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Upgrading Therapy Strategy Improves Pregnancy Outcome in Antiphospholipid Syndrome: A Cohort Management Study

Ariela Hoxha[1,2,*]   Maria Favaro[1,*]   Antonia Calligaro[1]   Teresa Del Ross[1]   Alessandra Teresa Ruffatti[3]
Chiara Infantolino[3]   Marta Tonello[1]   Elena Mattia[1]   Amelia Ruffatti[1]

[1] Department of Medicine-DIMED, Rheumatology Unit, University of Padua, Padua, Italy
[2] Department of Medicine, Internal Medicine Unit, San Bortolo Hospital, Vicenza, Italy
[3] Obstetrics and Gynaecology Unit, University Hospital Padua, Padua, Italy

Thromb Haemost

Address for correspondence Ariela Hoxha, MD, PhD, U.O.C di Reumatologia, Policlinico Universitario, Via Giustiniani 2, 35128 Padova, Italy (e-mail: arielahoxha@hotmail.com).

Abstract

The current study evaluates the efficacy and safety of different treatment strategies for pregnant patients with antiphospholipid syndrome. One hundred twenty-seven consecutive pregnancies were assessed; 87 (68.5%) with a history of pregnancy morbidity alone were treated with prophylactic low molecular weight heparin (LMWH) + low-dose aspirin (LDA, 100 mg) (group I) and 40 (31.5%) with a history of thrombosis and/or severe pregnancy complications with therapeutic LMWH + LDA (group II). LMWH doses were increased throughout the pregnancies depending on the patients' weight gain, and treatment was switched to a more intensive one at the first sign of maternal/fetal complications. The study's primary outcome was live births. There were no significant differences in live birth rate between group I (95.4%) and group II (87.5%). Even fetal complication rate was similar in the two groups; group II nevertheless had a higher prevalence of maternal and neonatal complications ($p = 0.0005$ and $p = 0.01$, respectively) and registered a significantly lower gestational age at delivery and birth weight ($p = 0.0001$ and $p = 0.0005$, respectively). Two patients in group I switched to group II therapy, six patients in group II switched to a more intensive treatment strategy (weekly plasma exchange + fortnightly intravenous immunoglobulins in addition to therapeutic LMWH + LDA). The multivariate analysis uncovered that triple antiphospholipid antibodies positivity was an independent factor leading to a more intensive therapy. All eight switched patients achieved a live birth. Study results revealed that adjusted LMWH doses and switching therapy at first signs of severe pregnancy complications led to a high rate of live births in antiphospholipid syndrome patients.

Keywords
► obstetric antiphospholipid syndrome
► low molecular weight heparin
► low-dose aspirin
► plasma exchange
► intravenous immunoglobulins
► pregnancy

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by vascular thrombosis and/or pregnancy morbidity associated with the presence in the blood of persistent antiphospholipid antibodies (aPL).[1] Since the early 1980s when recurrent pregnancy loss was first linked to APS,[2] many steps forward in our understanding of the heterogeneous family of aPL and related pregnancy complications have

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* *The first two authors contributed equally to the study.*

been taken. But despite increasing knowledge about the pathogenetic mechanism underlying aPL-related pregnancy morbidity, evidence from well-designed studies demonstrating the efficacy of various treatments continues to be limited.[3]

In accordance with the results of two clinical trials[4,5] and the findings of two meta-analysis,[6,7] prophylactic low-molecular weight heparin (LMWH) plus low-dose aspirin (LDA) are considered "standard therapy" for patients with positive aPL and recurrent pregnancy loss. Although specific clinical trials are lacking, women with a history of vascular thrombosis alone or associated with pregnancy morbidity are generally treated with therapeutic LMWH doses in association with LDA. As these protocols nevertheless fail in approximately 20 to 30% of pregnant APS patients,[8] additional treatments including intravenous immunoglobulin (IVIG), low-dose prednisolone, hydroxychloroquine, or apheresis procedures have at times been combined with the "standard therapy,"[9–14] but the data regarding their efficacy cannot be considered conclusive given the low number of cases that have been treated.

While it is generally agreed that pregnant APS patients should receive personalized treatment,[15,16] evidence-based guidelines for these patients continue to be lacking. The current study was designed as a management cohort study aiming to evaluate the efficacy and safety of different treatment strategies for pregnant APS patients in the attempt to provide some practical suggestions for attending physicians.

Materials and Methods

Study Population
This single-center, cohort study is based on the clinical records of consecutively presenting APS patients attending the Pregnancy Clinic of the Rheumatology Unit of the University of Padua, Padua, Italy, between August 1999 and May 2016. Two authors (A.H., M.F.) independently reviewed the clinical charts of the patients who were registered in a centralized database.

The women who satisfied the following criteria were enrolled in the study: (1) diagnosis of primary APS in accordance with the clinical and laboratory criteria outlined by the Sydney Consensus Statement[1] and (2) treatment with prophylactic LMWH plus LDA or therapeutic LMWH plus LDA initiated during the first trimester. In accordance to the international consensus criteria, pregnancy morbidity was defined as (1) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, and/or (2) one or more premature births of a morphologically normal neonate before the 34th week of gestation due to eclampsia or severe preeclampsia, or recognized features of placental insufficiency, and/or (3) three or more unexplained consecutive spontaneous abortions before the 10th week of gestation in patients in whom maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes have been excluded.[1] The patients were subdivided into two groups depending on the treatment that was prescribed:

- Group I (n = 87): APS women, with a history of pregnancy morbidity in the absence of thrombosis, treated with prophylactic LMWH plus 100 mg LDA.

- Group II (n = 40): APS women, with previous thrombosis and/or severe pregnancy complications as early-onset preeclampsia, hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, and intrauterine growth restriction (IUGR), treated with therapeutic LMWH plus 100 mg LDA.

The institutional review board for observational studies and the Audit Committee of the University Hospital of Padua approved the study design (Protocol Number: 6894/2013, February 7, 2013). The study was performed in accordance with the principles outlined in the Declaration of Helsinki. After being informed about the methodology and aims of the study, the patients were asked to sign informed consent forms.

Treatment Strategy
In the light of findings produced by our previous studies using adjusted LMWH dosage (enoxaparin),[17,18] prophylactic or therapeutic drug's dosage was increased as the pregnancy progressed and maternal body weight augmented. Patients with a body weight ranging from 55 to 65 kg received LMWH doses ranging between 4,000 and 6,000 U/daily (prophylactic dose) or twice daily (therapeutic dose), those with a body weight ranging from 66 to 85 kg received doses ranging between 6,000 and 8,000 U once/twice daily, and those with a body weight $\geq$ 86 kg received doses ranging between 8,000 and 10,000 U once/twice daily. In accordance with the manufacturer's recommendations, the once-/twice-daily doses never, in any case, exceeded the weight-adjusted dosage of 100 U/kg. Moreover, when early signs of pregnancy-related complications such as preeclampsia (new-onset hypertension $\geq$ 140/90 mm Hg and proteinuria $\geq$ 300 mg per 24-hour urine collection protein), placental insufficiency (abnormal Doppler flow velocimetry waveform analysis of uterine arteries), a platelet count more than 20% lower than the baseline value—the progressive decrease in platelets of 20% from baseline was arbitrarily considered as a warning signal on the basis of our clinical experience,[17,18] regardless of baseline platelet count— or thrombosis were detected, the patients were switched to a more intensive treatment protocol, that is, the patients being treated with prophylactic LMWH plus LDA (group I) were switched to therapeutic LMWH plus LDA (group II) and the patients being treated with therapeutic LMWH plus LDA (group II) were upgraded to an intensive treatment protocol consisting weekly plasma exchange plus fortnightly 1 g/kg/day IVIG in addition to therapeutic LMWH plus LDA.[9] Physical examination, fetal ultrasound studies, routine biochemistry tests, and coagulation screening were then performed every month until the 30th week of pregnancy and subsequently every 2 weeks. Moreover, from the 24th week of gestation the Doppler waveform was included in the testing protocol. From the 32nd week, cardiotocography for fetal surveillance was performed weekly.

Antiphospholipid Detection
Before the patients became pregnant, tests for the detection of aPL were performed and confirmed by a second test at least 12 weeks apart. Immunoglobulin (Ig) G/IgM anticardiolipin (aCL) and IgG/IgM anti- β2 glycoprotein I (anti-β2GPI) antibodies were measured using "home-made" enzyme-linked

immunosorbent assay as described elsewhere.[19] The results of aCL testing were expressed as IgG phospholipid or IgM phospholipid units using international reference material. The results of anti-β2GPI assays were calculated as arbitrary units using a standard curve obtained from a pool of positive samples calibrated to Koike's monoclonal antibodies (HCAL for the IgG and EY2C9 for the IgM anti-β2GPI). The cut-off values for medium/high titers for both aCL and anti-β2GPI antibodies were calculated using the 99th percentile obtained by testing 100 age-matched healthy women. Lupus anticoagulant (LAC) was detected following internationally accepted recommendations[20,21] using dilute Russell viper venom and dilute activated partial thromboplastin times as screening tests.

IgG and/or IgM isotype was considered single antibody positivity. Single aPL positivity thus referred to LAC or IgG/IgM aCL or IgG/IgM anti-β2GPI; double positivity referred to IgG/IgM aCL plus IgG/IgM anti-β2GPI or IgG/IgM aCL plus LAC or IgG/IgM anti-β2GPI plus LAC; and triple positivity referred to IgG/IgM aCL plus IgG/IgM anti-β2GPI plus LAC.

Outcomes

Live birth rate, defined as the number of live newborns surviving the first 27 days after birth, was the study's primary outcome. Secondary outcomes were maternal and fetal complications including platelet count more than 20% lower than the baseline value, preeclampsia,[22] eclampsia, HELLP syndrome, and IUGR.[23] It is true that this study refers to data collected in August 1999, but we retrospectively classified preeclampsia and IUGR using the 2013 American Congress of Obstetricians and Gynecologists guidelines.[22,23] Neonatal outcomes were assessed on the basis of gestational age at delivery, birth weight in percentiles, the Apgar score at 5 minutes, and neonatal complications.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software, version 22.0 (Chicago, Illinois, United States) and the GraphPad Prism version 5.00 (San Diego, California, United States). Data are shown as medians (ranges) or as numbers (percentages). Univariate comparisons of dichotomous data were performed using the chi-square or Fisher's exact test; the odds ratio (OR) with a 95% confidence interval (CI) was calculated. Comparisons between continuous variables were performed using the Mann–Whitney test and data are presented with median values and interquartile ranges (25th–75th percentiles). A stepwise forward conditional procedure was used for logistic regression analysis to evaluate the independent factors for switching therapy. A p-value of < 0.05 was considered statistically significant. The study is reported here following the STROBE guidelines.[24]

Results

One hundred twenty-seven consecutive pregnancies in 96 APS patients (median age = 36 years, range 25–47) were assessed. Baseline demographic, clinical, and laboratory features of the two groups of APS patients treated with prophylactic LMWH + LDA and therapeutic LMWH + LDA, respectively, are outlined in ►Table 1; to note single aPL positivity significantly prevailed in group I patients, while triple aPL positivity in group II ones. Maternal and fetal/neonatal outcomes of study population are illustrated in ►Table 2. The live birth rates were quite similar. The group II patients registered a significantly higher rate of maternal complications with respect to the group I ones as described in ►Table 2. Altogether, there were 13 maternal complications: 7 preeclampsia, 3 cases of platelet count more than 20% lower than the baseline value, 2 HELLP syndromes, and 1 thrombosis. Although there was no difference regarding fetal complications, the infants born to the group II patients had a significantly lower gestational age at delivery and birth weight compared with their counterparts. They also presented a significantly higher rate of neonatal complications due to prematurity, especially to respiratory distress.

Table 1 Demographic, clinical, and laboratory features of the two groups of antiphospholipid syndrome patients studied

	Group I	Group II	*p*-Value	OR (95%CI)
	$n = 87$	$n = 40$		
Age, median (range)	36 (25–47)	33.5 (27–42)	0.01	–
Ethnicity				
Caucasian, n (%)	82 (94.3)	39 (97.5)	0.6	0.42 (0.04–3.72)
Non-Caucasian, n (%)	5 (5.7)	1 (2.5)	0.6	0.42 (0.04–3.72)
Thrombosis, n (%)	0 (0)	20 (50.0)	< 0.0001	175 (10.15–3016)
Pregnancy morbidity, n (%)	87 (100)	9 (22.5)	< 0.0001	580.3 (32.78.10270)
Thrombosis and pregnancy morbidity, n (%)	0 (0)	11 (27.5)	< 0.0001	68.22 (3.89–1194)
Single aPL, n (%)	63 (72.4)	18 (45)	0.005	3.2 (1.47–7.0)
Double aPL, n (%)	23 (26.4)	8 (20)	0.5	1.43 (0.57–3.57)
Triple aPL, n (%)	1 (1.2)	14 (35)	< 0.0001	46.31 (5.8–369.2)
Previous pregnancy complications, n (%)	4 (4.6)	7 (17.5)	0.03	4.40 (1.2–16.04)

Abbreviations: aPL, antiphospholipid antibodies; CI, confidence interval; OR, odds ratio.
Note: Group I was treated with prophylactic low molecular weight heparin + low-dose aspirin; Group II was treated with therapeutic low molecular weight heparin + low-dose aspirin.

Table 2 Maternal and fetal/neonatal outcomes in the two groups of antiphospholipid syndrome patients studied

	Group I	Group II	*p*-Value	OR (95% CI)
	n = 87	*n* = 40		
Live birth, *n* (%)	83 (95.4)	35 (87.5)	0.1	2.88 (0.73–11.36)
Maternal complication, *n* (%)	3 (3.4)	10 (23.8)	0.0005	9.33 (2.40–36.23)
Labor[a]				
Vaginal, *n* (%)	34 (40.5)	4 (11.4)	0.002	5.27 (1.70–16.30)
Caesarean, *n* (%)	50 (59.5)	36 (88.6)	0.002	0.18 (0.06–0.58)
Fetal complication, *n* (%)	2 (2.4)	4 (10.5)	0.07	0.2 (0.03–1.15)
Week of gestation median (range)	38 (29–41)	37 (27–40)	0.0001	–
Weight (percentile) median (range)	50 (10–97)	50 (3–90)	0.1	–
Apgar at 5 min median (range)	9 (7–10)	10 (7–10)	0.3	–
Neonatal complication, *n* (%)	6 (7.2)	9 (25)	0.01	7.87 (2.52–24.51)
Switch to an upgrade therapy	2 (2.3)	6 (15.0)	0.01	7.5 (1.44–39.03)

Abbreviations: CI, confidence interval; OR, odds ratio.
Note: Group I was treated with prophylactic low molecular weight heparin + low-dose aspirin; Group II was treated with therapeutic low molecular weight heparin + low-dose aspirin.
[a]Fetal loss/miscarriages were excluded.

Finally, a significantly higher proportion of the group II participants needed to be switched to a more intensive therapy with respect to their counterparts (►**Table 2**).

No important side effects, in particular no hemorrhagic events, were observed in any of the patients.

Switching Therapy to Achieve a Better Pregnancy Outcome

Two group I patients were switched to group II therapy. Six group II patients were switched to the more intensive protocol,[9] all of them were treated with weekly plasma exchange plus fortnightly IVIG in addition to the already ongoing treatment with therapeutic LMWH plus LDA. All eight switched patients achieved a live birth. Their clinical and laboratory features along with pregnancy outcomes are outlined in ►**Table 3**. Four out of the eight (50%) were switched because of early-onset preeclampsia, three (37.5%) because of IUGR, and one (12.5%) because of cutaneous small vessels thrombosis. The median gestational age at the time of switching was 26 weeks (range 23–30). Triple aPL positivity was registered in one out of the two (50%) group I patients switched to group II, and in all (100%) of the group II patients switched to the more intensive protocol. History of thrombosis (66.7%) or severe preeclampsia (33.3%) was only observed in group II patients who switched to the more intensive protocol. The median gestational age at delivery of the switched patients considered together was 34.5 (range 23–30). The infants had a median birth weight of 2,233 g (range 1,640–2,700), a median percentile of 49 (range 10–75), and four (50%) neonatal complications, all due to prematurity.

Comparison of the clinical and laboratory characteristics between patients who had shifted to a more intensive therapy and those who did not (►**Table 4**) showed a significant prevalence of history of thrombosis ± pregnancy morbidity, previous pregnancy complications, triple aPL positivity, and

pregnancy complications in upgrading group, instead single aPL positivity significantly prevailed in the nonupgrading group. Logistic regression analysis demonstrated that triple aPL positivity was an independent factor for switching to a more effective therapy protocol ($p < 0.0001$, OR 98, 95% CI: 10.7–897.54).

Discussion

A careful and individual management of pregnancy in APS patients might improve the obstetric outcome. However, in cases of manifestations of severe complications such as pre-eclampsia or IUGR, an upgrading therapy strategy may be necessary.

While studies in the literature have reported a 70 to 80% of live birth rate in APS patients following fixed prophylactic or therapeutic doses of LMWH + LDA treatment,[3,8] findings from the current study demonstrate that using adjusted prophylactic or therapeutic doses of heparin throughout the pregnancies of these patients and switching therapy at the first signs of complications can achieve a higher rate of live births (94.5–87.5%, respectively). In a previous study, we reported[17] that adjusted, once-daily doses of LMWH together with LDA could be an efficacious treatment protocol for pregnant APS patients with no history of thrombosis to avoid pregnancy complications and to achieve a high live birth rate (97%) along with a satisfactory mean gestational age and birth weight.

The decision to use adjusted doses of LMWH is based on evidence that the bioavailability of subcutaneous heparin decreases during pregnancy due to pregnancy-related physiological changes such as elevations in: heparin-binding proteins, plasma volume, renal clearance, and heparin degradation by the placenta.[25,26] It should nevertheless be emphasized that the doses prescribed to our patients never exceeded the

Table 3 Clinical and laboratory features and pregnancy outcomes of the antiphospholipid syndrome patients whose therapy was switched due to early pregnancy complications

Patient	Age	Clinical history	Laboratory features	The reason for the switch	WG at switch	Live birth	Sex	WG at delivery	Weight percentile	Weight, g	Apgar at 5 minute	Neonatal complications
Switched from group I to group II												
FR[a]	35	FD at 30 WG	Single aPL	IUGR	27	Yes	F	34	25	2,175	10	RDS
ML	38	FD at 24 WG	Triple aPL	IUGR	27	Yes	M	34	10	1,800	NR	RDS
Switched from group II to high risk protocol therapy[b]												
SZ	31	Severe preeclampsia	Triple aPL	Preeclampsia	26	Yes	F	31	48	1,640	8	Pulmonary infection
FC	40	Thrombosis	Triple aPL	Cutaneous thrombotic microangiopathy	30	Yes	M	33	50	2,085	9	No
BA	37	Thrombosis	Triple aPL	Preeclampsia	24	Yes	M	35	60	2,700	9	No
BS	34	Thrombosis	Triple aPL	Preeclampsia	26	Yes	M	33	75	2290	7	RDS hyperbilirubinemia PDA
DAA[c]	28	Thrombosis	Triple aPL	Preeclampsia	26	Yes	M	35	60	2700	9	no
FF	36	Severe preeclampsia	Triple aPL	IUGR, anhydramnios	23	Yes	F	37	10	2300	10	Hypoglycemia

Abbreviations: aPL, antiphospholipid antibodies; FD, fetal death; IUGR, intrauterine growth restriction; NR, not reported; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; WG, week of gestations.
[a]Presence of heterozygous factor II.
[b]Consisted in therapeutic low molecular heparin + low dose aspirin + weekly plasma exchange + fortnightly immunoglobulin intravenously.
[c]Presence of heterozygous factor V Leiden.

Table 4 Comparison of clinical, laboratory features, and maternal/fetal outcomes in the patients with upgraded therapy compared with the nonupgraded therapy group

	Upgraded therapy group	Non-upgraded therapy group	p-Value	OR (95% CI)
	n = 8	n = 119		
TOAPS, n (%)	5 (62.5)	26 (21.8)	0.02	5.96 (1.33–26.62)
OAPS, n (%)	6 (75)	101 (84.8)	0.6109	0.53 (0.09–2.86)
Severe previous pregnancy complications, n (%)	3 (37.5)	8 (6.7)	0.02	8.32 (1.67–41.3)
Single aPL +ve, n (%)	1 (12.5)	80 (67.2)	0.003	0.06 (0.008–0.58)
Double aPL +ve, n (%)	0 (0)	31 (26.1)	0.1	0.16 (0.009–2.94)
Triple aPL +ve, n (%)	7 (87.5)	8 (6.7)	< 0.0001	97.13 (10.6–890.0)
Live birth, n (%)	8 (100)	111 (93.3)	1	1.29 (0.06–24.44)
Pregnancy complications, n (%)	8 (100)	9 (7.6)	< 0.0001	197.7 (10–57–3699.0)
Maternal complications, n (%)	5 (62.5)	8 (6.7)	0.0002	23.13 (4.66–114.7)
Fetal complications, n (%)	3 (37.5)	3 (2.5)	0.003	23.2 (3.70–145.2)
Week of gestations, median (range)	34 (31–37)	38 (27–41)	< 0.0001	–
Weight in gram, median (range)	2,233 (1,640–2,700)	3,050 (2,746–4,350)	0.0002	–
Weight in percentile, median (range)	49 (10–75)	50 (3–97)	0.4	–
Neonatal complications, n (%)	4 (50)	11 (9.2)	0.007	9.81 (2.15–44.84)

Abbreviations: aPL, antiphospholipid antibodies; CI, confidence interval; OAPS, obstetric pregnancy morbidity alone; OR, odds ratio; TOAPS, thrombosis and obstetric pregnancy morbidity.

prophylactic or therapeutic dosage recommended by the manufacture and that no noteworthy side effects were observed in our patients.

The study's novelty lies in the policy of upgrading therapy at the first signs of severe pregnancy-related complications, such as preeclampsia and placental insufficiency, or thrombosis. The eight (out of 127, thus 6.3%) patients studied who were switched to a more intensive therapy all achieved live births. Seven (87.5%) and 4 (50%) of the "switchers" presented, respectively, triple aPL positivity and a history of thrombosis, already well-known risk factors for pregnancy failure.[3,13,27] Interestingly, a large multicenter study[28] recently reported a live birth rate of only 30% in APS patients with triple aPL positivity, even in those treated with prophylactic or therapeutic LMWH + LDA.

Although the live birth rates in the two groups studied here were quite similar, group II including patients with more severe clinical histories and aPL profiles, presented a higher rate of pregnancy complications and a higher prevalence of patients needing upgrading.

In fact, a history of thrombosis and/or pregnancy complications, triple aPL positivity and complications during the considered pregnancies significantly prevailed in patients upgrading to a more intensive treatment with respect to those who did not. To note, live birth rate was not significantly different between the group updated therapy compared with the ones who did not need upgrading, so conferring to the switch therapy an important role in improving the live birth rate in complicated pregnancies, which generally have an unfavorable prognosis.[29] In addition, the multivariate analysis

uncovered that triple aPL positivity was an independent factor leading to a more intensive therapy.

It would seem from these data that upgrading the therapy protocol is a feasible option for high-risk aPL profile pregnancies at the first signs of pregnancy complications. It goes without saying that this approach implies close surveillance, to detect early clinical, instrumental, and/or laboratory signs of complications.[16,30,31]

Indeed, large numbers of investigators are acknowledging that the standard therapeutic regimen might not be sufficient in high-risk obstetric APS patients[10,15,27,32] to manage severe late pregnancy complications. This small cluster of patients may benefit from additional treatments such as IVIG, low-dose prednisolone, hydroxychloroquine, or apheresis procedures alone or combined[15,33] possibly initiated at the beginning of the pregnancy. At the same time, it is important to remember that prophylactic LMWH plus LDA treatment was sufficient in the patients with a history of pregnancy morbidity alone and single aPL positivity to produce a favorable pregnancy outcome.[27]

The limit of the study may be considered the unproven efficacy of upgrading to a more intensive therapy due to the absence of a not switching control group, but in this observational study we considered ethical the upgrading to a more intensive therapy when the first signs of a pregnancy complication appeared. While its strength is due to the high percentage of favorable pregnancy outcome observed in both the study groups and the lack of adverse events. In particular, therapeutic plasma exchange was performed as an outpatient procedure and was well tolerated without any notable side

effect. In fact, plasma exchange as other extracorporeal procedures is not free of adverse events; however, if some technical aspects due to the physiological changes of gestational status are taken into account and carefully considered, such as the increase of the circulating blood volume, the procedure is well tolerated as previously described.[34]

To conclude, the study showed that using adjusted LMWH doses and upgrading therapy at the first signs of pregnancy complications led to a high rate of live births in a relatively large group of APS patients. The study outlines the criteria for prescribing appropriate therapy for various subsets of these patients and for switching/upgrading the treatment protocol when it is no longer sufficient. Unfortunately, for the moment there are no evidence-based guidelines on the ideal additional treatment in refractory to conventional therapy in APS patients. The present results will hopefully help point the direction of future clinical trials investigating the efficacy and safety of the different therapies on large numbers of APS pregnant patients to identify the benefits and limits of different treatment strategies administered from the beginning of pregnancy.

What is known about this topic?

- Severe pregnancy complications, a history of thrombosis and pregnancy morbidity, and the presence of triple aPL positivity identify patients at high risk of pregnancy failure.
- Low molecular heparin plus low-dose aspirin are considered the standard of care of APS patients with recurrent pregnancy loss.
- There are up to 30% of pregnancies failure, in spite of treatment with standard of care.

What does this paper add?

- Adjusted low molecular weight heparin doses and upgrading therapy at the first signs of pregnancy complications improve the live births rate in APS patients.
- The study outlines the criteria for prescribing appropriate therapy for various subsets of APS patients and for switching/upgrading the protocol treatment when it is no longer sufficient, putting the first steps toward personalized therapy.

References

1 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 (02):295–306
2 Hughes GRV. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. Br Med J (Clin Res Ed) 1983;287(6399):1088–1089
3 de Jesus GR, Agmon-Levin N, Andrade CA, et al. 14th International Congress on Antiphospholipid Antibodies Task Force report on obstetric antiphospholipid syndrome. Autoimmun Rev 2014;13 (08):795–813
4 Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. Am J Obstet Gynecol 1996;174 (05):1584–1589
5 Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). BMJ 1997;314(7076):253–257
6 Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Cochrane Database Syst Rev 2005;2(02):CD002859
7 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(02):281–288
8 Lassere M, Empson M. Treatment of antiphospholipid syndrome in pregnancy–a systematic review of randomized therapeutic trials. Thromb Res 2004;114(5-6):419–426
9 Ruffatti A, Favaro M, Hoxha A, et al. Apheresis and intravenous immunoglobulins used in addition to conventional therapy to treat high-risk pregnant antiphospholipid antibody syndrome patients. A prospective study. J Reprod Immunol 2016;115:14–19
10 Ruffatti A, Hoxha A, Favaro M, et al. Additional treatments for high-risk obstetric antiphospholipid syndrome: a comprehensive review. Clin Rev Allergy Immunol 2017;53(01):28–39
11 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):6948–6951
12 Sciascia S, Branch DW, Levy RA, et al. The efficacy of hydroxychloroquine in altering pregnancy outcome in women with antiphospholipid antibodies. Evidence and clinical judgment. Thromb Haemost 2016;115(02):285–290
13 Mekinian A, Lazzaroni MG, Kuzenko A, et al; SNFMI and the European Forum on Antiphospholipid Antibodies. The efficacy of hydroxychloroquine for obstetrical outcome in anti-phospholipid syndrome: data from a European multicenter retrospective study. Autoimmun Rev 2015;14(06):498–502
14 Ruffatti A, Tonello M, Hoxha A, et al. Effect of additional treatments combined with conventional therapies in pregnant patients with high-risk antiphospholipid syndrome: a multicentre study. Thromb Haemost 2018;118(04):639–646
15 Chighizola CB, Gerosa M, Trespidi L, et al. Update on the current recommendations and outcomes in pregnant women with antiphospholipid syndrome. Expert Rev Clin Immunol 2014;10(11): 1505–1517
16 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(03):476–485

17 Ruffatti A, Gervasi MT, Favaro M, Ruffatti AT, Hoxha A, Punzi L. Adjusted prophylactic doses of nadroparin plus low dose aspirin therapy in obstetric antiphospholipid syndrome. A prospective cohort management study. Clin Exp Rheumatol 2011;29(03):551–554

18 Ruffatti A, Favaro M, Tonello M, et al. Efficacy and safety of nadroparin in the treatment of pregnant women with antiphospholipid syndrome: a prospective cohort study. Lupus 2005;14 (02):120–128

19 Ruffatti A, Olivieri S, Tonello M, et al. Influence of different IgG anticardiolipin antibody cut-off values on antiphospholipid syndrome classification. J Thromb Haemost 2008;6(10):1693–1696

20 Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulant. Thromb Haemost 1995;74 (04):1185–1190

21 Pengo V, Tripodi A, Reber G, et al; Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. Update of the guidelines for lupus anticoagulant detection. J Thromb Haemost 2009;7(10):1737–1740

22 Roberts JM, August PA, Bakris G, et al; American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122(05):1122–1131

23 Galan H, Grobman W; American College of Obstetricians and Gynecologists. ACOG Practice bulletin no. 134: fetal growth restriction. Obstet Gynecol 2013;121(05):1122–1133

24 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370 (9596):1453–1457

25 Barbour LA, Smith JM, Marlar RA. Heparin levels to guide thromboembolism prophylaxis during pregnancy. Am J Obstet Gynecol 1995;173(06):1869–1873

26 Casele HL, Laifer SA, Woelkers DA, Venkataramanan R. Changes in the pharmacokinetics of the low-molecular-weight heparin enoxaparin sodium during pregnancy. Am J Obstet Gynecol 1999;181 (5 Pt 1):1113–1117

27 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(09):1684–1689

28 Saccone G, Berghella V, Maruotti GM, et al; PREGNANTS (PREGNancy in women with ANTiphospholipid Syndrome) working group. Antiphospholipid antibody profile based obstetric outcomes of primary antiphospholipid syndrome: the PREGNANTS study. Am J Obstet Gynecol 2017;216(05):525.e1–525.e12

29 de Jesús GR, Rodrigues G, de Jesús NR, Levy RA. Pregnancy morbidity in antiphospholipid syndrome: what is the impact of treatment? Curr Rheumatol Rep 2014;16(02):403

30 De Carolis S, Botta A, Garofalo S, et al. Uterine artery velocity waveforms as predictors of pregnancy outcome in patients with antiphospholipid syndrome: a review. Ann N Y Acad Sci 2007; 1108:530–539

31 Alfirevic Z, Stampalija T, Gyte GM. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev 2013;11(11):CD007529

32 Bouvier S, Cochery-Nouvellon E, Lavigne-Lissalde G, et al. Comparative incidence of pregnancy outcomes in treated obstetric antiphospholipid syndrome: the NOH-APS observational study. Blood 2014;123(03):404–413

33 Ruffatti A, Salvan E, Del Ross T, et al. Treatment strategies and pregnancy outcomes in antiphospholipid syndrome patients with thrombosis and triple antiphospholipid positivity. A European multicentre retrospective study. Thromb Haemost 2014;112(04): 727–735

34 Marson P, Gervasi MT, Tison T, Colpo A, De Silvestro G. Therapeutic apheresis in pregnancy: General considerations and current practice. Transfus Apheresis Sci 2015;53(03):256–261