European Journal of Obstetrics & Gynecology and Reproductive Biology 234 (2019) 137–142

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

In vitro fertilization and autoimmunity: Evidence from an observational study

R. Di Rosa[a], S. Ferrero[b], N. Cifani[a], L. Ferri[a], M. Proietta[a], A. Picchianti Diamanti[a], F. Del Porto[a,*]

[a] "Sapienza", Università di Roma, Dipartimento di Medicina Clinica e Molecolare, Facoltà di Medicina e Psicologia, Ospedale Sant'Andrea, Via Grottarossa 1035-1039, 00189, Roma, Italy
[b] "Genera", Valle Giulia, Via Giuseppe de Notaris, 2, 00197, Roma, Italy

ARTICLE INFO

Article history:
Received 17 September 2018
Received in revised form 1 December 2018
Accepted 27 December 2018

Keywords:
Infertility
Antiphospholipid antibodies
Antiphospholipid antibody syndrome
Pregnancy
Systemic autoimmune diseases

ABSTRACT

Introduction: : The aim of this study was to evaluate the prevalence of antiphospholipid antibodies (aPLs) in infertile women undergoing *in vitro* fertilization (IVF).
Method of study: : From January 2012 to December 2017, 520 consecutive clinical records of infertile women undergoing IVF were evaluated. Among them, 100 consecutive clinical records of patients with positive autoantibodies were selected.
Results: : In 100/520 (19.23%) women, positive auto-antibodies were detected: 35/520 (6.73%) fulfilled classification criteria for a systemic disease. Positive aPLs were observed in 43 women (8.27%): 17/520 (3.27%) fulfilled diagnostic criteria for PAPS/APS, whereas patients with positive aPLs, who fulfilled diagnostic criteria for a systemic autoimmune disease other than APS were 18/520 (3.46%). LA and aCL were the main aPLs detected 53.49% and 44.19% respectively, whereas aB2GPI were found in 25.58%.
Conclusions: : we suggest that women with infertility may represent a subpopulation of patients with underhanded systemic autoimmune syndromes in which the main symptoms represented are obstetrical complications. We, therefore, recommend evaluating aPLs in all patients undergoing IVF with the aim of recognizing women at a higher risk of miscarriage or pregnancy morbidity.

Introduction

Early in pregnancy maternal immune system should lead to tolerance against paternal foreign antigens expressed by foetus so that implantation can proceed [1]. As a consequence, a good balance of immune system guarantees a physiological pregnancy development, so much that reinstatement of immune homeostasis in women affected by systemic autoimmune diseases strongly ameliorates foetal-maternal outcomes [2]. Obstetric antiphospholipid antibodies syndrome (OAPS) occurs in women with persistently positive antiphospholipid antibodies (aPLs) [3,4] and a history of one or more unexplained deaths of morphologically normal foetus at or beyond the 10th week of gestation (WG) or more than 3 unexplained consecutive miscarriages before the 10th WG. Also one or more premature delivery of a morphologically normal foetus before 34 W G because of eclampsia, severe pre-eclampsia, or recognized features of placental insufficiency represent one of the diagnostic criteria [3,4]. The international consensus laboratory criteria for antiphospholipid antibodies syndrome (APS) include the persistent presence of lupus anticoagulant (LA) and/or moderate or high positive IgG or IgM anticardiolipin,(aCL) (>40 GP L or MPL or >99thcentile) and/or anti-β2glycoprotein-1 (aβ2GPI) IgG and/or IgM antibodies (> 99thcentile) [3,4]. Despite the wide range of obstetric complications related to positive aPLs, APS is not inclued among causes of infertility. However, it is likely that defective embryonic implantation leading to very early miscarriages can appear as infertility [5]. In the last years, a wide spectrum of obstetric complaints not included among classification criteria [6], have been noted in women showing persistently positive aPLs. In particular, late pre-eclampsia, placental abruption, late premature birth (after 34 W G), or two or more unexplained *in vitro* fertilisation (IVF) failures [7]. Moreover, international consensus criteria for OAPS do not comprise non-classical aPL, or low titres of accepted aPLs such as aCL, and antiβ2-GPI antibodies, suggesting the existence of "non criteria" clinical and "non criteria" antibody patterns [7]. In such field, a European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS) has been drafted with the aim of assessing whether OAPS exists as a separate form of "classical" APS, showing clinical and laboratory criteria less restricive than those currently accepted

* Corresponding author.
E-mail address: flavia.delporto@uniroma1.it (F. Del Porto).

https://doi.org/10.1016/j.ejogrb.2018.12.042
0301-2115/

[8]. Excessively restrictive clinical and laboratory criteria, indeed, can limit the early identification of women at high risk of obsterical complications potentially lifethreatening for mothers and foetus. Results of EUROAPS showed that OAPS displays differential characteristics from classical APS, it has very good foetal–maternal outcomes when treated and seems to have different aPL-mediated pathogenic mechanisms [8]. On the basis of the points mentioned above, we evaluated the prevalence of aPLs in a population of women undergoing IVF.

Method of study

This was an observational retrospective study.

Among 520 women who underwent IVF at "Genera" Valle Giulia from January 2012 to December 2017, clinical records from 100 consecutive patients showing positive autoantibodies were evaluated. All patients underwent physical examination, routine tests, karyotype determination, ovarian reserve test, mammography, mammary ultrasound and hysteroscopy. Moreover, according to IVF center protocol, routine assesment of ANA, aCL IgG and IgM, aβ2GPI IgG and IgM, LA, anti-double stranded DNA, C3 and C4 complement fractions, rheumatoid factor and ENA profile, including anti-Ro, anti-La, anti-Jo1, anti-RNP, anti-Sm and anti-SCL70 antibodies were also performed and repeated after 12 weeks only in the presence of positive results.

All peripheral blood tests were performed before women started IVF hormonal stimulation. ANA were considered positive when detected at least twice at titres >1:80, aCL IgG or IgM at titres ≥40 GPL/MPL and /or aβ2GPI IgG or IgM (confirmed after 12 weeks from the first detection).

Clinical records of patients with positive auto-antibodies, but with genetic, anatomic, infective or hormonal causes of sterility were not considered.

All the patients had already been addressed toward the conform method of fertilization by IVF center and this study did not affect any diagnostic and therapeutic proceeding regarding IVF and pregnancy management.

An informed written consent was obtained from each patient before clinical record were evaluated. The study was performed according to the principles of the Declaration of Helsinki.

Results

We evaluated the first conseutive 100 clinical records (mean age 39.97 ± 4.63, median 40 years) of patients showing positive autoantibodies. Sixteen clinical records were promptly excluded since the patients discontinued IVF iter, so the data were incomplete. Among them, two showed positive aPLs. Twenty-one women showed positive ANA with no aPLs or clinical features of systemic autoimmune diseases. Ten patients fulfilled diagnostic criteria for a systemic autoimune disease (7 UCTD [12]; 2 SLE [9–11];1 Sjogren disease [13]), but did not display positive aPLs. In 6 patients only positive anti smooth muscle cell antibodies (ASMA) were detected. Four patients were diagnosed as affected by primary biliary cirrhosis (CBP): among them two women showed positive aCL IgM at high titres, but dropped out of futher clinical interventions.

In 43 clinical records (42/520- 8.6%) persistent positive aPLs at medium/high titres were found (Fig. 1 and Table 1). One of them did not proceed to ovarian stimulation, since an active lupus nephritis [14] was diagnosed. One woman who underwent ovodonation, displayed positive aPLs, but obsterical history did not fulfill clinical criteria for APS, thus infertility was mainly connected to age. Among the 43/520 selected women (8.27%) showing persistently positive aPLs (Table 1): 35/520 (6.73%) fulfilled classification criteria for a systemic disease (Tables 2 and 3). In particular, 14/520 (2.70%) of patients were affected by SLE [9–11] with only muco-cutaneous or muscoloskeletal symptoms/signs, among them 4 also fulfilled international consensus criteria for APS [3,4] and 10 showed positive aPLs without clinical features fulfilling APS criteria. Seven out of 520 (1.35%) were affected by UCTD [12], one of them fulfilled consensus criteria for APS and 6 showed only positive aPLs without clinical features fulfilling APS criteria. Two out of 520 patients (0.38%) were affected by Sjogren disease [13], both showing positive aPLs and not fulfilling clinical criteria for APS. Twelve out of 520 fulfilled criteria for PAPS (2.31%) [3,4]. Eight patients out of 520 (1.54%) showed positive aPLs at medium/high titres and obstetrical features, not included in international clinical classification criteria (Table 4).

In the whole, patients fulfilling diagnostic criteria for PAPS/APS were 17/520 (3.27%) (Table 3), whereas patients with positive aPLs and fulfilling diagnostic criteria for a systemic autoimmune disease other than APS were 18/520 (3.46%) (Table 3).

LA and aCL were the main aPLs detected 53.49% and 44.19% respectively, whereas aB2GPI were found in 25.58% of the patients (Table 5).

Intracytoplasmic sperm injection (ICSI) was the main method used for IVF (27/42 patients- 64.29%), whereas *in vitro* fertilization with embryo transfer (FIVET) was performed in 3/42 patients (7.14%), intrauterine insemination (IUI) in 5/42 women (11.90%) and 5 patients underwent ovodonation (OD), but were included since they fulfilled diagnostic criteria for APS [4] and recurrent

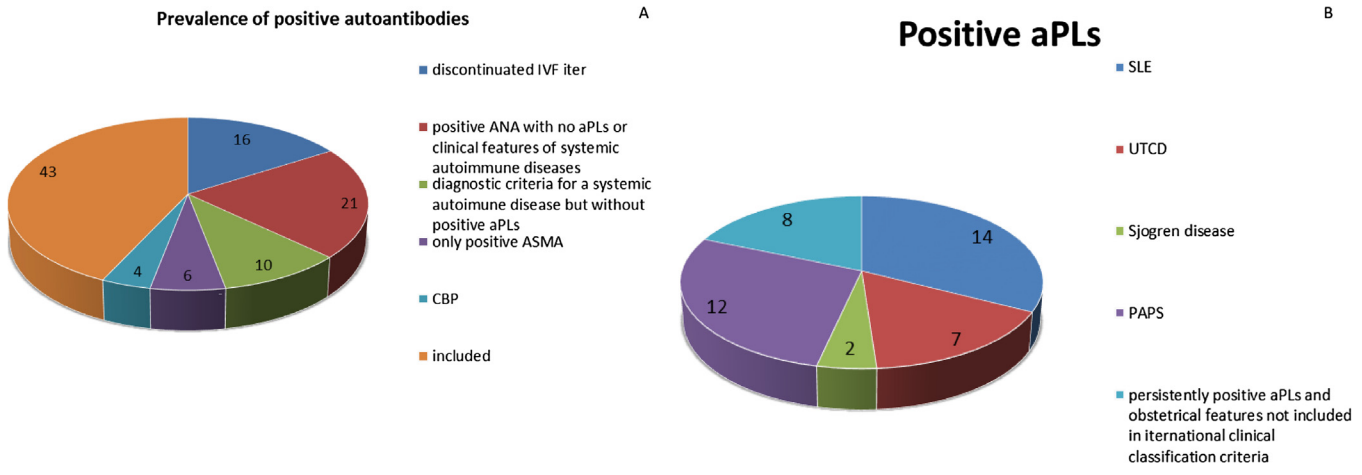

Fig. 1. A. Prevalence of positive autoantibodies in 100 consecutive women undergoingto IVF. B. Clinical characteristic of the 43 persistently aPLspositive women.

Table 1
aPLs and APS clinical criteria description in 43 persistently positive women.

n	age	ANA	aPL	APS clinical criteria	Other symptoms	diagnosis	IVF	BHCG	D
1	40	–	aCL IgM 35	DVT		PAPS	OD	–	–
2	33	1:80	aCL IgG 30	1 miscarriage < 10 W G	artralgia xerophtalmia, xerostomia, SS-B+	S.Sjogren, no clinical and no laboratory criteria for APS	ICSI	+	yes
3	42	1:640	LA	Recurrent IVF failure	artralgias, recurent oral aphtosis	SLE, no clinical criteria for APS	ICSI	+	yes
4	41		aCLIg M 20, LA	Recurrent miscarriages (5 < 10 W G)	Photosensitivity, polyartralgias	UTCD,APS	IUI	+	yes
5	40	1:160	aCLIgG 66.4	Recurrent IVF faiulure	acrocianosis, photosensitivity, arthralgias, malar rash, low complement	SLE, no clinical criteria for APS	FIVET	–	–
6	43	neg	aB2GPI IgG 91.8, aCLIgM 36	1 miscarriage at 8 W G	Raynaud phenomenon	UTCD, no clinical criteria for APS	ICSI	–	–
7	39	1:80	LA	2 miscarriage at 8 W G	Photosensitivity	UTCD, no clinical criteria for APS	ICSI	+	yes
8	37	neg	LA	DVT		PAPS	ICSI	+	yes
9	46	neg	LA	Recurrent IVF failure	–	No clinical criteria for APS	OD	+	yes
10	38	neg	aCL IgM 30	1 IVF failure	Photsensitivity, artrallgias, malar rash, Raynaud phenomenon	UTCD, no clinical and no laboratory ecriteria for APS	ICSI	+	yes
11	42	neg	aCLIgM	Recurrent miscarriages (4 < 10 W G)	–	PAPS	IUI	+	–
12	42	neg	LA	One foetal loss after 14 WG	artralgias	PAPS	FIVET	+	yes
13	43	1:80	aB2GPI IgG 50, IgM 19 aCL IgG 49 IgM 16	Recurrent IVF failure	Malar rash, artralgias, oral recurrebnt aphtosis,miastenia, diabetes	SLE, miastenia, no clinical criteria for APS	FIVET	+	yes
14	48	neg	aCL IgG 150, LA	Recurrent miscarriages (8 < 10 W G)	–	PAPS	OD	+	yes
15	37	neg	a CL IgM 102	sterility	–	No clinical criteria for APS	ICSI	+	yes
16	37	1:640	LA	Recurrent IVF failure	Malar rash, oral aphtosis, photosensitivity	SLE, no clinical criteria for APS	ICSI	+	yes
17	37	neg	LA	Recurrent miscarriages	artralgias	PAPS	ICSI	+	yes
18	43	neg	LA	sterility	Recurrent IVF failure	No clinical criteria for APS	ICSI	+	yes
19	46	neg	LA	2 foetal loss at 12 WG	none	PAPS	IUI	–	–
20	36	1:80	aB2GPI IgM 39.2, aCL IgG 60.5, aCL IgM 39.20	Sterility	Oral aphtosis, malar rash	SLE, no clinical criteria for APS	ICSI	–	–
21	37	neg	aCL IgG 25, LA	Recurent IVF faiulre	Oral aphtosis	UTCD, no clinical e no laboratory criteria for APS	ICSI	+	yes
22	44	1:80	aB2GPI IgG 15	Recurrent IVF failure	none	No clincal e no laboratory criteria for APS	OD	+	yes
23	42	neg	LA	One foetal loss after 16 WG	none	PAPS	ICSI	+	yes
24	40	1:320	LA	Recurrent miscarriages One foetal loss at 13 WG	Malar rash, oral aphtosis, artralgias	SLE, APS	ICSI	+	yes
25	41	1:80	aCL IgG 33 IgM 29	sterility	photosensitivity	UTCD, no clinical e no laboratory criteria for APS	ICSI	+	–
26	39	1:320	LA	Recurrent miscarriages	Arthritis, oral aphtosis, malar rash	SLE, APS	ICSI	+	yes
27	42	1:320	aCL IgM 50, LA	Recurrent miscarriges	Arthritis, photosensitivity	SLE, APS	IUI	+	yes
28	43	1:80	aCL IgG 27, LA	Recurrent IVF failure	arthritis	UTCD, no clinical criteria for APS	IUI	+	yes
29	42	1:160	LA	sterility	Arthritis,anemia,Raynaud phenomenon, SS-A	SLE, no clinical criteria for APS	ICSI	+	yes
30	41	neg	aB2GPI IgG 13 LA	One miscarriage at 8 W G, Recurrent IVF failure	none	No clinical criteria for APS	IUI	+	–
31	44	1:320	aCL IgM 105, aB2GP1 IgM 44	Recurrent IVF failure	Artrhalgias, oral aphtosis	SLE, no clinical criteria forAPS	ICSI	+	yes
32	39	1:80	SS-A, aB2GPI IgM 18	Recurrent IVF failure	Sicca syndrome	S. Sjogren, no clinical criteria for APS	ICSI	+	yes
33	43	neg	aCL IgG 40 GPL	Recurrent miscarriages (3 < 10 W G)		PAPS	ICSI	+	yes
34	34	neg	aCL IgM 86, aB2GPI IgG 20	Recurrent miscarriages		PAPS	ICSI	+	yes
35	47	1:80	aCL IgM 62, aB2GPI IgM 80	Recurrent IVF failure	Polyartralgia photosensitivity	SLE, no clnical criteria for APS	ICSI	+	yes
36	31		LA	Two miscarriages	APCA	No clinical criteria for APS	ICSI	+	yes
37	43		aCL IgM 40 GPL	Recurrent miscarriages		PAPS	ICSI	+	yes
38	44	1:160	LA once	One foetal loss at 29 WG		No clinical criteria for APS	OD	+	yes
39	36	1:160	LA, aCL IgM 18	Recurrent miscarriages		PAPS	ICSI	+	yes
40	43	1:320	LA, aB2GPI IgG 25	Recurrent IVF	Nephritis, dsDNA, polyartralgias, malar rash	SLE, APS	–	–	–
41	40	1:160	aCL IgM 45	One miscarriage <10 W G	Malar rash, arthralgias, anemia, thrombocytopenia	SLE, no clinical criteria for APS	ICSI	+	yes
42	38	1:160	LA, ANA aB2GPI 20 GPL	Sterility	Poliarthritis, malar rash, photosensitivity	SLE, no clinical criteria for APS	ICSI	+	yes
43	46		LAC	Infertility			OD	+	yes

Recurrent miscarriages: 3 before 10 W G.

Table 2
Women affected by a systemic autoimmune diseases diagnosed accordingly to international diagnostic criteria and fulfilling APS classification criteria.

	N°	age	Diagnosis	aPLs	ART	bHCG	delivery
1	1	40	Vascular PAPS	DVT + aCL IgM	OD	–	–
2	4	41	UTCD + APS	LA, aCL IgM + recurrent miscarriages	IUI	+	yes
3	8	37	Vascular PAPS	DVT + LA	ICSI	+	yes
4	11	42	Obstetric PAPS	aCL IgM + recurrent miscarriages	IUI	+	–
5	12	42	Obstetric PAPS.	LA + 1 miscarriage > 10 W G	FIVET	+	yes
6	14	48	Obstetric PAPS	LA, aCL IgG + recurrent miscarriages	OD	+	yes
7	17	37	Obstetric PAPS	LA + recurrent miscarriages	ICSI	+	yes
8	19	46	Obstetric PAPS	LA + 2 miscarriages at 12 WG	IUI	–	–
9	23	42	Obstetric PAPS	LA + 1 miscarriage after 16 WG	ICSI	+	yes
10	24	40	SLE + APS	LA + r miscarriages	ICSI	+	yes
11	26	39	SLE + APS	LA + r miscarriages	ICSI	+	yes
12	27	42	SLE + APS	LA, aCL IgM + r miscarriages	IUI	+	yes
13	33	43	Obstetric PAPS	aCL IgG + Recurrent miscarriages	ICSI	+	yes
14	34	34	Obstetric PAPS	aCL IgM, aB2GPI IgG + recurrent miscarriages	ICSI	+	yes
15	37	43	Obstetric PAPS	aCL IgM + recurrent miscarriages	ICSI	+	yes
16	39	36	Obstetric PAPS	LA, aCL IgM + recurrent miscarriages	ICSI	+	yes
17	40	43	SLE + APS	LA, aB2GPI IgG + recurrent miscarriages	–	–	–

Table 3
Women affected by a systemic autoimmune diseases diagnosed accordingly to international diagnostic criteria and evidence of persistently positive aPLs at medium-high titres, but not fillfilling APS classification criteria.

	N°	age	Diagnosis	Obsteric hystory	ART	bHCG	delivery
1	2	33	S.Sjogren + aCL IgG	one miscarriage < 10 W G	ICSI	+	yes
2	3	42	SLE + LA	rIVF failure	ICSI	+	yes
3	5	40	SLE + aCL IgG	r IVF failure	FIVET	–	–
4	6	43	UTCD + aCL IgMaB2GPI IgG	one miscarriage	ICSI	–	–
5	7	39	UTCD + LA	2 miscarriage at 8 W G	ICSI	+	yes
6	10	38	UTCD + aCLIgM	1 IVF failure	ICSI	+	yes
7	13	43	SLE + aB2GPI IgG&IgM + aCLIgG&IgM	+ r IVF failure	FIVET	+	yes
8	16	37	SLE + LA	r IVF failure	ICSI	+	yes
9	20	36	SLE + aB2GPI IgM, aCL IgG&IgM	Sterility, rIVF failure	ICSI	–	–
10	21	37	UTCD + LA, aCL IgM	r IVF failure	ICSI	+	yes
11	25	41	UTCD + aCLIgG&IgM	sterility	ICSI	+	–
12	28	43	UTCD + LA, aCL IgG 27	rIVF failure	IUI	+	yes
13	29	42	SLE + LA	sterility	ICSI	+	yes
14	31	44	SLE + aCLIgM, aB2GPI IgG	rIVF failure	ICSI	+	yes
15	32	39	Sindrome di Sjogren + aB2GPI IgG	rIVF failure	ICSI	+	yes
16	35	47	SLE + aCLIgM,aB2GPI IgM	rIVF failure	ICSI	+	yes
17	41	40	SLE + aCL IgM	one miscarriage	ICSI	+	yes
18	42	38	SLE + LA, ANA aB2GPI 20 GPL	Sterility	ICSI	+	yes

Table 4
Patients with peristently positive aPLs at medium high titres not fulfilling international consensus conference classification criteria for APS/PAPS.

	n°	age	Obstetrical features	aPLs	diagnosis	ART	bHCG	delivery
1	9	46	Recurrent FIV failure.	LA	–	OD	+	yes
2	15	37	Sterility	aCL IgM 105	–	ICSI	+	yes
3	18	43	Sterility	LA	–	ICSI	+	–
4	22	44	rIVF failure	aB2GPI IgG 15	–	OD	+	yes
5	30	41	Recurrent IVF failure + one spontaneous miscarriage(8 W G)	LA	–	IUI	+	–
6	36	31	two spontaneous miscarriage (9 W G)	LA	–	ICSI	+	yes
7	38	44	One fetal loss at 29 WG	LA once	–	OD	+	yes
8	43	46	Sterility	LA once		OD	+	yes

Table 5
Prevalence of LA, aCL and aB2GPI in 43 persistenlty aPLs positive women.

Positive autoantibodies	n. patients	%
Total aPLs	43	
LA	23/43	53.49
aCL IgG/IgM	19/43	44.19
aB2GPI IgG/IgM	11/43	25.58
Double positive	15/43	34.88
Triple positive	4/43	9.30

miscariages were the recognized cause of their obstetrical disorders.

Pregnancies were managed by a reliable and trustworthy gynaecologist according to international treatment protocols [2].

Implantation rate was 83.33% (35/42 women), wheras delivery rate was 76.19% (32/42).

Detailed data regarding delivery, maternal outcome and prenatal conditions were lacking, such that we could only reconstruct implantation rate and number of deliveries

Discussion

Our results showed that 19% (100/520) of infertile women undergoing IVF displayed a high prevalence of persistently positive serum auto-antibodies, mainly aPLs (43/520; 8.07%) and ANA (22/520;4.23%). Interestingly, 35/520 (6.73%) patients fulfilled diagnostic criteria for a systemic autoimmune diseases: 17/520 (3.27%) for APS or PAPS [3,4] and 18/520 (3.46%) for SLE [9–11], Sjogren [13] disease or UTCD [12], strongly suggesting that infertile women represent a particular subgroup of patients affected by a paucisintomatic systemic autoimmune disease, in which reproductive health and pregnancy are preferential targets. Prevalence of SLE and APS in the general population, indeed, are 130/100.000 and 50/100.000 respectively [15]. We can, therefore, speculate that in our population obstetric complications represented the main manifestations of a underhanded autoimmune disease, in which systemic symptoms were mostly limited to muscolo-skeletal and mucocutaneous involvement. In this field, it seems interesting to report that 4 women who underwent ovodonation fulfilled APS criteria, strongly suggesting that their infertility was attributable to OAPS more than to the age. Interestingly, these diagnoses were only made following IVF screening; aPLs, indeed, had never been evaluated in these patients, despite the highly suggestive obstetrical history, due to the absence of any systemic symptoms. Such an observation is further supported by epidemiologic evidence. Positive aPLs were detected in about 2% of health population, whereas their prevalence goes up to about 20% infertile women with a history of recurrent IVF failure [17]. Results obtained from EUROAPS strongly support our observations [8]. The european registry, indeed, demonstrated that OAPS shows differential clinical characteristics from classical APS and represents a specific subset within the APS disease [8].

It is generally accepted that a dysregulation of immune system negatively affects fertility. The role of immune system in reproductive health seems to be clear [18]. In early stages of pregnancy, maternal immune system should lead to tolerance, both in peripheral blood and at maternal/foetal placental interface, against paternal antigens expressed on foetus. Hormonal environment down regulates maternal natural killer (NK) T cell [19] and promotes the shift of immune response towards a T helper 2 pattern [20]. On the other hand, trophoblast expresses and releases soluble agents such as HLA-G, CD59, decay accelerating factor (DAF) and monocyte chemoattractant protein (MCP)-1, that are able to inhibit uterine NK and complement activation inside placenta [21]. Lack of uterine and peripheral blood NK depletion, a prevalent Th1 response and HLA-G downregulation have been related to miscarriages and recently also to recurrent IVF failure [21]. Thus, creating a link between pregnancy disorders, immunity and sterility. In this field it is well known that patients with a severe disease activity are at higher risk for maternal and foetal complications during pregnancy.

In our APS patients, treatment of underlying systemic autoimmune conditions seems to have led to a high implantation rate and a favourable pregnancy outcome. However, a limit to this study is that part of the data, mostly regarding progression of pregnancy, delivery, prenatal conditions and post partum maternal details were lacking. Thus, we could only suggest the presence of a relationship between aPLs and IVF technique success, but not draft definitive conclusions. To our knowledge, 31 studies have previously taken into consideration the possible connection between aPLs, infertility and IVF. The major limit of such manuscripts were the inclusion of all women undergoing IVF independently from infertility, obstetrical history and the evaluation of aPLs only once [5,22].

Antiphospholipid antibodies seem to be related to several pathological aspects of reproduction ranging from infertility to obsteric complications. It is now accepted that aPLs can cause pregnancy morbidity both by thrombotic and by a direct action upon trophoblast [5,23,24]. Moreover, it has been hypothesized that aPLs can cause infertility by compromising oocyte development after their secretion into follicular fluid24]. Nevertheless, the most accepted hypothesis is that aPLs might affect implantation by interfering with uterin decidualization and induce very early miscarriage [5].

Our results showed that LA was the main positive aPL. Most of the studies confirmed that LA is the main predictor of adverse pregnancy outcomes [25], being associated to extensive placental necrosis, infarction and thrombosis [26]. Double and triple positive aPLs were also shown to be related to a high risk of pregnancy loss. In our series, a high percentage of patients showed double o triple aPLs positivity. Among them 8/18 (44.45%) women displayed double positive aPLs and an obstetrical history suggestive, but not fulfilling diagnostic clinical criteria for APS. In agreement with EUROAPS suggestions, this observation, starts a discussion about patients fulfilling laboratory criteria, but with an incomplete clinical history to be diagnosed as APS. Further supporting this hypothesis, in 4.6% of our women an obsterical history compatible with APS, but not fulfilling clinical classification criteria, such as two miscarriages <10 W G, late onset pre-eclampsia, sterility or recurrent IVF failure [15,16] was observed, confirming that OAPS can include a wider range of obstetrical features than classic APS. Thus, we recommend performing an auto-antibody screening in all women undergoing IVF with the aim of identifying patients with positive aPLs early thus preventing clinical complications potentially life-threatening both for mothers and foetus.

In conclusion, we would suggest that women with infertility represent a subpopulation of patients with underhanded systemic autoimmune syndromes in which obstetrical complications represent the main symptoms. We, therefore, recommend evaluating auto-antibodies in all women undergoing IVF and performing a specialized clinical evaluation in all patients showing any positivity, with the aim of recognizing patients at higher risk of miscarriage, IVF failure, or pregnancy complications potentially life-threatening both to mothers and foetus. An accurate diagnosis, indeed, seems to represent an essential prerequisite for optimal clinical management of women undergoing IVF.

Conflict of interest

The authors have no actual or potential conflict of interest to declare, including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

References

[1] Bonney EA. Immune regulation in pregnancy: a matter of perspective? Obstet Gynecol Clin North Am 2016;43:679–98 Epub 2016 Oct 14.
[2] Andreoli L, Bertsias GK, Agamon-Levin N, Brown S, Cervera R, Costetad-Chalmaueu N, et al. EULAR recommendation 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. An Rheum Dis 2016;0:1–10.
[3] Wilson WA, Gharavi WE, Koike T, Lockshin MD, Branch DW, Piette JC, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999;42:1309–11.
[4] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.
[5] Chinhizola CB, de Jesus GR. Antiphospholipid antibodies and infertility. Lupus 2014;23:1232–8.

[6] Arachchillage DR, Machin SJ, Mackie IJ, Cohen H. Diagnosis and management of non-criteria obstetric antiphospholipid syndrome. Thromb Haemost 2015;113(January1):13–9.
[7] Buckingham KL, Chamley LW. A critical assessment of the role of antiphospholipid antibodies in infertility. J Reprod Immunol 2009;80 (June1-2)132–45, doi:http://dx.doi.org/10.1016/j.jri.2008.11.005 Epub 2009 Feb 25.
[8] Alijotas-Reig J, Ferrer-Oliveras R. The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): a preliminary first year report. Lupus 2012;21:766–8.
[9] Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
[10] Tan EM, Cohen AS, Fries JF, Masi AT, Mcshane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25(11):1271–7.
[11] Petri M, Orbai A-M, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64(8):2677–86.
[12] Mosca M, Tani C, Vagnani S, Carli L, Bombardieri S. The diagnosis and classification of undifferentiated connective tissue diseases. J Autoimmun 2014;48-49: 50-2.
[13] Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis 2016;2017(76):9–16.
[14] Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;35(6):630–40.
[15] Yetman DL. Antiphospholipid antibody panels andrecurrent pregnancy loss: prevalence of aCL compared with other antiphospholipid antibodies. Fertil Steril 1996;66(4):540–6.
[16] Duncan L. Epidemiology of the antiphospholipid syndrome. In: Cervera R, editor. Antiphospholipid syndrome in systemic autoimmune diseases. 2nd ed. Amsterdam: Elsevier; 2016. p. 17–30.
[17] Levine AB, Lockshin MD. Assisted reproductive technology in SLE and APS. Lupus 2014;23:1239–41.
[18] Pantham P, Abrahams VM, Chamley LW. The role of anti-phospoholipid antibodies in autoimmune reproductive failure. Reproduction 2016;151:R79–90.
[19] Beer AE, Kwak JY, Ruiz JE. Immunophenotypic profiles of peripheral blood lymphocytes in women with recurrent pregnancy losses and in infertile women with multiple failed in vitro fertilization cycles. Am J Reprod Immunol 1996;35:376–82127.
[20] Rieger L, Hofmeister V, Probe C, et al. Th1 and Th2-like cytokine production by first trimestre decidual large granular lymphocytes is influen-ced by HLA-G and HLA-E. Mol Hum Reprod 2002;8:255–6142.
[21] Morgan BP, Holmes CH. Immunology of reproduction: protecting the placenta. Curr Biol 2000;10:R381–3.
[22] Chighizola CB, de Jesus GR. Branch DW the hidden world of anti-phospholipid antibodies and female infertility: a literature appraisal. Autoimmun Rev 2016;15(June6):493–500.
[23] Girardi G. Role of tissue factor in the maternal immunological attack of the embryo in the antiphospholipid syndrome. Clin Rev Allergy Immunol 2010;39:160–5.
[24] Girardi G Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody induced fetal loss by inhibiting complement activtion. Nat Med 2004;10:1222–6.
[25] Yelnik CM, Laskin CA, Porter TF, Branch DW, Buyon JP, Guerra MM, et al. Lupus anticoagulant is the main predictor of adverse pregnancy outcomes in aPL-positive patients:validation of PROMISSE study results. Lupus Sci Med 2016;3 (January1)e000131, doi:http://dx.doi.org/10.1136/lupus-2015-000131 eCollection 2016.
[26] kkaya Reyhan Diz-Kucu. Lupus anticoagulant, thrombosis, and death. Blood 2015;125:3371–2.