ORIGINAL INVESTIGATIONS

Assessment of the prevalence of systemic lupus erythematosus in women with reproductive health problems in the Russian Federation. Results of the multicenter pilot PRISMA study

Reshetnyak T.M.[1,2], Trofimov E.A.[3], Abdulganieva D.I.[4], Astakhova A.D.[5], Enikeeva G.R.[6], Seredavkina N.V.[1], Zonova E.V.[7], Bugrova O.V.[8], Zlobin M.V.[9], Klimenko A.A.[10,11], Ilivanova E.P.[12], Ostroushko I.A.[13], Glukhova S.I.[1], Pozharov I.V.[14], Nekrasova N.B.[15,16], Mutovina Z.Yu.[17], Trofimova A.S.[3], Yakupova S.P.[4], Remnev A.E.[18], Lila A.M.[1,2]

[1]V.A. Nasonova Research Institute of Rheumatology, Moscow; [2]Russian Medical Academy of Continuing Professional Education, Ministry of Health of Russia, Moscow; [3]North-Western State Medical University named after I.I. Mechnikov, Ministry of Health of Russia, Saint Petersburg, Russia; [4]Kazan State Medical University, Ministry of Health of Russia, Kazan; [5]Lapino Clinical Hospital "Mother and Child", Moscow; [6]City Clinical Hospital №13, Republic of Bashkortostan, Ufa; [7]Novosibirsk State Medical University, Ministry of Health of Russia, Novosibirsk; [8]Orenburg State Medical University, Ministry of Health of Russia, Orenburg; [9]N.A. Semashko Nizhny Novgorod Regional Clinical Hospital, Nizhny Novgorod; [10]Pirogov Russian National Research Medical University, Ministry of Health of Russia, Moscow; [11]City Clinical Hospital №67 named after L.A. Vorokhobov, Moscow Healthcare Department, Moscow; [12]Leningrad Regional Clinical Hospital, Saint Petersburg; [13]Voronezh Regional Clinical Hospital №1, Voronezh; [14]M.F. Vladimirsky Moscow Regional Research Clinical Institute, Moscow; [15]Scientific Center of Laser Medicine LLC, Rostov-on-Don; [16]Clinical Diagnostic Center "Zdorovye", Rostov-on-Don; [17]Moscow Clinical Scientific Center, Hospital №52, Moscow Healthcare Department, Moscow; [18]AstraZeneca Pharmaceuticals LLC, Moscow

[1]34A, Kashirskoe Shosse, Moscow 115522, Russia; [2]2/1, Barrikadnaya Street, Build. 1, Moscow 125993, Russia; [3]41, Kirochnaya Street, Saint Petersburg 195015, Russia; [4]49, Butlerova Street, Kazan 420012, Russia; [5]111, 1st Uspenskoe Shosse, Lapino, Odintsovsky Urban Okrug, Moscow Region 143081, Russia; [6]28, Nezhinskaya Street, Ufa 450112, Russia; [7]52, Krasny Prospekt, Novosibirsk 630091, Russia; [8]6, Sovetskaya Street, Orenburg 460014, Russia; [9]190, Rodionova Street, Nizhny Novgorod 603093, Russia; [10]1, Ostrovityanova Street, Moscow 117513, Russia; [11]2/44, Salyama Adilya Street, Moscow 123423, Russia; [12]45, Lunacharskogo Avenue, Build. 2A, Saint Petersburg 194291, Russia; [13]151, Moskovsky Prospekt, Voronezh 394066, Russia; [14]61/2, Shchepkina Street, Moscow 129110, Russia; [15]132, Krasnoarmeyskaya Street, Rostov-on-Don 344010, Russia; [16]70/3, Dolomanovsky Lane, Rostov-on-Don 344011, Russia; [17]3, Pekhotnaya Street, Moscow 123182, Russia; [18]21, 1st Krasnogvardeysky Proezd, Build. 1, Moscow 123112, Russia

Objective: *to assess the prevalence of systemic lupus erythematosus (SLE) in the Russian population of patients with reproductive health problems (RHP).*

Material and methods. *Patients were enrolled in 2023–2024 at 15 clinical centers in 5 federal districts of the Russian Federation. Women referred by a gynecologist, reproductive specialist, or general practitioner to a rheumatologist to rule out a systemic autoimmune rheumatic disease (SARD) were included. The study comprised two visits: the first screening visit and the second (final, 2–6 weeks later) visit, during which SARD verification was performed. Descriptive statistics methods were used for data analysis. The frequency of features in two independent study groups was compared using χ^2 (Pearson's test), odds ratios with 95% confidence intervals. The association between antibody levels and clinical manifestations was assessed by constructing a regression model.*

Results and discussion. *Of 631 women examined, 612 (97.0%) met the inclusion criteria; 19 women were excluded because they did not have RHP (infertility or pregnancy loss) and/or signs of SARD. Antinuclear factor (ANF) was determined in 590 of 612 women. ANF positivity was detected in 238 (40.3%) of 590 patients. Of these 238 women, antinuclear antibodies were detected in 71, and decreased complement component levels were found in 55 (C3 in 28 and C4 in 27). SARD was diagnosed in 71 (11.6%) cases: SLE in 27 (4.4%) (definite in 23 and probable/incomplete in 4), mixed connective tissue disease was newly diagnosed in 36 (5.9%), Sjugren's disease in 4 (0.7%), and systemic sclerosis in 4 (0.7%). Among ANF-positive patients with RHP, 167 (70.2%) of 238 had no SARD.*

Conclusion. *In this multicenter pilot study, the frequency of SLE in the Russian population among women with RHP was 4.4% (27 of 612 women), and the overall frequency of SARD was 11.6% (71 of 612). ANF positivity occurred more than three times (40.3%) more often than newly diagnosed SARD cases, indicating the need for further studies to clarify the reasons for ANF occurrence in women of childbearing age with RHP and for their longitudinal follow-up.*

Keywords: *systemic lupus erythematosus; systemic autoimmune rheumatic diseases; reproductive health problems; antinuclear factor; multicenter pilot study.*

Contact: *Tatyana Magomedalievna Reshetnyak;* ***t_reshetnyak@yahoo.com***

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Systemic lupus erythematosus (SLE) predominantly affects women of childbearing age, and preserving their reproductive health is a key priority for practicing rheumatologists. Research into reproductive system disorders in SLE is becoming increasingly important as assisted reproductive technology become more sophisticated and widely available. [1, 2] Support for patients with SLE who have reproductive issues is only possible through a multidisciplinary approach involving gynecologists, andrologists, reproductive specialists, endocrinologists, immunologists, obstetricians, and other specialists.

In women with SLE, fertility (the ability to conceive and give birth to a child) may be impaired. Long-term treatment with cyclophosphamide is one of the known factors that reduce fertility in women with SLE. Reversible subfertility may develop during treatment with non-steroidal anti-inflammatory drugs. The psychosocial effects of the condition can also affect fertility. High-activity SLE is often accompanied by menstrual irregularities (amenorrhea and temporary infertility), and the presence of antiphospholipid (aPL) antibodies leads to pregnancy loss (early and late miscarriages, intrauterine fetal death, etc.). However, a number of issues regarding the impact of SLE on fertility and the realization of reproductive potential require further research. [3, 4]

The importance of timely diagnosis of SLE cannot be overstated. For patients with reproductive issues, verification of SLE is not a priority; as a result, the diagnosis and initiation of timely, effective SLE treatment may be significantly delayed. This contributes to the development of organ damage, negatively affecting the quality of life, fertility, and pregnancy outcomes. [5, 6] Studies aimed at improving the quality of medical care for these patients and therefore enhancing the reproductive health in women with SLE are absolutely necessary, and this served as the basis for this article.

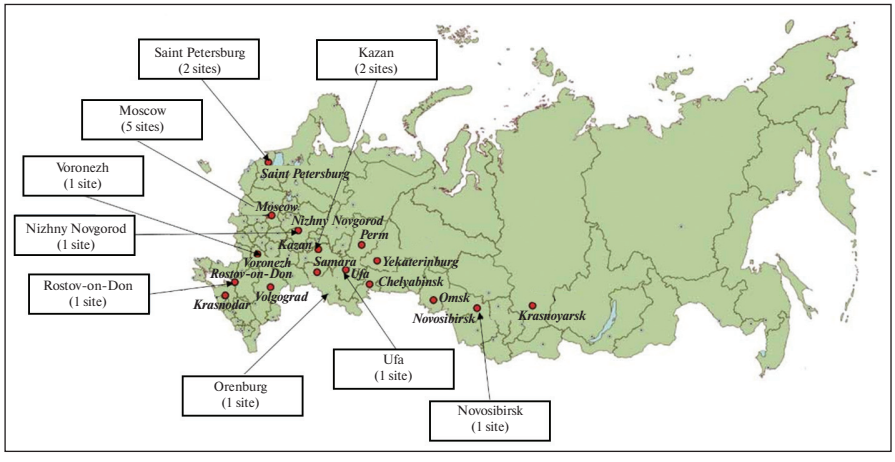

Fig. 1. *Regions participating in the PRISMA study*

The aim of the study is to evaluate the prevalence of SLE in the Russian female patient population with reproductive issues.

Materials and methods. A multicenter prospective pilot study PRISMA (The Prevalence Evaluation of Systemic Lupus Erythematosus in Russian Patients With Reproductive Issues) was conducted. Patients were enrolled in 2023–2024 at 15 clinical sites in 5 federal districts of the Russian Federation. The study included women who had been referred to a rheumatologist by a gynecologist, reproductive specialist, or general practitioner to rule out systemic autoimmune rheumatic disease (SARD). The regions that participated in the study are shown in Fig. 1.

A total of 631 women were examined, and 612 (97.0 %) patients were enrolled in the study. Another 19 women did not meet the inclusion criteria (they did not exhibit signs of SARD and reproductive issues). To rule out SLE, 612 patients with reproductive issues were examined. The study design is shown in Fig. 2.

An individual case report form was completed for each woman and included demographic data, complaints, comorbidities, the 1997 and 2012 SLE diagnostic criteria, [7, 8] treatment history prior to and during study enrollment, and obstetric and gynecological history, in accordance with diagnostic criteria. [9, 10] Concomitant non-rheumatic comorbidities were recorded based on source medical records. The history of viral infections was assessed based on the examination findings by a gynecologist or reproductive specialist.

Inclusion criteria: age 19–45 years; suspected SARD; history of obstetric and gynecological complications; signed informed consent to participate in the study.

Exclusion criteria: age > 45 years; an acute infectious disease, or a relapse of a chronic infectious disease, or any other condition that, in the physician's opinion, could affect the accuracy of immunology test results; SLE or another SARD previously confirmed by a rheumatologist.

The study included two visits: the first was a screening visit, and the second was the final visit (2–6 weeks later), during which the SARD diagnosis was verified.

The anthropometric and clinical characteristics of the women enrolled in the study are presented in Table 1.

Non-rheumatic comorbidities were reported in 387 (63.2%) of the 612 patients; the most common of which were a history of viral infections (26.3%) and thyroid disorders (19.9%). Information regarding the history of viral infections was based on data from previous examinations due to reproductive issues. Of the 161 women with a history of viral infections, 37 (23%) had polymerase chain reaction test results.

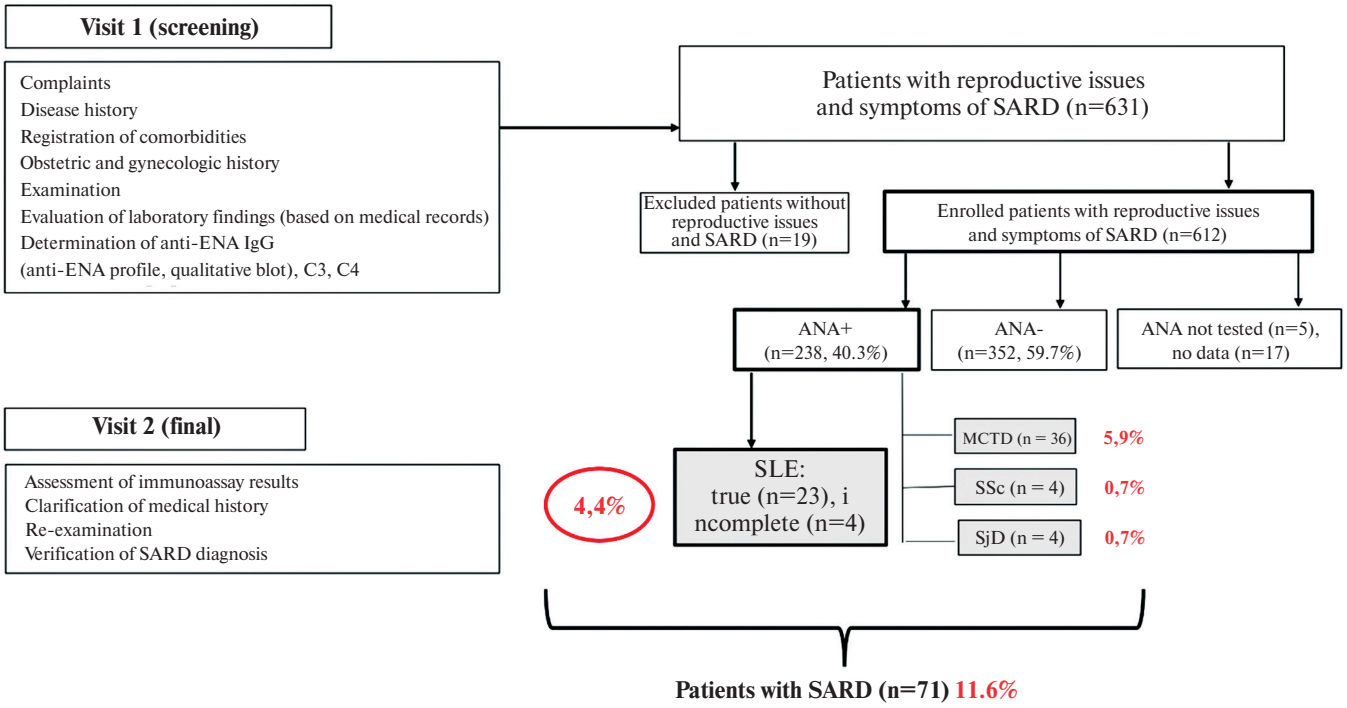

Fig. 2. *Study design. ENA (extractable nuclear antigen) – extractable nuclear antigens; ANF – antinuclear factor; MCTD – mixed connective tissue disease; SSc – systemic sclerosis; SD – Sjögren's disease.*
The percentage of women was calculated from the number included in the study (n=612)

A total of 225 (36.8%) patients were diagnosed with infertility; the most common causes of which were endometriosis, cervical ectropion, polycystic ovary syndrome, and menstrual irregularities. A history of other gynecological disorders was reported in 138 (22.5%) of the 612 women.

The list of "Other disorders" includes conditions affecting other organ systems. "Infections and infestations" include chronic infections (chronic urogenital infection), as well as one case each of syphilis, parasitic infestation, viral hepatitis B, and herpes zoster. There were patients with multiple comorbidities.

Seventy percent (70%) of the women had a history of pregnancy (Table 2). Obstetric issues (pregnancy loss) were observed in 402 (65.6%) of 612 cases. Spontaneous abortions accounted for the majority of obstetric abnormalities (57.7%). Eighty-three (83) (19.3%) of 430 women had a history of pregnancy loss after 10 weeks of gestation.

The clinical symptoms of SARD were reported in 254 women. The predominant clinical and laboratory findings suggestive of SLE and serving as the grounds for referral to a rheumatologist were arthralgia (41.5%), arthritis (7.2%), skin changes, including erythematous rashes resembling acute cutaneous lupus erythematosus and photodermatitis (20.4%), myalgia (11.9%; Fig. 3), and ANA positivity (n = 238, 38.9%). Isolated Raynaud's phenomenon was reported in 20 (3.7%) of 612 women.

ANAs were determined by indirect immunofluorescence (IIF) using Hep2 cells (human laryngeal carcinoma epithelial cells) as the substrate. The maximum ANA titer, as well as the intensity and type of immunofluorescence, were taken into account. The content of 16 anti-ENA IgG antibodies (anti-ENA profile) was determined by qualitative immunoblot (IB) assay for antinuclear antibodies (ANAs), which included testing for anti-Sm antibodies (anti-Sm), anti-double-stranded DNA antibodies (anti-dsDNA), anti-ribonucleoprotein antibodies (anti-RNP), anti-SSA (Ro) 52 kDa and 60 kDa antibodies (anti-SSA), anti-SSB (La) antibodies (anti-SSB), anti-cardiolipin antibodies (aCL), anti-centromere B antibodies (anti-CENT-B), anti-proliferating cell nuclear antigen antibodies (anti-PCNA), anti-ribosomal P antibodies (anti-RibP), and anti-mitochondrial M2 antibodies (AMA-M2).

In the second stage of the study, ANA-positive women were examined for SARD: SLE, SSc, SjD, dermatomyositis, MCTD, overlap syndromes. [11] Women with obstetric abnormalities but without signs of SARD who met the diagnostic criteria for antiphospholipid syndrome were isolated. [9, 12]

Statistical data analysis Given the observational nature of the study, a single dataset was used for analysis — the full analysis set (FAS). The analysis included all female patients who met the inclusion and exclusion criteria and had at least baseline data (complete or partial) collected during visit 1. No data imputation methods were used in this study as data were collected at only one time point following the baseline. Descriptive statistical methods were used for numerical variables: number of non-missing values (N), minimum value (min), maximum value (max), arithmetic mean (M), and the standard deviation (SD).

Absolute frequencies (n/N) and percentages are presented for all categorical variables (based on the available sample size). If necessary, the exact 95% Clopper-Pearson confidence interval is also provided.

To analyze differences in the frequencies between two independent groups of study subjects, we used the chi-square test (Pearson's test) and the odds ratio (OR) with a 95% CI.

Table 1. Characteristics of patients included in the study (n=612)

Parameter	Value
Age, years, Me; 95% CI; min–max	34; 32.9–33.9; 19–45
Body weight, kg; Me; 95% CI; min–max	63; 64.8–67.0; 40–130
Height, cm; Me; 95% CI; min–max	165; 165.2–166.2; 145–196
BMI, kg/m^2, Me; 95% CI; min–max	22.85; 23.60–24.40; 15.43–44.98
History of viral infections (rubella, herpes simplex virus type 2, Epstein–Barr virus, retroviruses, cytomegalovirus)	161 (26.3)
Thyroid disorders	122 (19.9)
Hypertension	37 (6.1)
Pregestational diabetes mellitus	17 (2.8)
Kidney disease with renal failure	9 (1.3)
Pulmonary hypertension	4 (0.7)
Infertility	225 (36.8)
Neoplasms benign, malignant and unspecified (including cysts and polyps) of the genitals	72 (11.8)
Pelvic infections and infestations	38 (6.2)
Surgical and other medical procedures	15 (2.5)
Endocrine disorders (ovarian dysfunction, hyperprolactinemia)	8 (1.3)
Congenital, familial, and genetic disorders (uterine malformation, dermoid cyst)	5 (0.5)
Other disorders	267 (43.6)

Note. The data are shown as n (%) unless otherwise specified. Me, median; CI, confidence interval; BMI, body mass index.

Comorbidities were encoded by System Organ Class and Preferred Terms according to the Medical Dictionary for Regulatory Activities (MedDRA).

Results. ***Immunological disorders.*** ANA positivity was the most common reason to undergo examination for SARD. ANA test results were obtained for 590 of 612 women. Of the 590 cases, 238 (40.3%) tested positive, while the remaining 352 (59.7%) tested negative. ANA was not tested in 5 (0.8%) of 612 patients, and in 17 (2.8%) the result was not known. The minimum ANA titer was 1/320 and the maximum ANA titer was 1/5120. ANA positivity was associated with reproductive issues. They were found in 184 (77.3%) of 238 ANA-positive patients and in 127 (36%) of 352 ANA-negative patients (OR 0.16; 95% CI 0.11–0.23; $p < 0.001$). Signs suggestive of SLE (see Fig. 3), which served as the grounds for referral to a rheumatologist, were observed in 196 (82.4%) of 238 women with ANA and in 58 (16.4%) of 352 without ANA (OR 0.04; 95% CI 0.01–0.06; $p < 0.001$).

Other causes of ANA positivity (n = 51, 21.4%) included chronic infections (n = 30), a history of viral infections (n = 14), and thyroid disorders (autoimmune thyroiditis, n = 7).

Various non-rheumatic chronic comorbidities were also reported in ANA-negative women (n = 29, 8.2%).

The effects of ANA positivity on pregnancy outcomes are shown in Table 3. Stillbirths occurred significantly more frequently in ANA-positive women than in ANA-negative women (35.3% vs. 6.5%), and cases of infertility were also slightly more common (42.9% vs. 34.9%, respectively). At the same time, pregnancy loss before and after week 10 of gestation was more common in ANA-negative women (see Table 3). Namely, early miscarriage was reported in 164 (46.6%) of 352 women without ANA and in 73 (30.7%) of 238 with ANA (OR 1.97; 95% CI 1.4–2.8; $p < 0.001$).

ANA-positive patients were tested for other antibodies (Table 4).

In ANA-positive women, anti-SSA (60 kDa) and anti-dsDNA antibodies were the most commonly detected. Anti-dsDNA antibodies with ELISA and IB assays were detected in 6.7% and 1.9% of patients, respectively. This discrepancy can be attributed to differences in the sensitivity and specificity of the methods.

SARD. During the second visit, patients who met the criteria for SARD were selected from 238 ANA-positive women. This group included 71 (29.8%) women: 23 (34.3%) with SLE, 36 (50.7%) with MCTD, 4 (6%) with SSc, and 4 (6%). Four other ANA-positive women also had hematological and immunological abnormalities (Coombs-positive anemia, leukopenia, thrombocytopenia, and decreased complement component C3 and C4 levels), leading to a diagnosis of incomplete SLE. [13]

Newly diagnosed SARD was reported in 11.9% of 612 women. The prevalence of newly diagnosed SLE was 4.4% (95% CI 1.1–2.5).

Table 2. Frequency of obstetric complications in patients included in the study

Parameter	n/N (%)
History of pregnancy, n (%):	
No	182/612 (29.7)
Yes	430/612 (70.3)
Pregnancies, Me; 95% CI; min–max*	2; 2–3; 1–12
Abortion for medical reasons, n (%):	
No	300/430 (69.8)
Yes	130/430 (30.2)
Abortions, Me; 95% CI; min–max*	1; 1–2; 0–8
Elective abortion, n (%):	
No	370/430 (86.0)
Yes	70/430 (14.0)
Abortions, Me; 95% CI; min–max*	1; 1–2; 1–4
Spontaneous abortion, n (%):	
No	182/430 (42.3)
Yes	237/430 (57.7)
Miscarriages, Me; 95% CI; min–max*	1; 1–2; 1–12
Live birth, n (%):	
No	233/430 (54.7)
Yes	197/430 (45.8)
Live births, Me; 95% CI; min–max*	1; 1–2; 1–6
Stillbirth, n (%):	
No	323/430 (75.1)
Yes	107/430 (24.2)
Stillbirths, Me; 95% CI; min–max*	1; 1–1; 1–3
FGR, n (%):	
No	388/430 (90.2)
Yes	42/430 (9.8)
FGR cases, Me; 95% CI; min–max*	1; 1–2; 1–3
Preterm birth, n (%):	
No	394/430 (91.6)
Yes	36/430 (9.4)
Preterm births, Me; 95% CI; min–max*	1; 1–1; 1–2
Preeclampsia, n (%):	
No	408/430 (94.9)
Yes	22/430 (6.1)
Preeclampsia cases, Me; 95% CI; min–max*	1; 1–1; 1–2
Gestation with neonatal death, n (%):	
No	414/430 (96.3)
Yes	16/430 (4.7)
Neonatal deaths, Me; 95% CI; min–max*	1; 1–2; 1–3
Delivery, n (%):	
Caesarean section	71/197** (36.0)
Normal delivery	126/197 (64)

Note. CIs were calculated for patients with the attribute; n, number of women with or without the attribute; N, total number used to calculate the percentage (%); *, parameters calculated for a single woman; **, number of patients who had or did not have a normal delivery among women with live births; pregnancy outcomes were calculated based on the total number of pregnancies. FGR, fetal growth restriction.

In the remaining 167 (70.2%) ANA-positive women, despite the presence of certain symptoms (arthralgia, skin rashes, myalgia, photosensitivity) that may occur in SLE, the SARD diagnosis was not confirmed (see Fig. 3). As shown in Fig. 3, the most common complaint was arthralgia, which was reported by 254 (41.5%) of the 612 women. At the same time, signs of arthritis were observed in 44 (17.3%) of the 254 women with arthralgia; hair loss and various skin rashes were the next most common symptoms. Twenty-three (23) patients met the 1997 ACR (American College of Rheumatology) diagnostic criteria for SLE, while 4 had < 4 diagnostic criteria for SLE; therefore, they were diagnosed with incomplete SLE.

A comparison of SLE diagnostic criteria in patients with confirmed SLE and ANA-positive women without SARD is shown in Fig. 4.

The most common clinical signs in women with SLE were butterfly-shaped erythema, arthritis and serositis, primarily pleuritis,

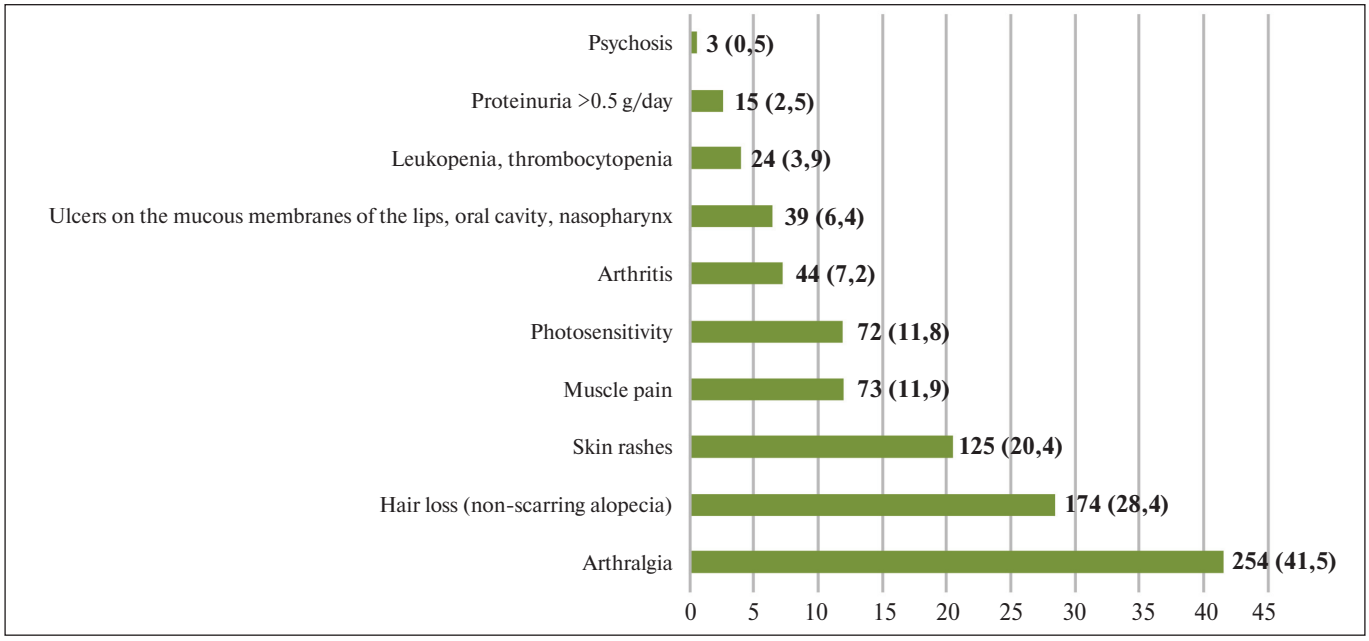

Fig. 3. *Frequency of clinical symptoms suspicious for SARD in patients included in the study (n=612), n (%)*

which was accompanied by pericarditis in 2 women. Photosensitivity was observed in both SLE and ANA+ without SLE.

The incidence of infertility and pregnancy outcomes in ANA-positive women with SLE and other SARDs are shown in Table 5. Pregnancy loss was reported in 184 (77.3%) of the 238 patients with ANA, and infertility was observed in just under half of them (see Table 5). Spontaneous abortions were statistically significantly associated with SARD, while infertility was associated with SLE.

Discussion. SLE is a chronic autoimmune disease with multisystem involvement that is associated with significant morbidity and increased mortality. There are at least 5 million people with SLE worldwide. [14] There is no data available on the overall prevalence of SLE in the Russian Federation. According to data from the territorial registry of the Republic of Crimea, the prevalence of SLE was 5.59 per 100,000 people in 2013, while the incidence rate was 0.29 per 100,000 in 1994 to 2003, 0.49 per 100,000 in 2004 to 2013, peaking at 1.35 per 100,000 in 2010. [15]

In our study, various non-rheumatic comorbidities were reported in 63.2% of women. Just over a quarter of them showed signs of having had viral infections. Thyroid disorders were diagnosed in 20% of the patients. Various atopic skin and musculoskeletal manifestations have been described as extraglandular signs of thyroid pathology. [16] The presence of comorbidities (past viral infections and thyroid disorders were the most commonly reported in the study group) indicates a high prevalence of symptoms mimicking SARD.

The high rate of ANA positivity (40.3%) in our patients with reproductive issues may be attributed to previous viral infections. In some cases, the response of the immune system to a pathogen can cause organ damage (immunopathology) or lead to autoimmune disorders. There are several mechanisms causing virus-induced autoimmune disorders, including molecular mimicry. [17, 18] Viral infections, including the recent pandemic of the novel coronavirus infection and the associated post-COVID syndrome (long COVID), can manifest as various non-specific clinical syndromes accompanied by immunological abnormalities. [19]

In addition, 22.5% of the women had gynecological disorders, with endometriosis and cervical ectropion being particularly common; moreover, more than a third of the women (36.8%) suffered from infertility. According to the literature, endometriosis is frequently associated with autoimmune disorders, providing further evidence of the role of immune dysfunction in the pathogenesis of this disease. [20, 21] Our data regarding the high prevalence of comorbidities (including SARD) in women with reproductive issues are consistent with reports on the role of various factors in the mechanisms of infertility and pregnancy outcomes.

SLE has traditionally been considered a contraindication to pregnancy. However, improvements in medical care have made pregnancy possible for the majority of women with this disease. At the same time, women with SLE continue to experience a higher incidence of pregnancy complications, leading to increased morbidity and mortality in both the fetus and the mother compared to women without SLE. [22–26] There have been isolated reports of sexual dysfunction in SLE, but these findings are inconsistent. [27] Infertility may be a symptom of an underlying chronic disease. According to data from the US National Registry, up to 15% of

Table 3. Presence of RHP depending on ANF positivity, n (%)

Symptom/sign	ANA+ (n=238)	ANA- (n=352)
Spontaneous abortion before week 10 of gestation	73 (30.7)	164 (46.6)*
Pregnancy loss after week 10 of gestation	9 (3.9)	58 (16.5)
Stillbirth	84 (35.3)*	23 (6.5)
Infertility	102 (42.9)	123 (34.9)

Note. Some women exhibited multiple concomitant symptoms. *, $p < 0.05$.

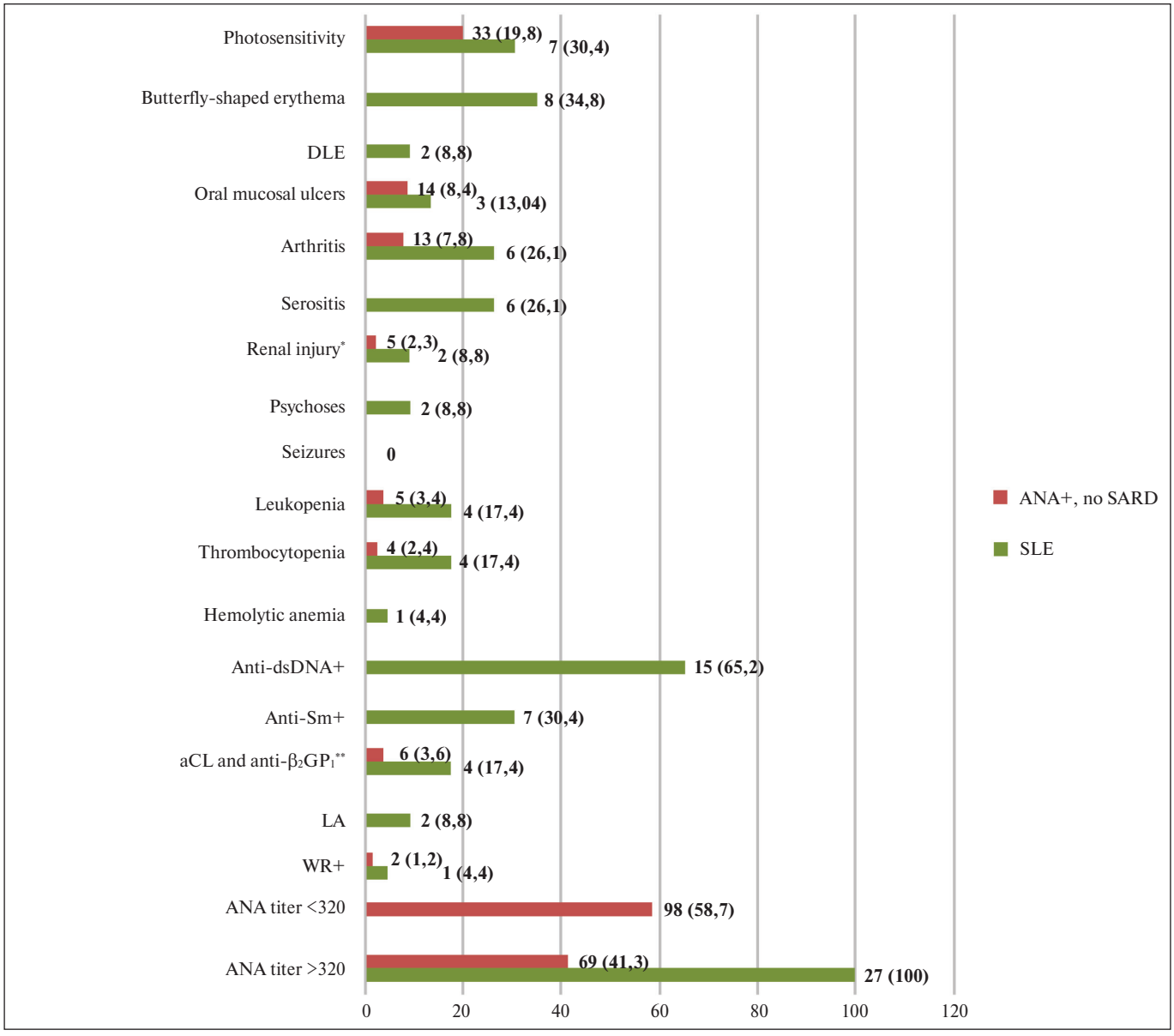

Fig. 4. *Frequency of SLE classification criteria in patients with definite SLE (according to the 1997 ACR criteria) and in ANF-positive women without SARD, n (%). DLE – discoid lupus erythematosus; WR – Wassermann reaction.* * *– chronic pyelonephritis;* ** *– aCL and anti-β2GP1 were tested once; p>0.05*

married couples suffer from infertility, and roughly the same percentage of women of reproductive age seek medical help for infertility each year. [28]

In our study, ANA positivity was statistically significantly associated with reproductive issues, and symptoms mimicking SARD were statistically more frequently observed in women with ANA. ANA positivity observed in 40.3% of cases was the primary reason for testing to rule out SARD; in 82.4% of women, it was accompanied by other clinical and laboratory signs of autoimmune disease. In our cohort, the incidence of infertility among ANA-positive and ANA-negative women was comparable (42.9% and 32.9%, respectively). There have been isolated reports on the incidence of infertility in SARD, particularly in SLE. [3, 4, 27]

We analyzed the prevalence of ANA positivity and its association with obstetric and gynecologic history. As is well known, ANAs are a heterogeneous group of autoantibodies that react with various components of the cell nucleus. [29] ANAs are detected by IIF using Hep2 cells in 25–30% at titer 1:40, in 10–15% at 1:80, and in 5% of healthy individuals at titer ≥ 1:160. ANAs are detected at titer ≥ 1/40 in 25–30% of healthy relatives of SARD patients. Elevated ANA levels are observed in SARD, inflammatory liver and thyroid disease, infections (including latent ones), oncological processes, and when taking certain medications. [30] Our data confirm a high prevalence of ANAs in women with reproductive issues.

A number of studies have noted a link between recurrent fetal loss syndrome and the presence of ANAs in the blood. In a meta-analysis by M.B. Cavalcante et al., [31] the prevalence of ANAs detected by IIF was significantly higher in the group with recurrent fetal loss syndrome — 20.6% (288 of 1,400 examined) vs. the

Table 4. Frequency of different antibodies detected in ANF-positive patients according to immunological testing

Antibodies	n/N (%)
Anti-SSA (60 kDa)	21/222 (9.5)
Anti-dsDNA (ELISA)	15/223 (6.7)
Anti-SSA (52 kDa)	12/214 (5.6)
Anti-SSB	11/218 (5.1)
Anti-Sm	7/218 (3.2)
AMA-M2	6/214 (2.8)
Anti-CENP-B	5/214 (2.3)
Anti-dsDNA (IB)	4/215 (1.9)
Anti-RNP/anti-Sm	4/216 (1.9)
Anti-RibP	4/214 (1.9)
Anti-Scl70	3/214 (1.4)
Anti-nucleosome antibodies	2/214 (0.9)
Anti-histone antibodies	1/214 (0.5)
Anti-PM-Scl	1/214 (0.5)
Anti-PCNA	0/214 (0)
Anti-Jo1	0/213 (0)
aPL (ELISA)	83/124 (66.9)
aCL IgG	30/124 (24.2)
aCL IgM	59/124 (47.6)
Total anti- 2GP1	40/69 (58.0)
LA	18/58 (31.0)
C3 hypocomplementemia	28/37 (75.7)
C4 hypocomplementemia	27/36 (75.0)

Note. n, number of positive patients; N, number of examined patients; ELISA, enzyme-linked immunosorbent assay; anti-Scl70, anti-Scl70 (topoisomerase-I) antibodies; anti-PM-Scl, antibodies that primarily target two exosome complex proteins: PM/Scl100 (protein similar to RNase D) and PM/Scl75 (one of proteins similar to RNase PH); anti-Jo1, antibodies against the Jo1 cytoplasmic antigen, IgG class autoantibodies directed against a cytoplasmic enzyme involved in the synthesis of transfer RNA; anti- 2GP1, antibodies against 2-glycoprotein 1; LA, lupus anticoagulant.

control group — 6.7% (72 of 1,080). The number of women with stillbirths in our study was significantly higher among ANA-positive women.

The cause of infertility may also be linked to autoimmune disorders, which can result from past infections and other comorbidities. On average, 10% of infertile couples have unexplained infertility. A systematic review conducted by A. Deroux et al., [32] using the keywords "infertility" and "autoimmunity," "reproductive technology, assisted reproduction, in vitro fertilization, and autoimmunity" found that ANA and/or aPL antibodies were more common in the population of infertile women; serum autoantibodies were associated with premature ovarian failure, which in itself is responsible for impaired fertility. Among autoantibodies, anti-ovarian antibodies may be detected, which may be present in the ANA panel.

It was surprising not only that one-third of the women included in the study tested positive for ANAs, but also that SARD was detected in patients with reproductive issues. The criteria for newly-diagnosed SARD in ANA positivity were met in 29.8% of patients (71 of 238): 50.7% had MCTD (36 out of 71),

Table 5. The Frequency of infertility and pregnancy outcomes in ANF positive women with SLE and other SARDs

Parameter	ANA+ patients			
	no SARD (n=167)	with other SARDs (n=44)	with SLE (n=27)	Total (n=238)
Spontaneous abortion, n (%) Miscarriages, min–max*	36 (21.6) 1–6	25 (56.8)** 1–6	12 (37.1) 1–5	73 (30.7)
Stillbirth, n (%)	2 (2.6)	4 (9.1)	1 (3.7)	84 (35.3)
Fetal growth restriction, n (%) Stillbirths, min–max*	5 (6.6) 1–3	1 (2.3) 1–1	0 0	9 (7.5)
Neonatal death, n (%) Neonatal deaths, min–max*	1 (1.3) 1–3	1 (2.3) 1–1	0 0	12 (5.04)
Infertility, n (%)	80 (47.9)	1 (2.3)	21 (77.8)**	102 (42.9)

Note. *, parameters calculated for a single woman; **, $p < 0.001$ (OR 0.21; 95% CI 0.10–0.42).

34.3% had SLE, 6% had SSc, and 6% had SjD. MCTD reported in half of the ANA-positive women with SARD in our study indicates the need for further monitoring of these patients. The diagnosis of MCTD is complicated by the fact that it can take several years for the full clinical presentation of a rheumatic disease (SLE, SSc, rheumatoid arthritis, or SjD) to emerge after the initial symptoms appear. [33, 34] In our study, 70.5% of ANA-positive women did not have SARD, although non-specific symptoms were reported; the percentage of women with SARD and, separately, with SLE exceeded the incidence rates in the general population. In a cohort of 612 women, the incidence of newly diagnosed SARD was 11%, and that of newly diagnosed SLE was 4.4%.

This study has a number of limitations. This was a cross-sectional study without follow-up of ANA-positive women; the immunology testing involved the determination of antinuclear antibodies in the IB assay without confirmation by ELISA. The presence of aPL antibodies and the predominance of women testing positive for SSA (60 kDa) necessitated further testing to verify the diagnosis.

Conclusion. In the multicenter pilot study, the prevalence of SLE among female patients in the Russian population with reproductive issues was 4.4% (27 of 612 women); the overall prevalence of SARD was 11.6% (71 of 612). The incidence of ANA positivity was more than 3 times higher (40.3%) than that observed in patients with newly-diagnosed SARD, indicating the need for further investigation into the causes of reproductive issues in women of childbearing age and for their dynamic follow-up.

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REFERENCES

1. Решетняк ТМ, Кошелева НМ, Насонов ЕЛ. Системная красная волчанка и беременность: до, во время гестации и после родов. Научно-практическая ревматология. 2023;61(3):292-297.
Reshetnyak TM, Kosheleva NM, Nasonov EL. Systemic lupus erythematosus and pregnancy: Before gestation, during and after childbirth. *Nauchno-Prakticheskaya Revmatologia*. 2023;61(3):292-297 (In Russ.).
2. Амирбекова Ж, Гаглоева Г, Жиенбаева А и др. Беременность при системной красной волчанке: обзор литературы. Репродуктивная медицина (Центральная Азия). 2023;(1):116-125.
Amirbekova Zh, Gagloeva G, Zhienbaeva A, et al. Pregnancy in systemic lupus erythematosus: review of literature. *Reproduktivnaya meditsina (Tsentral'naya Aziya)*. 2023;(1):116-125. (In Russ.).
3. Власова ГА, Перминова СГ, Кошелева НМ, Назаренко ТА. Репродуктивная функция у женщин с иммуновоспалительными ревматическими заболеваниями. Акушерство и гинекология. 2019;(10):51-9.
Vlasova GA, Perminova SG, Kosheleva NM, Nazarenko TA. Reproductive function in women with immuno-inflammatory rheumatic diseases. *Akusherstvo i ginekologiya*. 2019;(10):51-9. (In Russ.).
4. Власова ГА, Перминова СГ, Кошелева НМ, Веюкова МА. Влияние терапии иммуновоспалительных ревматических заболеваний на репродуктивную функцию. Акушерство и гинекология. 2021;(7):53-60.
Vlasova GA, Perminova SG, Kosheleva NM, Veyukova MA. The impact of therapy for immune-inflammatory rheumatic diseases on reproductive function. *Akusherstvo i ginekologiya*. 2021;(7):53-60. (In Russ.).
5. Лила АМ, Трофимов ЕА, Лила ВА. Системная красная волчанка: особенности течения у беременных и варианты терапии. Современная ревматология. 2015;9(3):43-47.
Lila AM, Trofimov EA, Lila VA. Systemic lupus erythematosus: Specific features of its course and therapy options. *Modern Rheumatology Journal*. 2015;9(3):43-47. (In Russ.).
doi: 10.14412/1996-7012-2015-3-43-47.
6. Кошелева НМ, Матьянова ЕВ, Федорова ЕВ, Клименченко НИ. Исходы беременности у больных ревматоидным артритом и системной красной волчанкой. Часть I. Материнские исходы. Научно-практическая ревматология. 2019;57(2):180-185.
Kosheleva NM, Matyanova EV, Fedorova EV, Klimenchenko NI. Pregnancy outcomes in patients with rheumatoid arthritis and systemic lupus erythematosus. Part I. Maternal outcomes. *Nauchno-Prakticheskaya Revmatologiya*. 2019;57(2):180-185. (In Russ.).
7. Petri M, Orbai AM, Alarcon GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*. 2012 Aug;64(8):2677-86. doi: 10.1002/art.34473.
8. Hochberg MC. Updating the American college of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1997 Sep;40(9):1725. doi: 10.1002/art.1780400928.

9. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* 2006 Feb;4(2):295-306. doi: 10.1111/j.1538-7836.2006.01753.x.
10. Женское бесплодие. Клинические рекомендации. Акушерство и гинекология. 2025;10 (Приложение).
Female Infertility. Clinical Guidelines. *Akusherstvo i ginekologiya.* (In Russ.). 2025;10 (Supplement).
11. Диффузные болезни соединительной ткани и другие системные воспалительные заболевания соединительной ткани. В кн.: Насонова ВА, Бунчук НВ, редакторы. Руководство по внутренним болезням. Ревматические болезни. Москва; 1997. С. 160-218.
Diffuse connective tissue diseases and other systemic inflammatory connective tissue diseases. In: Nasonova VA, Bunchuk NV, editors. A guide to internal medicine. Rheumatic diseases. Moscow; 1997. P. 160-218.
12. Решетняк Т.М. Антифосфолипидный синдром: диагностика и клинические проявления (лекция). Научно-практическая ревматология. 2014; 52 (1): 56-71.
Reshetnyak TM. Antiphospholipid syndrome: Diagnosis and clinical manifestations (a lecture). *Nauchno-Prakticheskaya Revmatologia.* 2014;52(1):56-71. (In Russ.).
13. Панафидина ТА, Попкова ТВ, Лила АМ, Насонов ЕЛ. Неполная системная красная волчанка. Собственное наблюдение и обзор литературы. Научно-практическая ревматология. 2023;61(6): 678-688.
Panafidina TA, Popkova TV, Lila AM, Nasonov EL. Incomplete systemic lupus erythematosus. Own observation and literature review. *Nauchno-Prakticheskaya Revmatologia.* 2023;61(6):678-688. (In Russ.).
14. Etchegaray-Morales I, Mendoza-Pinto C, Arellano-Avendaco FJ, et al. Epidemiology of systemic lupus erythematosus in Latin America. *Reumatol Clin (Engl Ed).* 2024 Dec; 20(10):560-566. doi: 10.1016/j.reumae.2024.11.003.
15. Шадуро ДВ, Белоглазов ВА, Петров АВ, Алиев КА. Современная клинико-эпидемиологическая характеристика системной красной волчанки по данным территориального регистра. Клиническая медицина. 2017;(2):140-147.
Shaduro DV, Beloglazov VA, Petrov AV, Aliev KA. Modern clinical epidemiological characteristic of lupus erythematosus based on the data of regional registry. *Klinicheskaya meditsina.* 2017;(2):140-147. (In Russ.).
16. Niehues T, von Hardenberg S, Velleuer E. Rapid identification of primary atopic disorders (PAD) by a clinical landmark-guided, upfront use of genomic sequencing. *Allergol Select.* 2024 Oct 2:8:304-323. doi: 10.5414/ALX02520E.
17. Fousteri G, Dave Jhatakia A. Viral Infections and Autoimmune Disease: Roles of LCMV in Delineating Mechanisms of Immune Tolerance. *Viruses.* 2019 Sep 21; 11(10):885. doi: 10.3390/v11100885.
18. Olivares-Hernandez A, Figuero-Perez L, Miramontes-Gonzalez JP, et al. Immune System Disorders, Cancer and Viral Infections: A New Treatment Opportunity for the Immune Checkpoint Inhibitors. *Life (Basel).* 2021 Dec 15;11(12):1400. doi: 10.3390/life11121400.
19. Greenhalgh T, Sivan M, Perlowski A, Nikolich JŤ. Long COVID: a clinical update. *Lancet.* 2024 Aug 17;404(10453):707-724. doi: 10.1016/S0140-6736(24)01136-X.
20. Blanco LP, Salmeri N, Temkin SM, et al. Endometriosis and autoimmunity. *Autoimmun Rev.* 2025 Mar 26;24(4):103752. doi: 10.1016/j.autrev.2025.103752.
21. Lukac S, Schmid M, Pfister K, et al. Extragenital Endometriosis in the Differential Diagnosis of Non-Gynecological Diseases. *Dtsch Arztebl Int.* 2022 May 20;119(20): 361-367. doi: 10.3238/arztebl.m2022.0176.
22. Moyer A, Edens C. Impact of Systemic Lupus Erythematosus on Conception: Insights into infertility, fertility preservation, assisted reproductive technology and pregnancy outcomes. *Semin Reprod Med.* 2024 Sep; 42(3):209-227. doi: 10.1055/s-0044-1793827.
23. He WR, Wei H. Maternal and fetal complications associated with systemic lupus erythematosus: An updated meta-analysis of the most recent studies (2017-2019). *Medicine (Baltimore).* 2020 Apr;99(16):e19797. doi: 10.1097/MD.0000000000019797.
24. Трофимов ЕА. Антифосфолипидный синдром: особенности течения у беременных и принципы лечения. Вестник НовГУ. 2016;6(97):63-67.
Trofimov EA. Antiphospholipid syndrome: features of the course in pregnant women and treatment principles. *Vestnik NovGU.* 2016; 6(97):63-67. (In Russ.).
25. Vinet E, Clarke AE, Gordon C, et al. Decreased live births in women with systemic lupus erythematosus. *Arthritis Care Res (Hoboken).* 2011 Jul;63(7):1068-72. doi: 10.1002/acr.20466.
26. Krasselt M, Baerwald C. Sex, symptom severity and quality of life in rheumatology. *Clin Rev Allergy Immunol.* 2019 Jun;56(3): 346-361. doi: 10.1007/s12016-017-8631-6.
27. Xia XY, Liu ST, Song ZC, et al. Current investigation of the high prevalence of sexual dysfunction in female patients with systemic lupus erythematosus: a cross-sectional study. *Rheumatol Int.* 2024 Oct;44(10):2147-2157. doi: 10.1007/s00296-024-05690-6.
28. Carson SA, Kallen AN. Diagnosis and management of infertility: a review. *JAMA.* 2021 Jul 6;326(1):65-76. doi: 10.1001/jama.2021.4788.
29. Pashnina IA, Krivolapova IM, Fedotkina TV, et al. Antinuclear autoantibodies in health: autoimmunity is not a synonym of autoimmune disease. *Antibodies (Basel).* 2021 Feb 25;10(1):9. doi: 10.3390/antib10010009.
30. Решетняк ТМ, Шумилова АА, Кошелева НМ. Клиническое значение антинуклеарных антител. Лечебное дело. 2021; (4):96-103.
Reshetnyak TM, Shumilova AA, Kosheleva NM. *Lechebnoe delo.* 2021;(4):96-103. (In Russ.).
31. Cavalcante MB, Cavalcante CTMB, Sarno M, et al. Antinuclear antibodies and recurrent miscarriage: systematic review and meta-analysis. *Am J Reprod Immunol.* 2020 Mar;83(3):e13215. doi: 10.1111/aji.13215.
32. Deroux A, Dumestre-Perard C, Dunand-Faure C, et al. Female infertility and serum auto-antibodies: a systematic review. *Clin Rev Allergy Immunol.* 2017 Aug;53(1):78-86. doi: 10.1007/s12016-016-8586-z.
33. Десинова ОВ, Старовойтова МН, Гусева ИА и др. Особенности перекрестной формы системной склеродермии с ревматоидным артритом (ССД-РА overlap-синдром). Научно-практическая ревматология. 2007;45(4):18-23.
Desinova OV, Starovoytova MN, Guseva IA, et al. Features of systemic sclerosis-rheumatoid arthritis overlap syndrome (SS-RA overlap syndrome). *Nauchno-prakticheskaya revmatologiya.* 2007;45(4):18-23. (In Russ.).
34. Barber MRW, Drenkard C, Falasinnu T, et al. Global epidemiology of systemic lupus erythematosus. *Nat Rev Rheumatol.* 2021 Sep; 17(9):515-532. doi: 10.1038/s41584-021-00668-1.

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Reshetnyak T.M. https://orcid.org/0000-0003-3552-2522
Trofimov E.A. https://orcid.org/0000-0003-3236-4485
Abdulganieva D.I. https://orcid.org/0000-0001-7069-2725
Astakhova A.D. https://orcid.org/0009-0004-9052-2183
Enikeeva G.R. https://orcid.org/0009-0002-4151-8546
Seredavkina N.V. https://orcid.org/0000-0001-5781-2964
Zonova E.V. https://orcid.org/0000-0001-8529-4105
Bugrova O.V. https://orcid.org/0000-0001-9478-8916
Zlobin M.V. https://orcid.org/0000-0002-8200-3293
Klimenko A.A. https://orcid.org/0000-0002-7410-9784
Ilivanova E.P. https://orcid.org/0000-0002-9312-3768
Ostroushko I.A. https://orcid.org/0009-0002-4338-8933
Glukhova S.I. https://orcid.org/0000-0002-4285-0869
Pozharov I.V. https://orcid.org/0000-0003-0777-8977
Nekrasova N.B. https://orcid.org/0009-0003-8533-261X
Mutovina Z.Yu. https://orcid.org/0000-0001-5809-6015
Trofimova A.S. https://orcid.org/0000-0001-5926-7912
Yakupova S.P. https://orcid.org/0000-0002-8590-4839
Remnev A.E. https://orcid.org/0009-0007-7349-395X
Lila A.M. https://orcid.org/0000-0002-6068-3080