The global antiphospholipid syndrome score in women with systemic lupus erythematosus and adverse pregnancy outcomes

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Abstract

Objective

To validate the global antiphospholipid syndrome score (GAPSS) in a cohort of women with systemic lupus erythematosus (SLE) and antiphospholipid antibodies (aPL).

Methods

This retrospective study included 143 women ever pregnant with SLE who presented in our outpatient clinic were included. Data on cardiovascular risk factors and aPL status were retrospectively collected and their individual GAPSS score was calculated.

Results

Significantly higher GAPSS values were found in women with any placental medicated complication (such as foetal death, placental abruption, prematurity, pre-eclampsia or intrauterine growth restriction (IUGR)) (GAPSS 8.2±3.0 vs. 3.5±3.0, p<0.001). Significantly higher GAPSS values were also found in those with recurrent miscarriages (RM) <10 weeks, foetal death, placental abruption, prematurity, pre-eclampsia or IUGR) (GAPSS 8.3±4.5 vs. 3.2±2.6, p<0.001). Patients with 3 or more consecutive early miscarriages (<10 weeks), foetal death, miscarriage <10 weeks' gestation, premature birth (<34 weeks), pre-eclampsia (<34 weeks), stillbirth, and placental infarction had significantly higher GAPSS values compared to those without previous pregnancy complications. The odds ratio of having any pregnancy morbidity when having a GAPSS value ≥8 was 20 compared to those with a GAPSS of ≤1 (p<0.001).

Conclusion

Women with a history of aPL-related pregnancy complications had higher GAPSS values in this retrospective cohort compared to women without pregnancy complications. This study is the first step to assess the clinical utility of the GAPSS score in pregnancy. A prospective validation is needed.

Key words

antiphospholipid syndrome, systemic lupus erythematosus, pregnancy, pregnancy complications, pregnancy morbidity, global antiphospholipid syndrome score

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease which is characterised by a multitude of autoantibodies including antiphospholipid antibodies (aPL). SLE is a systemic disease, can affect any organ and has preponderance for women in their childbearing age (1, 2). Pregnancy complications, such as early and late pregnancy losses, foetal growth restriction (FGR), and pre-eclampsia are more commonly seen in women with SLE, in particular those with aPL, compared to healthy subjects (3).

A proportion of patients with SLE also have APS, which is classified by the persistent presence of aPL in patients with thrombotic events and/or pregnancy morbidity. The current classification criteria for APS include three laboratory tests: lupus anticoagulant (LA), anticardiolipin (aCL) and anti-β2 glycoprotein-I (β2GPI) (4) which have to be present on more than two occasions at least 12 weeks apart (4). The pregnancy morbidity in APS includes unexplained recurrent early miscarriage, foetal deat and late obstetrical manifestation such as pre-eclampsia, premature birth or FGR associated with placental insufficiency (obstetric APS) (5).

The persistent presence of aPL is a risk factor for the development of aPL related clinical manifestations (6). Not all individuals with persistent aPL will develop thrombosis or pregnancy complications. Therefore, identifying patients at high risk of developing aPL related clinical manifestations remain a main challenge and represents still an unmet clinical need. This may be relevant for the immediate treatment of patients, but may also be useful for the classification of subgroups in the setting of clinical trials.

Our group recently developed a risk score for clinical manifestations of APS [the global APS score (GAPSS)], which is a tool to quantify the risk of aPL related clinical manifestations. The GAPSS encompasses the combination of independent cardiovascular risk factors and the individual aPL profile in non-pregnant patients (7). Our study was performed to address the possible utility of the GAPSS model in women with SLE who have a history of aPL related adverse pregnancy outcomes.

Material and methods

Patients

This retrospective chart driven cohort study included 143 consecutive women who meet the following criteria: 1) ever pregnant with SLE according to the current ACR criteria (8); 2) were followed-up in our outpatient 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 (with at least 5 visit records available); 3) data on pregnancy complications, cardiovascular risk factors, aPL status were available for retrospectively collection. Data collection, to include aPL status and cardiovascular assessment, was based on information reported at the last available visit. The data collection was closed at May 2017. Demographic, clinical and laboratory characteristics are summarised in Table I.

Cardiovascular risk factors assessment

Cardiovascular risk factors were assessed following the National Institute for Health and Care Excellence (NICE) guidelines (9). In detail, enrolled patients underwent a physical examination, blood pressure determination and phlebotomy for vascular risk factors. Arterial hypertension was defined as an appropriately sized cut-off (9), high blood pressure (systolic blood pressure >140 mmHg/diastolic blood pressure >90 mmHg) on at least two occasions or use of oral antihypertensive medications. Serum total and high-density lipoprotein cholesterol levels were determined with standardised enzymatic methods and interpreted according to a cut-off value for a total cholesterol of over 6.5 mmol/L.

Autoantibody detection

The tested aPL profile included LA, aCL (IgG and IgM isotypes) and anti-ß2 glycoprotein I (IgG and IgM isotypes) antibodies. The aCL, anti-ß2GPI and anti-phosphatidylserine/prothrombin antibodies (aPS/PT) were detected by enzyme linked immunosorbent as-

say (ELISA, INOVA Diagnostic, San Diego, CA). Plasma samples were tested for the presence of LA according to the recommended criteria from the recommendation of the International Society on Thrombosis and Haemostasis (ISTH) Subcommittee on Lupus Anticoagulant/Phospholipid-Dependent Antibodies (10, 11).

GAPSS calculation

The individual GAPSS was calculated for each patient at diagnosis. The GAPSS score was calculated by adding each risk factor score: 3 for hyperlipidaemia, 1 for arterial hypertension, 5 for aCL IgG/IgM, 4 for ß2GPI IgG/IgM, 3 for aPS/PT IgG/M and 4 for LA (12) as previously reported (7, 13). After its first description, GAPSS was prospectively validated (13). The score included routine aPL tests and aPS/PT. The data are presented as GAPSS score.

Definitions on maternal and foetal pregnancy complications

For the purpose of this study the following definitions were used*: Recurrent miscarriage*: >3 consecutive pregnancy losses before the end of 10 weeks' gestation; *foetal death*: pregnancy loss after 10 weeks' gestation but before the end of 24 weeks of gestation; *preterm birth*: birth between 24 and 36+6weeks; *pre-eclampsia*: defined according to international criteria (14); stillbirth: baby born with no sign of life at or after 28 weeks' gestation; *placental infarction*: presence of thrombosis without evidence of inflammation on biopsy; p*regnancy morbidity (PM):* defined as any of the above mentioned pregnancy complications.

Statistical analysis

Categorical variables are presented as number (%) and normally distributed variables are presented as mean (SD). 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 considered as statistically significant. Linear and logistic regressions were performed. The statistical analyses were performed using SPSS v. 23.0 (IBM, Armonk, NY, USA).

Table I. Patient information: demographics, clinical details relevant for the global antiphospholipid score (GAPSS) and previous pregnancy morbidity.

Patients characteristics	All (n=143)	%
Age, years (median, range)	45 (range 25–77)	
Ethnicity (White:Black:Afro-Caribbean:Colombian:Asian)	119:6:11:1:4	
Clinical details		
SLE disease duration, mean (S.D.), years	13.4 (9.3)	
Obstetric APS according to Sydney Criteria	50	35%
Clinical details relevant to GAPPS		
Cardiovascular risk factor (any), n	84	58%
Smoking, n	39	27%
Arterial hypertension, n	44	31%
Hyperlipidaemia, n	31	22%
Diabetes, n	4	3%
Outcome details		
Pregnancies, n	382	
Pregnancy morbidity (any), n	54	14%
Consecutive early recurrent (>3) miscarriages before 10 weeks gestation, n	9	2%
Any miscarriage, n	39	10%
Foetal death (after 10 weeks gestation), n	25	7%
Prematurity (before week 34 gestation), n	15	4%
Pre-eclampsia, n	19	5%
Intrauterine death (after 28 weeks gestation), n	10	3%
Placental infarction on histology, n	5	1%

Theory

We hypothesise that women with SLE who have a history of aPL related adverse pregnancy outcomes have higher GAPSS values. GAPSS values might help identify the patients that are at higher risk of developing APS-related clinical manifestations.

Results

A total of 143 consecutive women with SLE and aPL with a median age of 45 (range 25–77) years at the last available visit at the time of data collection were included in the study. The average disease duration is 13.4 years ±9.3 (mean, S.D) and 84 patients (58%) had a history of any cardiovascular risk factor. Amongst those 39 (27%) patients were smokers, 44 (31%) patients had arterial hypertension, 31 (22%) had hyperlipidaemia and 4 (3%) had diabetes mellitus. Our cohort of 143 patients had a total of 382 pregnancies and 54 patients (14%) had any pregnancy morbidity. Fifty (35%) patients fulfil the classification criteria for obstetric APS (3). Nine patients (2%) had recurrent early first trimester losses (>3), 39 patients (10%) had any pregnancy loss, 25 patients (7%) had a history of foetal death (after 24 weeks of gestation), 15 (4%) had a history of preterm birth before week 34 of gestation, 19 (5%) had a previous pre-eclampsia, 10 (3%) had a history of stillbirth (after 28 weeks gestation), 5 (1%) had a placental infarction. Patient demographics are summarised in Table I.

GAPSS scores

The GAPSS values were calculated for each individual (Table II). Significantly higher GAPSS values (reported in percentage increase) were seen in patients with the following pregnancy history when compared to those without a history of pregnancy complications: 134% higher GAPSS values were found in those with placental mediated complications (such as foetal death, placental abruption, prematurity, pre-eclampsia or intrauterine growth restriction) (mean GAPSS 3.5±3.1 *vs*. 8.2±4.5, $p<0.001$).

Moreover, we found 163% higher GAPSS values in patients with recurrent early miscarriages (≥3), foetal death, placental abruption, prematurity, pre-eclampsia or intrauterine growth restriction) (mean GAPSS 3.2±2.6 *vs*. 8.4±4.5, $p<0.001$). Findings also remained significant when looking at single outcomes. We found 96% higher GAPSS in women with three or more consecutive miscarriages of

Table II. Calculation of the Global APS score (GAPSS).

The Global APS Score (GAPSS) was created to help assess the risk of developing aPL-related clinical manifestations. This score derived from the combination of independent risk factors for thrombosis and pregnancy loss, taking into account the aPL profile (criteria and non-criteria aPL), the conventional cardiovascular risk factors, and the autoimmune antibodies profile.
It has been demonstrated that risk profile in APS can be successfully assessed, suggesting that GAPSS can be a potential quantitative marker of APS-related clinical manifestations.

Hyperlipidaemia	3
Arterial hypertension	1
aCL IgG/IgM	5
Anti-β2GPI IgG/IgM	4
aPS/PT IgG/IgM	3
LA	4

aCL: anticardiolipin, LA: lupus anticoagulants.

<10 weeks gestation compared to those without (mean GAPSS 9.4 *vs*. mean GAPSS 4.8, p=0,002), 34% higher GAPSS in patients with any miscarriages compared to patients without (mean GAPSS 6.3±4.2 *vs*. mean GAPPS 4.7±4.3, p=0.045); 136% higher GAPSS values in those with previous foetal death (mean GAPSS 9.1±3.9, *vs*. mean GAPSS 3.8±3.4, p<0.001), 139% higher GAPSS values in those with previous pregnancy loss <10 weeks gestation (mean GAPSS 9.1±4.2 *vs*. mean GAPSS 3.8±3.4, p<0.001), 64% higher GAPSS values in those with premature birth (<34 weeks) (mean GAPSS 7.8±4.8 *vs*. mean GAPSS 4.8±4.1, p=0.011), 66% higher GAPSS in patients with a history of pre-eclampsia (PET<34 weeks) (mean GAPSS 7.9±5.2 *vs*. mean GAPSS 4.7±4, p=0.002), 90% higher GAPSS in patients with a previous stillbirth (mean GAPSS 9.1±5.2 *vs*. mean GAPSS 4.8±4.1, p=0.002), 116% higher GAPSS in patients with previous placental infarction compared to those without a history of placental infarction (mean GAPSS 10.6±4.3 *vs*. mean GAPSS 4.9±4.2, p=0.004). The results are graphically illustrated in Figure 1. Linear regression model analysis showed that foetal death is the main driver of this association. A logistic regression showed, that the odds ratio (OR) of having any pregnancy morbidity when having a GAPSS score ≥8 was 20 compared to those with an GAPSS of ≤1 (p<0.001).

Discussion

To the best of our knowledge this is the first study to address the performance of the GAPSS in a cohort of women with SLE and aPL who have ever have been pregnant. We found significantly higher GAPSS values in those with SLE and aPL with previous pregnancy complications compared to those without pregnancy complications.
The GAPSS is a risk score model based on six factors in total (four laboratory entities (*i.e*. the aPL status) and two clinical diagnoses (arterial hypertension and hyperlipidaemia)), which have been shown to increase the likelihood of having thrombosis or pregnancy loss in SLE. GAPSS encompasses

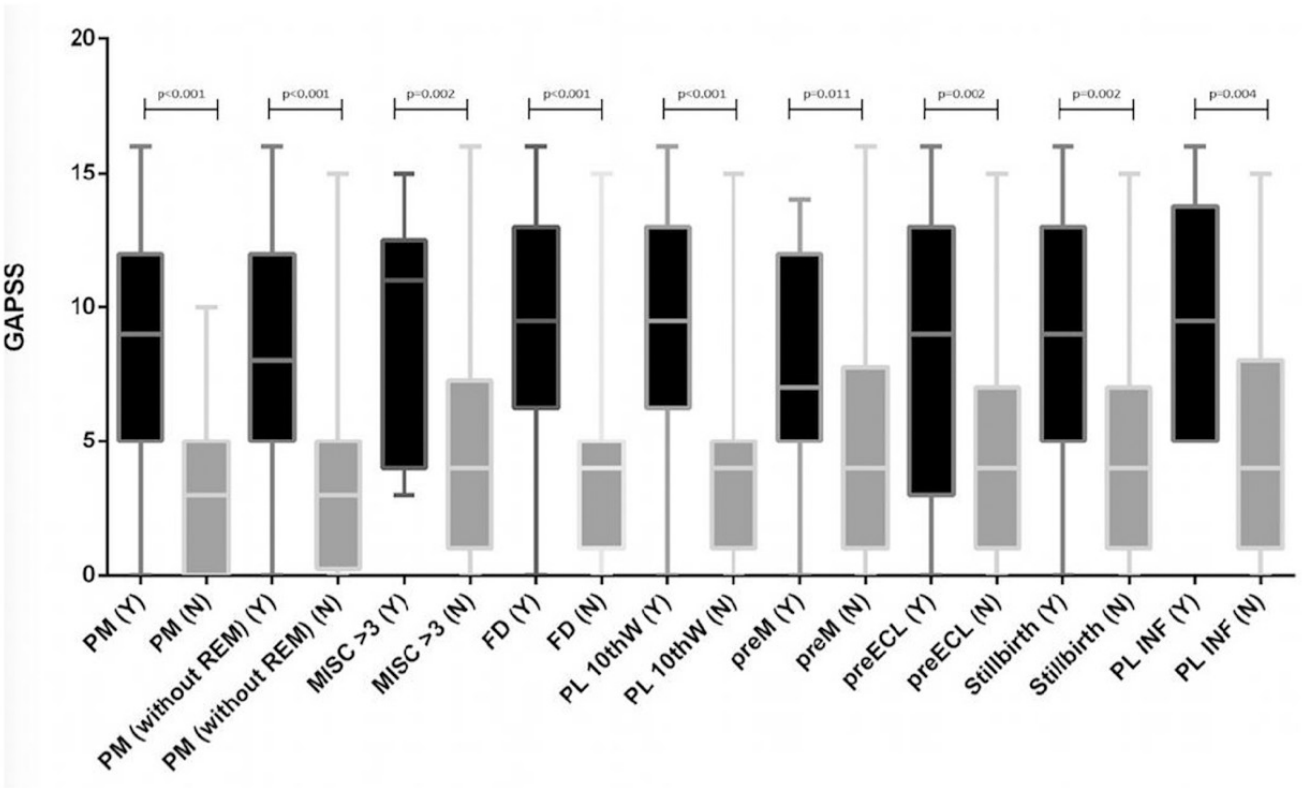

Fig. 1. Graphic illustration of the global antiphospholipid syndrome scores (GAPSS) in women with and without pregnancy morbidity.
FD: foetal death after 10 weeks before the end of 28 weeks; Stillbirth: intrauterine death after 28 weeks; MISC >3: recurrent (3 or more) consecutive miscarriages before 10 weeks; PL 10^{th}W: pregnancy loss <10 weeks; PM (without REM): pregnancy morbidity (including foetal death, placental abruption, prematurity, pre-eclampsia or intrauterine growth restriction); preM: premature birth before 34 weeks; preECL: pre-eclampsia; PL INF: placental infarction on histology; PM: pregnancy morbidity (any).

the individual aPL profile, both including criteria and non-criteria aPL and the conventional cardiovascular risk factors including arterial hypertension and the presence of hyperlipidaemia.

GAPSS was originally developed in a SLE cohort including 211 consecutive SLE patients. Since the first retrospective validation studies suggesting its utility, GAPSS has been retrospectively and prospectively validated by us and others (15). Amongst the retrospective validation studies was a study assessing GAPSS' utility in APS patients at risk of myocardial infarction16 and a prospective validation in patients with aPL at risk of stroke (16, 17).

However, to date, no studies have specifically looked into whether the GAPSS would be of use in women with or without previous aPL-related pregnancy morbidity. Our results show that higher GAPSS scores are found in women with any previous aPL related pregnancy complications compared to those without.

How are these results useful? Firstly, they are in line with the well-established association of pregnancy morbidity (such as pre-eclampsia and foetal death) with the increased risk of maternal premature cardiovascular disease later in life, which has been reported in women without (18) and more recently in women with SLE (19, 20). Secondly, in the past, clinical trials investigating therapeutic approaches in aPL-positive women have suffered for a vast heterogeneity in the studied populations (*e.g.* heterogeneity in aPL profile, aPL definition, cardiovascular risk factor), making results difficult to extrapolate. From this perspective, GAPSS might represent a practical tool to improve homogeneity when analysing data (*e.g.* stratifying patients according to their GAPSS range).

A striking observation was that any aPL-related pregnancy morbidity was associated with significantly higher GAPSS results. Another interesting observation was, that the highest difference in mean GAPSS was found in women with a previous history of placental infarctions on placental biopsy. Secondly, our results add to the body of studies which may prompt the question if we should be more aggressive in treating modifiable risk factors such as hyperlipidaemia and arterial hypertension in women with SLE and aPL with a previous history of maternal placental syndromes (19, 20). The answer will depend on interventional studies, which yet are to be conducted.

Given the retrospective design of the present study, our finding of high GAPSS values in women with previous pregnancy morbidity does not explain causality. It is likely that women with a previous history of pregnancy complications are more likely to develop hyperlipidaemia and hypertension (21) (and therefore confound our results), but we would expect the non-modifiable GAPSS variables such as the presence of the individual aPL subclasses (which weight more in the GAPSS score) to balance these findings.

The limitation of our study is the retrospective design and the observational character. While we applied methodological rigor in data mining and extracting, we cannot exclude some level of inaccuracy when data were retrieved. However, this is an intrinsic limitation of retrospective chart review study. When specifically referring to pregnancy outcomes, we acknowledge that some recall bias regarding our patients' pregnancy history can exist. However, in our experience women are most often very well aware of pregnancy outcomes and are able to recall at what gestational age their babies are born. Furthermore, the GAPSS score was calculated at the last available visit and this aspect might potentially influence the outcome results of the study. Indeed, the cross-section nature of the study strongly impacts on the extrapolated observations. Similarly, the time between the aPL status and cardiovascular assessment and the pregnancies very heterogenous. However, the rate of adverse pregnancy outcomes in our cohort are what we would expect in an SLE cohort and are in line with rates from other groups (22-24).

Conclusions

Where do our results take us?

SLE women with a history of aPL-related pregnancy complications had higher GAPSS values in this retrospective cohort compared to women without pregnancy complications. The clinical utility of the GAPSS score in pregnancy and should be validated in a prospective cohort in order to assess if our results translate into prospective cohorts. Future projects could assess if there is a correlation between GAPSS score and disease activity assessment tools.

Further research is needed, but our findings provide the first step to prompt a prospective evaluation of the GAPSS in pregnant women with SLE.

Key messages

- We found 43 to 171% higher GAPSS in women with previous aPL related pregnancy complications
- The odds ratio of having any pregnancy morbidity when having a GAPSS score ≥8 was 20 compared to those with an GAPSS of ≤1 ($p<0.001$)
- The GAPSS seems a promising tool for risk stratification in pregnancy in women with SLE

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