Psychosocial burden in young patients with primary anti-phospholipid syndrome: an Italian nationwide survey (the AQUEOUS study)

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Abstract

Objective

The AQUEOUS (Anti-phospholipid syndrome: a QUEstionnaire for yOUng patientS) study aimed to assess how the diagnosis of primary anti-phospholipid syndrome (PAPS) affects the psychosocial status of young patients.

Methods

Subjects with PAPS aged 18–45 years were invited to compile an ad hoc designed questionnaire and the Short Form-12 to assess quality of life (QoL).

Results

Ninety-two patients (83.7% females) were recruited in 10 Italian centres. Vascular and obstetric manifestations were equally represented. Nearly half of the patients perceived the need for psychological support, 89.2% when considering women after pregnancy complications. Social activities and working efficiency were reduced in APS patients, also intimacy was threatened. In all cases, fatigue appeared to be the main determinant. PAPS affected family planning, due to fears of treatment side-effects, disease hereditariness, inability to care for the newborn child. Fertility appeared to be conserved: the median time to pregnancy was 2 months; assisted reproduction techniques were pursued by 5 women. Our survey documented significantly lower rates of hospitalisation and learning disabilities in 51 children born after APS diagnosis as compared to 48 children born before. PAPS patients displayed lower QoL in physical and, to a greater extent, mental scores compared to the general Italian population. Both components were significantly lower in women and in patients with fatigue.

Conclusion

The AQUEOUS study assessed for the first time the unmet needs of young PAPS patients, enabling the development of a future "youth-focused" strategy to reduce disease burden.

Key words

anti-phospholipid syndrome, young patients, psychosocial burden, unmet needs, survey

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Introduction

The diagnosis of anti-phospholipid syndrome (APS) can be formulated whenever an individual with a suggestive clinical history is found to be persistently positive for one or more tests for anti-phospholipid antibodies (aPL). When APS is diagnosed in subjects without any additional underlying systemic autoimmune conditions, it is referred to as primary APS (PAPS). The international community acknowledges three tests to detect circulating aPL: IgG and/or IgM against β2 glycoprotein I (anti-β2GPI) and cardiolipin (aCL) at medium-high titres plus the functional assay lupus anticoagulant (LA) (1). The pro-thrombotic potential of aPL reaches the greatest magnitude in the younger population, where the burden of traditional cardiovascular risk factors is lower: aPL were calculated to mediate 17.4% of cardiovascular events occurring in individuals before 50 years, increasing the thrombotic risk by 5.48-fold (2). Subjects with thrombotic APS receive life-long anticoagulation to prevent thrombotic recurrences (3). Furthermore, aPL provide the main acquired risk factors for obstetric complications: early and late pregnancy losses and premature birth due to eclampsia, severe pre-eclampsia, or placental insufficiency (4). Despite adequate treatment, 20% of pregnant women experience adverse obstetric outcome (5).

APS usually presents in early adulthood: in the largest series, the median age at disease onset was 31 years (6). Being diagnosed as APS carries several difficulties, which might threaten the well-being of the individual under many aspects: patients should accept a chronic disease, sometimes coping with post-thrombotic sequelae and/or non criteria manifestations, sometimes facing reiterated reproductive failure. Long-term anticoagulation strongly affects every-day routine, due to frequent INR monitoring and interference on activity of vitamin K antagonists (VKAs) by alcohol, temporary illness, exercise and smoking (7). The impact of a chronic diagnosis might be particularly burdensome when received in early adulthood, a critical time in which APS onset might affect education, work, social life, intimacy and family planning. A higher prevalence of depression and anxiety in young people with rheumatic diseases compared to adults has been described (8) but studies specifically addressing this topic in PAPS are lacking.

By means of an *ad hoc* questionnaire investigating several disease-specific aspects, the AQUEOUS (Anti-phospholipid syndrome: a QUEstionnaire for yOUng patientS) study assessed how the diagnosis of PAPS affects the psychosocial status of young patients, investigating their experiences, difficulties and needs. The AQUEOUS study was promoted by SIRyoung, a commission instituted by the Italian Society for Rheumatology (SIR) to promote research efforts and foster the collaboration with young patients' organisations.

Patients and methods

Patients

Subjects with a diagnosis of PAPS (thrombotic, obstetric or both) aged between 18 and 45 years were considered eligible for study inclusion. Patients were invited to participate to the survey that included i) an *ad hoc* questionnaire and ii) the Short Form (SF)-12 to assess quality of life (QoL). Clinical details of all participants were recorded: demographic data, clinical manifestations of APS, treatments and aPL tests, performed in local laboratories (1).

Questionnaire

A self-administered questionnaire was designed in female and male versions. The female version included 107 (7 open-ended and 100 multiple-choice) questions organised in 13 sections. The male version included 12 sections, for a total of 90 (7 open-ended and 83 multiple-choice) questions. The questionnaires had been revised for content/construct validity, feasibility and lay language by an independent group of APS patients.

All patients signed an informed consent. This study was conducted in compliance with the Declaration of Helsinki and was approved by the local ethics committees.

Effects of anticoagulant treatment

The impact of anticoagulant treatment was measured through a 12-item questionnaire, derived from the Anti-Clot Treatment Scale (ACTS). Patients were asked to rate their experiences of anticoagulant treatment during the past 4 weeks on a 5-point scale of intensity (9).

Quality of life

SF-12 is made up of eight subscales that measure physical and psychological aspects of life: role-physical function, physical functioning, bodily pain, role-emotional function, general health perception, vitality, social functioning, and mental health (10). The SF-12 allowed the assessment of the influence of disease on patients' physical condition, psychological and social well-being (11, 12). A score from 0 (worse) to 100 (best) was calculated for each dimension. Two subscales were computed as different weighted sums of dimension scores (mental [MCS] and a physical component summary [PCS] scores) to obtain a mean of 50 with a standard deviation (SD) of 10 in a healthy general population (9). PCS and MCS scores can be classified in 3 health categories: good health (scores above 50), bad health (between 30 and 50) and very bad health (below 30).

Statistical analysis

Continuous data were expressed as median (interquartile range [IQR]) while categorical data were presented as percentages. The association between categorical variables was assessed by chi-squared or Fisher's test, as appropriate. The correlation between continuous variables was tested by Spearman's test. Potential differences in continuous variables between two or more subgroups were investigated using Mann-Whitney or Kruskal-Wallis test, respectively. Some variables were further categorised as follows: age >30 years *versus* age <30 years, disease duration >5 years *versus* <5 years, academic degree or higher *versus* no academic degree. *p*-values lower than 0.05 were considered as statistically significant. Statistical analysis was performed using GraphPadPrism for Mac v. 6.0c (La Jolla, CA, USA).

Table I. Demographic, clinical and laboratory characteristics of recruited subjects.

	Women (n=77)	Men (n=15)	All (n=92)
Age (years)	38 (33-43)	42 (38-43.5)	39 (33-43)
BMI	23.4 (20.8-27.3)	25.2 (22.4-26.9)	23.4 (21.2-28.9)
Disease duration (years)	4 (1-11)	9 (6-11.75)	5 (1-11)
Diagnostic delay (months)	6 (3-8)	2 (0-5)	5 (3-8)
Thrombosis (patients)	38 (49.3%)	15 (100%)	53 (57.6%)
Single event	26/38 (68.4%)	10/15 (66.6%)	36/53 (67.9%)
Recurrent events	12/38 (31.6%)	5/15 (33.3%)	17(53 (32.1%)
Arterial (patients)	14/38 (36.8%)	2/15 (13.3%)	16/53 (30.2%)
Arterial (events)	15	2	17
AMI	2/15 (13.3%)	0/2 (0%)	2/17 (11.8%)
Stroke	10/15 (66.6%)	0/2 (0%)	10/17 (58.8%)
Others	3/15 (20%)	2/2 (100%)	5/17 (29.4%)
Venous (patients)	22/38 (56.9%)	13/15 (86.6%)	35/53 (66%)
Venous (events)	23	14	37
DVT	21/23 (91.3%)	13/14 (92.9%)	34/37 (91.9%)
PE	2/23 (8.3%)	1/14 (7.1%)	3/37 (8.1%)
Arterial + venous (patients)	1/38 (2.6%)	0/15 (0%)	1/53 (1.9%)
CAPS (patients)	1/38 (2.6%)	0/15 (0%)	1/53 (1.9%)
Organ damage	12/38 (31.6%)	6/15 (40%)	18/53 (34%)
Venous insufficiency	1/12 (8.3%)	3/6 (50%)	4/18 (22.2%)
Limb weakness	4/12 (33.3%)	1/6 (16.6%)	5/18 (27.7%)
Reduced sight/blindness	1/12 (8.3%)	1/6 (16.6%)	2/18 (11.1%)
Heart failure	2/12 (16.6%)	1/6 (16.6%)	3/18 (16.6%)
Renal Insufficiency	2/12 (16.6%)	–	2/18 (11.1%)
Others	2/12 (16.6%)	–	2/18 (11.1%)
Obstetric manifestations	53 (68.8%)		
Early pregnancy loss*	9 (16.9%)		
Late pregnancy loss	26 (49.1%)		
Premature birth	22 (41.5%)		
Preeclampsia	14 (26.4%)		
Laboratory features			
Positive LA	53/77 (68.8%)	14/15 (93.3%)	67/92 (72.8%)
Positive aCL IgG	47/77 (61%)	11/15 (73.3%)	58/92 (63%)
Positive aCL IgM	24/77 (31.2%)	4/15 (26.6%)	28/92 (30.4%)
Positive anti-β2GPI IgG	40/77 (51.2%)	13/15 (86.6%)	53/92 (57.6%)
Positive anti-β2GPI IgM	29/77 (37.7%)	4/15 (26.6%)	33/92 (35.9%)
Triple aPL positivity	36/77 (46.8%)	10/15 (66.6%)	46/92 (50%)

Continuous variables are expressed as median IQR; categorical variables are expressed as number (%). BMI: body mass index; AMI: acute myocardial infarction; DVT: deep venous thrombosis; PE: pulmonary embolism; CAPS: catastrophic anti-phospholipid syndrome; aCL: anti-cardiolipin antibodies; aPL: antiphospholipid antibodies; IQR: interquartile range; LA: lupus anticoagulant.

Results

Ninety-two patients fulfilling the inclusion criteria were included in the AQUEOUS study. Patients were predominantly female (83.7%), and were recruited in 10 Italian rheumatologic centres. The demographic details and clinical data of included patients are listed in Table I. Thrombosis and pregnancy complications were equally represented, being observed in 53 subjects; 16 women had experienced both thrombotic and obstetric manifestations. Autoimmune thyroiditis was the most common comorbidity (8.7%), followed by systemic arterial hypertension (4.3%). One patient was affected by a major depressive disorder on psychiatric treatment while a diagnosis of fibromyalgia had been formulated in 5 patients (3 males). However, approximately 33% of patients complained of symptoms suggestive of fibromyalgia (mainly fatigue and headaches), but rheumatologists investigated these manifestations only in one third of patients.

Towards APS diagnosis

Most patients (60.1%) received APS diagnosis after consulting one or two physicians, with a median diagnostic delay of about 6 months. Rheumatologists and immunologists formulated the majority of diagnoses (53.9%), followed by obstetricians (22.5%) and haematologists (12.3%).

Doctor-patient communication

Many respondents (75%) had been informed about the potential disease complications at diagnosis; rheumatologists regularly investigated pregnancy desire (81.8%). Physicians satisfactorily discussed the issues related to anticoagulation: less than 10% of the women (n=7) did not receive information about the management of anticoagulation during pregnancy; 28 patients (30.4%) were not aware of the availability of direct oral anticoagulants (DOACs). Rheumatologists mostly gave information about this novel class of drugs.

Psychological impact

Sixty-six subjects (71.7%) felt that APS might have impacted their psychological well-being (infrequently [75.8%], often [12.1%] or always [10.6%]). Most respondents stated that a diagnosis of APS implied – often (46.7%) or always (6.6%) – barely manageable difficulties. However, subjects with APS were generally satisfied with their lives, felt to hold the command of their existence (75%), believed to have reached important targets (64.1%) and were optimistic about their future (66.3%). The rate of life disappointment was significantly higher among patients with organ damage (52.6%, p=0.0012, χ^2=15.58), with most patients not expecting to achieve important goals (68.4%, p=0.0049, χ^2=12.86) and being seldom optimistic about their future (52.6%, p=0.0071, χ^2=12.07). Patients preferred not to allude to their condition when dealing with strangers (68.5%) and during job interviews (53.3%), much less frequently with friends (15.2%), colleagues (13%) and new partners (9.8%). The reasons preventing open communication were: fearing to inspire compassion (34.8%) and avoiding taking advantage of the disease (19.6%). Approximately half of patients (45.6%) perceived the need of psychological support but only 27 subjects (64%) had access to professional care, mainly due to lack of spare time. The rate of patients warranting psychological support increased up to 89.2% when considering women after pregnancy complications. Only 15 women (26.8%) had access to professional care; frequently, the main sources of support were the partners and the parents (48.2%). Approximately half of the women felt that the sanitary personnel were not adequately prepared for this task.

Age, disease duration and the education level did not affect the psychological burden conveyed by APS diagnosis.

Education, work and finances

Most patients (60.9%) completed secondary studies, with 24 (26%) even obtaining a higher-level education. Ten individuals received APS diagnosis before completing education; only in two cases (20%) the disease was found to cause delay in educational career. Patients believed that informing teachers of their condition would have been beneficial; no patient felt discriminated in educational environments.

Most patients (93.5%) have had a job. Of these 86 individuals, only 37 subjects (43%) denied any impact of the diagnosis on their working ability; the remaining patients declared that APS affected their working ability sometimes (42%), often (9.4%) and always (3.6%). Most patients (55.8%) did not inform their employer of their condition, and only 26 subjects (30%) have always spoken openly of their disease before starting a job. According to many patients (72%), APS was not a cause to quit a job; having APS forced 21 subjects to resign once (7%), sometimes (12.8%) or often (4.7%).

Most patients (72%) were able to provide for themselves and their families financially, thanks to their salaries or the spouse's income. Social welfare and families were the most common sources of financial support.

Social life

Most respondents (52.2%) stated that APS diagnosis never affected social life. The remaining 44 patients declared that carrying APS exerted a negative impact on sociality sometimes (40.1%), often (4.4%) and always (3.3%). Fatigue provided the main reason for an unfulfilling social life, being reported by all the 44 patients with a poor sociality, without significant differences between genders. In case of necessity, respondents sought the assistance of partners (51%) and parents (44%); social services were seldom an option (2.2%).

The burden of anticoagulant treatment

Of the 41 patients receiving anticoagulant treatment, 34 were on VKAs and 7 on DOACs (rivaroxaban [2], apixaban [2], dabigatran [1], two subjects were switched from apixaban to rivaroxaban); 5 additional patients refused the switch to DOACs. The prescription of DOACs among APS patients was discouraged by rheumatologists and haematologists. As detailed in Table II, the majority of patients reported that anticoagulation impacted every-day life never or rarely, even though 58.5% acknowledged the difficulties in following treatment. Age did not affect the impact of anticoagulation on daily life, except for the possibility of bruising which particularly bothered younger patients (p=0.0004, χ^2=20.5). Patients with higher education level rated more positively the impact of anticoagulant treatment on daily life (p=0.0121, χ^2= 12.83), although were also more limited in vigorous physical activities by the risk of bleeding (p=0.038, χ^2=10.15). Subjects with longer disease duration felt more the inconvenience of practical aspects due to treatment such as arranging medical appointments or blood tests (p=0.009, χ^2=13.3). The impact of anticoagulation treatment did not differ upon organ damage.

A concurrent anticoagulant treatment did not affect family planning in 22 out of 37 anticoagulated women (59.5%). However, 6 women (16.2%) decided not to have children because of anticoagulation, while other 9 women (24.3%) underwent a lower number of pregnancies than previously planned. Thirty women (81%) were briefed on the management of anticoagulation during gestation; these insights affected the decision to pursue a pregnancy in 15 cases (50%), mostly positively (66.6%).

Intimacy and contraception

Relationships were rarely terminated because of APS diagnosis (3.6%). The disease was found to interfere with sexual life by a minority of patients (38.4%), mostly due to fatigue, even though this

Table II. Daily impact of anticoagulation therapy during the previous 4 weeks.

	Not at all	A little	Moderately	Quite a bit	Extremely
How much does the possibility of bleeding as a result of anti-clot treatment limit you from taking part in vigorous physical activities? (*e.g.* exercise, sports, dancing, etc.).	19 (46.3%)	7 (17.1%)	12 (29.3%)	2 (4.9%)	1 (2.4%)
How much does the possibility of bleeding as a result of anti-clot treatment limit you from taking part in your usual activities? (*e.g.* work, shopping, housework, etc.).	20 (48.8%)	9 (22%)	9 (22%)	3 (7.2%)	0 (0%)
How bothered are you by the possibility of bruising as a result of anti-clot treatment?	12 (29.3%)	11 (26.8%)	7 (17.1%)	6 (14.6%)	5 (12.2%)
How bothered are you by having to avoid other medicines (*e.g.* aspirin) as a result of anti-clot treatment?	10 (24.4%)	8 (19.5%)	13 (31.7%)	7 (17.1%)	3 (7.3%)
How much does anti-clot treatment limit your diet? (*e.g.* food or drink, including alcohol).	14 (34.1%)	7 (17.1%)	12 (29.3%)	6 (14.6%)	2 (4.9%)
How much of a hassle (inconvenience) are the daily aspects of anti-clot treatment? (*e.g.* remembering to take your medicine at a certain time, taking the correct dose of your medicine, following a diet, limiting alcohol, etc.).	12 (29.3%)	17 (41.5%)	7 (17.1%)	1 (2.4%)	4 (9.7%)
How much of a hassle (inconvenience) are the occasional aspects of anti-clot treatment? (*e.g.* the need for blood tests, going to or contacting the clinic/doctor, making arrangements for treatment while travelling, etc.).	8 (19.5%)	19 (46.3%)	10 (24.4%)	2 (4.9%)	2 (4.9%)
How difficult is it to follow your anti-clot treatment?	5 (12.2%)	12 (29.3%)	11 (26.8%)	9 (22%)	4 (9.7%)
Overall, how much of a negative impact has your anti-clot treatment had on your life?	7 (17.1%)	14 (34.1%)	13 (31.7%)	5 (12.2%)	2 (4.9%)
How confident are you that your anti-clot treatment will protect your health? (*e.g.* prevent blood clots, stroke, heart attack, DVT, embolism)	3 (7.2%)	14 (34.1%)	10 (24.4%)	9 (22%)	5 (12.2%)
Overall, how much of a positive impact has your anti-clot treatment had on your life?	1 (4.9%)	2 (4.9%)	10 (24.4%)	18 (43.9%)	10 (24.4%)

impact is infrequent in 81.3% of cases. Physicians were reluctant to discuss issues related to contraception: most women (n=48, 62.3%) did not receive any insights into fertility control. Gynaecologists emerged as the professional figures most commonly investigating these aspects (50.7%), followed by rheumatologists (31.2%). Nevertheless, the knowledge on the available contraception methods was satisfactory, and only 15 women never employed any birth control measure. Estro-progestinic pill was the most used method before the diagnosis; afterwards, no woman continued the pill and male condom was the method of choice in 56.4% of cases; intrauterine devices were utilised in 8 women.

Fertility and assisted reproduction techniques

The median number of conceptions per patient was 2 [2-2]; data on 116 conceptions could be retrieved from the questionnaires. The median time to pregnancy was 2 months [1-4]. In five cases, the time to conception was greater than 24 months.

ARTs were pursued by 5 women (6.5%), due to female and idiopathic infertility (40%), and both partners (20%) infertility, for overall 15 procedures: 4 intra-uterine insemination (fertilisation rate: 50%), 5 *in vitro* fertilisation and embryo transfer (fertilisation rate: 100%) and 6 intra-cytoplasmic sperm injection (fertilisation rate: 50%). Of these procedures, two (13.3%) culminated in a live birth; no maternal thrombotic events occurred.

Family planning

Most patients lived with their partners and children (n=56, 60.9%); 17 subjects shared home with the partner (18.5%), 10 lived on their own (10.9%) and 7 individuals were at their parents' house (7.6%). In 44.6% of cases, APS exerted a negative impact on family planning, a figure that was significantly higher in females than in man (χ^2=10.051; p=0.0015). Such deleterious effect was mainly due to APS obstetric complications (42%), the fears of not to properly care for a neonate (33.3%), to harm the baby due to APS or medications (22.2%) or to transmit the syndrome (10.3%). The rate of pregnancy voluntary termination was similar before and after APS diagnosis (8 and 6, respectively). Pregnancy was terminated because of disease implications in 3 cases, due to high obstetric risk (75%) and drug teratogenicity (25%).

Children and their health

Sixty-one patients (66.3%, 55 women and 9 men) had 99 children, with a median number of 2 children per subject. Three children had been adopted. There was no difference in the numbers of children born before *versus* after APS diagnosis. Features of neonates at birth, and details on psychological development and comorbidities are presented in Table III.

Quality of life

Data on QoL were available for 86 patients (Fig. 1). According to official

Table III. Characteristics at birth, causes of hospitalisation, neuropsychiatric development of children born to parents with APS.

	Before diagnosis (n=48)		*p*-values*	After diagnosis (n=51)		*p*-values*	*p*-values**
	Fathers	Mothers		Fathers	Mothers		
n	10	38	NA	10	41	NA	NA
Gender (M/F)	3 (30%)/7 (70%)	15 (39.5%)/23 (60.5%)	NA	4 (40%)/6 (60%)	22 (53.7%)/19 (53.7%%)	NA	NA
Gestational week	38 (38-38.5)	36 (33-38)	0.0251	38 (37-39.75)	37 (36-38)	NS	NS
Weight (grams)	3350 (3200-3400)	2480 (1450-3305)	0.0452	3315 (3090-3640)	2990 (2615-3292.5)	0.06	NS
Hospitalisation in the first 12 months	–	8 (21% Prematurity (6), bronchiolitis (1), inguinal hernia (1)	NS	1 (10%) Respiratory dystress	1 (2.4%) Prematurity	NS	0.0203
Learning/ neuropsychiatric disorder	–	5 (13.2%) Dyslexia (2), dysorthography (1), psychomotor delay (2)	NS	–	–	NA	0.0517
Diagnosis of any disease	1 (10%) Asthma	2 (5.3%) Asthma, thyroiditis	NS	–	5 (12.2%) Phenylketonuria, atopic dermatitis (2), urticaria, vesicoureteral reflux	NS	NS

Continuous variables are expressed as median [IQR]; categorical variables are expressed as number (%).
* Statistical analysis was performed comparing children born to APS fathers to children born to APS mothers.
** Statistical analysis was performed comparing children born before APS diagnosis to children born after APS diagnosis.
M: males; F: females; NA: not available; NS: not significant.

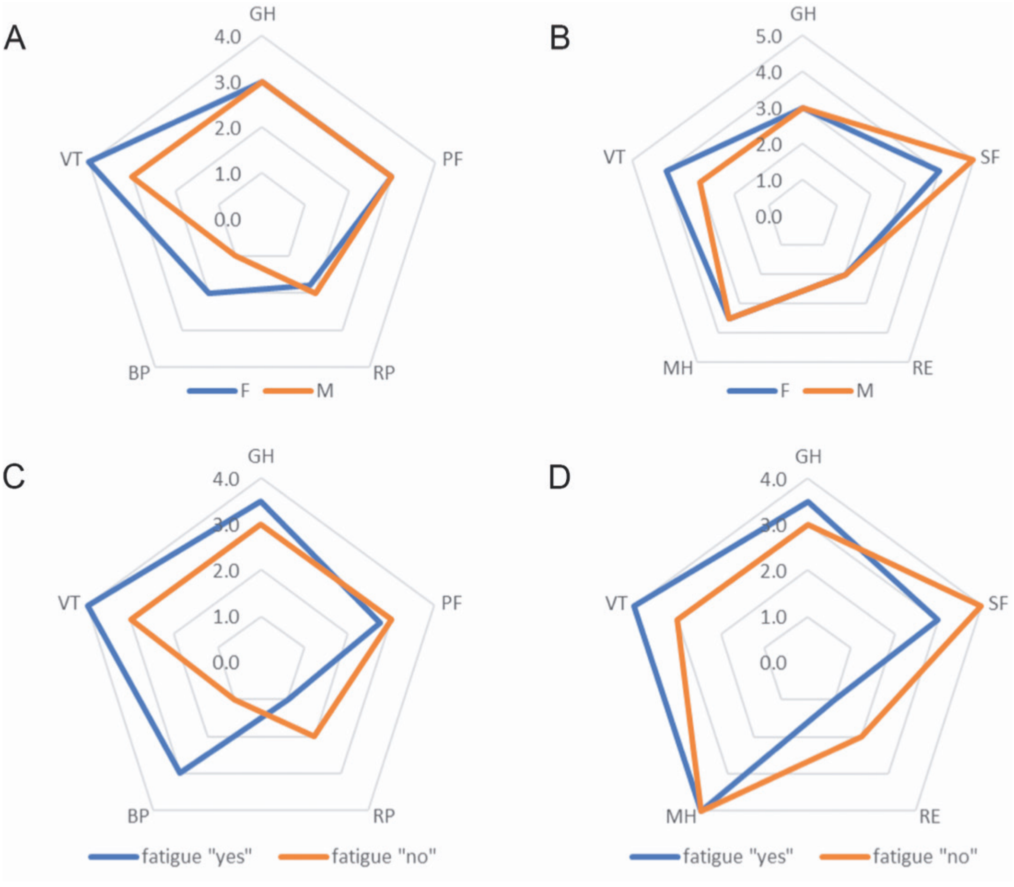

Fig. 1. Graphic comparisons of SF-12 dimension scores according to gender and fatigue.
SF-12 is a 12-item general health questionnaire that yields an 8-scale profile of health: physical function (PF), social function (SF), role-emotional (RE), role-physical (RP), bodily pain (BP), general health (GH), mental health (MH), and vitality (VT). These can be combined into two component summary measures: physical (PCS) and mental (MCS). GH and VT contribute to both components; PF, RP and BP compose PCS, whereas RE, MH and SF constitute MCS.
A: PCS in women and men (median values 47.4 [IQR 38.5–55.3] and 53.8 [IQR 50.1–55.8], respectively)
B: MCS in women and men (median values 44.0 [IQR 34.5–52.9] and 54.9 [IQR 35.6–57.3], respectively)
C: PCS in patients with and without fatigue (median values 52.4 [IQR 40.7–55.3] and 54.7 [IQR 49.4–55.9], respectively)
D: MCS in patients with and without fatigue (median values 44.82 [IQR 36.2–52.8] and 52.2 [IQR 41.6–55.9], respectively)

national statistics (https://www.istat.it/it/archivio/207259), PAPS patients presented lower mean PCS and MCS scores compared to general Italian population (PCS 46.8 *vs.* 51.2, MCS 44.0 *vs.* 49.2). 44.2% of patients had to limit their daily activities due to physical impairment. PCS and MCS were significantly lower in women than in men (p=0.0505, U=337 and p=0.048, U=335.5) and in patients with fatigue *versus* those not reporting fatigue (p<0.0001, U=418.0 and p=0.0003, U=511, respectively). Women with previous pregnancy loss presented lower MCS (p=0.0227, U=364.5) but conserved PCS. No significant differences emerged when PCS/MCS scores were compared among patients grouped upon diagnosis, thrombosis, anticoagulation treatment, organ damage, premature birth, number of positive aPL tests and fibromyalgia. PCS and MCS were found not to correlate with age at diagnosis, age at disease onset, and diagnostic delay.

Discussion

The nationwide, observational, cross-sectional AQUEOUS study explored for the first time the multi-faceted impact of the diagnosis of PAPS, a potentially devastating disease featuring increased morbidity and mortality, when received between 18 and 45 years of age. These are the most productive years, when the individual pursues education and training, starts work commitment, engages in mature relationships, and assumes greater responsibilities. According to our data, social activities and working efficiency were restricted in APS patients, and even intimacy was threatened. In all cases, fatigue appeared to be the main determinant, being reported by approximately half of the patients. Fatigue was identified as a still neglected clinical manifestation of APS, providing one of the main findings emerged in this study. Surely, such an unexpected high frequency of fatigue should be further investigated using dedicated tools such as the validated questionnaire FACIT-Fatigue. PAPS also affected family planning, especially when the diagnosis was received by the female partner, due to fears of treatment side effects, disease hereditariness, and inability to care for the newborn. Another source of great concern for PAPS patients related to the potential impact of the disease and treatments on health status of babies. Our survey documented a lower rate of hospitalisation and learning disabilities in babies born after APS diagnosis compared to those born before. These findings are highly relevant given the paucity of previous data: an association between maternal aPL positivity and learning disabilities in the offspring was reported in some studies (13-15). Importantly, the questionnaire investigated additional aspects potentially affecting family planning, such as fertility. Several rheumatologic conditions impair the ability to conceive, manifesting with prolonged time to pregnancy and higher requirement of ARTs (16). Available data on fertility in APS women come from two reports suggesting a potentially reduced ovarian reserve (17, 18). This is the first study to assess time to conception and ART requirement in PAPS, evincing a conserved fertility: the median time to conception was 2 months and the need of ARTs not frequent. The procedures were not burdened by significant adverse event, consistently with literature: none of the 3 available studies reported a significant raise in the thrombotic hazard (19-21).

Our survey did not highlight any detrimental effect of PAPS diagnosis in domains as education and finance; even the relationships with the partner and other relatives were preserved, being the family the main psychological and financial source of support. To note, negative forms of spousal supports appeared to be significantly associated with psychological distress (22). Furthermore, the AQUEOUS questionnaire gathered data on the different shades of social support – emotional and informational – that PAPS patients experience in family life and in outer environments such as medical, educational and working settings. Most importantly, this survey emphasised that patients with PAPS warranted a tighter emotional support, especially when dealing with pregnancy complications. This should not be surprising: obstetric adverse outcomes are a recognised cause of anxiety (23-25). It is pivotal to provide all relevant information about potential outcome and treatment option, as already outlined by other authors (26). Nevertheless, this seemed not to be enough: patients required a professional support; those who sought help from a psychologist admitted a great benefit. Secondly, informational support from APS-devoted rheumatologists was often adequate. Importantly, time to diagnosis was preserved, and patients were diagnosed after consulting one or two physicians. This is relevant, as delayed diagnosis was shown to affect patients' health and to correlate with organ damage (27, 28). In our cohort, patients were well informed on the potential clinical manifestations of the syndrome and issues related to anticoagulation. Many respondents were aware of the availability of DOACs, but the use of novel anti-coagulants was low (7.6%), in agreement with updated recommendations (3). Criticisms still related to contraception, despite the efforts by SIR to distribute a dedicated leaflet (https://www.reumatologia.it/medicina-di-genere). Unfortunately, approximately half of rheumatologists were reluctant to address this issue, even though favouring an open discussion is known to relieve anxiety and discourage self-exclusion (17). Rheumatologists should also be aware that fibromyalgia is a strong determinant of patients' health even in PAPS. In our cohort, a formal diagnosis of fibromyalgia was pursued rarely, but the prevalence could have been underestimated as more than one third of patients reported suggestive symptoms. According to previous data, one fifth of PAPS patients have fibromyalgia, displaying worse QoL and higher incidence of depression compared to controls, despite preserving the social interaction (29). Notably, given the very low prevalence of major mood disorder in the AQUEOUS cohort, it can be assumed that our findings are not biased by concomitant psychiatric comorbidity. Deeper insights into these aspects of the disease should be promoted among rheumatologists, as the adequate knowledge of practitioners on disease-specific items not only impacts the diagnostic and therapeutic approach (27, 30), but also reduces the process of invalidation – the rejection of the condition – by family and friends, and associates with better psychological adjustment to chronic illness (31). The relevance of informational support applies even to non-medical settings: many patients acknowledged that they would have benefitted, during educational years, of awareness and understanding from teachers. However, most patients did not feel hampered to talk about their disease, especially with strangers and at work: given the hidden nature of their disability, they expect lack of understanding, and try to avoid commiseration.

As a whole, the support offered to young Italian patients with PAPS was acceptable, differently from what emerged in in a recent UK survey: PAPS patients declared to receive insufficient support (31).

In agreement with available literature, we evinced an impaired QoL among PAPS patients (27, 32-33). In our cohort, QoL resulted reduced in both mental and physical domains (33), with a greater impairment in MCS. This finding already emerged in reports focusing on PAPS (27) or other chronic diseases (35, 36). QoL was particularly impaired among females (34) and patients with fatigue, while we could not evince any difference in terms of QoL between patients stratified upon a formal diagnosis of fibromyalgia, further suggesting that this condition is underdiagnosed among PAPS patients. We did not observe a lower QoL in patients with thrombosis, in agreement with a single report (32). All remaining studies described a worse QoL in subjects with a previous vascular event, especially if arterial (33, 34). In our cohort, anticoagulated patients had a similar QoL to those not receiving VKAs, and anticoagulation treatment was well tolerated by patients. This could be considered as a surprising finding, since anticoagulation has been reported to exert a detrimental effect on QoL, irrespectively of the underlying diagnosis (35, 37). However, this deleterious effect tends to minimise over time, thanks to a physiological process of psychological adjustment (36, 38). At a deeper analysis, differences in the impact of anticoagulation emerged: educated individuals appreciated to a higher extent the protection conferred by treatment; younger subjects were more prone to worry about the aesthetic consequences of anticoagulation while patients with longer disease duration were more disturbed by the practical implications of anticoagulant therapy.

In our cohort, organ damage was evident in 18 patients (19.6%), who endured a heavier psychological impact of APS diagnosis. Indeed, these subjects reported a higher rate of disappointment with their existence, pessimistic feelings about future and inability of achieve life goals, even though no correlation with QoL could be observed. This finding is not concordant with previous studies, which identified organ damage as one of the main determinants of QoL. In PAPS, organ damage occurs early in disease course (26); across different cohorts, its prevalence ranges between 20 and 38.4% (26, 39-42). An accurate tool to estimate organ damage is lacking in PAPS. Indeed, the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI) was proven to underestimate aPL-related organ damage (39, 43). A novel physician-reported chronic damage index, named DIAPS, was developed to better capture the severity of thrombotic–related manifestations of the syndrome but to date has been applied exclusively in the Latin-American population (44). Given the lack of validated tools, we did not apply any index to evaluate aPL-related organ damage. Another limitation of this study includes the use of SF-12, a generic tool to evaluate QoL. Unfortunately, no disease-specific questionnaire is yet available for APS, and SF-12 was shown to be valid and reproducible.

Overall, the AQUEOUS study led to a better understanding of the unmet needs of young patients with PAPS; hopefully this survey will allow clinicians to develop a "youth-focused" holistic approach to reduce disease burden, as already pursued at European level with PARE (45).

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