Joint project between SSC Women’s Health Issues in Thrombosis and Hemostasis) and SSC Lupus anticoagulant/antiphospholipid antibodies

Person responsible (Chair / Investigators): Maha Othman (SSC Women’s Health Issues in Thrombosis and Hemostasis) and Katrien Devreese (SSC Lupus anticoagulant/antiphospholipid antibodies)

Principal investigators: Cristina Belizna, Patricia Casais, Johanna Gebhart, Sam Schulman.

NAME OF PROJECT:

Current treatments practice in women with obstetric APS and women with obstetrical morbidity and “non-criteria” APS and adverse obstetrical outcomes: CORA international registry

Description

The application is included in the broad remit of ISTH/SSC supported research and is a proposal for an international register with respect to current treatment practices in obstetrical antiphospholipid syndrome (APS), refractory obstetrical APS (defined as unsuccessful pregnancies despite standard treatment with low doses aspirin (LDA) and low molecular weight heparins (LMWH), and in women with prior adverse pregnancy outcomes who do not meet Sydney clinical or laboratory APS criteria.

APS is characterized by the confirmed presence of antiphospholipid antibodies (aPL) (lupus anticoagulant (LA), anticardiolipin antibodies (aCL), anti-beta2 glycoprotein I antibodies (anti-β2GPI) and clinical manifestations such as thrombosis, and/or pregnancy morbidity (1). APS may occur in the context of a background autoimmune disease, mainly systemic lupus erythematosus (SLE) (secondary APS), or isolated defined as primary APS.

Nowadays, 78-80% of pregnancies in obstetrical APS are successful with conventional treatment with LDA and LMWH (2, 3). Lessons from two large international studies with respect to the morbidity and mortality in APS (2) and on the analyses of the clinical features, laboratory data and fetal-maternal outcomes (3) underlined the need of a better knowledge and understanding of treatment strategies in refractory cases. Patients with APS may develop significant morbidity and mortality despite current treatment. Therefore, it is imperative to identify prognostic factors and therapeutic measures to prevent these complications.

Several laboratory findings have been associated with poor pregnancy outcomes: triple aPL positivity, double aPL positivity, LA positivity, false positive IgM for CMV, anti-β2GPI domain 1
antibodies and hypocomplementemia (4-6). Triple positivity is confirmed as the most significant risk factor (4, 7). Endothelial dysfunction with inflammatory and procoagulant phenotypes is associated with clinical manifestations both in primary and secondary APS (8).

EULAR recent recommendations for the management of APS raised the issues of several grey areas for the treatment approaches in APS (9). Currently, in women with prior obstetric APS combination treatment with LDA and prophylactic dosage LMWH is recommended during pregnancy. However, in patients with recurrent pregnancy complications, strategies such as increasing the dose of LMWH to therapeutic dose, addition of hydroxychloroquine (HCQ) or of low-dose prednisolone in the first trimester are employed, but high-quality evidence is limited. Moreover, the role of immunoglobulins also remains to be evaluated. The efficacy of various dosages of aspirin (i.e.: 75, 100, 150, (160) mg daily) is also a topic of interest.

Another area of uncertainty is the management of obstetrical APS women considered with low-risk aPL profile (10). The management of the patients presenting with isolated aCL or anti-β2GPI antibodies at low-medium titers, particularly if transiently positive, is still a matter of debate. Several studies have showed that, in some situations, patients may show clinical features of APS but associated with temporary positive or persistently negative titers of criteria aPL (11-28). Nevertheless, the negativity for classic aPL criteria does not exclude that other antibodies may be present or involved in the onset of thrombosis. The most studied antibodies are those against phosphatidylethanolamine, phosphatidic acid, phosphatidylserine, phosphatidylinositol, vimentin/cardiolipin complex, and annexin A5, anti domain 1, 4, 5 of β2GP1 (11-28). The diagnosis of seronegative APS is usually made by exclusion, but its recognition is important in order to adopt the most appropriate therapeutic strategy to increase the rate of successful pregnancies.

Aim of the study

The main objective of this international registry is to evaluate management and outcomes of obstetric APS and to determine physicians practice patterns regarding women with adverse pregnancy outcomes who do not meet Sydney clinical or laboratory APS criteria.

Secondary objectives are:

- to evaluate the occurrence of adverse effects of therapy
- to identify clinical and laboratory parameters associated with adverse pregnancy outcomes.
SSC Subcommittee Project/Collaborative Project

-compare outcomes in patients with non-criteria titers and/or non-criteria aPL

We aim to collect data from clinicians who are in charge of patients with obstetrical APS worldwide. The participating clinicians will be invited to enter data obtained from the medical records of the patients using the ISTH REDCap data collection system.

We will submit the project to be an ISTH SSC endorsed international registry so that interested clinicians across the world can contribute to data collection on treatment practices and therefore allow a better understanding of this entity. There are no randomized controlled trials or adequately powered prospective studies to determine the optimal anticoagulation management for these patients except studies about the role of HCQ (29, 30). These data will complement the information, which will be obtained from randomized controlled trials on HCQ and allow cumulating knowledge and experience across the world.

Design and methodology (Data expected to collect, sample size and statistical analysis):

We propose an international, multicenter, 3 year-register study. The study population will include patients with all types of obstetrical APS (incident and prevalent cases) and women with prior adverse pregnancy outcomes who do not fulfill Sydney clinical or laboratory criteria of APS. Table 1 shows “non-criteria” definitions of clinical manifestations and laboratory parameters.

Two cohorts will be followed:

1. women with obstetric APS defined according to standard Sydney criteria with successful as well as adverse obstetrical outcomes despite standard treatment.
2. women with obstetrical morbidity and aPL but not fulfilling clinical and/or laboratory criteria for obstetric APS (Table 1).

For both cohorts, the registry will admit retrospective cases defined as pregnancies occurred up to five years before reporting and prospective cases defined as women who are pregnant at the moment of enrollment in the registry.

Participation of specialists from multidisciplinary teams (obstetricians, gynecologists, vascular medicine, clinical hematologists, biologists, immunologists, internists) from international centers from several countries is welcome and expected. The investigators will check for eligibility according to the inclusion criteria and give information about the study (orally and information letter) and eventually will collect blood samples in some centers where available. Upon agreement, patients will sign an informed consent. After informing the patient and obtaining her signature on the informed consent form, the investigator will complete a
computerized inclusion form, available 24/7 over the Internet via the e-CRF (secure access previously granted to each pre-declared investigating center).

Data will be collected with respect to aPL positivity and titers, patients age, clinical obstetrical and/or thrombotic manifestations, associated autoimmune diseases, type of treatment, response to treatment, number of recurrent episodes of pregnancy morbidity, number of unscheduled hospitalizations, number of side effects at inclusion, and during follow-up.

*Laboratory tests*

All lab tests will be performed locally. As aPL are dependent on assay used, we will include in the registry: the titers of the aPL and units, the method of measurement, the local reference values, the method of reference values calculation, the interpretation by the local investigator as low-medium-high aPL titers.

This will include both classical aPL and non-conventional aPL (defined in Table 1).

We are aware that these antibodies will rarely be available as many centers do not perform them; but when available, these antibodies will be entered in the database.

For LAC we will include the data on dRVVT and aPTT (ratios of screen, mix and confirm; with local cut-off values), to see whether the dRVVT and/or aPTT system is positive; as aPTT positivity can be false positive if CRP is elevated. Also, use of anticoagulants during LAC measurement will be mentioned (in order to interpret LAC correctly, since false positive and false negative may occur with VKA, or false positive with DOAC). However, this situation is expected to be very rare as pregnant patients should neither be on VKA or on DOACs.

*Statistical analysis*

The statistical analysis will be realized by means of the software Excel version 2010 of Microsoft (Redmond Washington the United States) and of the software IBM SPSS statistics version 23 (Chicago Illinois the United States). For the comparative analysis of the groups, Student’s t-test will be used for the quantitative variables, having verified beforehand the equality of the variances for the studied parameters, and the Chi² test or Fisher’s exact test (in case of fewer than 30 cases in any cell) for the nominal qualitative variables. For variables with a skewed distribution, Mann-Whitney test will be used. Collected variables shall be described globally and per group.
The subgroups analysis will be performed in:

1. Women with LA
2. Women with triple aPL (aCL and anti-beta2GPI same isotype)
3. Women with a concomitant autoimmune disorder.
4. Women with low aPL risk profile (single positive aPL)
5. Women with double positive aPL (aCL and anti-beta2GPI of same isotype (LAC negative)
6. Women with “seronegative” APS but with clinical APS Sydney criteria
7. Women with classical APS aPL antibodies but not meeting clinical APS Sydney criteria.
8. Women with non-criteria aPL types and or titers

In addition, multiple regression models will be used to determine odds ratio and 95% CI (prognostic factors). Linear regression models will be used to determine titers associated with adverse outcomes.

An interim analysis will be performed on an annual basis and data will be presented during the SSC subcommittees meetings.

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):

The inclusion criteria will be

- Patients with obstetrical APS according to Sydney criteria
- Patients with clinical Sydney criteria for obstetrical APS and “non-criteria” aPL titers
- Patients with confirmed positive criteria aPL, but not meeting clinical criteria for APS.
- Age > 18 years
- All obstetric events happened within the last 5 years
- Patients have signed the informed consent form.

Criteria of exclusion
SSC Subcommittee Project/Collaborative Project

- Adverse pregnancy outcomes due to obstetrical, gynecological, genetic, endocrine or infectious cause.
- Patients with aPL and no prior adverse pregnancy outcome.
- Women with early abortions in the context of assisted reproduction.
- Women who were never tested for aPL

Considering the number of centers having agreed to participate to date and the period of inclusion, approximately 4-5 patients per month and per center are expected. The expected total number to be included is 2000 patients.

**Expected timeline: Project stage/set up**

Finalization of the project: December 2020

Launch of the project: March 2021 Duration: 36 months

SSC Subcommittee Project/Collaborative Project

Finalization/statistical analysis: March 2024

Reporting: research results and project milestones will be reported at the Subcommittee’s annual SSC meeting and annual progress report made to the Executive Committee starting July 2021

**Expected outcomes**

The results will be submitted as a Society publication, both SSC Communication and original research on behalf of the SSC. Depending on the outcome, also a Recommendation of the SSC could be proposed.

All publications resulting from the research will be published in an ISTH journal.

**Description of project set/up and management, needed infrastructure and resources:**

The project will be led by the SSC Women’s Health Issues in Thrombosis and Hemostasis and SSC Lupus Anticoagulant/antiphospholipid antibodies. A computerized register with an inclusion form, on Redcap available 24/7 over the Internet via the e-CRF (secure access previously granted to each pre-declared investigating center) will be created. Data will be recorded by each investigator.
The knowledge translation of the project results will be through communications at congresses and international conferences and via different publications.
Table 1: Non-criteria clinical and laboratory definitions

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Laboratory parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with confirmed positive criteria</strong>&lt;br&gt;aPL, but &lt;3 pregnancy losses before 10\textsuperscript{th} week of gestation</td>
<td>Non-criteria aPL are antibodies against: phosphatidylethanolamine, phosphatidic acid, phosphatidylserine, phosphatidylinositol, antiphosphatidylserin/prothrombin (aPS/PT), vimentin/cardiolipin complex, and/or annexin A5, anti domain 1, 4, 5 of B2GP1.</td>
</tr>
<tr>
<td><strong>Pre-eclampsia after sem 34</strong></td>
<td>Non-criteria aPL titers will be defined such as 95\textsuperscript{th} percentile; and/or aCL and/or antiB2 GP1 titers less than 40 ui.</td>
</tr>
</tbody>
</table>


