Reproductive Life Stages and Female Sex-Specific Patterns in Uveitis Activity: Data From the AIDA Network Uveitis Registry

CARLA GAGGIANO, ALEJANDRA DE-LA-TORRE, SILVANA GUERRIERO, RAFAEL TIERRADENTRO-ALAPE, GAAFAR RAGAB, ANGIE FORERO-URIBE, STEFANIA COSTI, ROSANNA DAMMACCO, MARIA PIA PAROLI, MOHAMED THARWAT HEGAZY, EMANUELA DEL GIUDICE, JURGEN SOTA, ANDREA HINOJOSA-AZAOLA, LUCIANA BREDA, ANTONIO VITALE, ALEX FONOLLOSA, ADELE CIVINO, STEFANO GENTILESCHI, MARCO CATTALINI, ANGELA MAURO, VALERIA CAGGIANO, SOAD HASHAD, JESSICA SBALCHIERO, PIERO RUSCITTI, MARIA SOLE CHIMENTI, MARIA TARSIA, HENRIQUE AYRES MAYRINK GIARDINI, ALESSANDRO CONFORTI, SAMAR THARWAT, FRANCESCO CARUBBI, ABDELHAFEEZ MOSHRIF, JOSÉ HERNÁNDEZ-RODRÍGUEZ, LAMPROS FOTIS, SERENA BUGATTI, SULAIMAN AL-MAYOUF, ANASTASIOS KARAMANAKOS, MATTEO PIGA, FRANCESCA MINOIA, MARIA CRISTINA MAGGIO, GIAN DOMENICO SEBASTIANI, GIOVANNI CONTI, PATRIZIA BARONE, PERLA AYUMI KAWAKAMI-CAMPOS, GIUSEPPE LOPALCO, FRANCESCO LA TORRE, MARIA FRANCESCA GICCHINO, SEZA OZEN, EZGI DENIZ BATU, BRUNO FREDIANI, LUCA CANTARINI, AND CLAUDIA FABIANI

AJO.com Supplemental Material available at AJO.com.
Accepted for publication November 9, 2025.

From the Rheumatology Unit, Department of Medical Sciences (C.G., J.S., A.V., S.G., V.C., J.S., B.F., L.C.), Surgery and Neuroscience, University of Siena, Siena University Hospital, European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center, Siena, Italy; Neuroscience Research Group (NEUROS) (A.D.T., R.T.A., A.F.U.), Neurovitae Center for Neuroscience, Institute of Translational Medicine (IMT), School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia; Department of Translational Medicine and Neurosciences (DiBraiN) (S.G., R.D.), Bari University, Bari, Italy; Internal Medicine Department (G.R., M.T.H.), Rheumatology and Clinical Immunology Unit, Faculty of Medicine, Cairo University, Egypt; Unit of Pediatric Rheumatology (S.C.), ASST Gaetano Pini-CTO, Milan, Italy; Uveitis Unit (M.P.P.), Department of Sense Organs, Eye Clinic, Sapienza University of Rome, European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center, Rome, Italy; Pediatric and Neonatology Unit (E.D.G.), Department of Maternal Infantile and Urological Sciences, Sapienza University of Rome, Latina, Italy; Departamento de Inmunología y Reumatología (A.H.A.), Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; Pediatric Rheumatology Unit (L.B.), S.S. Annunziata Hospital, Chieti, Italy; Department of Ophthalmology (A.F.), Biocruces Bizkaia Health Research Institute, Cruces University Hospital, University of the Basque Country, Barakaldo, Bizkaia, Spain; Department of Retina (A.F.), Instituto Oftalmológico Bilbao, Bilbao, Spain; Paediatric Rheumatology and Immunology (A.C.), Vito Fazzi Hospital, Lecce, Italy; Pediatric Clinic (M.C.), University of Brescia and Spedali Civili di Brescia, European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory, and Autoimmune Diseases (RITA) Center, Brescia, Italy; Pediatric Rheumatology Unit (A.M.), Department of Childhood and Developmental Medicine, Fatebenefratelli-Sacco Hospital, Milan, Italy; Tripoli Children Hospital (S.H.), University of Tripoli, Tripoli, Libya; Division of Rheumatology (P.R.), Department of Clinical Sciences and Applied Biotechnology, University of L'Aquila, L'Aquila, Abruzzo, Italy; Rheumatology, Allergology and Clinical Immunology (M.S.C.), Department of System Medicine, University of Rome "Tor Vergata", Rome, Italy; Clinical Pediatrics (M.T.), Siena University Hospital, European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center, Siena, Italy; Rheumatology Division (H.A.M.G.), Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil; Ospedale San Paolo di Civitavecchia (A.C.), U.O. Medicina Generale, Civitavecchia, Rome, Italy; Rheumatology and Immunology Unit (S.T.), Internal Medicine Department, Mansoura University, Mansoura, Egypt; Department of Internal Medicine (S.T.), Faculty of Medicine, Horus University, New Damietta, Egypt; Department of Life (F.C.), Health & Environmental Sciences and Internal Medicine and Nephrology Unit, Department of Medicine, University of L'Aquila and ASL Avezzano-Sulmona-L'Aquila, San Salvatore Hospital, L'Aquila, Italy; Rheumatology Department (A.M.), Faculty of Medicine, Al-Azhar University, Assuit, Egypt; Autoinflammatory Diseases Clinical Unit (J.H.R.), Department of Autoimmune Diseases, Hospital Clinic of Barcelona, IDIBAPS, University of Barcelona, European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center, Barcelona, Spain; Third Department of Paediatrics (L.F.), National and Kapodistrian University of Athens, General University Hospital "Attikon", European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center, Athens, Greece; Department of Internal Medicine and Therapeutics (S.B.), Università di Pavia, and Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center, Pavia, Italy; Department of Pediatric RheumatoV, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; Department of Pediatrics (S.A.M.), College of Medicine, Alfaisal University, Riyadh, Saudi Arabia; Department of Rheumatology (A.K.), Evangelismos General Hospital, Athens, Greece; Rheumatology Unit (M.P.), Department of Medical Sciences, Policlinico of the University of Cagliari, Cagliari, Italy; Pediatric Immuno-Rheumatology Unit (F.M.), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center, Milan, Italy; University Department PROMISE "G. D'Alessandro" (M.C.M.), University of Palermo, Palermo, Italy; Rheumatology Unit (G.D.S.), Azienda Ospedaliera San Camillo Forlanini, Roma, Italy; Pediatric Nephrology and Rheumatology Unit (G.C.), Azienda Ospedaliera Universitaria (AOU) "G. Martino", University of Messina, Messina, Italy; Pediatric Rheumatology Unit (P.B.), Department of integrated Maternal-Child and Reproduction Activity AOU "Policlinico-San Marco" Catania, Italy; Department of Ophthalmology (P.A.K.C.), Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J) Policlinic Hospital (G.L.), University of Bari, Bari, Italy; Department of Pediatrics, Pediatric Rheumatology Center (F.L.T.), Giovanni XXIII Pediatric Hospital, University of Bari Aldo Moro, Bari, Italy; Department of Woman (M.F.G., E.D.B.), Child and of General and Specialized Surgery,

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2025.11.009

• OBJECTIVE OR PURPOSE: To investigate whether noninfectious uveitis (NIU) activity varies across reproductive life stages (RLS) according to sex.
• DESIGN: Observational, retrospective, cross-sectional registry-based study.
• SUBJECTS, PARTICIPANTS, AND/OR CONTROLS: The study recruited female patients with NIU (regardless of anatomical location or underlying etiology) as the main study group and male patients as controls to allow sex-based comparisons. They were enrolled in the AIDA Network Uveitis Registry between 2020 and 2025.
• METHODS, INTERVENTION, OR TESTING: RLS (prepuberal, early puberty, late puberty, reproductive, perimenopause, and podtmenopausal) were approximated using age intervals derived from epidemiological data. Study outcomes were flare frequency, anterior chamber cells (ACC), anterior chamber flare, vitreous haze, new posterior segment inflammatory signs, and immunosuppressive treatment (IST) exposure.
• RESULTS: Four hundred twenty-five female and 275 male patients were included. Median (IQR) relapse number in 12 months was 0.8 (1.3) [min 0.0-max 2.0] in prepuberty, 1.0 (2.0) [0.0-5.0] in early puberty, 0.0 (1.0) [0.0-5.0] in late puberty, 0.5 (1.0) [0.0-8.0] in reproductive age, 1.0 (1.0) [0.0-10.0] in perimenopause, and 0.5 (1.0) [0.0-7.5] in post-menopause ($P = .014$). There was a statistically significant interaction between RLS and sex ($P = .044$), with a perimenopausal peak retained only in women. In subjects with active anterior involvement, differences in the distribution of ACC grades among RLS were observed, with a peak in prepuberty and early puberty ($P = .004$). Proportions of subjects receiving IST were higher in prepuberty and puberty than in the remaining RLS ($P = .012$).
• CONCLUSIONS: RLS are clinically relevant modifiers of uveitis activity and should guide patient education, risk stratification, and therapy. Early puberty and perimenopause increase relapse risk; pediatric cases show more severe anterior inflammation and require more systemic IST. (Am J Ophthalmol 2026;282: 292–304. © 2025 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/))

University of Campania Luigi Vanvitelli, Naples, Italy; Department of Pediatrics (S.O.), Hacettepe University, Ankara, Turkey; Ophthalmology Unit (C.F.), Department of Medical Sciences, Surgery and Neuroscience, University of Siena, Siena University Hospital, European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center, Siena, Italy

Inquiries to Luca Cantarini, Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinics, Department of Medical Sciences, Surgery and Neurosciences, University of Siena. Rheumatology Unit, Siena, Italy; e-mail: cantarini@unisi.it

Inquiries to Claudia Fabiani, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Ophthalmology Unit, Siena, Italy; e-mail: claudia.fabiani@aidanetwork.org

INTRODUCTION

Noninfectious uveitis is a leading cause of visual morbidity worldwide. Its unpredictable course, characterized by recurrent relapses and chronic inflammation, often results in irreversible ocular damage despite significant therapeutic advances over recent decades. While genetics, autoimmune predisposition, and environmental factors are well-established contributors to its pathogenesis and progression, growing evidence indicates that endocrine and reproductive factors also influence ocular inflammatory activity.[1]

This influence is expected to play a critical role in women, given the complexity of the female hormonal milieu throughout life, which includes short-term cyclical variations as well as major changes during puberty, pregnancy, postpartum, lactation, and perimenopause. These reproductive transitions affect immune function through mechanisms that remain only partially understood. Experimental and clinical studies have demonstrated that high concentrations of estrogen and progesterone exert immunosuppressive effects by promoting Th2 polarization and regulatory T-cell activity, while suppressing Th1 and Th17 responses.[2-4] Conversely, hormonal withdrawal phases, such as the late luteal phase, postpartum period or perimenopause, could be linked to inflammatory rebounds, partly driven by declines in sex steroids, cortisol fluctuations, and surges in pro-inflammatory prolactin (Figure 1).[1,3,5]

Despite these insights, most existing studies are limited to small cohorts, retrospective analyses, or animal models, focusing mainly on specific uveitis types such as human leukocyte antigen (HLA)-B27-associated uveitis or juvenile idiopathic arthritis (JIA)-associated uveitis, and primarily examining disease course during puberty or pregnancy.[6-11] The broader impact of reproductive stages on uveitis activity across sexes and including multiple etiologies has not yet been systematically assessed.

In this context, we utilized the international AIDA Network Uveitis Registry[12] to investigate whether uveitis activity varies across reproductive life stages (RLS) throughout the lifespan, whether disease activity patterns differ between women and men, and whether specific anatomic compartments are disproportionately affected. Our ultimate aim is to identify life stages associated with heightened relapse risk and to inform individualized monitoring and treatment strategies for women with uveitis.

METHODS

This is an observational, retrospective, registry-based study. Patients with noninfectious uveitis were enrolled in the

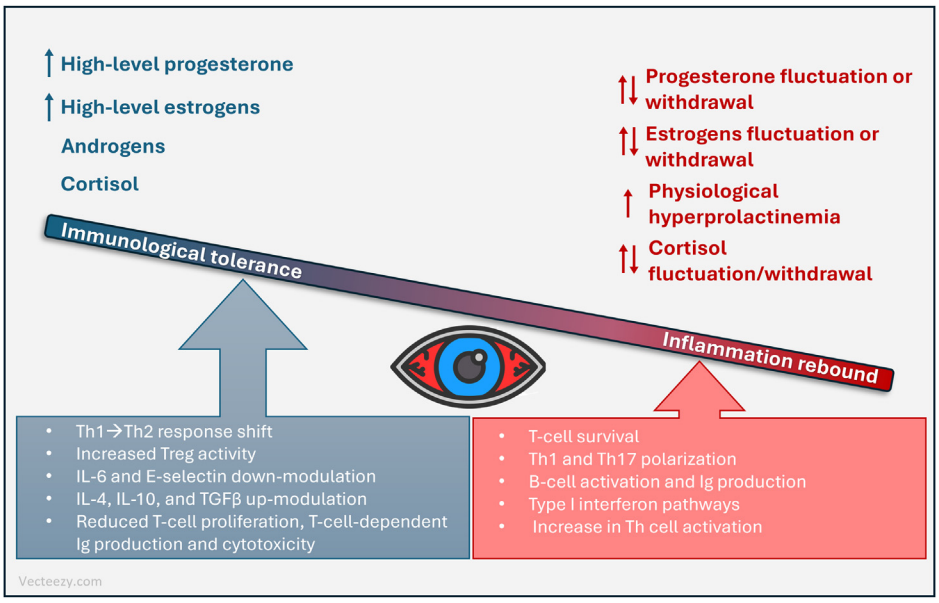

FIGURE 1. A potential interplay between reproductive hormones and the immune system in modulating uveitis course in females. List of abbreviations: Ig = Immunoglobulins; IL = Interleukin; TGF = Transforming Growth Factor; Th = T-helper lymphocytes; Treg = T-regulatory lymphocytes.

AIDA Network Uveitis Registry between 2020 and 2025 by 22 centers from 8 Countries.

The protocol of the AIDA Network registries (ClinicalTrials.gov ID: NCT05200715) was approved prospectively by the Ethics Committee of Siena University Hospital (Ref. 14951), and by the Ethics Committees of the participating investigator centers. Patients (or their parents/legal guardians) must provide written consent after receiving appropriate information to be eligible for the registry. This study complies with the principles outlined in the Declaration of Helsinki.

• **AIMS AND OUTCOMES:** The primary aim of the study was to assess the association between RLS (prepuberal, early puberty, late puberty, reproductive, perimenopausal, and postmenopausal) and the frequency of uveitis flares in the whole cohort and according to biological sex. The outcome analyzed was the total number of uveitis flares in the last 12 months reported at registry enrolment, as defined by the Standardization of Uveitis Nomenclature (SUN) criteria.[13]

The secondary aim was to evaluate the association between RLS and inflammation severity during disease activity phases in the whole cohort and according to biological sex. Outcomes were identified as follows: anterior chamber cell (ACC) grade (0-4) and anterior chamber flare grade (0-4+) at the evaluation when active anterior or panuveitis were observed according to the SUN criteria[13]; vitreous haze grade (0-4) according to the SUN criteria[13] and presence of new active disease signs at fundus examination when active intermediate, posterior, or panuveitis were observed.

Exploratory objectives were to describe immunosuppressive treatment (IST) history across RLS and to describe the proportion of female patients with worsened, stable, or improved disease course after menarche, during pregnancy (by trimester), and after menopause.

• **STUDY POPULATION AND REPRODUCTIVE STAGE CLASSIFICATION:** Female patients with a diagnosis of noninfectious uveitis (NIU) (regardless of anatomical location or underlying etiology) were included in the main study group. Male patients were included as a control group to allow sex-based comparisons. For this study, sex was defined with reference to a set of biological attributes associated with physical and physiological features such as chromosomal genotype, hormonal levels, internal and external anatomy as designated at birth. Subjects with a history of gender-affirming hormone therapy were excluded from the study due to the potential impact of immunological effects of the therapy.[14]

The definition of RLS refers to the distinct phases in a woman's reproductive lifespan, characterized by physiological and hormonal changes, which influence fertility status and endocrine function. Many potential criteria have been evaluated for defining stage boundaries, including menstrual cycles, hormonal measurements, symptoms, fertility, and ovarian imaging. However, despite significant efforts, accurate staging criteria supporting the classification of women in research are still not available.[15] In this study, in the absence of direct hormonal data, RLS were approximated using age intervals derived from epidemiological data: prepuberal stage <8 years, early puberty from ≥8

to ≤12 years, late puberty from >12 to <18 years, reproductive stage from ≥18 to <44 years, perimenopause (including late reproductive STRAW stages −3b and −3a, early −2 and late −1 menopausal transition stages, and early post-menopause +1a and +1b) from ≥44 to <56 years, and post-menopausal stage ≥56 years.[15-20] These same age intervals were applied to male patients to allow age and sex-based comparisons, acknowledging that male puberty typically begins later and andropause is more gradual and variable than menopause, while keeping the focus on female patients as the main study group.

• **DATA HANDLING AND ANALYSIS:** For the primary analysis (frequency of uveitis flares), only patients with disease duration greater than 12 months at the time of enrolment were included. Stratification by sex was applied. Sensitivity analyses were performed including only patients with disease duration between 1 and 5 years to assess the influence of chronicity and only patients undergoing systemic IST. Flares were recorded separately for each eye over the 12 months preceding enrolment. For patients with unilateral uveitis, the flare count of the affected eye was used as the patient-level value. For bilateral uveitis, because the registry did not indicate whether flares in the 2 eyes occurred simultaneously or as distinct episodes, the mean number of flares between the right and left eyes was used as a conservative estimate of disease activity. This approach aimed at minimizing potential double-counting of synchronous bilateral flares that could otherwise overestimate patient-level inflammatory burden. For the secondary analysis (inflammation severity), inflammation markers from all patients were analyzed using data from the registry visits tied to treatment initiation or escalation due to uveitis activity (onset or relapse). The eye level anatomic class was recorded, including the number of unaffected eyes for descriptive purposes. However, secondary analysis was conducted at the patient level. In cases of bilateral uveitis, the eye with the higher inflammation grade was used for analysis. Patients with no ophthalmological data collected during uveitis activity were excluded.

Treatment exposure was analyzed at the time of enrolment qualitatively (exposed versus non exposed) and only patients with disease duration greater than 12 months were included.

• **STATISTICAL ANALYSIS:** Statistical analysis was conducted in the JASP environment (version 0.19.3.0). Descriptive analysis included counts, frequencies, mean, standard deviation (SD), median, interquartile interval (IQR), minimum and maximum values. The Shapiro-Wilk test was used to assess the normality of data distribution. Associations between categories were analyzed through contingency tables and the chi-squared test. The distributions of nonparametric continuous or ordinal variables across more than 2 groups were compared via the ANOVA Kruskal-Wallis test. Multiple fixed factors were included in the analysis (ie, sex * reproductive stages) to evaluate interactions in the ANOVA test. Ethnic background was recorded for all participants (Table 1); however, due to the very low representation of nonwhite ethnicities, ethnicity was not included as a fixed factor in the ANOVA Kruskal–Wallis model, as this would have resulted in unreliable group distributions and unstable interaction estimates. Only patients with available data for the outcome of interest were included (complete-case analysis). A *P*-value <.05 was considered statistically significant.

RESULTS

• **DESCRIPTIVES:** The study included 700 patients with noninfectious uveitis (NIU), 425 women and 275 men. Among them, 444 were included in the primary analysis and 429 in the secondary analysis (total 664 evaluations during uveitis activity). Demographic and clinical characteristics of the cohort are reported in Tables 1 and 2. Anterior segment inflammation was observed in 545 patients (77.9%), intermediate or posterior segment involvement in 275 (39.3%). Uveitis was idiopathic in 337 patients (48.1%), while it was associated with a systemic disease in 280 (40.0%) (missing information in 83 cases).

• **PRIMARY ANALYSIS: FREQUENCY OF UVEITIS FLARES:** Four hundred forty-four patients were included in the primary analysis, while 256 were excluded because of disease duration of less than 12 months ($n = 130$), disease duration not available ($n = 47$), or flare frequency data not available ($n = 79$). A baseline comparison of included and excluded patients is available in Table S1. Patients were assessed for registry enrollment after a median disease duration of 4.8 years (IQR 10.0) [min 1.0-max 64.3]. Their median age at enrolment was 37.5 (IQR 38.9) years [min 5.0-max 89.9]. They were classified according to the estimated RLS at the time of enrolment based on their age (Figure 2). The key demographic and clinical features of this subgroup of patients are compared according to RLS in Table 3. A female predominance was observed in the prepuberty, late puberty, and reproductive age groups ($P = .026$). Both median age at disease onset, age at the enrolment, and disease duration were lower in the prepuberty and early puberty groups ($P < .001$).

The median number of relapses in the 12 months preceding the enrolment was 0.5 (IQR 1.0) [min 0.0-max 10.0]; it was 0.8 (1.3) [0.0-2.0] in prepuberal age, 1.0 (2.0) [0.0-5.0] in early puberty, 0.0 (1.0) [0.0-5.0] in late puberty, 0.5 (1.0) [0.0-8.0] in reproductive age, 1.0 (1.0) [0.0-10.0] in perimenopausal age, and 0.5 (1.0) [0.0-7.5] in post-menopausal age ($P = .014$). Additionally, a statistically significant interaction was found between RLS and sex in the ANOVA analysis ($P = .044$). The distribution of relapses number

TABLE 1. Demographic and Clinical Characteristics of the Cohort

	Entire Cohort		Primary Analysis Cohort (Number of Flares)	Secondary Analysis Cohort (Severity of Flares)
Biological Sex	Female	Male		
Patients, n.	425	275	444	429
Ethnicity, n. (%)				
White	274 (64.5)	193 (70.2)	330 (74.3)	244 (56.9)
Hispanic	101 (23.8)	47 (17.1)	64 (14.4)	121 (28.2)
Arab	23 (5.4)	16 (5.8)	23 (5.2)	29 (6.8)
Asian	2 (0.5)	2 (0.7)	2 (0.5)	2 (0.5)
Black	0 (0)	2 (0.7)	2 (0.5)	1 (0.2)
Native American	0 (0)	1 (0.4)	0 (0.0)	1 (0.2)
Other	2 (0.5)	0 (0)	1 (0.2)	2 (0.5)
Missing	23 (5.4)	14 (5.1)	22 (5.0)	29 (6.8)
Age at onset, years Median (IQR)	32.9 (39.1)	30.1 (37.4)	29.0 (35.7)	33.4 (33.8)
[min-max]	[1.4-82.5]	[1.1-86.7]	[1.4-86.7]	[1.1-86.7]
Age at enrolment, years Median (IQR)	38.0 (38.8)	38.9 (38.3)	37.5 (38.9)	38.4 (40.2)
[min-max]	[2.9-89.9]	[1.6-87.9]	[5.0-89.9]	[1.6-89.9]
Systemic disease associated with uveitis, n. (%)	185 (43.5)	95 (34.6)	203 (45.7)	146 (34.0)
Bilateral uveitis, n. (%)	263 (63.2)	153 (56.5)	264 (59.5)	262 (61.1)
Anatomic classes, n. eyes (%)				
Anterior uveitis	399 (46.9)	196 (35.6)	403 (46.0)	328 (38.2)
Intermediate uveitis	54 (6.4)	63 (11.5)	51 (5.7)	87 (10.1)
Panuveitis	161 (18.9)	105 (19.1)	147 (16.6)	217 (25.3)
Posterior uveitis	48 (5.7)	41 (7.5)	70 (7.9)	45 (5.2)
Missing	92 (10.8)	62 (11.3)	100 (11.3)	77 (9.0)
Fellow eyes without uveitis	95 (11.2)	78 (14.2)	105 (11.8)	99 (11.5)
Associated corneal involvement, n. eyes (%)	3 (0.4)	1 (0.2)	3 (0.3)	1 (0.1)
Associated scleral involvement, n. eyes (%)	8 (0.9)	4 (0.7)	9 (1.0)	4 (0.5)
Systemic or regional therapy up to the enrolment, n. (%)	253 (59.5)	155 (56.4)	289 (65.1)	122 (28.4)

across RLS in the entire cohort and split by sex are visualized in Figure 3.

As a sensitivity analysis, number of relapses in the 12 months before enrolment was analyzed according to RLS and sex in the subgroup of patients with disease duration 1 to 5 years ($n = 230$) (Supplemental Figure S1). The median disease duration was 2.4 years (IQR 1.8) [min 1.0-4.9]. The difference in the number of relapses across RLS was not statistically significant in the entire cohort ($P = .105$). However, statistical significance was maintained when considering the interaction of RLS and sex ($P = .044$).

As a sensitivity analysis, number of relapses in the 12 months before enrolment was analyzed according to RLS and sex in the subgroup of patients exposed to systemic immunosuppressive treatment up to the enrolment ($n = 289$) (Supplemental Figure S2). Statistical significance was maintained both in the entire cohort ($P = .027$) and when considering the interaction of RLS and sex ($P = .021$). A sensitivity analysis restricted to female patients ($n = 265$) was conducted to assess the impact of male categorization. Relapse frequency in the 12 months before enrolment showed a similar pattern across RLS as in the primary analysis ($P = .086$) (Supplemental Figure S3).

• **SECONDARY ANALYSIS: INFLAMMATION SEVERITY DURING UVEITIS ACTIVITY:** 429 patients included in the secondary analysis were evaluated by an ophthalmologist during active uveitis phases ($n = 664$ evaluations). Anterior involvement in at least one eye was observed in 546 evaluations (83.0%), intermediate or posterior involvement in at least one eye in 322 (54.0%).

In subjects with anterior involvement, differences in the distribution of both ACC and anterior chamber flare grades among RLS were observed ($P = .004$ and $P = .053$, respectively) (Figure 4A and B). Differences in both ACC and anterior chamber flare grades were not maintained when considering the interaction of RLS and sex ($P = .780$ and $P = .122$, respectively).

In subjects with intermediate or posterior involvement, no statistically significant differences were observed in the distribution of vitreous haze grades among RLS both in the entire cohort ($P = .557$) and stratifying by sex ($P = .412$) (Figure 4C). In addition, no statistically significant differences were observed in the percentage of subjects with new active disease signs at fundus examination both in the entire cohort ($P = .379$) and stratifying by sex ($P = .207$ for the female sex; $P = .440$ for the male sex).

TABLE 2. Uveitis Etiology Breakdown According to Reproductive Life Stages in the Entire Cohort

Uveitis Etiology N. Patients (%)	Prepuberal	Early Puberty	Late Puberty	Reproductive	Perimenopausal	Post-menopausal
Idiopathic	9 (42.9)	43 (55.8)	49 (55.7)	93 (43.9)	59 (45.7)	84 (47.5)
JIA	9 (42.9)	23 (29.9)	30 (34.1)	21 (9.9)	–	–
SpA	–	3 (3.9)	4 (4.6)	28 (13.2)	19 (14.7)	16 (9.0)
IBD	–	–	–	7 (3.3)	5 (3.9)	2 (1.2)
PsA	–	–	1 (1.1)	7 (3.3)	13 (10.1)	4 (2.3)
RA	–	–	–	2 (1.0)	5 (3.9)	6 (3.4)
Sarcoidosis	1 (4.8)	1 (1.3)	1 (1.1)	7 (3.3)	2 (1.6)	11 (6.2)
Iatrogenic	–	–	–	1 (0.5)	4 (3.1)	11 (6.2)
CTD	–	–	–	–	1 (0.8)	5 (2.8)
Behçet's disease	–	–	–	4 (1.9)	1 (0.8)	4 (2.3)
AID	–	–	–	3 (1.4)	2 (1.6)	4 (2.3)
Vasculitis	–	–	–	2 (1.0)	3 (2.3)	7 (4.0)
MS	–	–	–	4 (1.9)	–	–
Oculo-specific clinical entity*	–	5 (6.5)	3 (3.4)	21 (9.9)	11 (8.5)	11 (6.2)
Others	–	1 (1.3)	1 (1.1)	9 (4.3)	5 (3.9)	7 (4.0)
Missing	2 (9.5)	2 (2.6)	1 (1.1)	8 (3.8)	2 (1.6)	6 (3.4)

*Oculo-specific clinical entities included the following: Birdshot chorioretinopathy ($n = 7$), Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE)/Acute Multifocal Ischemic Choriocapillaritis (AMIC) ($n = 1$), Fuchs' Heterochromic Iridocyclitis ($n = 4$), HLA-B27 associated uveitis (ocular only) ($n = 4$), Vogt-Koyanagi-Harada syndrome ($n = 1$), Multiple Evanescent White Dot Syndrome (MEWDS) ($n = 1$), Ocular ischemic syndrome ($n = 1$), Pars Planitis (Idiopathic intermediate uveitis) ($n = 2$), Punctate Inner Choroidopathy (PIC) ($n = 4$), Serpiginous choroiditis ($n = 2$), Susac Syndrome ($n = 1$), Sympathetic ophthalmia ($n = 1$), Uveitis-glaucoma-hyphema (UGH) syndrome (Ellingson syndrome) ($n = 2$), Vogt-Koyanagi-Harada syndrome ($n = 16$), Not-specified ($n = 4$).List of abbreviations: AID = autoinflammatory diseases; CTD = connective tissue diseases; IBD = inflammatory bowel diseases; JIA = juvenile idiopathic arthritis; MS = multiple sclerosis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SpA = seronegative Spondylarthritis. Note that each patient may have more than one disease associated with uveitis

TABLE 3. Key Demographic and Clinical Features of Patients Included in the Primary Analysis are Compared According to Reproductive Life Stages

	Prepuberal	Early Puberty	Late Puberty	Reproductive	Perimenopausal	Post-menopausal	*P*-Value
Patients, n. (%)	12 (2.7)	49 (11.0)	57 (12.8)	132 (29.7)	82 (18.5)	112 (25.2)	–
Female sex, n. (%)	8 (66.7)	23 (47.9)	38 (66.7)	92 (69.7)	43 (52.4)	61 (54.5)	.026
Age at onset, years							
Median (IQR)	3.6 (1.6)	6.9 (3.2)	8.9 (5.5)	25.9 (18.5)	41.3 (10.5)	57.5 (16.9)	<.001
[min-max]	[2.7-5.7]	[2.2-10.6]	[2.0-16.4]	[1.4-41.2]	[4.7-52.7]	[6.1-86.7]	
Age at enrolment, years							
Median (IQR)	6.1 (1.2)	9.7 (2.3)	14.6 (2.3)	33.3 (11.6)	48.5 (6.8)	66.1 (12.0)	<.001
[min-max]	[5.0-7.8]	[8.0-12.0]	[12.1-17.9]	[18.0-43.9]	[44.0-55.9]	[56.1-89.9]	
Disease duration, years							
Median (IQR)	2.0 (0.6)	2.9 (3.1)	5.3 (6.1)	5.8 (10.8)	5.5 (13.2)	5.4 (13.8)	<.001
[min-max]	[1.1-3.5]	[1.0-10.2]	[1.0-13.7]	[1.0-32.9]	[1.1-50.3]	[1.0-64.3]	
Systemic disease associated with uveitis, n. (%)	8 (66.7)	21 (42.9)	25 (43.9)	62 (48.1)	40 (48.8)	47 (42.3)	.634
Bilateral uveitis, n. (%)	9 (75.0)	35 (71.4)	36 (63.2)	77 (58.3)	50 (61.0)	57 (51.0)	.156
Anterior involvement (in at least one eye) n. (%)	12 (100.0)	43 (87.8)	42 (73.7)	103 (78.6)	61 (78.2)	86 (80.4)	.254
Intermediate or posterior involvement (in at least one eye), n. (%)	2 (16.7)	20 (47.6)	22 (45.8)	53 (45.7)	26 (38.2)	35 (39.3)	.381
Systemic or regional therapy up to the enrolment, n. (%)	11 (91.7)	40 (83.3)	45 (80.4)	82 (66.1)	45 (63.4)	66 (62.3)	.012

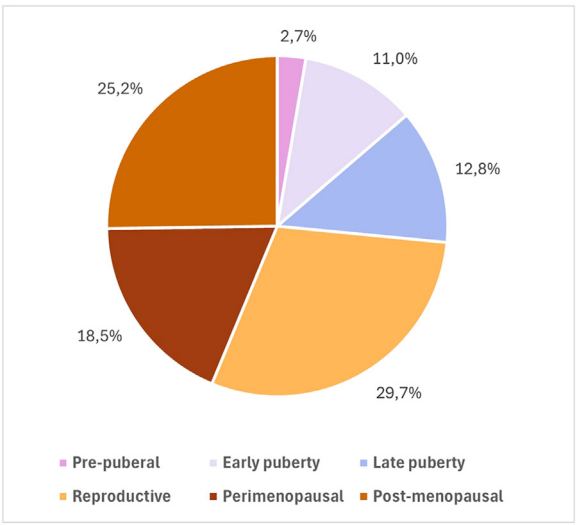

FIGURE 2. Patients included in the primary analysis classified according to the estimated reproductive life stage at the time of enrolment.

• **EXPLORATORY ANALYSIS:** At the time of enrolment, 289 out of 444 patients (65.1%) were exposed to systemic or regional IST. The proportions of subjects who received at least one systemic or regional therapy ($P = .012$), conventional ($P < .001$) or biologic ($P = .002$) disease-modifying anti-rheumatic drugs (DMARDs) were higher in prepuberal and puberal stages than in the remaining RLS (Figure 5). Table S2 compares the frequency of treatment exposure across RLS in patients with disease duration equal or greater than 12 months and affected by nonsystemic forms of uveitis.

Uveitis onset was reported during pregnancy or soon after delivery in 7 patients (4.5% of female patients with onset during reproductive age). Data on uveitis course patterns were available for 31 patients after menarche, 12 during pregnancy, and 21 after menopause. Given the limited sample size, these data are presented in exploratory form in Table S3.

DISCUSSION

Our results suggest that uveitis activity varies significantly across RLS, with a clear interaction between sex and RLS, underscoring that reproductive biology should not be considered a background variable but an active disease course modifier. Specifically, disease activity peaked at early puberty in both sexes and in the perimenopausal phase in the female group, a pattern that was retained when controlling for disease duration and for systemic IST exposure. The as-

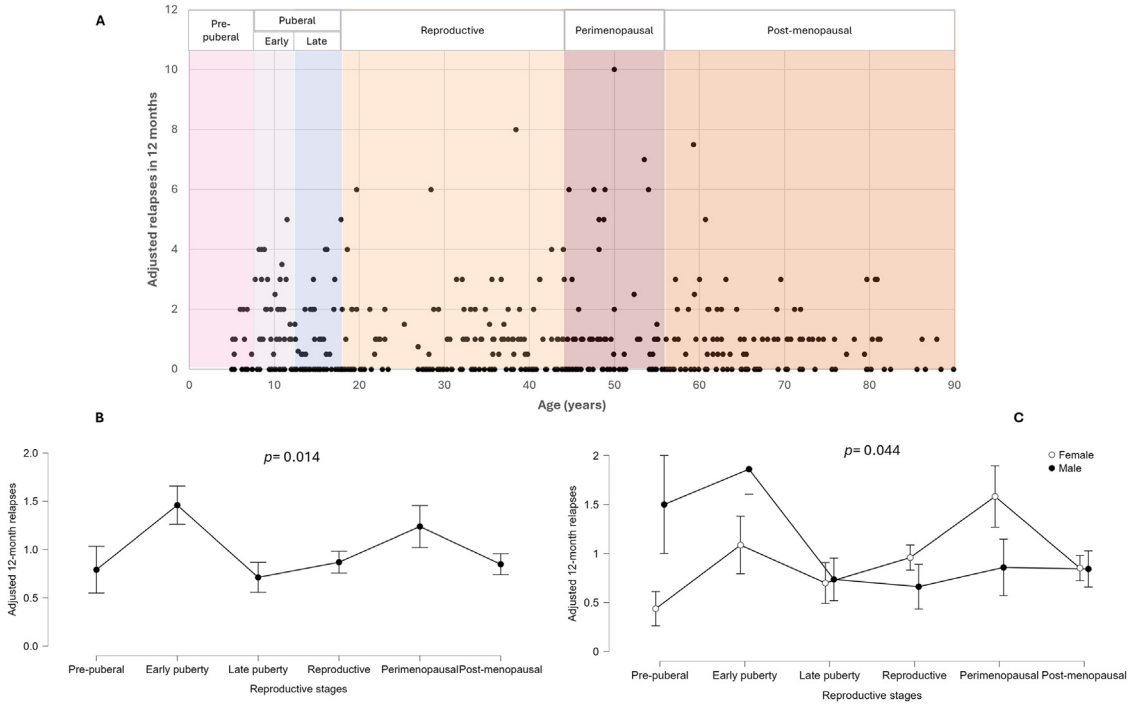

FIGURE 3. Distribution of relapses across reproductive life stages in the entire cohort (A and B) and split by sex (C). Panels B and C show means and standard deviations. The adjusted number of relapses is shown, which means accounting for the laterality of uveitis in each patient: the exact number of relapses in 12 months is shown for unilateral uveitis, the mean number of right and left eye relapses in 12 months for bilateral uveitis.

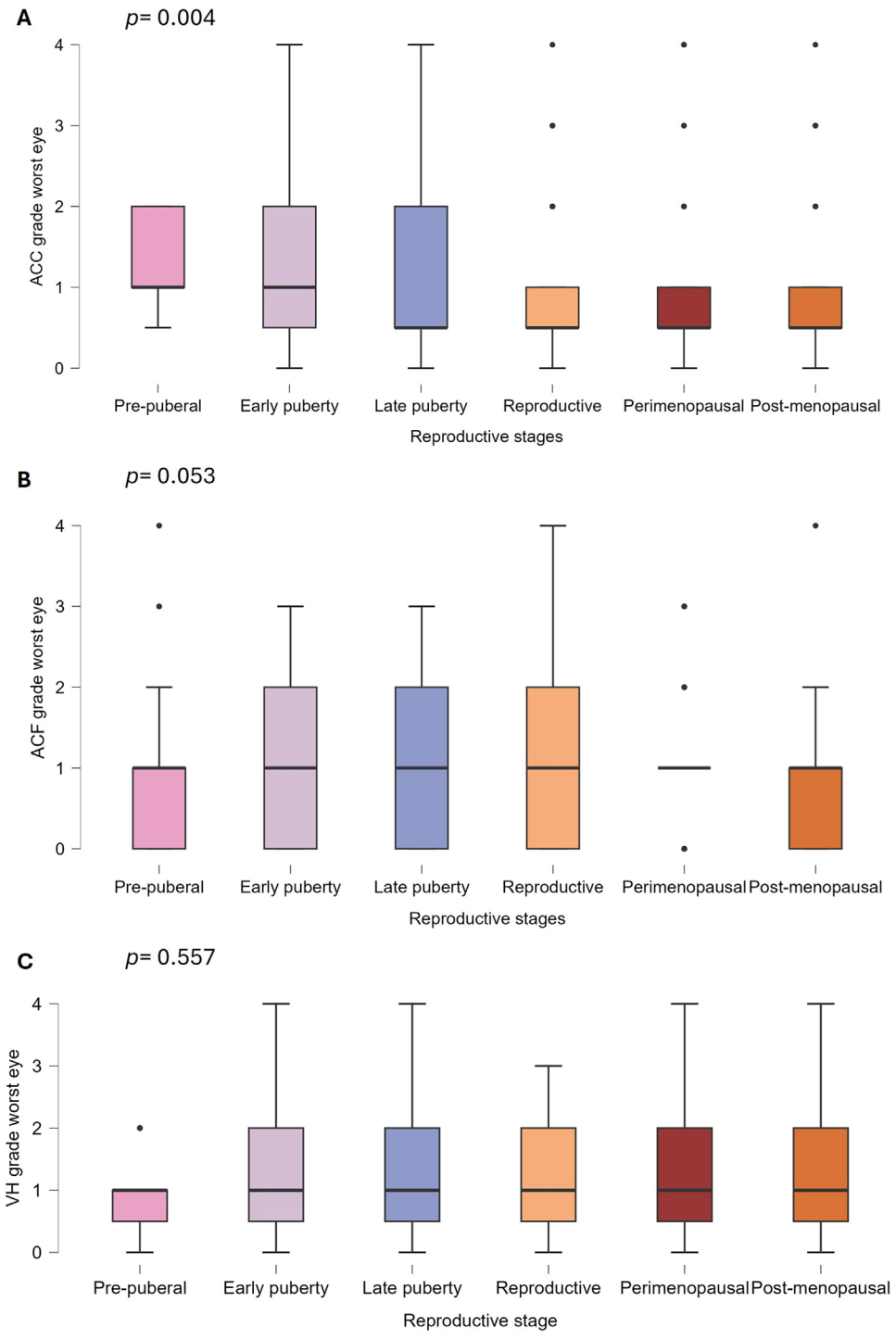

FIGURE 4. Differences in the distribution of anterior chamber cells (ACC) grade (A) and anterior chamber flare (ACF) grade (B) across reproductive life stages in subjects with active anterior involvement. Differences in the distribution of vitreous haze grades (C) across reproductive life stages in subjects with active intermediate or posterior involvement.

sociation was particularly evident in the anterior segment, where ACC and, to a lesser degree, anterior chamber flare grades differed across RLS, whereas vitreous haze grades and new signs of inflammation in the posterior segment were not influenced. Moreover, patients in early puberal stage required more advanced IST, aligning with previous evidence that puberty is a critical period of immune dysregulation in uveitis.[7] It should be noted that RLS categories reflect physiological transitions specific to the female sex, which are not biologically equivalent for the male one. Male pa-

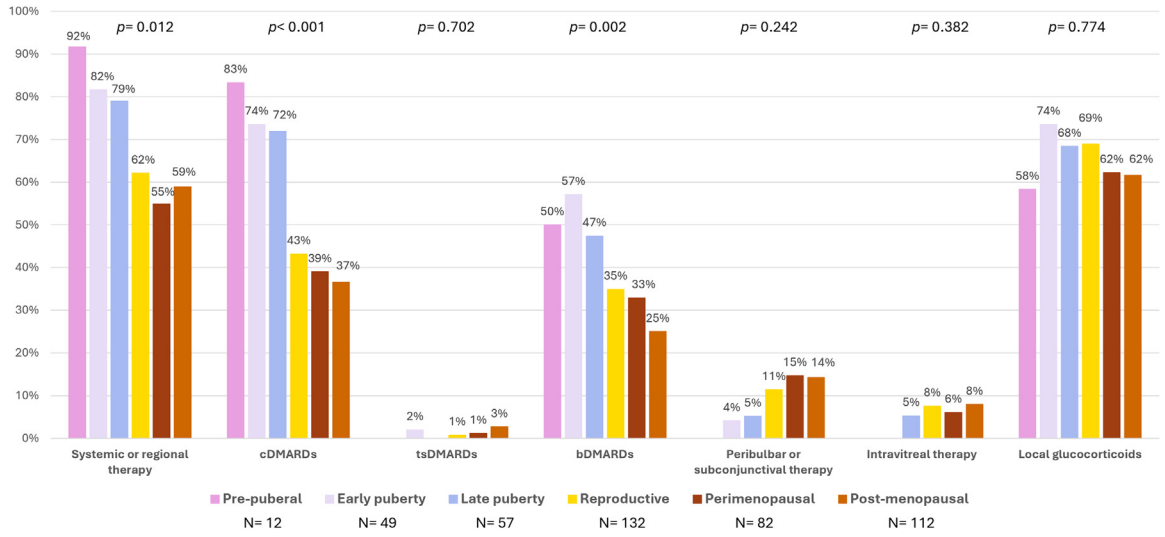

FIGURE 5. Proportions of subjects with disease duration greater than 12 months who received systemic or regional therapies stratified by reproductive life stages. List of abbreviations: bDMARDs = biologic disease-modifying anti-rheumatic drugs; cDMARDs = conventional disease-modifying anti-rheumatic drugs; tsDMARDs = targeted synthetic disease-modifying anti-rheumatic drugs.

tients were assigned to the same age-based groups for analytical consistency, but stage-related patterns observed in men should be interpreted cautiously, as they may not represent true hormonal-based variations of uveitis course.

Our findings of increased disease activity and treatment exposure at early puberty reflect the biphasic course of JIA-associated uveitis, in which disease activity decreases in late childhood but re-emerges around early adolescence,[7] but also the emergence of specific types of uveitis epidemiologically linked to adolescence and young adulthood such as acute anterior uveitis in HLA-B27+ subjects. It has been demonstrated that pubertal hormonal transitions shape disease onset and activity in other autoimmune diseases, including juvenile systemic lupus erythematosus, JIA, autoimmune thyroid disease, type 1 diabetes, and Sjögren's disease[3,4,21]; in addition, beyond sex steroids, puberty is accompanied by global immune maturation and sex-specific changes in the abundance of T-cell subsets, monocytes and B-cells, providing a plausible biological framework for these observations.[4,21]

Although our registry did not capture intra-cycle variations, it could be hypothesized that, within the reproductive stage, short-term hormonal fluctuations can meaningfully alter inflammatory risk, potentially diluting stage-level associations. In this regard, a historical prospective study suggested that acute anterior uveitis attacks cluster in the late luteal phase, although the lack of direct hormonal measurements and the difficulties in identifying the actual "onset" of uveitis flares limited this approach.[5,22] Another important potential confounder in the reproductive stage analysis is the wide range of uveitis etiologies observed in this period, as shown in Table 2. Reported causes span from idiopathic disease to ex-JIA, spondyloarthritis, inflammatory bowel disease, psoriatic arthritis, rheumatoid arthritis, sarcoidosis, iatrogenic uveitis, Behçet's disease, autoinflammatory disorders, vasculitides, multiple sclerosis, and other systemic or ocular conditions. Such heterogeneity in underlying disease may influence the natural course of uveitis, affecting both relapse risk and exposure to IST.

Pregnancy and postpartum hormonal variations were difficult to assess in our registry due to very low counts and lack of variables confirming the exact temporal relationship with uveitis flares. Our small pregnancy subset showed a reduction in uveitis activity in the second and third trimesters, in line with prior case series.[23-26] Given the limited sample size and retrospective information, these findings should be interpreted cautiously and considered exploratory, warranting confirmation in larger prospective cohorts. Historical studies of experimental autoimmune uveitis in mice demonstrated that pregnancy status suppresses uveitis activity via Th1-Th2 response shift and estrogen-mediated interleukin (IL)-6 and E-selectin down-modulation which reduce anterior cellular infiltration.[11,27] Progesterone is generally regarded as an immunosuppressive and anti-inflammatory hormone as well, especially at the high concentrations measured in pregnancy. It reduces Th1/Th17 differentiation, T-cell proliferation and T-cell dependent antibody production and cytotoxicity while enhancing Treg activity and IL-10 production, thereby promoting immunological tolerance.[2,3] On the contrary, the postpartum period was marked by new-onset disease or relapses in a small subset of our cohort, mirroring the well-established flare window within 3 to 4 months postpartum

reported in the literature.[10,26,28] This rebound could be biologically driven not only by the abrupt withdrawal of estrogens and progesterone, but also the fall in cortisol level and rising proinflammatory prolactin during lactation.[1]

In our cohort, uveitis activity across the perimenopausal period appeared variable, with a peak observed in the female sex group and a more stable course in male controls of the same age interval. Data about natural menopause effects on uveitis course are limited, but exogenous hormonal interventions suggest a link with disease activity modulation in previous studies. A large U.S. claims analysis found that female hormonal therapy modestly increased the risk of incident uveitis in peri– and post-menopausal women.[29] On the other hand, also aromatase inhibitors, which cause profound estrogen depletion in post-menopausal women treated for estrogen receptor-positive breast cancer, have been repeatedly associated with uveitis and cystoid macular edema.[30-32] Both in the physiological and pathological contexts, estrogens exert concentration- and tissue-dependent effects on immune regulation, which may contribute to explaining the patterns of uveitis activity across reproductive life.[3] As already mentioned, estrogen pharmacological or high concentrations, such as those reached during pregnancy, promote an anti-inflammatory environment. Conversely, at physiological or fluctuating levels, estrogens may have pro-inflammatory properties by stimulating T-cell survival, Th1 and Th17 differentiation, supporting B-cell activation and immunoglobulin production, and enhancing type I interferon pathways.[1,3] Clinically, this complex spectrum of effects is reflected in the difficulty of correlating specific reproductive life phases with an increased/ decreased risk of uveitis flares.

Our sex and stage interaction, especially in the perimenopausal stage, also likely reflects the protective role of androgens. Testosterone is generally regarded as immunosuppressive, increasing the negative selection of autoreactive thymocytes via Aire upregulation and TGFβ production, enhancing Treg activity, promoting Th2 response with IL-4 and IL-10, and attenuating Th1/Th17 responses.[1,3] Experimental and clinical data suggest that higher androgen levels may protect against autoimmune conditions, though their interactions with genetic background are complex. Interestingly, an early hypothesis proposed a link between HLA-B27 and elevated testosterone levels, potentially explaining the male predominance in acute anterior uveitis despite the broader female bias in noninfectious autoimmune disease.[6]

In our cohort, the distribution of anterior versus intermediate/posterior uveitis showed slight variability across RLS, with a nonsignificant trend toward a higher frequency of anterior involvement in prepubertal patients. Although these differences did not reach statistical significance, a potential impact of anatomical subtype on flare frequency cannot be ruled out. Observed differences in ACC grades across RLS suggest that hormonal transitions may modulate the severity of anterior segment inflammation. This finding aligns with the well-known association of anterior uveitis, particularly in children and adolescents, with immune-mediated diseases known to be sensitive to hormonal changes, such as early-onset JIA and HLA-B27-related uveitis.[1] In contrast, the lack of significant variation in vitreous haze and active funduscopic findings across RLS in patients with intermediate or posterior involvement may indicate either that posterior segment inflammation is less susceptible to hormonal influence, or that the outcome measures used are less sensitive or more prone to interobserver variability.[33] Additionally, structural changes in the posterior segment may evolve more slowly and may not reflect short-term fluctuations in systemic hormonal states.

Our study has some limitations that should be acknowledged to allow a correct interpretation of the results. The main limitation is the lack of direct hormonal measurements in the registry. The pragmatic use of age-based categories as proxies for RLS may have led to misclassification, particularly during puberty and perimenopause, where substantial inter-individual variability exists, arising from both physiological differences and the potential effects of hormonal therapy. Furthermore, applying female-centric reproductive categories to men for comparative purposes may have obscured meaningful disease trajectories in the male group and potentially introduced spurious trends in the male group. To assess the potential impact of this approach, a sensitivity analysis restricted to women alone was performed, yielding results consistent with the primary analysis. The study primary outcome was based on retrospective cross-sectional recall and assuming that RLS at enrolment reflected the hormonal environment over the preceding year. This approach may have introduced recall bias and variability in documentation availability, potentially leading to imprecise estimation of relapse frequency and reduced sensitivity for detecting differences among RLS. A prospective longitudinal design would better establish a causal inference, but it was not feasible within the AIDA registry, which was launched in 2020. Because the registry lacked information on the timing of bilateral flares, using the per-eye mean for bilateral uveitis was a conservative approach that may have underestimated total disease activity, particularly in groups with a higher proportion of patients with bilateral disease. Moreover, the observed differences between included and excluded patients with regard to flare frequency analysis suggest a possible selection bias toward a patient phenotype characterized by white ethnicity, early-onset uveitis, systemic disease association, absence of intermediate or posterior involvement and undergoing systemic IST, potentially limiting external generalizability; future studies with more complete datasets could be designed in the future to specifically assess the impact of these demographic and clinical factors on disease course and outcomes. Although ethnic variation is known to influence both uveitis phenotypes and reproductive development, ethnicity had to be excluded from the analysis due to

limited representation of minority groups; while it would be possible to categorize participants as white versus nonwhite, such a dichotomization would provide limited insight, as the nonwhite group would remain heterogeneous. Lastly, treatment exposure was a potential confounder which was addressed in sensitivity analysis; however, details on dose, duration, adherence, and temporal relation to flares were not available. Also, the potential impact of certain immunosuppressants on reproductive function, as well as inter-center variability in treatment practices, have not been addressed in this study and should be future research objectives.

Nevertheless, our findings carry important implications for clinical practice by providing a lifespan overview of uveitis trajectories in the female population capable of informing patient management, treatment timing, and follow-up strategies. The observation that disease activity peaks around early puberty, with higher exposure to systemic IST in this age group, highlights the need for closer surveillance and cautious therapeutic planning in adolescents. At this stage, clinicians should account for the dynamic hormonal environment, along with growth-related factors and potential challenges with treatment adherence when balancing efficacy against long-term safety. The sex-specific peak at the perimenopausal stage suggests that women in midlife may represent another at-risk group, warranting proactive monitoring, patient counseling, and timely therapeutic adjustments when hormonal fluctuations precipitate disease reactivation. In our small pregnancy subset, the tendency toward reduced activity during gestation and potential relapses postpartum reinforces the importance of preconception counseling and structured postpartum follow-up to promptly detect and manage disease fluctuations. Taken together, these insights support a model in which RLS function as a clinically relevant modifier of uveitis activity, which should be explicitly integrated into patient education, risk stratification, and individualized treatment planning.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

CARLA GAGGIANO: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **ALEJANDRA DE-LA-TORRE:** Writing – review & editing, Validation, Data curation. **SILVANA GUERRIERO:** Writing – review & editing, Validation, Data curation. **RAFAEL TIERRADENTRO-ALAPE:** Writing – review & editing, Validation, Data curation. **GAAFAR RAGAB:** Writing – review & editing, Validation, Data curation. **ANGIE FORERO-URIBE:** Writing – review & editing, Validation, Data curation. **STEFANIA COSTI:** Writing – review & editing, Validation, Data curation. **ROSANNA DAMMACCO:** Writing – review & editing, Validation, Data curation. **MARIA PIA PAROLI:** Writing – review & editing, Validation, Data curation. **MOHAMED THARWAT HEGAZY:** Writing – review & editing, Validation, Data curation. **EMANUELA DEL GIUDICE:** Writing – review & editing, Validation, Data curation. **JURGEN SOTA:** Writing – review & editing, Validation, Data curation. **ANDREA HINOJOSA-AZAOLA:** Writing – review & editing, Validation, Data curation. **LUCIANA BREDA:** Writing – review & editing, Validation, Data curation. **ANTONIO VITALE:** Writing – review & editing, Validation, Data curation. **ALEX FONOLLOSA:** Writing – review & editing, Validation, Data curation. **ADELE CIVINO:** Writing – review & editing, Validation, Data curation. **STEFANO GENTILESCHI:** Writing – review & editing, Validation, Data curation. **MARCO CATTALINI:** Writing – review & editing, Validation, Data curation. **ANGELA MAURO:** Writing – review & editing, Validation, Data curation. **VALERIA CAGGIANO:** Writing – review & editing, Validation, Data curation. **SOAD HASHAD:** Writing – review & editing, Validation, Data curation. **JESSICA SBALCHIERO:** Writing – review & editing, Validation, Data curation. **PIERO RUSCITTI:** Writing – review & editing, Validation, Data curation. **MARIA SOLE CHIMENTI:** Writing – review & editing, Validation, Data curation. **MARIA TARSIA:** Writing – review & editing, Validation, Data curation. **HENRIQUE AYRES MAYRINK GIARDINI:** Writing – review & editing, Validation, Data curation. **ALESSANDRO CONFORTI:** Writing – review & editing, Validation, Data curation. **SAMAR THARWAT:** Writing – review & editing, Validation, Data curation. **FRANCESCO CARUBBI:** Writing – review & editing, Visualization, Data curation. **ABDELHAFEEZ MOSHRIF:** Writing – review & editing, Validation, Data curation. **JOSÉ HERNÁNDEZ-RODRÍGUEZ:** Writing – review & editing, Validation, Data curation. **LAMPROS FOTIS:** Writing – review & editing, Validation, Data curation. **SERENA BUGATTI:** Writing – review & editing, Validation, Data curation. **SULAIMAN AL-MAYOUF:** Writing – review & editing, Validation, Data curation. **ANASTASIOS KARAMANAKOS:** Writing – review & editing, Validation, Data curation. **MATTEO PIGA:** Writing – review & editing, Validation, Data curation. **FRANCESCA MINOIA:** Writing – review & editing, Validation, Data curation. **MARIA CRISTINA MAGGIO:** Writing – review & editing, Validation, Data curation. **GIAN DOMENICO SEBASTIANI:** Writing – review & editing, Validation, Data curation. **GIOVANNI CONTI:** Writing – review & editing, Validation, Data curation. **PATRIZIA BARONE:** Writing – review & editing, Validation, Data curation. **PERLA AYUMI KAWAKAMI-CAMPOS:** Writing – review & editing, Validation, Data curation.

GIUSEPPE LOPALCO: Writing – review & editing, Validation, Data curation. **FRANCESCO LA TORRE:** Writing – review & editing, Validation, Data curation. **MARIA FRANCESCA GICCHINO:** Writing – review & editing, Validation, Data curation. **SEZA OZEN:** Writing – review & editing, Validation, Data curation. **EZGI DENIZ BATU:** Writing – review & editing, Validation, Data curation. **BRUNO FREDIANI:** Writing – review & editing, Validation, Data curation. **LUCA CANTARINI:** Writing – review & editing, Supervision, Conceptualization. **CLAUDIA FABIANI:** Writing – review & editing, Supervision, Conceptualization.

Acknowledgments: Sixteen authors of this work (Carla Gaggiano, Jurgen Sota, Antonio Vitale, Stefano Gentileschi, Valeria Caggiano, Jessica Sbalchiero, Maria Tarsia, Bruno Frediani, Luca Cantarini, Claudia Fabiani, Maria Pia Paroli, Marco Cattalini, José Hernández-Rodríguez, Lampros Fotis, Serena Bugatti, and Francesca Minoia) belong to institutions which are members of the European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA), namely Azienda Ospedaliero-Universitaria Senese (Siena, Italy), Spedali Civili di Brescia (Brescia, Italy), Hospital Clinic of Barcelona (Barcelona, Spain), General University Hospital "Attikon" (Athens, Greece), Fondazione IRCCS Policlinico San Matteo (Pavia, Italy), and Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan, Italy). This study complies with the principles outlined in the Declaration of Helsinki. The protocol of the AIDA Network registries (NCT05200715) has been approved by the Ethics Committee of Siena University Hospital (Ref. 14951), and by the Ethics Committees of the participating investigator centers. Patients (or their parents/legal guardians) must provide written consent after receiving appropriate information to be eligible for the registry.
Funding/support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Declaration of competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on a reasonable request.

REFERENCES

1. Sen HN, Davis J, Ucar D, et al. Gender disparities in ocular inflammatory disorders. *Curr Eye Res*. 2015;40(2):146–161. doi:10.3109/02713683.2014.932388.
2. Liu X, Gu C, Lv J, et al. Progesterone attenuates Th17-cell pathogenicity in autoimmune uveitis via Id2/Pim1 axis. *J Neuroinflammation*. 2023;20(1):144. doi:10.1186/s12974-023-02829-3.
3. Moulton VR. Sex Hormones in Acquired Immunity and Autoimmune Disease. *Front Immunol*. 2018;9:2279. doi:10.3389/fimmu.2018.02279.
4. Yang Q, Kennicott K, Zhu R, et al. Sex hormone influence on female-biased autoimmune diseases hints at puberty as an important factor in pathogenesis. *Front Pediatr*. 2023;11:1051624. doi:10.3389/fped.2023.1051624.
5. Sanghvi C, Aziz K, Jones NP. Uveitis and the menstrual cycle. *Eye (Lond)*. 2004;18(5):451–454. doi:10.1038/sj.eye.6700713.
6. James WH. Sex ratios and hormones in HLA related rheumatic diseases. *Ann Rheum Dis*. 1991;50(6):401–404. doi:10.1136/ard.50.6.401.
7. Hoeve M, Kalinina Ayuso V, Schalij-Delfos NE, et al. The clinical course of juvenile idiopathic arthritis-associated uveitis in childhood and puberty. *Br J Ophthalmol*. 2012;96(6):852–856. doi:10.1136/bjophthalmol-2011-301023.
8. Paroli MP, Fabiani C, Spinucci G, et al. Severe macular edema in patients with juvenile idiopathic arthritis-related uveitis. *Case Rep Ophthalmol Med*. 2013;2013:803989. doi:10.1155/2013/803989.
9. Kump LI, Cervantes-Castañeda RA, Androudi SN, et al. Patterns of exacerbations of chronic non-infectious uveitis in pregnancy and puerperium. *Ocul Immunol Inflamm*. 2006;14(2):99–104. doi:10.1080/09273940500557027.
10. Rabiah PK, Vitale AT. Noninfectious uveitis and pregnancy. *Am J Ophthalmol*. 2003;136(1):91–98. doi:10.1016/s0002-9394(03)00110-7.
11. Agarwal RK, Chan CC, Wiggert B, Caspi RR. Pregnancy ameliorates induction and expression of experimental autoimmune uveitis. *J Immunol*. 1999;162(5):2648–2654.
12. Casa FD, Vitale A, Guerriero S, et al. Autoinflammatory Diseases Alliance (AIDA) Network. Development and Implementation of the AIDA International Registry for Patients with Non-Infectious Uveitis. *Ophthalmol Ther*. 2022;11(2):899–911. doi:10.1007/s40123-022-00459-1.
13. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol*. 2005;140(3):509–516. doi:10.1016/j.ajo.2005.03.057.
14. White AA, Lin A, Bickendorf X, et al. Potential immunological effects of gender-affirming hormone therapy in transgender people - an unexplored area of research. *Ther Adv Endocrinol Metab*. 2022;13:20420188221139612. doi:10.1177/20420188221139612.
15. Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab*. 2012;97(4):1159–1168. doi:10.1210/jc.2011-3362.
16. Campisi SC, Marchand JD, Siddiqui FJ, et al. Can we rely on adolescents to self-assess puberty stage? a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2020;105(8):dgaa135. doi:10.1210/clinem/dgaa135.
17. De Sanctis V, Elhakim IZ, Soliman AT, et al. Methods for rating sexual development in girls. *Pediatr Endocrinol Rev*. 2016;14(1):27–32. doi:10.17458/PER.2016.SESEEM.MethodsforRating.
18. Sotos JF, Tokar NJ. Appraisal of testicular volumes: volumes matching ultrasound values referenced to stages of genital development. *Int J Pediatr Endocrinol*. 2017;2017:7. doi:10.1186/s13633-017-0046-x.

19. Perimenopause SN. From Research to Practice. *J Womens Health (Larchmt)*. 2016;25(4):332–339. doi:10.1089/jwh.2015.5556.
20. Brinton RD, Yao J, Yin F, et al. Perimenopause as a neurological transition state. *Nat Rev Endocrinol*. 2015;11(7):393–405. doi:10.1038/nrendo.2015.82.
21. de Gruijter NM, Naja M, Peckham H, et al. A systematic review exploring the bidirectional relationship between puberty and autoimmune rheumatic diseases. *Pediatr Rheumatol Online J*. 2021;19(1):47. doi:10.1186/s12969-021-00528-y.
22. Elgohary MA. Female sex hormones and uveitis. *Eye (Lond)*. 2005;19(9):1013–1015. doi:10.1038/sj.eye.6701706.
23. Chan CC, Reed GF, Kim Y, et al. A correlation of pregnancy term, disease activity, serum female hormones, and cytokines in uveitis. *Br J Ophthalmol*. 2004;88(12):1506–1509. doi:10.1136/bjo.2004.048595.
24. Chiam NP, Hall AJ, Stawell RJ, et al. The course of uveitis in pregnancy and postpartum. *Br J Ophthalmol*. 2013;97(10):1284–1288. doi:10.1136/bjophthalmol-2013-303358.
25. Giorgiutti S, Jamilloux Y, Gerfaud-Valentin M, et al. The course of non-infectious uveitis in pregnancy: a retrospective study of 79 pregnancies. *Graefes Arch Clin Exp Ophthalmol*. 2023;261(5):1391–1398. doi:10.1007/s00417-022-05949-3.
26. Sharon Y, Adler A, Tiosano A, et al. The effect of pregnancy on the course of uveitis in single and multiple pregnancies. *Graefes Arch Clin Exp Ophthalmol*. 2023;261(3):803–808. doi:10.1007/s00417-022-05829-w.
27. Miyamoto N, Mandai M, Suzuma I, et al. Estrogen protects against cellular infiltration by reducing the expressions of E-selectin and IL-6 in endotoxin-induced uveitis. *J Immunol*. 1999;163(1):374–379.
28. Xu X, Ray I, Tang E, et al. Impact of pregnancy and the postpartum period on noninfectious uveitis flare-ups. *Ocul Immunol Inflamm*. 2025:1–5. doi:10.1080/09273948.2025.2532826.
29. Sobrin L, Yu Y, Susarla G, et al. Risk of noninfectious uveitis with female hormonal therapy in a large healthcare claims database. *Ophthalmology*. 2020;127(11):1558–1566. doi:10.1016/j.ophtha.2020.04.034.
30. Nguyen KH, Smith AK, Kim BT, Browne AW. A case report of cystoid macular edema, uveitis and vitreomacular traction in a patient taking Anastrozole. *Am J Ophthalmol Case Rep*. 2022;25:101339. doi:10.1016/j.ajoc.2022.101339.
31. Serban D, Costea DO, Zgura A, et al. Ocular side effects of aromatase inhibitor endocrine therapy in breast cancer - a review. *In Vivo (Brooklyn)*. 2022;36(1):40–48. doi:10.21873/invivo.12674.
32. Almafreji I, Smith C, Peck F. Review of the literature on ocular complications associated with aromatase inhibitor use. *Cureus*. 2021;13(8):e17565. doi:10.7759/cureus.17565.
33. Kempen JH, Ganesh SK, Sangwan VS, Rathinam SR. Interobserver agreement in grading activity and site of inflammation in eyes of patients with uveitis. *Am J Ophthalmol*. 2008 Dec;146(6):813 8.e1. doi:10.1016/j.ajo.2008.06.004.