg prednisone), indeed there was only one study [18] using low dose of steroids (≤10 mg prednisone), thus we used 20 mg of prednisone as threshold for low-medium dose of steroids. The meta-analysis of these 4 studies also showed that low/medium-dose prednisone tended to decrease the rate of abortions [OR 0.659 (0.169-2.564, p=0.55], although it did not reach statistical significance. (**Figure 1b).** There was evidence of high heterogeneity (I^2 82%.) among the studies included.

Safety and tolerability of glucocorticoid treatment

As detailed in **Table 4**, adverse events related to glucocorticoids varied notably in the different studies, depending on the dosage used and the duration of treatment. As shown in **Table 4**, not all studies reported information on fetal or maternal morbidities. However, preeclampsia, gestational diabetes and premature birth were the most common morbidities recorded. The meta-analysis showed that glucocorticoids increased the frequency of preeclampsia and gestational diabetes with an OR of 2.966 (1.364-6.448), p=0.006 **(Figure 2a)** and an OR of 3.803 (1.791-8.073), p=0.001 **(Figure 2b),** respectively. However, it is worth noting that most studies (all but our own) reporting such effects involved high dose steroids.

The meta-analysis revealed a non-significant increase in pre-term birth associated with corticosteroid treatment [OR= 3.252 (0.674-15.7), p =0.142], possibly reflecting those studies that used low doses of prednisone (**Figure 2c**).

DISCUSSION

APS has been clearly associated with pregnancy morbidities, such as recurrent pregnancy losses, stillbirths or placental complications. Pathogenic mechanisms include the presence of thrombosis [35;36], though this only explains a small percentage of complications, as well as inflammatory mechanisms that include interactions with trophoblasts [37]. aPL promoted an antiangiogenic profile [38], reduced cell proliferation and migration [39] and also favored the secretion of inflammatory cytokines and complement activation [40], consequently hindering trophoblast growth and resulting in placental dysfunction. In line with the hypothesis of an underlying thrombotic cause for pregnancy morbidities, clinical investigators have evaluated the effects of LDA and LMWH in these patients. In fact, both LDA and LMWH are currently the standard treatment for women with obstetric APS. It has recently been

proposed that the effectiveness of LMWH stems not only from the inhibition of thrombus formation, but also from the inhibition of complement activation [41]. Despite standard treatment with LDA and LMWH, a non-negligible proportion of patients with obstetric APS do not achieve a successful pregnancy [42]. Among the different therapeutic options in patients refractory to standard treatment, glucocorticoids have been postulated as a valuable option in multiple studies [12;29-31;34]. The rationale for their use includes the blockade of the autoimmune–induced inflammatory factors that impact not only trophoblast implantation and infiltration, but also placental implantation and placental dysfunction. Indeed, historically glucocorticoids have been widely used in refractory obstetric APS with conflicting results (**Table 4).**

Several uncontrolled studies including case reports and series with women with positive aPL treated with glucocorticoids (in combination with LDA and/or LMWH and/or other treatments) have reported positive results with an increase in successful pregnancy rate [8;9;12-16; 29; 43; 48]. However, there are also some studies with negative results [19; 44] as well as three randomized clinical trials [20; 45; 21] and their meta analysis [49] which do not support the use of glucocorticoids as they showed no improvement in live birth rates, but rather an increase in fetal and maternal morbidities.

Despite the unfavourable results of the randomized trials, evidence from observational evidence support a potential role for glucocorticoids. Recently, Mekinian et al. [17] published a favorable outcome (OR 0.30 95% CI 0.11-0.82, p=0.019) associated with corticosteroid and Ye [18] also suggested the benefit (regarding pregnancy loss and also placental dysfunction-related diseases) of adding low dose prednisone and HCQ to standard therapy in refractory obstetric APS. Rufatti et al [34] have recently published a cohort of primary APS treated with either prednisone and/or HOQ or IvIG and/or plasmapheresis to conventional treatment. They found higher benefit with parenteral

regimen, however treatment with low-dose prednisone had a pregnancy success rate of 75%. In our cohort, and according to the meta-analysis results, low-dose prednisone therapy, particularly when discontinued around 12 weeks of gestation and in tandem with the standard treatment with LDA and LMWH, seems to improve pregnancy success in those patients with refractory obstetric APS. However, statistical significance was not reached, probably due to the high heterogeneity of the studies included in the meta-analysis, which makes it difficult to reach any solid conclusions.

The safety of corticosteroid treatment in refractory APS has varied according to the different dose schedules. Initial studies involved small case series or observational studies that used high-dose glucocorticoids throughout the entire pregnancy in addition to LDA (and LMWH in some cases) reported a high rate of adverse events such as IUGR or preeclampsia [8;9;11;13].

The evidence from randomized control trials also confirmed these observations [18,19, 42] . Empson et al. [46] carried out a meta-analysis of these three clinical trials and concluded that prednisone and LDA resulted in a significant increase in prematurity (RR 4.83, 95% CI 2.85-8.21). One must take into account that these studies were still using medium to high doses of steroids during the entire pregnancy, which is different from our treatment protocol. Han et al. [47] evaluated fetal and maternal morbidities associated with the use of prednisone (10 mg/day; maintained until weeks 12 to 14 with subsequent reduction over 4 weeks) in a cohort of 72 women with recurrent spontaneous abortion. They found no increase either in the rates of preeclampsia, gestational diabetes, abruptio placenta, preterm birth before 34 weeks, or in the rate of low or high birth weights for gestational age. Unlike what has been previously

suggested, this therapeutic intervention did not show an increase in pregnancy morbidities.

Although high doses of steroids are associated with severe pregnancy morbidities, studies that utilized low-dose prednisone (≤10 mg/day) appear to be safe for both the mother and the fetus, especially when discontinued around the first trimester. These were the results reported by Geva [49]. Ye [18] and Han [47], as well as by ourselves.

Our study has some limitations, mainly due to its size, retrospective design and lack of randomization. Moreover, interaction interaction effects between multiple treatments could not be explored. However, our cohort is well-defined, consisting of eleven women with confirmed APS based on the Sidney criteria. All of them were attended at the same rheumatology unit using a consistent treatment protocol (some of them were referred to the unit from the assisted reproductive clinic thus explaining the high rate of assisted reproduction techniques in the cohort). This, in addition to the wide and exhaustive literature search we conducted, as well as the meta-analysis results stratified according to the corticosteroid dose, makes our conclusions reliable, at least until well-designed clinical trials are conducted.

In conclusion, although our study suggests that a limited course (<12 weeks) of low-dose prednisone, in addition to the standard treatment with LDA and LMWH, might improve the pregnancy success rate in patients with refractory obstetric APS with a good safety profile, these results should be interpreted with caution. In view of the results of the meta-analysis, the efficacy and safety of low doses of corticosteroids in patients with refractory APS must be confirmed in studies with an adequate design. However, treatment with high doses of steroids significantly increases the frequency of maternal and fetal morbidities, thus precluding any recommendation of their use.

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Ethical statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Local Ethics Committee of Cantabria (2018.029, 28th May 2018).

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FIGURE LEGENDS

Figure 1. Forest plot showing: a) Differences in the frequency of pregnancy loss between those treated and non-treated with glucocorticoids; b) Differences in the frequency of pregnancy loss between those treated and non-treated with glucocorticoids stratified by the use of high or low-to-medium steroid doses.

Figure 2. Forest plot showing the differences in the frequency of preeclampsia (a), gestational diabetes (b), and pre-term birth (c) between pregnancies treated and non-treated with glucocorticoids.

Table 1 Clinical and serological data on the APS cohort

	APS cohort (n,%)	**APS treated with CS (n=6)**	**APS non treated with CS (n=5)**
Age, y (mean SD)	34.1 ± 4.8	37.85 ± 3.76	33.78 ± 4.68
CV risk factors (n=11)			
• Hypertension	1 (9.1)	0 (0)	1 (20)
• Diabetes	0 (0)	0 (0)	0 (0)
• Dyslipidemia	0 (0)	0 (0)	0 (0)
• Tobacco use	4 (36.4)	2 (33.3)	2 (40)
• Obesity	2 (18)	1 (16.7)	1 (20)
Associated diseases (n=11)			
• Thyroid disease	5 (45.5)	2 (33.3)	1 (20)
APS manifestations (n=11)			
• Thrombosis	1 (9.1)	1 (16.7)	0 (0)
• Obstetric manifestations			
• Early pregnancy loss	11 (100)	6 (100)	5 (100)
• Fetal death	2 (18.2)	1 (16.7)	1 (20)
• Premature birth	1 (9.1)	0 (0)	1(20)

Serological characteristics (n=10)			
• aCL	5 (50)	3 (60)	2 (40)
IgG aCL	3 (30)	1 (20)	2 (40)
IgM aCL	2 (20)	2 (40)	0 (0)
• aB2GP I	7 (70)	4 (80)	3 (60)
IgG aB2GP I	5 (50)	2 (40)	2 (40)
IgM aB2GP I	6 (60)	4 (80)	2 (40)
• LA	2 (20)	1 (20)	1 (20)
• Number of positive antibodies:			
1 aPL	7 (70)	3 (60)	4 (80)
2 aPL	2 (20)	1 (20)	1 (20)
3 aPL	1 (10)	1 (20)	0 (0)

CV: cardiovascular, aCL: anticardiolipin antibodies, aB2GPI: antiB2 glycoprotein I, LA: lupus anticoagulant, aPL: antiphospholipid antibodies

Table 2. Main data on the 47 pregnancies studied in the 11 patients with APS.

	Pregnancies studied (n=47)
Maternal age (yr)	34.1±4.8
Method of conception (n,%) • Spontaneous • In vitro fertilization Ovodonation	 28 (59.6) 11 (23.4) 8 (17)
Pregnancy outcomes (n,%) • Abortion • Fetal death • Delivery	 32 (68.1%) 3 (6.4%) 12 (25.5%)
Age at delivery (wk)	37.8 ± 3.1
Weight at birth (gr)	3106 ± 422
Maternal morbidities (n,%) • Gestational diabetes • Preeclampsia	 3/17 (17.7) * 1/12 (8.3) #
Fetal morbidities (n, %) • Abruptio placenta • IUGR • Oligohydramnios • PRM	 0 0 0 1 (8.3)

IUGR: intrauterine growth restriction, PRM: premature rupture of membranes. * We considered 17 as the denominator since 30 pregnancies that were not treated with glucocorticoids resulted in abortions; thus, there was no time to develop gestational

diabetes. # We considered 12 as the denominator since 30 pregnancies in the non-treated group and 5 patients in the steroid-treated group ended in abortion; thus, these patients were not susceptible to suffering preeclampsia.

Table 3. Treatment regimens used for the 26 pregnancies.

Concomitant treatments	**Pregnancies treated with glucocorticoids (n=13)**	**Pregnancies on any non-corticosteroid treatment (n=13)**
ASA	0	2
LMWH	0	1
ASA+LMWH	3	7
ASA + LMWH + IvIG	1	3

ASA: acetylsalicylic acid, LMWH: low molecular weight heparin, IvIG: intravenous immunoglobulins

Table 4. Literature review, including studies that used glucocorticoids in obstetric APS patients.

Author	Type of study	Study population	n	Treatment	Results	Adverse/other events
Lubbe et al [8] 1983	Case series	Lupus anticoagulant + RSA	6	40-60 mg/day prednisone + 75 mg/day ASA	↑ successful pregnancy rate in 83.3%	1 preeclampsia (20%) 1 premature birth (20%)
Branch et al [9] 1985	Case series	Lupus anticoagulant+ RSA	8	40-50 mg/day prednisone + 81 mg/day ASA	↑ successful pregnancy rate in 59.3%	3 IUGR (60%) 5 preeclampsia + premature birth (100%)
Frampton et al [43] 1987	Case report	aPL + RSA 10	1	20 mg/day prednisolone + 900 mg/week ASA + 300 mg/day dipyridamole + plasmapheresis	↑ successful pregnancy rate in 100%	None

Author	Type of study	Study population	n	Treatment	Results	Adverse/other events
Lockshin et al [19] 1989	Non-randomized clinical trial	aCL IgG	25	1) No treatment 2) 80 mg/day ASA 3) 80 mg/day ASA + 30 mg/day prednisone 4) 60 mg/day prednisone	82% fetal death in women treated with prednisone vs 50% in those not treated with prednisone (p=0.01); women whose pregnancies ended in abortions ↑ successful pregnancy rate in those treated with ASA	IUGR (only in those treated with glucocorticoids)
Semprini et al [10] 1989	Case series	Lupus anticoagulant + 1 fetal death	14	Prednisone + LMWH (no data on dosage)	↑ successful pregnancy rate in 78.12%	3 IUGR (33.3%)
Ordi et al [11] 1989	Case series	APS	7	ASA 50 mg/day + prednisone 20 mg/day (variable)	↑ Successful pregnancy rate in 78%	Premature birth (32-36 weeks) 100% Cushing syndrome (86%)

Author	Type of study	Study population	n	Treatment	Results	Adverse/other events
Hasegawa et al [12] 1992	Case series	APS + ≥ 2 abortions	29	40 mg/day prednisolone + 81 mg/day ASA	↑ Successful pregnancy rate in 68% ($p < 0.01$)	4 IUGR (30.8%)
Silveira et al [13] 1992	Case series	aCL + RSA	11	40 mg/day prednisolone + 81 mg/day ASA	↑ successful pregnancy rate in 84.4%	1 IUGR (8.3%) 1 preeclampsia (8.3%) 4 premature birth(33.3%)
Branch et al [44] 1992	Cohort	APS	54	1) 10-80 mg/day prednisone + 81 mg/day ASA 2) 10.000-20.000 U/day LMWH + 81 mg/day ASA 3) 10-60 mg/day prednisone+ 10.000-20.000 U/day LMWH+ 81 mg/day ASA 4) Others or Iv Ig	No differences among the 4 groups	Gestational diabetes in 8/48 prednisone-treated pregnancies vs 0/22 of non-treated ($p<0.05$) No differences in preeclampsia, fetal distress, premature rupture of membrane

Author	Type of study	Study population	n	Treatment	Results	Adverse/other events
Passaleva et al [28] **1992**	Non-randomized clinical trial	aPL + RSA	22	1) 20 mg/day fluocortolone x5 times/week + 100 mg/day ASA 2) 100 mg/day ASA 3) No treatment	↑ Successful pregnancy rate in 70.9% in group 1	None
Kwak et al [29] **1992**	Non-randomized clinical trial	aPL + RSA	94	1) 10-40 mg/day prednisone + 10.000 U/day LMWH + 80 mg/day ASA pre-conceptional 2) Same treatment post-conceptional 3) No treatment	Successful pregnancy rate in group 1 (73.8%) > group 2 (44.1%) ($p < 0.05$) and group 3 (11.1%) ($p < 0.00001$)	Low birth weight

Author	Type of study	Study population	n	Treatment	Results	Adverse/other events
Cowchock et al [20] 1992	Randomized clinical trial	Obstetric APS	20	1) 40 mg/day prednisone + 80 mg/day ASA 2) 17.000 U/day LMWH + 80 mg/day ASA	Successful pregnancy rate was 75% in both groups	Significantly increased frequency of preeclampsia, gestational diabetes, MPR and pre-term birth in group 1
Landy et al [30]1992	Non-randomized clinical trial	aPL + obstetric morbidities	51	1) LDA or LMWH + prednisone (5-60 mg/day) 2) Prednisone 5-60 mg/day 3) ASA 4) No treatment	Successful pregnancy rate was 90.9% in combination therapy	48.6% adverse events in those treated with prednisone (monotherapy or combination) 10 patients with gestational diabetes

Author	Type of study	Study population	n	Treatment	Results	Adverse/other events
Many et al(31) 1992	Non-randomized clinical trial	APS	31	1) Prednisone 30 mg/day + ASA 100 mg/day 2) Prednisone 30 mg/day + ASA 100 mg/day or dipyridamole 22 mg/day+ LMWH 3) Prednisone 20-40 mg/day or ASA 100 mg/day or LMWH 4) No treatment	↑ Successful pregnancy rate (51.9% with treatment vs 6.8% with no treatment vs 69.1% with combination therapy).	Overall in patients on any treatment: 14 low weight at birth, 16 C-section, 3 hypertension, 1 vertebral fracture, 2 infections, 18 cushingoid face
Silver et al [45] 1993	Randomized clinical trial	aPL + RSA	34	1) 20 mg/day prednisone + 81 mg/day ASA 2) 81 mg/day ASA	↑ successful pregnancy rate in 70%	Higher rate of preterm birth in group 1 (p = 0.003). Prednisone as independent risk factor of pre-term birth (p=0.0016)
Menashe Y et al [50] 1993	Case series	Refractory APS	4	ASA + Dipyridamole + prednisone + warfarin or heparin	Successful pregnancy rate 100 %	1 vertebral fracture 2 pre-term birth

Author	Type of study	Study population	n	Treatment	Results	Adverse/other events
Marco et al [14] 1995	Case series	aPL + ≥ 2 abortions	14	20 mg/day prednisone + 125 mg/day ASA	↑ Successful pregnancy rate in 75.5%	None 4 IUGR (14.3%)
Harger et al [15] 1995	Case series	Lupus anticoagulant + ≥ 2 abortions	21	20 mg/day prednisone + ASA	↑ Successful pregnancy rate in 72%	6 Hypertension (21.4%) 3 PRM (10.7%) 13 Pre-term births (65%)
Laskin et al [21] 1997	Randomized controlled trial	aPL + ≥ 2 abortions	202	1) 0.5-0.8 mg/kg/day prednisone + 100 mg/day ASA 2) Placebo	No differences in successful pregnancy rate ($p = 0.19$)	Increased frequency of hypertension ($p = 0.05$), gestational diabetes ($p = 0.02$) and premature birth ($p < 0.001$) in group 1

Author	Type of study	Study population	n	Treatment	Results	Adverse/other events
					Successful pregnancy rate 77.8%	
Reece et al [32] 1997	Non-randomized clinical trial	aPL	18	1) 80 mg/day ASA 2) Prednisone (10-25mg/day // >25 mg/day) + 80 mg/day ASA	↑ Successful pregnancy rate from 75 to 100% in patients with <2 abortions and low aPL titers with treatment	ND
Vaquero et al [22] 2001	Non randomized clinical trial	APS	82	1) 15-20 mg/day prednisone + 100 mg/day ASA 2) 1 g/Kg/month IvIg until 32 weeks	No differences in successful pregnancy rate	Increased rate of hypertension and gestational diabetes in group 1 ($p < 0.05$)
Houng et al [33] 2001	Cohort	APS	47	Treatment with ASA, LMWH, IvIg, plasmapheresis, HCQ, prednisone (7-60 mg/day) and their combinations	↑ successful pregnancy rate in 65% compared with previous rate	Corticoids associated with severe prematurity ($p=0.005$), preeclampsia ($p=0.014$) and IUGR ($p=0.005$)

Author	Type of study	Study population	n	Treatment	Results	Adverse/other events
Empson et al [46] 2002	Meta-analysis	aPL	3 studies (Cowchock(23), Silver (48) Laskin(24))	Prednisone + ASA vs LMWH + ASA Prednisone + ASA vs ASA or placebo	No differences in the rate of pregnancy loss	Increased prematurity rate in those treated with prednisone and ASA (RR 4.83, IC 2.85-8.21)
Bramham et al [16] 2011	Case series	Refractory APS	18	LMWH+ ASA + 10 mg/day prednisolone until week 14	↑ Successful pregnancy rate in 57% ($p < 0.05$)	5 IUGR (21.4%) 2 preeclampsia (8.7%) 2 premature births (8.7%)
Watanabe [48] 2014	Case series	Refractory APS	3	10-20 mg/d prednisolone+ IvIg+ ASA +LMWH	Successful pregnancy rate 100%	1 premature birth (placenta previa)
Mekinian et al [17] 2017	Cohort	Refractory APS	49	ASA + LMWH +/- corticoids +/- HCQ	Corticoids were associated with favorable outcomes (OR 0.3 95% CI 0.11-0.82, p=0.019)	Treatment with corticoids and HCQ decreased the frequency of preeclampsia (p = 0.01)

Author	Type of study	Study population	n	Treatment	Results	Adverse/other events
Song et al [42] 2017	Case series	Refractory APS	123	Prednisone 5 mg/day + ASA 74 mg/day pre-conceptional + LMWH after pregnancy confirmation	Successful pregnancy rate 87.9%	4 Premature birth, 3 preeclampsia, 1 gestational diabetes, 6 PMR
Ye et al [18] 2017	Cohort	Refractory APS	267	1) HCQ 400 mg/day + Prednisone 10 mg/day + ASA 75 mg/day + LMWH 2) ASA 75 mg/day + LMWH	↓ pregnancy loss rate, placental dysfunction and low weight in group1 ↑ pregnancies over 24 weeks and weight at birth in group 1 ↑ Successful pregnancy rate in group 2	Decreased rates of preeclampsia/eclampsia in group 1.
Ruffatti et al [34] 2018	Cohort	Primary high risk APS	194	1) Oral treatment (HCQ and /or 10-20 mg /day prednisone 2) Iv treatment (IvIG and/or plasmapheresis)	In group 1 HCQ was linked to a higher live birth rate with respect to the other treatments	ND

RSA: recurrent spontaneous abortion, ASA: acetylsalicylic acid, IUGR: Intrauterine growth restriction, aPL: antiphospholipid antibodies, LMWH: low molecular weight heparin, APS: antiphospholipid syndrome, aCL: anti-cardiolipin antibodies, PRM: premature rupture of membranes, ND: no data, IvIG: intravenous immunoglobulins, HCQ: hydroxychloroqu