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Placental lesions in patients with antiphospholipid antibody syndrome: experience of a single tertiary-care Italian reference center

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Introduction: Abnormal placentation contributes to obstetric morbidity in antiphospholipid antibodies syndrome (APS). The placenta is the main target of antiphospholipid antibodies (aPL) in obstetric APS and is the site of dysfunctional inflammatory responses and thrombosis. Standard treatment for APS during pregnancy includes low-dose aspirin (LDA) plus low molecular weight heparin (LMWH) and, in refractory cases, hydroxychloroquine (HCQ). Recently, a systematic review of the literature identified five main pathological placental lesions in APS patients: placental infarction, decidual vasculopathy, decidual inflammation, increase of syncytial knots due to syncytiotrophoblast death, and decrease in vasculosyncytial membranes. The aims of this study were to investigate whether placental lesions associate with obstetrical outcomes in a cohort of APS patients.

Methods: 130 pregnant APS patients evaluated between 2009 and 2023 at the High-Risk Obstetrics Outpatient Clinic of San Raffaele Hospital, Milan, were enrolled. Placental samples from 25 spontaneously conceived pregnancies in APS patients were collected from January 2017 to May 2023 and analyzed.

Results: All (n = 130) patients were on LDA and 110/130 (85%) on both LDA and LMWH. Twenty-six patients (20%) also received HCQ. In these patients, signs of placental inflammation (preterm birth and preterm premature rupture of membranes) were less frequently observed. Of the 25 placental samples analyzed, 19 (76%) patients had primary APS, while 6 patients had APS secondary to SLE. All patients were treated with LDA and LMWH. In patients with concomitant systemic lupus erythematosus (SLE) or in refractory APS, HCQ was added. Histological analysis of placental tissue revealed increased syncytial knots in 17/25 (68%) placentas, decreased vasculosyncytial membranes in 11/25 (44%), infarction in 8/25 (32%), presence of macrophages

Abbreviations
APS, anti-phospholipid antibodies syndrome; SLE, systemic lupus erythematosus; Apl, antiphospholipid antibodies; aCL, anticardiolipin antibodies; aβ2GPI, anti–beta2-glycoprotein I antibodies; aPS-PT, anti-phosphatidylserine-prothrombin antibodies; LLAC, lupus like anticoagulant; BMI, body mass index; aGAPSS, adjusted global antiphospholipid syndrome score; PE, pulmonary embolism; DVT, deep venous thrombosis; IFD, intrauterine fetal death; IUGR, intrauterine growth restriction; APO, adverse pregnancy outcomes; HCQ, hydroxychloroquine; LDA, low-dosage aspirin; LMWH, low molecular weight heparin; gw, gestation week; OR, odds ratio; P, P value; CI, confidence interval; SD, standard deviation.

and decidual inflammation in 2/25 (8%), and atherosis or reduction of spiral artery remodeling in 3/25 (12%). We also observed at least two coexisting placental lesions in 12/25 (48%) placentas. In the placenta of patients treated with HCQ we did not observe any decidual inflammation at histology.

Conclusion: Placental anomalies have occurred in patients with APS despite close and optimal obstetric monitoring. It is thus tempting to speculate that HCQ may have beneficial effects on pregnancy by decreasing the risk of deciduitis in patients with APS.

KEYWORDS

pregnancy, miscarriages, antiphospholipid antibodies syndrome, placental histology, hydroxychloroquine

Key message

Pregnancies in women with Antiphospholipid Syndrome (APS) are considered high-risk and are closely associated with adverse pregnancy outcomes. Despite standard therapy with LDA and LMWH—and the addition of HCQ in selected cases—histopathological analysis of placentas from APS patients often reveals signs of maternal and fetal malperfusion.

Introduction

Antiphospholipid syndrome is an autoimmune systemic disorder characterized by vascular thrombosis and pregnancy morbidity in the presence of a persistent positivity of antiphospholipid antibodies (1).

The Revised Sapporo Classification Criteria define APS as the presence of at least one clinical and one laboratory criterion. Clinical criteria encompass vascular thrombosis (venous, arterial, or small vessel) and pregnancy morbidity (early recurrent miscarriage, fetal death, or premature birth before the 34th week due to conditions like preeclampsia/eclampsia or placental insufficiency). Laboratory criteria involve confirmed persistent positivity of lupus anticoagulant, anticardiolipin antibodies (IgG or IgM), or anti-β2GPI antibodies (IgG or IgM) (2). Recently, the classification criteria for APS have been updated by EULAR (3).

The Global APS Score (GAPSS) is commonly used to assess thrombotic and obstetric risk in APS patients and takes into account aPL profile and conventional cardiovascular risk factors (4). Obstetric APS is associated with miscarriage, IFD, IUGR, preeclampsia, and preterm delivery (5). Fetal loss is the most common complication, and obstetric APS stands as a leading, treatable cause of recurrent pregnancy loss (6, 7). Women with triple aPL positivity, history of vascular thrombosis and concomitant SLE and/or other autoimmune diseases are at higher risk for pregnancy complications (5, 8).

In obstetric APS, antiphospholipid antibodies target the placenta, essential for fetal development, leading to complications arising from abnormal placentation (9–11). APS interferes with trophoblast proliferation and viability, spiral artery remodeling, and vasculosyncytial membrane formation, resulting in maternal/fetal malperfusion (12) leading to issues such as preeclampsia and IUGR. During the transition from cytotrophoblasts to syncytiotrophoblasts, phosphatidylserine glycoprotein is exposed on the cell surface (13). In patients with APS, aPL can bind to cytotrophoblasts and the decidua. Several studies show a decrease in trophoblast proliferation within placental explants and an increase in trophoblast death, leading to more debris released as syncytial knots (14, 15). The balance of trophoblast quantity is crucial for nutrient supply to the fetus through vasculosyncytial membranes, spiral artery remodeling, and normal decidual function (16, 17). Alteration of these factors can lead to preeclampsia, suggesting a link between aPL and these pathological gestational conditions. Inflammation of the decidua in APS can be attributed to macrophages clustering around extravillous trophoblasts (18). In mice, excessive decidual inflammation may also result from classical complement cascade activation due to aPL deposition (19, 20). Complement components C3 and C5 are crucial for mediating aPL-induced thrombosis (21, 22). Complement activation often leads to hypocomplementemia in primary APS patients (23), likely acting as an intermediate step for platelet and endothelial activation. Both inflammatory and thrombotic mechanisms play a crucial role in the pathophysiology of APS. The intricate relationship between these mechanisms has been the subject of several excellent reviews, highlighting their complex interactions and combined impact on the disease process (24–26).

Five main pathological lesions characterize the placenta from APS pregnancies: placental infarction caused by spiral artery thrombosis, decidual vasculopathy characterized by atherotic changes in uterine spiral arteries and lack of remodeling by trophoblasts, inflammation of the decidua, increase in syncytial knots due to syncytiotrophoblast death, and decrease in vasculosyncytial membranes (27). These lesions can be classified according to their pathogenesis into inflammatory and vascular lesions (13). These categories can be further classified into maternal and fetal, and into acute and chronic lesions (28). Changes in the anatomy and function of the placenta, depending on the timing of the injury during pregnancy, can lead to recurrent miscarriage in the early phases, or preterm delivery, preeclampsia, and IUGR in the later phases of pregnancy.

Combination therapy with LDA and LMWH is the standard treatment during pregnancy (29) due to its capacity of improving live birth rate. Yet, 30% of patients still experience pregnancy complications (30). Additional strategies, including HCQ supplementation, have been proposed for refractory cases, exhibiting promise in reducing pregnancy loss and complications in selected patients (31, 32).

HCQ indeed has multifaceted beneficial effects on pregnancy complications, including anti-aggregant, anti-inflammatory, and immune-regulatory properties. It diminishes aPL binding to syncytiotrophoblasts (33–35). Additionally, HCQ safeguards pregnancy by inhibiting complement activation in the placenta (36). Sciascia et al. (32) associated HCQ treatment with reduced pregnancy complications in aPL-positive patients. However, whether HCQ treatment improves the main pathological lesions in the placenta from APS pregnancies remains to be elucidated. Moreover, it is not completely clear whether these placental abnormalities associate with specific pregnancy outcomes. Therefore, the aims of this study were to assess the presence of placental lesions in the placentas collected from APS patients, to investigate whether HCQ treatment protects against abnormal placentation, and to determine the impact of APS-related placental lesions on fetal growth and development, including the incidence of preeclampsia, IUGR and preterm delivery.

Materials and methods

Population

We performed a monocentric prospective observational study of pregnancies in women with a diagnosis of APS according to the Sapporo criteria (2). We included also patients with at least two abortions in the presence of a low titer of aPL. Data were collected from 130 pregnancies involving 96 APS patients who were followed at the High-Risk Obstetrics Outpatient Clinic of San Raffaele Hospital in Milan, Italy, from 2009 to May 2023. All pregnancies were closely monitored from conception to the post-partum clinical examination (40 days after delivery). Early miscarriage was defined as fetal loss before 10 gestational weeks, while late miscarriage was identified as fetal loss occurring after 10 gestational weeks. IFD was defined as fetal death after 20 weeks. The study was conducted in accordance with the Declaration of Helsinki, after approval by the Institutional Ethical Committee (protocol "MED-Mol" N. 62/INT/2021), and all patients signed a written informed consent.

All included patients had positivity for classical aPL (2). LLAC was detected according to international guidelines (37). aCL, aβ2GPI IgG and IgM antibodies and, when possible, also aPS/PT IgG and IgM were assessed by ELISA (QUANTA Lite ACA IgG and IgM, and β2-GPI IgG and IgM). All tests were conducted at the Department of Laboratory Medicine of our Institution, following validated procedures. INOVA Diagnostic Inc. provided aPS/PT IgG and IgM and were assessed on serum samples obtained at the first visit, immediately before or at the beginning of pregnancy. Medium aPL was defined as 20–40 U/ml, high aPL was defined as above 40 U/ml. For non-criteria a PL (aPS/PT), the cut off for defining positive aPL titer was 30 U/ml.

Pregnancy management

Gestational age was calculated as the time from the last menstrual cycle confirmed by ultrasound during the first trimester. If a strong discrepancy was noted between gestational and sonographic dating in a spontaneous pregnancy, the latter was used to date the pregnancy. At delivery, data regarding fetal and neonatal growth was collected. Preterm birth was defined as delivery occurring below 37 gestational weeks. APO were defined as: (a) fetal death occurring >10 weeks of gestation not explainable by chromosomal abnormalities, anatomical malformations, or congenital infections; (b) neonatal death occurring before hospital discharge due to complications of prematurity and/or placental insufficiency; (c) preterm birth occurring <37 weeks due to placental insufficiency, gestational hypertension, or (d) preeclampsia during gestation or puerperium (38). Ultrasonography was performed at 12 GW, 20 GW, 32 GW, 36 GW, and when fetal and/or maternal conditions required it. Every pregnancy was carefully monitored for the onset of arterial hypertension and/or preeclampsia (defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy as a *de novo* rise in systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg in the second half of pregnancy, and proteinuria ≥300 mg/24 h). IUGR was defined according to the World Health Organization classification as a child with weight at delivery <10th growth centile compared to the standard weight for sex and gestational age of 34 GW. Clinical Doppler ultrasound data (Pulsatility Index) were also collected during ultrasonography examination.

All patients during the enrolled pregnancies were treated with LDA (100 mg) from preconception and prophylactic LMWH (4,000 U daily) from the first US scan. LMWH was added according to EULAR recommendations (30). In patients with previous PE and/or DVT therapeutic dosage of LMWH were administrated. HCQ was added in APS secondary to SLE and/or in APS refractory to standard therapy (5, 31, 32, 39).

Placental histology

During the latter part of our recruitment process (2017–2023), after delivery, placentas underwent specific and not routine histological analyses aimed at assessing the main placental lesions described in APS (27). This approach enabled us to correlate histological findings with the clinical characteristics of the patients and pregnancies outcomes. Placentas were collected after cesarean birth or vaginal delivery and immediately fixed in 4%-neutral buffered formalin. All placentas were examined macroscopically and microscopically. Formalin-fixed placental weight and the percentage of macroscopic lesions on their surface were determined. Subsequently, two samples of the umbilical cord, fetal and placental membranes, and at least two samples of macroscopically normal placental tissue were taken from a central part of a placental cotyledon and from a peripheral area. Additional samples were also taken. Samples were processed and embedded in paraffin wax for histology.

Statistical analysis

Descriptive statistics were performed for all variables. Comparisons between groups were investigated using chi-square

test or student *T*-test for categorical and continuous variables respectively. Logistic regression was employed to determine whether HCQ treatment protected against placental lesions. Statistical significance was set at p values < 0.05.

Results

Patient characteristics

A total of 130 pregnancies in 96 patients with APS were included. Of these, 102 (78%) had primary APS while 28 (22%) had APS secondary to SLE. In twenty-four pregnancies (18%) was reported a previous thromboembolic diagnosis (i.e., venous thrombosis or pulmonary thromboembolism) and in 107 (82%) a history of APO. Only 8 patients did not have a previous pregnancy, while of the remaining 122 pregnancies, 68 (56%) had a previous liveborn baby. Overall, after being cared for in our Outpatient Clinic, 105 (81%) pregnancies culminated in an at-term delivery of a healthy child.

One hundred and ten (85%) pregnancies had a medium-high preconceptional aPL titer, while 20 (15%) had a low aPL titer. 29/130 pregnancies were conducted with triple aPL positivity. In these patients a statistical significant higher rate of previous thrombosis were reported (10 DVT/PE in 29 APS with triple aPL positivity vs. 14 DVT/PE in APS with single or double aPL positivity, $p = 0.045$). In 79 (61%) cases at least one previous early miscarriage was reported, 41 (32%) at least one late miscarriage and 18 (14%) IFD. The rate of successful anamnestic pregnancies was 56% (68/122). All patients and pregnancies characteristics are reported in Table 1.

During the index pregnancy, all patients received LDA 100 mg daily. In 109 (84%) pregnancies LMWH was added and in 26 (20%) were prescribed also hydroxychloroquine. 14/26 received HCQ for a SLE diagnosis and 12/26 received HCQ due to a previous refractory APS despite standard therapy with LDA and LMWH.

A total of 105 (81%) pregnancies gave birth to liveborn infants, 24 (18%) were diagnosed with early miscarriage and one patient had an IFD. Fetal/neonatal outcomes are detailed in Table 1.

TABLE 1 Clinical and laboratory characteristics of the cohort.

	Entire cohort	Patients whose placentas were analyzed	*P* value
Medical history	*N* = 130	*N* = 25	
Maternal age at conception (years)	33.58 ± 4.76	34.00 ± 5.06	0.23
Primary APS	102 (78)	19 (76)	0.78
aGAPSS (at conception)	9.41 ± 4.38	8.76 ± 4.17	0.24
>1 aPL positivity	54 (42)	15 (60)	0.09
Triple aPL positivity	29 (22)	8 (32)	0.29
High titer of aPL	110 (85)	19 (76)	0.30
Borderline aPL titer	20 (15)	6 (24)	0.72
aCL IgG/IgM	117 (90)	22 (88)	0.76
aβ2GPI IgG/IgM	52 (40)	12 (48)	0.40
LLAC and/or aPS/PT	29 (22)	7 (28)	0.53
TE-APS	24/130 (18)	1/25 (4)	0.07
Obstetrial medical history	***N* = 122**	***N* = 24**	
Previous newborn rate	68 (56)	12 (50)	0.61
≥2 miscarriages	65 (53)	16 (66)	0.23
≥3 miscarriages	37 (30)	9 (37)	0.49
IUGR/preeclampsia	7 (6)	4 (17)	0.06
Preterm birth	11 (9)	4 (16)	0.26
IFD	18 (15)	2 (8)	0.40
Therapy during pregnancy	***N* = 130**	***N* = 25**	
LDA + LMWH	110 (85)	25 (100)	0.13
HCQ	26 (20)	11 (44)	<0.05
Pregnancy characteristics	***N* = 130**	***N* = 25**	
Low complement level	13 (10)	3 (12)	0.76
Week of delivery	37.7 ± 2.8	37.4 ± 2.5	0.31
Liveborn infant	105 (81)	25 (100)	0.06
Birth weight (g)	2,953 ± 747	2,818 ± 593	0.20
Placental weight (g)	487 ± 152	441 ± 129	0.08
Miscarriage	24 (18)	0	NA
	***N* = 105 (newborn)**	***N* = 25 (newborn)**	
IUGR/preeclampsia	15 (14)	3 (12)	0.93
Preterm birth	16 (15)	4 (16)	0.92
IFD	1 (1)	0	NA

Continuous variables were expressed as mean ± SD, while categorical variables as absolute frequency (percentage).

TABLE 2 Placental histology.

Placental lesions	
Increased syncytial knots	17 (68%)
Decreased vasculosyncytial membranes	11 (44%)
Infarction	8 (32%)
Impaired spiral artery remodeling	3 (12%)
Decidual inflammation	2 (8%)
≥2 placental lesions	12 (48%)

Variables as absolute frequency (percentage).

Placental analyses

Twenty-five placentas of deliveries occurring during the last year of recruitment underwent specific placental analyses. Table 1 reports the clinical features, previous obstetrical history, and obstetrical outcomes of the pregnancies whose placentas were collected. No difference in patient and pregnancy characteristics was found between the entire cohort and the cohort of patients whose placentas were analyzed, suggesting that placental analyses were performed in a sample that was representative of the entire cohort (Table 1).

Mean placental weight was 441 ± 129 g. Frequencies of occurrence of each placental lesion among increased syncytial knots, decreased vasculosyncytial membranes, infarction, impaired spiral artery remodelling, and decidual inflammation were described in Table 2. Increased syncytial knots were the most frequent finding, being present in 17 (68%) placentas. Notably, 48% of placentas displayed more than two lesions.

The titer of aCL IgG was significantly higher in pregnancies whose placenta displayed syncytial knots (p 0.04, Table 3). In addition, a tendency towards higher aCL IgG titers were observed in pregnancies whose placentas had more than two

types of lesions (p 0.07, Table 3). No statistically significant differences were observed in the detection of more than two placental lesions between patients with primary APS and those with APS associated with SLE.

All patients with a history of thromboembolic event had placental infarction despite therapy (p 0.04, Table 3). Placental infarction was an independent predictor of placental weight at delivery independent of maternal age, its occurrence being associated with lower placental weight (p 0.04, Table 4). Also, a tendency was observed towards lower neonatal weight in the presence of placental infarction (p 0.08).

At logistic regression analyses, HCQ therapy during pregnancy did not predict any of the placental lesions analyses (Table 5). However, none of the pregnancies occurred in patients who received HCQ (11 out of 25) had decidual inflammation of the placenta, which was present in two of the 25 placentas analyzed (Table 5). Figure 1 depicts the main placental histological lesions.

Discussion

In this study of APS pregnant patients, we observed a high rate of successful pregnancy outcomes, largely due to specialized multidisciplinary care and specific therapeutic interventions. The low incidence of maternal complications and high live birth rates

TABLE 3 Pregnancies characteristics (n = 25) based on the presence or absence of placental lesion.

		≥2 histological placental lesions			Infarction			Decreased vasculosyncytial membranes			Increased syncytial knots		
	Overall	No	Yes	*P*	No	Yes	*P*	No	Yes	*P*	No	Yes	*P*
Age at delivery (years)	34 (32–36)	36 (32.8–37.8)	33 (32–35)	0.11	35 (32–37)	32.5 (32–35.2)	0.48	32.5 (32–35.8)	36 (33.5–38.5)	0.19	35 (33–37.8)	34 (32–36)	0.28
BMI (kg/m^2)	21.4 (19.1–22.8)	22.1 (20.3–25.9)	20 (19.1–21.8)	0.23	21.4 (19.1–22.8)	21.1 (19.4–22.1)	0.93	21.1 (18.6–22.3)	21.8 (19.6–22.9)	0.48	22.3 (20.5–31.4)	20.8 (18.4–21.8)	0.08
Miscarriages	2 (1–3)	2.5 (1–3.2)	2 (1–2)	0.42	2 (1–4)	1.5 (1–2)	0.11	2 (1–2.8)	2 (1.5–4)	0.18	2 (1–2.5)	2 (1–3)	1
aGAPSS	8 (5–12)	8 (4.5–12.5)	8.5 (5.8–11.2)	0.59	8 (5–10.5)	10.5 (8.2–12)	0.22	10.5 (7.2–12.2)	5 (5–8)	0.19	8 (5–16)	8 (5–12)	0.8
aCL IgM titer	4.2 (0–28)	1.6 (0–28)	12.6 (1.5–26.2)	0.73	7.4 (0–28)	3.1 (1.5–10.4)	0.91	5.8 (1.2–33.8)	2 (0–25.3)	0.46	14 (0–28.8)	4.2 (0.8–23.1)	0.92
aCL IgG titer	7.4 (0–32)	0 (0–10.4)	25 (5.6–38.2)	0.07	0 (0–16.8)	32 (24–488)	0.15	13.6 (0–34.5)	0 (0–18)	0.44	0 (0–0)	16.8 (3.7–37.1)	0.04
B2GP1 IgM titer	1 (0–33.9)	1.5 (0–45)	0.5 (0–9.2)	0.51	1.5 (0–45)	0.5 (0–1)	0.32	0.6 (0–7.4)	1 (0–45)	0.76	22.5 (0–45.8)	1 (0–13.2)	0.71
β2GP1 IgG titer	6 (0–25.6)	21 (2.2–25.6)	5.7 (0–40)	0.80	5.4 (0–23)	50 (4.5–1,481)	0.39	14.8 (1.7–54.2)	6 (0–22)	0.59	21.5 (5.2–22.8)	5.4 (1.1–33.3)	0.95
aPS-PT IgM titer	29 (0–43.4)	29 (7.5–38)	20.4 (2.2–67.5)	0.94	25 (4.5–37.3)	53 (7.5–131.5)	0.50	36.7 (11.2–96)	10.7 (0–31)	0.13	31 (25–32.6)	22 (0–51.5)	0.73
aPS-PT IgG titer	5 (0–10)	5 (0–10)	3 (0–8.2)	0.94	6 (0–9.5)	0 (0–112.5)	0.84	0 (0–10.8)	6 (0–7.5)	0.94	7.5 (5–26)	0 (0–9.2)	0.22
APS secondary to SLE	6 (24)	2 (16.7)	4 (30.8)	0.72	4 (23.5)	2 (25)	1	3 (21.4)	3 (27.3)	1	2 (25)	4 (23.5)	1
≥2 miscarriages	16 (64)	8 (66.7)	8 (61.5)	1	12 (70.6)	4 (50)	0.58	8 (57.1)	8 (72.7)	0.7	5 (62.5)	11 (64.7)	1
LLAC	7 (28)	3 (25)	4 (30.8)	1	3 (17.6)	4 (50)	0.23	6 (42.9)	1 (9.1)	0.15	2 (25)	5 (29.4)	1
PE/DVT	3 (12)	0 (0)	3 (23.1)	0.25	0 (0)	3 (37.5)	0.04	3 (21.4)	0 (0)	0.31	1 (12.5)	2 (11.8)	1
≥1 miscarriage <10 gw	18 (72)	9 (75)	9 (69.2)	1	13 (76.5)	5 (62.5)	0.80	9 (64.3)	9 (81.8)	0.60	6 (75)	12 (70.6)	1
≥1 miscarriage >10 gw	8 (32)	5 (41.7)	3 (23.1)	0.57	6 (35.3)	2 (25)	0.95	5 (35.7)	3 (27.3)	0.98	3 (37.5)	5 (29.4)	1
IFD	2 (8)	1 (8.3)	1 (7.7)	1	1 (5.9)	1 (12.5)	1	1 (7.1)	1 (9.1)	1	2 (25)	0 (0)	0.17
Low complement	4 (16)	2 (16.7)	2 (15.4)	1	3 (17.6)	1 (12.5)	1	3 (21.4)	1 (9.1)	0.77	1 (12.5)	3 (17.6)	1
≥3 aPL positivities	8 (32)	4 (33.3)	4 (30.8)	1	4 (23.5)	4 (50)	0.38	7 (50)	1 (9.1)	0.08	2 (25)	6 (35.3)	0.95
≥2 aPL positivities	15 (60)	6 (50)	9 (69.2)	0.57	9 (52.9)	6 (75)	0.54	10 (71.4)	5 (45.5)	0.36	4 (50)	11 (64.7)	0.79

Continuous variables are expressed as median (interquartile range), while categorical variables as absolute count (percentage).

TABLE 4 Logistic and linear regression analyses predicting obstetrical outcomes.

	IUGR-preeclampsia/ preterm		GW at delivery		Neonatal weight at delivery		Placental weight	
	OR (95% CI)	*P*	Estimate (SE)	*P*	Estimate (SE)	*P*	Estimate (SE)	*P*
Infarction	5.72 (0.65–80.92)	0.13	−0.82 (1.08)	0.46	−419.24 (231.14)	0.08	−106.76 (49.01)	0.04
Decreased vasculosyncytial membranes	0.87 (0.08–7.08)	0.89	−0.17 (1.04)	0.86	184.81 (231.96)	0.43	59.46 (49.71)	0.24
Increased syncytial knots	0.37 (0.03–3.97)	0.40	1.47 (1.09)	0.19	5.12 (256.46)	0.98	−55.73 (54.64)	0.24
≥2 placental lesions	3.81 (0.42–84.64)	0.28	−0.18 (1.08)	0.87	−352.77 (231.05)	0.14	−110.22 (47.48)	0.03

TABLE 5 Logistic regression investigating whether HCQ treatment predicts each placental lesion, after adjusting for age at conception.

HCQ therapy	OR (CI 95%)	*P* value
Infarction	1.69 (0.27–12.87)	0.58
Decreased vasculosyncytial membranes	0.68 (0.11–3.86))	0.66
Increased syncytial knots	0.39 (0.04–2.63)	0.35
≥2 placental lesions	0.63 (0.11–3.66)	0.60

underscore the importance of specialized care in managing APS pregnancies. Standard therapy LDA and LMWH has been shown to significantly reduce the rates of miscarriages and late pregnancy complication (7, 30). Previous studies have consistently shown that standard therapy results in successful pregnancy outcomes in approximately 75%–80% of women with APS (40), a substantial improvement compared to their prior obstetric histories (10, 41, 42).

Despite these advancements, about 22% of APS women do not respond to conventional treatment with LDA and LMWH (40) and continue to experience adverse pregnancy events such as miscarriages, IFD, IUGR and preeclampsia. To address these refractory cases, additional treatments have been explored, including higher doses of LMWH, corticosteroids, intravenous immunoglobulin, plasma exchange, complement inhibitors, antitumor necrosis factor alpha, and HCQ (43).

HCQ has garnered particular interest due to its favorable safety profile during pregnancy, affordability, and ease of oral administration (31). Known for its anti-inflammatory and antithrombotic properties, HCQ is an old antimalarial drug that inhibits platelet aggregation and modulates immune responses (39, 44, 45).

Its potential role in reducing decidual inflammation—a key factor in adverse pregnancy outcomes—is especially significant. Several studies have shown that HCQ can improve obstetrical outcomes in APS patients (31, 39).

In our cohort, 25 placentas of pregnancies in APS patients underwent specific histological analysis. These pregnancies are representative of the typical population evaluated at our Clinic. Histological analysis of placentas from APS patients treated with HCQ revealed no instances of decidual inflammation, suggesting that HCQ may mitigate immune-mediated placental damage. This data need do be confirmed in a larger cohort of APS pregnant patients.

The presence of higher median titers of aCL IgG in placentas of pregnancies with two or more histological lesions and in those with increased syncytial knots, suggests that aCL IgG titers might serve as markers for predicting specific placental pathologies. Furthermore, all patients with a history of thromboembolic events exhibited placental infarction despite therapy, highlighting the ongoing risk of vascular complications in APS and the necessity of considering thromboembolic history in managing these cases.

Our findings align with previous literature indicating that placental lesions such as infarctions, impaired spiral artery remodeling, and decidual inflammation are common in APS and

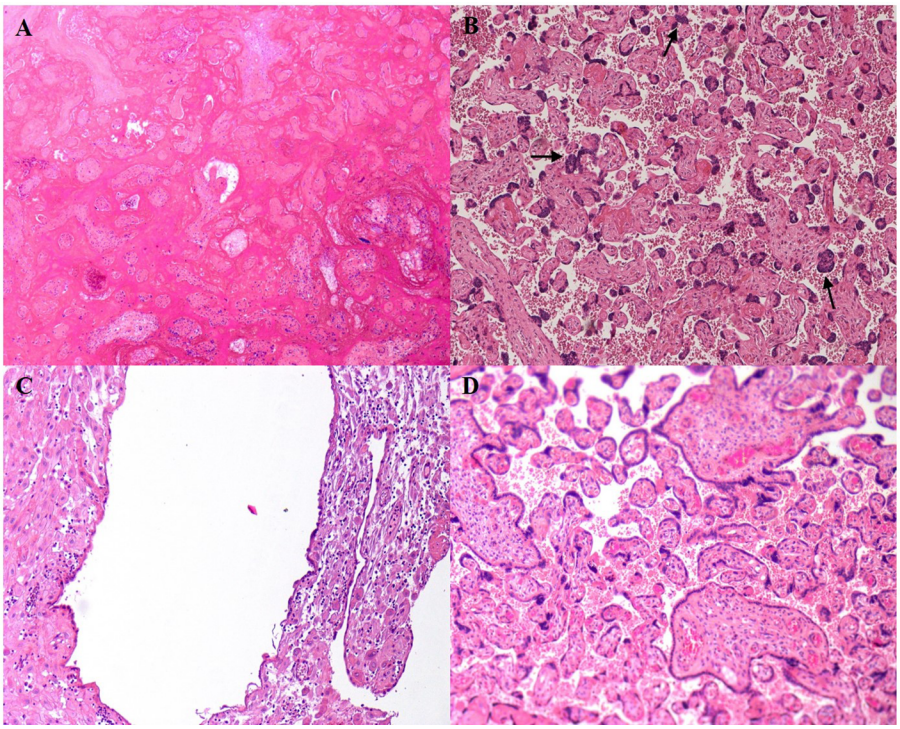

FIGURE 1
Placental histological lesions. **(A)** Placental infarction: the tissue is made up of ischemic "ghost" villi with mild inflammation in the lower-right part of the image. **(B)** Syncitial knots (arrows). **(C)** Deciduitis: lymphocytic inflammatory infiltrates in chorionic plate. **(D)** Normal placental tissue.

contribute to poor pregnancy outcomes (40). These lesions are believed to result from the direct binding of aPL to trophoblasts and other placental structures, leading to inflammation, thrombosis, and impaired placental development (10).

The role of HCQ in reducing these lesions is supported by its anti-inflammatory and antithrombotic effects. HCQ has been shown to decrease the binding of aPL to syncytiotrophoblasts and restore the expression of annexin A5, a protein that forms a protective anticoagulant shield on the placental surface (34, 44). Additionally, HCQ inhibits complement activation, which is crucial in mediating aPL-induced placental damage (36). These mechanisms suggest that HCQ may help preserve placental function and improve pregnancy outcomes in APS patients (46).

Given the known benefits of HCQ, initiating this treatment at the beginning of pregnancy with refractory APS, in addition to standard therapy, appears beneficial. The safety of HCQ during pregnancy is well-documented (45) and its efficacy in refractory APS is recognized (32). However, further studies with larger sample sizes are necessary to confirm these findings and elucidate the mechanisms by which HCQ may reduce placental lesions and improve pregnancy outcomes in APS patients.

Future research should focus on larger cohorts to better understand the impact of HCQ on placental pathology and adverse pregnancy outcomes. Detailed histopathological analyses and comprehensive clinical data will be critical for validating and expanding upon our findings. Understanding the specific pathways through which HCQ exerts its protective effects will help optimize treatment strategies for APS patients and potentially improve maternal and fetal outcomes.

In conclusion, our study underscores the significant impact of specialized multidisciplinary care in managing pregnancies affected by APS. The moderate-to-low levels of aPL titers observed in the 25 pregnancies may indicate a cohort with a potentially lower risk of adverse pregnancy outcomes (47). However, as the literature suggests (48), low aPL titers are more strongly associated with previous recurrent miscarriages. Our preliminary data also confirm the safety of using HCQ during pregnancy for both the mother and the fetus. Additionally, HCQ appears to offer extra benefits by reducing placental lesions. Larger studies are essential to fully understand the role of HCQ in improving pregnancy outcomes for APS patients, and the inclusion of detailed histopathological analyses and larger cohorts will be crucial for future research.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

The studies involving humans were approved by Ospedale San Raffaele Ethical Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

VC: Writing – review & editing, Writing – original draft, Methodology, Formal Analysis, Data curation, Conceptualization. RD: Writing – review & editing, Writing – original draft, Formal Analysis, Data curation. GI: Writing – original draft, Data curation. SG: Writing – original draft, Methodology, Conceptualization. MP: Writing – original draft, Data curation. NT: Writing – original draft, Data curation. RL: Writing – original draft, Data curation, Conceptualization. FP: Writing – original draft, Data curation. MC: Writing – review & editing, Supervision, Data curation, Conceptualization. PC: Writing – review & editing, Supervision, Data curation, Conceptualization. P-RQ: Writing – review & editing, Supervision, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/flupu.2024.1459172/full#supplementary-material

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