











# Use of a screening questionnaire for systemic lupus erythematosus among pregnant women in a Mexican population

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## ABSTRACT

**Objective** To conduct a diagnostic assessment of pregnant women using a screening questionnaire for SLE.

**Materials and methods** This was an analytical cross-sectional study carried out at the National Institute of Perinatology between 1 November 2019 and 28 February 2020, using a screening questionnaire for SLE. Antinuclear antibody and anti-double stranded DNA antibody tests and a clinical assessment by a rheumatologist were conducted for participants who obtained  $\geq 4$  positive responses on the questionnaire. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the screening questionnaire for SLE were calculated.

**Results** The questionnaire survey was conducted with 540 pregnant patients, 22 of whom (4.1%) had  $\geq 4$  positive responses. An antinuclear antibody test was conducted in all aforementioned 22 patients; 17 (77.3%) showed titres of  $\geq 1:80$ . Of the 22 patients, 19 (86.4%) underwent clinical assessment by a rheumatologist. The patients were classified according to the SLE classification criteria: 7/19 (36.9%) met the revised 1997 American College Rheumatology (ACR) criteria, 8/19 (42.1%) met the Systemic Lupus International Collaborating Clinics criteria and 7/19 (36.9%) met the 2019 ACR/EULAR criteria (sensitivity=0.86, specificity=0.97, PPV=0.77 and NPV=1 for antinuclear antibody titre of  $\geq 1:80$ ; sensitivity=0.88, specificity=0.98, PPV=0.37 and NPV=1 for SLE according to the 2019 ACR/EULAR criteria).

**Conclusions** The questionnaire showed high sensitivity and specificity in the diagnosis of SLE. Given its usability and cost:benefit ratio, this strategy should be used for all patients coming in for their first visit to determine who requires antinuclear antibody testing and who needs to be referred to a rheumatologist.

## BACKGROUND

SLE is a chronic multisystem autoimmune disease of unknown aetiology that mainly affects women of reproductive age. It is defined by its clinical characteristics and the presence of autoantibodies directed against one or more components of the cell nucleus.<sup>1,2</sup> SLE increases the risk of miscarriage, fetal death,

## Key messages

### What is already known about this subject?

▶ Antinuclear antibody tests may yield positive results in patients with other autoimmune diseases or even in individuals with no symptoms. Therefore, the diagnosis of SLE must be based on clinical and immunological data.

### What does this study add?

▶ The presence of four or more positive responses showed high sensitivity and specificity for the diagnosis of SLE during pregnancy.  
 ▶ Screening questionnaires with less than four positive responses showed a high negative predictive value; based on this, we do not recommend making antinuclear antibodies in patients with a negative questionnaire.

### How might this impact on clinical practice or future developments?

▶ The screening questionnaire for SLE shows high sensitivity and high specificity for the diagnosis of SLE. Given its usability and cost:benefit ratio, this test should be used in all patients coming in for a first visit, to improve the selection of patients who are required antinuclear antibody testing and those referred to a rheumatologist.

pre-eclampsia, intrauterine growth retardation and preterm birth.<sup>3,4</sup> The presence of anti-Ro and anti-La antibodies can cause fetal heart block and neonatal lupus.<sup>5</sup> The prognosis of both the mother and fetus improves when SLE is inactive for at least 6 months before pregnancy and when the renal function of the mother is stable and normal.<sup>3,6</sup>

The highest incidence is observed in people aged between 15 and 45 years. The prevalence varies widely from 1/250 to 1/2000.<sup>7</sup> Exacerbation during pregnancy ranges from 20% to 30%.<sup>8,9</sup> Recognising lupus activity and flare-ups in pregnant women may be difficult

due to the physiological changes of pregnancy, which tend to overlap with disease activity.<sup>10 11</sup>

The use of lupus activity indexes is hindered by similar difficulties, as physiological changes during pregnancy were not considered when these instruments were being developed. Specific tools have been developed to determine lupus activity during pregnancy, although their utility remains limited. Assessment by a rheumatologist and the use of clinical judgement and medical expertise continue to be the best tools for assessing disease severity.<sup>11</sup>

Antinuclear antibody testing is used as a screening method for systemic autoimmune diseases and it can yield accurate results in 99.3% of patients with lupus. The 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for SLE require antinuclear antibodies at a titre of  $\geq 1:80$  by indirect immunofluorescence.<sup>12</sup> While this is a relatively accessible test, its widespread use can lead to a poor cost:benefit ratio, resulting in diagnostic errors and high economical costs. Antinuclear antibody testing could be efficient if conducted in a preselected subpopulation.<sup>13</sup>

Liang *et al* described a two-step model for identifying patients with SLE in the general population.<sup>14</sup> This model involved a 10-question questionnaire based on the revised 1997 American College Rheumatology (ACR) criteria.<sup>14 15</sup> The questions are formulated in a simple and clear language to detect the presence or absence of arthritis, Raynaud's phenomenon, mucocutaneous manifestations, haematological manifestations, pleurisy, proteinuria and seizures. The proposed SLE screening strategy involved the use of a general questionnaire and those who obtained  $\geq 4$  points on the questionnaire underwent antinuclear antibody test. Patients with positive questionnaire results but negative results on the antinuclear antibody tests were informed that the possibility of SLE was extremely low, so no further tests were required. Patients with a positive questionnaire and positive antinuclear antibodies were referred to a rheumatologist for clinical assessment and lupus diagnosis. The result of  $\geq 4$  positive responses had a sensitivity of 87.2%, specificity of 98.1% and PPV of 79% for the detection of SLE in the general population.<sup>12</sup>

The Spanish version of the questionnaire was validated by Seoane-Mato *et al*<sup>16</sup> in the 2016 EPISER Study (prevalence of rheumatic diseases in adult population in Spain), which showed a prevalence of lupus in adults aged 20 years and above residing in Spain at 0.21%, that is, 210 cases per 100 000 inhabitants.<sup>17 18</sup> In addition, the questionnaire was used in another study to determine the prevalence of lupus in a population living in Florencia, Italy; the study included a population of 71 204 individuals aged 18 years and above and reported a prevalence of lupus of 71 per 100 000 inhabitants.<sup>19</sup>

This study aimed to determine whether the two-step screening strategy proposed by Liang *et al*, that is, a questionnaire followed by antinuclear antibody test, is adequate for identifying pregnant patients with SLE and

ensuring timely referral and monitoring by a rheumatologist. In clinical practice, clinicians rely on the classification criteria for SLE developed by the European League Against Rheumatism/American College of Rheumatology for the diagnosis.

## MATERIALS AND METHODS

An analytical cross-sectional study was conducted to assess the efficacy of the diagnostic tests carried out in the National Institute of Perinatology between 1 November 2019 and 28 February 2020. The study population comprised pregnant women who visited the Division of Maternal-Fetal Medicine for an ultrasonography. All patients who agreed to participate were asked to complete the SLE screening questionnaire (Spanish version).

### Statistical analysis

The sensitivity (S), specificity (E), positive predictive value (PPV) and negative predictive value (NPV) were calculated for various numbers of positive responses on the screening questionnaire. Epi Info V.7.2.3.1 was used to describe the variables; StatCalc was used to elaborate 2×2 tables and determine the performance of the diagnostic test.

The analysis showed that highest sensitivity and highest specificity were obtained with  $\geq 4$  responses, so this result was chosen as a cut-off point for the questionnaire response. After obtaining informed consent from the patients, a sample of peripheral blood was collected from the subjects with  $\geq 4$  positive responses and stored at  $-70^{\circ}\text{C}$  for further processing. The antinuclear antibody test was carried out by indirect immunofluorescence using HEp-2 cells as the substrate at the Laboratory of Immunology of the National Institute of Medical Science and Nutrition "Salvador Zubirán." Titres of  $\geq 1:80$  were considered positive, regardless of the type of pattern. The anti-double-stranded DNA antibody test was carried out using the ELISA test (Orgentec Diagnostika). Titres above the 95th percentile in our population were considered positive.

Patients with  $\geq 4$  positive responses on the screening questionnaire were clinically assessed by a rheumatologist. In light of the clinical assessment and antinuclear antibody results, the following classification criteria for SLE were used: revised 1997 ACR criteria, 2012 SLICC (Systemic Lupus International Collaborating Clinics) criteria and 2019 ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) criteria.

## RESULTS

The study population comprised 540 pregnant patients with an average age of  $29.2 \pm 7.1$  years, gestational age of  $24.2 \pm 7.9$  weeks at the time of the questionnaire survey and an average of  $2.4 \pm 1.5$  previous pregnancies; 52 (9.63%) patients had a family history of rheumatoid disease. **Table 1** shows the patients' characteristics, pregnancy data and the distribution of questionnaire responses.

**Table 1** Comparison between patients with SLE and without SLE

	Without SLE n=533	With SLE n=7	P value
Age at the time of inclusion	29.2±7.1	26±4.2	0.11
Gestational age at the time of questionnaire survey	24.2±7.9	23.2±7.7	0.37
Previous pregnancies	2.5±1.5	1.4±0.5	0.075
History of autoimmune diseases other than SLE (%)	50 (9.4)	2 (28.6)	0.08
Total of positive responses	<b>N (%)</b>	<b>N (%)</b>	<b>P value</b>
Have you ever suffered from arthritis or joint swelling for more than 3 months?	16 (3)	4 (57)	<0.0001
Have your fingers turned pale, purple/blue or numb in the cold?	80 (15)	5 (71)	<0.0001
Have you ever had sores in your mouth for more than 2 weeks?	19 (3)	3 (43)	<0.0001
Have you been diagnosed with low blood cell count (anaemia, low white cell count or low platelet count)?	53 (10)	4 (57)	<0.0001
Have you ever had a prominent rash (red skin) on your cheeks for more than a month?	18 (3.4)	5 (71)	<0.0001
Does your skin become excessively red, more than expected, after being out in the sun?	40 (7)	4 (57)	<0.0001
Have you ever had pain when you breathe deeply for several days?	21 (4)	3 (43)	<0.0001
Have you been told that you 'release' protein in your urine?	58 (11)	6 (86)	<0.0001
Have you ever had rapid and abundant loss of hair?	130 (24)	5 (71)	0.004
Have you ever had seizures or crisis?	24 (5)	1 (14)	0.22

We observed that for the diagnosis of SLE, the first nine questions of the screening questionnaire showed statistical significance when compared with the responses of the group of patients without SLE. It is noteworthy that seizures showed no statistically significant difference between the groups with and without SLE (table 2), even that it shows similar prevalence (14%) to the prevalence reported of seizures associated with SLE by Appenzeller *et al.*<sup>20</sup> of 11.6% (20); therefore, we suggest conducting an antinuclear antibody test in patients with positive screening results to reduce the risk of false positives.

It is important to mention that three of the seven patients with SLE and positive questionnaire already had a SLE diagnosis, and in the negative group, one patient

had previous SLE diagnosis, so this has to be taken into consideration because it could generate some bias or influence the answers given at the time the patients answer the questionnaire. The gestational age of the questionnaire depends on the gestational age when the patients start surveillance in the maternal fetal medicine unit. Not one of the seven patients with SLE had other rheumatological disease. The principal type of antinuclear antibody was the fine speckled.

**Table 2** Clinic characteristics of patients with SLE

Case	Age	GA	G	B	A	SLE	ORD	AB	Positive
1	29	32	2	1	0	1	NO	FS	6
2	21	15.3	1	0	0	0	NO	FS	4
3	33	28	2	0	1	1	NO	M	5
4	24	13	2	1	0	0	NO	H	6
5	23	28	1	0	0	0	NO	FS, C	5
6	28	29	1	0	0	0	NO	H, C	10
7	24	17.4	1	0	0	1	NO	FS	6

A, abortion; AB, antibodies; B, birth; C, cytoplasmic; FS, fine speckled; G, gestation; GA, gestational age; H, homogeneous; M, mitochondrial; ORD, other rheumatological disease.

**Table 3** Positive answers of the patients with positive questionnaire

Question/case	1	2	3	4	5	6	7	Total
1	+	+	-	+	-	+	-	4
2	-	+	+	-	+	+	+	5
3	-	-	-	+	+	+	-	3
4	+	+	+	-	-	+	+	5
5	+	+	+	+	-	+	+	5
6	+	-	-	-	+	+	+	4
7	-	-	+	+	-	+	-	3
8	+	-	+	+	+	+	+	6
9	+	-	-	+	+	+	+	5
10	-	-	-	-	-	+	-	1
<b>Total</b>	<b>6</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>5</b>	<b>10</b>	<b>6</b>	

**Table 4** Screening questionnaire and antinuclear antibody test diagnostic performance with different cut-off points

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR +	LR -
≥2 Positive responses	100	78.8	5.8	100	4.72	0
≥3 Positive responses	85.7	91.2	11.3	99.8	9.74	0.16
≥4 Positive responses	85.7	97	27.3	99.8	28.6	0.15

LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

**Table 3** demonstrates that the question with more positive answers in the SLE group patients was the question number 8, “Have you been told that you ‘release’ protein in your urine?”, and the least frequent positive answer was the number 10, “Have you ever had seizures or crisis?”.

The diagnostic performance of the screening test was assessed using different cut-off points: ≥2 positive responses had a sensitivity of 100% and specificity of 78%, ≥3 positive responses had a sensitivity of 85.7% and specificity of 91.2%, and ≥4 positive responses had a sensitivity of 85.7% and specificity of 97%. The cut-off point of ≥4 positive responses was selected. However, the fact that ≥2 positive responses showed high sensitivity should be considered (**table 4**). The two-step screening strategy proposed by Liang *et al*, whereby the presence of ≥4 positive responses to the questionnaire

were compared with antinuclear antibodies, is regarded as an imperfect gold standard to determine diagnostic test indicators.

Antinuclear antibody test was conducted for 22 patients with positive screening results out of which 17 (77.3%) showed positive results, and 19 (86.4%) were assessed by a rheumatologist. Based on the different classification criteria for SLE, diagnosis was determined as follows: 7/19 (36.9%) met the revised 1997 ACR criteria, 8/19 (42.1%) met the SLICC criteria and 7/19 (36.9%) met the 2019 ACR/EULAR criteria. Within the group of patients with negative screening results, 1 (0.20%) patient had a prior diagnosis of SLE.

In the group with negative screening results, question 9 received the highest number of positive responses (23.6%), while in the group of positive screening results,

**Table 5** Comparison between the group with positive and negative findings on the screening test

	Negative result (<4 positive responses) n=518 (95.9%)	Positive result (≥4 positive responses) n=22 (4.1%)	P value
Age at the time of inclusion	29.1±7.1	28.0±7.0	0.932
Gestational age at the time the questionnaire was conducted	24.2±7.9	23.3±7.4	0.506
Previous pregnancies	2.5±1.5	2.2±1.3	
History of autoimmune diseases other than SLE	48 (9)	3 (14)	<0.0001
Total of positive responses	<b>N (%)</b>	<b>N (%)</b>	
Have you ever suffered from arthritis or joint swelling for more than 3 months?	14 (2.7)	8 (36.4)	<0.0001
Have your fingers turned pale, purple/blue or numb in the cold?	69 (13.3)	17 (77.3)	<0.0001
Have you ever had sores in your mouth for more than 2 weeks?	14 (2.7)	8 (36.4)	<0.0001
Have you been diagnosed with low blood cell count (anaemia, low white cell count or low platelet count)?	43 (8.3)	15 (68.2)	<0.0001
Have you ever had a prominent rash (red skin) on your cheeks for more than a month?	14 (2.7)	9 (40.9)	<0.0001
Does your skin become excessively red, more than expected, after being out in the sun?	29 (5.6)	15 (68.2)	<0.0001
Have you ever had pain when you breathe deeply for several days?	16 (3.1)	8 (36.4)	<0.0001
Have you been told that you ‘release’ protein in your urine?	54 (10.4)	11 (50)	<0.0001
Have you ever had rapid and abundant loss of hair?	122 (23.6)	13 (59.1)	<0.0001
Have you ever had seizures or crisis?	20 (3.9)	5 (22.7)	<0.0001

question 2 received the highest number of positive responses (77.3%) (table 5).

## DISCUSSION

The screening strategy for SLE must meet the following criteria: high sensitivity to detect the highest number of patients in a population and high specificity to avoid misclassification of healthy subjects; likewise, predictive values must be high to ensure a test has an acceptable cost:benefit ratio.<sup>21</sup> In this study, the two-step screening strategy proposed by Liang *et al*,<sup>14</sup> which was used first on a mixed population, was used to determine the effectiveness of the screening questionnaire in the diagnosis of SLE. The questionnaire survey included 540 patients; 22 (4.07%) obtained positive screening results. In the study published by Liang *et al*, 167 (58.8%) out of 284 patients obtained positive results. However, the study included 110 patients who were not diagnosed with lupus and 118 patients with confirmed lupus. In the study conducted by Benucci *et al*, out of 32 521 patients who completed the questionnaire, 30 (0.09%) obtained positive results. However, their study included men and women from the general population, aged 18 years and above.

The most frequent occurrence of positive response within the group with negative screening results was to question 9 on rapid and abundant hair loss (23.6%), while the most frequent occurrence of positive response within the group with positive screening results was to question 2 on fingers turning pale, purple/blue or numb in the cold (77.3%). These results are very similar to those of Liang, who found 80% positive responses to question 2 within the group of patients with lupus. However, within the group with negative screening results, question 2 received the most frequent positive responses at a frequency of 9%, followed by question 9 at a frequency of 3%.

The diagnostic test performance of the screening questionnaire alone is as follows: sensitivity=0.88; specificity=0.98; PPV=0.37. Our results are better than those reported by Liang who showed a sensitivity of 0.87, specificity of 0.98 and PPV of 0.14. The diagnostic test performance of the screening questionnaire and antinuclear antibody test is as follows: sensitivity=0.86; specificity=0.97; PPV=0.77. These results are similar to those reported by Liang, who showed a sensitivity of 0.95, specificity of 0.95 and PPV of 0.79.

Based on the results obtained and given that antinuclear antibody testing is more accessible than assessment by a rheumatologist, we suggest conducting an SLE screening questionnaire survey for pregnant patients during their first visit. The presence of  $\geq 4$  positive responses should be used as a cut-off for further testing. An antinuclear antibody test must be requested for these patients; those with a positive antinuclear antibody test results must be referred to a rheumatologist. This strategy can help improve patient selection and reduce the number of false-positive results. We suggest referring patients with positive questionnaire results to a rheumatologist even before getting

the results of the antinuclear antibody test. However, this will depend on whether the specialist at the centre is following the screening strategy. Of note, this strategy increases sensitivity at the expense of specificity and false positives. The cut-off point of  $\geq 4$  positive responses was used for the antinuclear antibody test and assessment by a rheumatologist, as it showed the highest specificity, but the presence of  $\geq 2$  positive responses showed a sensitivity of 100%. We suggest referring patients with  $\geq 2$  positive responses to an antinuclear antibody test and assessment by a rheumatologist, especially when positive responses are not subjective events such as hair loss and hands turning pale, blue or purple, both of which are common events during pregnancy. This alternative approach may lead to one in 25 women having false-positive ANA, which could cause unnecessary anxiety and more expenses for the institution to continue the tests to detect one out of 25 patients with positive questionnaire. In this case, we consider that the high sensitivity of  $\geq 2$  positive responses a expenses of the low specificity is not worth it.

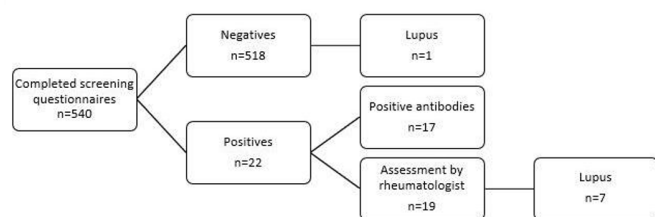
A screening programme for lupus has benefits such as determining the actual prevalence of lupus in the population of patients that visits the Institute, and this can help direct resources and efforts towards the care and monitoring of these patients and ensuring early diagnosis and treatment to reduce risks related to SLE. This study proposes a way to improve lupus diagnosis; the large number of patients is a strength, but as expected, SLE cases are limited, which limits the strengths of the findings.

One limitation of this study was that during assessment by a rheumatologist, some patients reported difficulties in interpreting the questionnaire questions. To avoid this, we suggest that patients complete the questionnaire during their first visit with the assistance of their physician, so that clarifications can be provided, when needed, to ensure the patients are giving objective responses.

This study does not seek to transfer the results to the general population. The main limitation of our study is the fact that, for methodological purposes, patients with negative screening results were considered as to have negative antinuclear antibody status and negative lupus status. The antinuclear antibody test may yield positive results in patients with other autoimmune diseases or even in individuals with no symptoms. Therefore, the diagnosis of SLE should be based on clinical and immunological data and not exclusively on the presence or absence of antinuclear antibodies. Likewise, all proposed classification criteria were compared with the expert opinion of a lupus specialist, which is considered a gold standard for SLE diagnosis. However, our method is based on approved criteria that can improve patient selection and ensure timely care and assessment.

## CONCLUSIONS

The screening questionnaire for SLE shows high sensitivity and high specificity for the diagnosis of SLE. Given



**Figure 1** Patient distribution.

its usability and cost:benefit ratio, this test should be used in all patients coming in for a first visit, to improve the selection of patients who are required antinuclear antibody testing and those referred to a rheumatologist. Early diagnosis of SLE can decrease maternal and fetal complications related to this disease; therefore, we recommend the use of this two-step screening programme for all patients.

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**Patient consent for publication** Not required.

**Ethics approval** This study was reviewed by the Ethics Committee of the Division of Maternal-Fetal Medicine of the National Institute of Perinatology "Isidro Espinosa de los Reyes". This committee authorised the informed consent and the processing of the data to maintain the anonymity of the participants and their information.

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**Data availability statement** Data are available in a public, open access repository. Data are available on reasonable request.

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