Pregnancy success rate and response to heparins and/or aspirin differ in women with antiphospholipid antibodies according to their Global AntiphosPholipid Syndrome Score

Pregnancy success rate and response to heparins and/or aspirin differ in women with antiphospholipid antibodies according to theirGlobal AntiphosPholipid Syndrome Score

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Abstract

Background:

Current standard of care (SoC) in pregnancy for women with antiphospholipid antibodies (aPL) includes treatment with low dose aspirin (75–100mg/day), often associated with low molecular heparin or unfractionated heparin according to their previous clinical history. However, despite the current SoC, up to 30% of women continue to have pregnancy complications. The Global AntiphosPholipid Syndrome Score (GAPSS) is a risk stratification score developed in view of risk subdividing aPL positive patients according to their cardiovascular profile. GAPSS values range from 0 – 12. Our aim was to investigate the individual clinical response to SoC in women with aPL after stratifying them according to their GAPSS value. We hypothesize, that those women with higher GAPSSvalue are lesslikely to respond to SoC.

Methods: One-hundred-fourty-threewomen with aPL ever pregnant treated with SoC therapy were included. Data on cardiovascular risk factors and aPL positivity were retrospectively collected. The individual GAPSS was calculated for each patient by calculating the sum of each risk factor score, as follows: 3 for hyperlipidaemia, 1 for arterial hypertension, 5 for anticardiolipin IgG/IgM, 4 for anti-β2glycoprotein I IgG/IgM, 3 for anti-phosphatidylserine/prothrombin antibodies IgG/IgM and 4for lupus anticoagulant.The patients GAPSS was then grouped according to the patients' GAPSS into low risk (<6), medium risk (6-11) and high risk (≥12).

Results:

The analysis included 143 patients (mean age 30.8±6.4) with SLE (122;85.3%) and/or aPL positivity, for a total of 352 pregnancies.

Overall, we observed a live birth rate of 70.5%, with a total of live birth of 248 out of the 352 pregnancies. Forty-five patients (31%) experienced at least one event of PM, defined as early or late.

Patients were stratified according to GAPSS values, in order to identify a low risk group (GAPSS <6, n=72), a medium risk group (GAPSS 6-11, n=66) and a high risk group (GAPSS≥12, n=5).

When considering patients who ever experienced PM while treated with SoC, all patients in the high risk group experienced PM, while patients in the medium group had a significant higher rate of PM when compared to the low risk group [29 (43.9%) patients V.s. 11 (15.3%), respectively; p<0.001]. When analysing the number of pregnancies in the three groups, patients in the high risk group had significantly lower live birth rates, when compared to the other groups [11(40.7%) life births V.s. 100(62.1%) and 137(82.5%), respectively; p<0.05]. Furthermore, patients with medium risk group also had significantly lower live birth rates, when compared to the lower risk group (p<0.001).

Conclusions:

GAPSS might be a valuable tool for identifying patients with a higher likelihood of response to SoC.

1. Introduction

Autoimmune diseases, such as systemic lupus erythematosus (SLE) often concern young women during their childbearing years and,for quite some time,these women have been advised against getting pregnant[1]. To date, with the improvement of antibody testing, careful medical and obstetric management and appropriate standard of care (SoC), most of these women can have successful pregnancies. In particular, the number of pregnancies in women with SLE in the USA is estimated at 4500 per year[2].

When planning a pregnancy in patients with any known connective tissue disease, ENA profiling is required, as the presence of maternal anti-Ro/SSA antibodies is strongly associated with the development of neonatal cutaneous lupus and fetal complete congenital heart block (CHB)[3]. Additionally, antiphospholipid antibodies (aPL) testing is mandatory, as their positivity is linked to an increased risk of developing pregnancy morbidity, which includes recurrentfirst trimester pregnancy loss, intrauterine growthrestriction, preeclampsia, prematurebirth and intrauterine death (IUD)[4][5][6].CurrentSoC in pregnancy for patients withSLE and/or aPLpositivitàincludes treatment with low dose aspirin (75–100mg/day) oftencombined withlowmolecularheparin or unfractionatedheparinaccording to theirpreviousmedicalhistory. Successful pregnancies, however, does not mean uneventful, as up to 30% of women continue to havepregnancy complications despite the current SoC[7].In women refractory to aspirin and heparin, additional therapies, such as hydroxychloroquine[8], low-doses steroids [7], intravenous immunoglobulins [9], and higher dosages of low molecular or unfractionated heparin may be used at the discretion of the treating physician. Therefore,the identification of patients that are at greater risk to develop pregnancy complications despite the SoC who maybenefit from additional therapeutic approaches is an unmet clinical need.

Our group conceived and validated theglobal antiphospholipid syndrome score (GAPSS)[10][11][12], as a risk score for predictingaPL-related clinical manifestations (thrombotic and/or pregnancy morbidity). The GAPSS score takes into account the combination of tradition cardiovascular risk factors andtheindividual aPL profile. These include hyperlipidaemia, arterial hypertension, lupus anticoagulant (LA), anticardiolipin (aCL), anti-beta2 glycoprotein-I (anti-β2GPI), and anti-phosphatidylserine/prothrombin (aPS/PT)antibodies.

In this study, we aimed to investigate whether pregnancy success rate and response to SoC differ in women according to the GAPSS scorein women with SLE and/or aPL positivity.

2. Methods

2.1 Patients

This retrospective cohort study included 143 consecutive women ever pregnant with SLE and/or aPLwho presented to our outpatient clinic pregnancy clinic under the Department of Rheumatology, Guy's and St Thomas' NHS Foundation Trust, London, UK and the S. Giovanni Bosco Hospital, University Hospital, Turin, Italy. The study was conducted under the principles set forth in the Helsinki Declaration of 1975, as revised in 2013.Data on pregnancy complications, cardiovascular risk factors, aPL positivity were retrospectively collected from patient notes.

Study inclusion criteria included:

a) Women with a diagnosis of SLE according to the current ACR criteria[13] and/or women with confirmed aPL positivity (at least twice 12 weeks apart), ever pregnant.

b) Women who received treatment according to SoC (see definition below) during pregnancy

SoC definition

- Women with aPL positivity and no history of pregnancy morbidity: Low-dose aspirin (75–100 mg/day)
- Previousobstretric APS[5]: low-dose aspirin (75–100 mg/day) plus LMWH at thromboprophylactic doses (e.g., subcutaneous enoxaparin 40 mg/day, subcutaneous dalteparin 5000 U/day, or subcutaneous tinzaparin 4500 U/day) or unfractionated heparin
- Previous thrombotic APS[5]: low-dose aspirin (75–100 mg/day) plus LMWH at therapeutic doses (e.g., subcutaneous enoxaparin 1 mg/kg every 12 h or 1.5 mg/kg/day or subcutaneous dalteparin 100 U/kg every 12 h or 200 U/kg/day)

2.2 Cardiovascular risk factors assessment

Cardiovascular risk factors of the study population were assessed following the NICE guidelines[14]. In detail, enrolled patients underwent a physical examination, blood pressure determination, and phlebotomy in order to assess vascular risk factors. Arterial hypertension was defined as an appropriately sized cut-off [14], high blood pressure on at least two occasions, and/or use of oral antihypertensive medications. Serum total and high-density lipoprotein cholesterol levels were determined according to standardized methods and interpreted according to current cut-off values [14].

2.3 Previous Autoantibody detection

The aPL profile, at the diagnosis, included aCL, LA and anti-ß2 glycoprotein I (anti-ß2GPI) antibodies. The aCL and anti-ß2GPI were detected by ELISA as previously described [15,16]. Both IgG and IgM aPS/PT were assayed semiquantitatively using commercial ELISA kits (QUANTA Lite®, Inova Diagnostic), in accordance with manufacturer's instructions. Plasma samples were tested for the presence of LA according to the recommended criteria from the International Society on

Thrombosis and Haemostasis (ISTH) Subcommittee on Lupus Anticoagulant/Phospholipid-Dependent Antibodies [17,18].

2.4 GAPSS calculation

The cumulative GAPSS was calculated for each patient as previously reported, by adding together all points corresponding to the risk factors [10]. The score has a range from 0 to 20 and equals the sum of assigned weighted points to six variables, defined as arterial hypertension (1 point), dyslipidemia (3 points) and positivity to aCL (5 points), anti-ß2GPI (4 points), aPS/PT (3 points) and LA (4 points).

The patients GAPSS was then grouped according to the patients' GAPSS into low risk (<6), medium risk (6-11) and high risk (≥12).

2.5 Statistical analysis

Categorical variables are presented as number (%) and continuous variables are presented as mean (S.D.). Categorical agreement and degree of linear association was analyzed. The significance of baseline differences was determined by the chi-squared test, Fisher's exact test or the unpaired t-test, as appropriate. A two-sided *p*-value <0.05 was statistically significant. All statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY, USA).

3. Results

The analysis included 143 patients (mean age 30.8±6.4) with SLE and/or aPL positivity, for a total of 352 pregnancies. More in detail, 122 patients (85.3%) were diagnosed with SLE and 21 (14.7%) patients werepersistently aPL positive with no concomitant sign/symptom of an autoimmunecondition. Demographic, clinical and laboratory characteristics are summarized in Table 1.

Overall, we observed a live birth rate of 70.5%, with a total of live birth of 248 out of the 352 pregnancies. Forty-five patients (31%) experienced at least one event of pregnancy morbidity (PM), defined as early or late.

When stratifying patients according to GAPSS values, 72 patients (50.3%) had GAPSS values lower than 6 (low risk), 66 patients (46.2%) had GAPSS scores between 6 and 11 (medium risk) and 5 patients (3.5%) and GAPSS values higher or equal to 12 (high risk).

When considering patients who ever experienced PM while treated with SoC, all patients in the high risk group experienced PM, while patients in the medium group had a significant higher rate of PM when compared to the low risk group [29 (43.9%) patients V.s. 11 (15.3%), respectively; $p<0.001$]. When analysing the number of pregnancies in the three groups, patients in the high risk group had significantly lower live birth rates, when compared to the other groups [11(40.7%) life births V.s. 100(62.1%) and 137(82.5%), respectively; $p<0.05$]. Furthermore, patients with medium risk group also had significantly lower live birth rates, when compared to the lower risk group [100 (62.1%) live births; $p<0.001$)].

When analysing the pregnancy outcomes according to previous SLE clinical manifestations, we did not observeany association with PM. Nevertheless, patients with previous LN had experienced more frequentlylate pregnancy complications, butthe difference was not statistically significant ($p=0.211$).

Figure 1 resumes the results of PM and live births divided in the three groups according to GAPSS scores.

The use of other medications (including steroids, azathioprine, hydroxycloroquine) was not found to be statistically different between women with PM when compared to those without.

4. Discussion

In this study, when focusing on pregnancy outcomes of patients with SLE and/or aPL positivity, we report an overall live birth rate of 70.5%. Interestingly, when stratifying patients for GAPSS, patients with low risk profile (GAPSS <6) had a live birth up to 82.5%, significantly higher than patients that presented with and higher risk profile according to GAPSS (GAPSS≥12) that had live birth rates up to 40.7%.

When looking critically at our results our observed live birth rate was 70%, as expected in a populationwith SLE/aPL, however, one should notice the marked difference in pregnancy outcome in the different subgroups of patients. Similarly, the discrepancy between the published literature and the "real life" emphasizes the need to better classify the patients according to the stratification of obstetric risk[19][20]. Such a heterogeneity in pregnancy outcome might create a challenge for physicians caring for women with autoimmune disorders such as SLE or APS. Identifying patients at higher risk for both maternal /fetal complications is still an unmet need for physicians. Similarly, the definition of the risk profile subgroups for pregnancy failure will provide an objective tool for tailoring the management of patients on an individual base.

Overall, our results demonstratedthat women with higher GAPSS values are those with higher rate of PM, suggesting that the GAPSS could represent an accurate, practical strategy for risk stratification that could be implemented into routine pregnancy care settings for women with SLE/aPL.

Some points are worth considering. Firstly, early detection of at-risk women provides the opportunity for targeted intervention to reduce risks in pregnancy. Whilethe current management is mainly based on the use of aspirin often in combination with heparins according to the patients previous medical history, the use of additional strategies to improve pregnancy outcome is mainly based on not controlled studies[7][21,20]and mainly relies on physicians' judgment[22][23]. Based on our results, the identification of high risk pregnancy might be based on a quantitative and

reproducible approach, suggesting that women with GAPSS> 12 might represent to a subset of higher risk for PM, potentially requiring therapeutic strategies in addition to SoC.

Secondly, this retrospective analysis might pave the way for future prosperitystudies considering different therapeutic approaches forpatients with aPL according to their risk for future event. In line with these observations, in fact, recent evidence supports the fact that patients with aPL might respond to treatment differently according to their risk profile. When referring to the management of thrombotic APS, for instance, whilepreliminary experiences seemed to support the use of direct anticoagulant agents[24], emerging evidence highlighted the risk of this approach in patients at high risk as those with triple positivity[25]. It is worth considering that patients aPL triple positivityhave a GAPSS>12, further supporting the potential role of GAPSS as a tool to guide therapeutic choices.

Thirdly, several studies have evaluated biochemical markers to demonstrate predictive ability with positive results for PM in women with aPL[26–28]. While identification of additional more complex and costly biochemical markers is potentially useful, clinical application may be limited by cost and feasibility. Applying the GAPSS implies no additional cost nor extra testing and therefore minimal patient/physician inconvenience.

Finally, a simple and reproducible risk score such as GAPSS might help identifying not only patients that are at higher risk of developing pregnancy complications despite SoC, but also those patients that might develop during the follow-up thrombotic manifestations[29]. We acknowledge that this study had some limitations. First, the intrinsic nature of a retrospective study might limit the reproducibility of the results. Secondly, the study population was, to a certain degree, heterogeneous, since both patients with a diagnosis of SLE and aPL positive patients without SLE were enrolled. Larger series will be critical to further characterize the behavior of these diseases in

pregnancy, as well as their impact on mother and fetus alike. However, when analyzing pregnancy outcome dividing patients for previous SLE-related clinical manifestation, we did not observe any statistical significant difference. Similarly, it was out of the scope of this study to asses if the use of azathioprine or steroids might impact on pregnancy outcome. Also, up to 93% of patients with SLE were receiving HCQ, limiting any further analysis on the role of this medication in this cohort.

In conclusion, in the last two decades, a great improvement was certainly achieved in the outcome of pregnancies in women with SLE and/or aPL. This success is probably due to multidisciplinary teams devoted to the tight control of women with these conditions. A preconception risk stratification is recognized as crucial. The results obtained in this study confirmed the role of GAPSS as a easy, reliable tool for risk stratification.

In the absence of controlled trials and with very limited prospective studies available,GAPSS might be a valuable tool for the treating clinician for identifying patients at higher risk of developing any event of PM who might need additional therapeutic approach other than SoC.

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Legend of Tables and Figures

Table 1. Clinical and demographic characteristics of the cohort, divided according to GAPSS.

Figure 1. Pregnancy morbidity rates and Live births divided in the three groups according to the levels of GAPSS [low risk group (GAPSS <6), a medium risk group (GAPSS 6-11) and a high risk group (GAPSS≥12)].

	GAPSS <6 (n=72)	GAPSS 6-12 (n=66)	GAPSS ≥13 (n=5)
Demographics			
Age, mean (±S.D.)	30,7 (±5,9)	30,6 (±6,2)	34 (±11,1)
Diagnosis			
SLE, n (%)	55 (76%)	52 (79%)	4 (80%)
aPL positive, n (%)	17 (24%)	14 (21%)	1 (20%)
CardiovascularRiskFactors			
Hyperlipidemia, n (%)	14 (19%)	18 (27%)	2 (40%)
ArterialHypertension, n (%)	13 (18%)	28 (42%)	1 (20%)
Smoking, n (%)	19 (26%)	15 (23%)	2 (40%)
Diabetes, n (%)	1 (1%)	1 (2%)	1 (40%)
aPLProfile			
LA, n (%)	0	32 (48%)	3 (60%)
aCLIgG/IgM, n (%)	10 (14%)	33 (50%)	5 (100%)
Anti-Beta2GPI IgG/IgM, n (%)	2 (3%)	10 (15%)	4 (80%)
Triple Positive, n (%)	0	0	2 (40%)
aPS/PT IgG/IgM, n (%)	7 (10%)	11 (17%)	1 (20%)

Table 1. Clinical and demographic characteristics of the cohort, divided according to GAPSS.

Global AntiPhospholipid Syndrome Score (GAPSS); Standard Deviation (S.D.); Systemic Lupus Erythematosus (SLE); Antiphospholipid antibodies (aPL); Lupus Anticoagulant (LA); anticardiolipin antibodies (aCL); Anti-Beta2Glycoprotein I (anti-Beta2GPI);

Figure 1

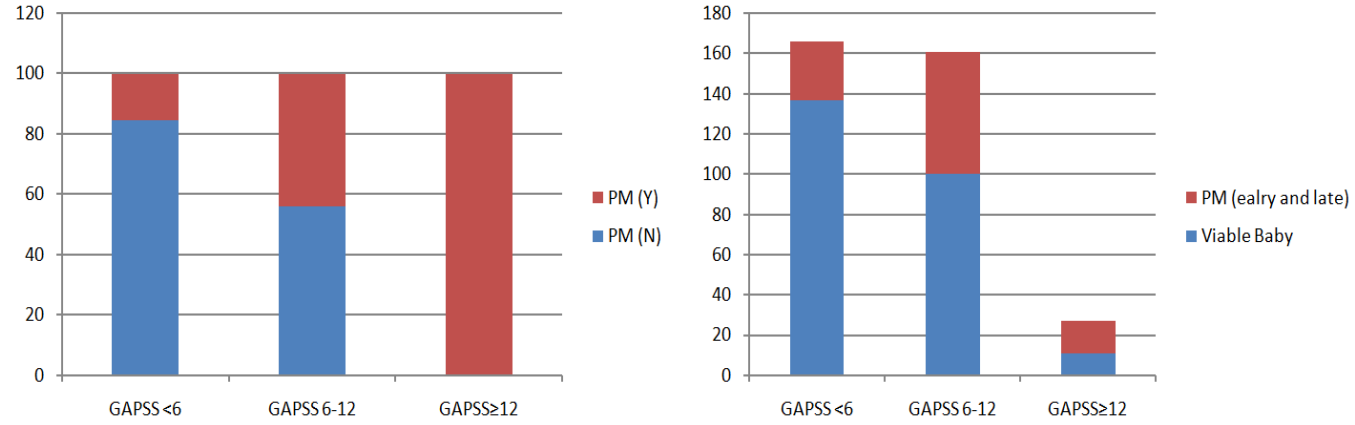

Figure 1. Pregnancy morbidity rates and Live births divided in the three groups according to the levels of GAPSS [low risk group (GAPSS <6), a medium risk group (GAPSS 6-11) and a high risk group (GAPSS≥12)].
Panel A. Rates of Patients that ever experienced pregnancy morbidity (expressed as percentages).
Panel B. Live births and pregnancy morbidity (early and late) in the three groups(expressed as numbers).
PM- Pregnancy Morbidity: GAPSS – Global AntiPhospholipid Score

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