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Comparison of Estradiol Levels in Female Adolescents with and Without Systemic Lupus Erythematosus

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ABSTRACT: Systemic lupus erythematosus (SLE) often affects females during adolescence. Evidence on circulating estradiol and disease activity in adolescent females with SLE is inconsistent. This cross-sectional study included 44 female adolescents aged 8–18 years: 22 with SLE and 22 without SLE. Participants were recruited at a tertiary hospital in Makassar, Indonesia, from January to April 2026. Serum estradiol was measured using enzyme-linked immunosorbent assay. Demographic, nutritional, and menstrual-cycle characteristics were recorded, and SLE activity was assessed using SLEDAI. ANCOVA adjusted for age and menstrual-cycle phase. Estradiol concentrations were higher in the SLE group than in the non-SLE group, but not significantly (p=0.105). Median concentrations were 64.67 pg/mL (50.10–107.80) and 56.37 pg/mL (36.50–95.20), respectively. After adjustment, estimated marginal means were 63.35 pg/mL and 59.71 pg/mL, with no significant difference (F=0.370, p=0.547, partial η^2=0.010). Estradiol did not differ by nutritional status, menstrual-cycle phase, or disease-activity categories, and correlated neither with SLEDAI nor with age or %BW/H. Circulating estradiol alone was not associated with SLE status or disease activity. Larger studies warranted.

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease driven by complex interactions among genetic, environmental, immunological, and hormonal factors. Juvenile-onset SLE may have a more severe clinical course than adult-onset disease, making adolescence an important period for understanding disease mechanisms.[1–3] Puberty is accompanied by marked increases in estradiol and profound changes in reproductive and immune function. Estradiol can modulate immune-cell activation, cytokine production, B-cell responses, and Toll-like receptor signaling, providing a biological basis for its potential involvement in SLE pathogenesis.[4–6] However, clinical evidence regarding circulating estradiol in SLE remains inconsistent. Lower estradiol levels have been reported in women with SLE, while other studies have demonstrated associations between estradiol-related pathways, inflammatory mediators, and disease activity.[7,8] Moreover, combined hormonal and receptor profiles may better reflect disease severity than estradiol concentration alone.[9]

These findings are particularly relevant during adolescence, when estradiol varies substantially with pubertal maturation and menstrual-cycle phase. Recent evidence also suggests that differences in estradiol between women with and without SLE may depend on menstrual-cycle phase.[10] Nevertheless, evidence specifically addressing estradiol concentrations in adolescent females with SLE remains limited. Therefore, this study aimed to compare serum estradiol levels between the SLE group and non-SLE

group and to evaluate their relationship with disease activity assessed using SLEDAI, while considering age, nutritional status, and menstrual-cycle phase.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

A cross-sectional comparative study was conducted to compare serum estradiol concentrations between female adolescents with SLE and those without SLE and to assess the association between estradiol levels and disease activity in the SLE group. The primary outcome was the difference in serum estradiol concentrations between the two groups, while the secondary outcome was the association between serum estradiol concentration and disease activity assessed using the SLEDAI score. The study was conducted at the pediatric outpatient clinic and inpatient ward of a tertiary hospital in Makassar, Indonesia, from January to April 2026. Estradiol measurements were performed at a university-affiliated research laboratory using an enzyme-linked immunosorbent assay (ELISA).

2.2 Participants and Sampling

The target population comprised female adolescents aged 8–18 years with or without SLE. Participants were recruited consecutively from the pediatric outpatient clinic and inpatient ward. The SLE group included patients diagnosed by a pediatric rheumatology and immunology consultant who fulfilled the 2012 Systemic Lupus International Collaborating Clinics classification criteria (≥4 criteria, including at least one clinical and one immunologic criterion, or biopsy-proven lupus nephritis with antinuclear antibody or anti-double-stranded DNA positivity) or the 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology criteria (positive antinuclear antibody at ≥1:80 as the obligatory entry criterion and a classification score ≥10). The non-SLE group comprised age-eligible female adolescents recruited from the same hospital outpatient and inpatient settings who had no SLE or other chronic/autoimmune diseases and presented with mild, nonsystemic acute conditions. Thus, they represented hospital-based non-SLE controls rather than healthy population controls.

Participants were excluded if they had another autoimmune disease, ovarian cyst, or malignancy, while for the non-SLE group, participants with conditions potentially affecting estradiol metabolism, including a history of hormonal therapy or systemic glucocorticoid use, were not included as these were considered exclusion criteria. Written informed consent was obtained from parents or legal guardians before enrollment.

2.3 Sample Size

The minimum sample size was calculated using a two-sample mean comparison formula for independent groups, assuming an alpha level of 0.05, 80% power, an expected estradiol difference of 15 pg/mL, and standard deviations of 20 and 15 pg/mL in the SLE and non-SLE groups, respectively. The resulting minimum sample size was 22 participants per group, yielding a total minimum sample of 44 participants.

2.4 Clinical and Anthropometric Assessment

Age, body weight, height, nutritional status, menstrual-cycle phase, and serum estradiol concentration were recorded for all participants. Nutritional status was classified using predefined criteria based on percentage of actual body weight relative to ideal body weight for height (%BW/H) and BMI-for-age according to the 2000 Centers for Disease Control and Prevention (CDC) growth reference. Menstrual-cycle phase was determined from the first day of the last menstrual period and categorized as menstrual (days 1–5), follicular (days 6–14), luteal (days 15–28), prolonged (>28 days without menstruation), or premenarcheal. For participants with SLE, disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). The total score was categorized as remission/no activity (score 0), mild activity (1–5), or moderate-to-severe activity (6–19).

2.5 Serum Estradiol Measurement

Approximately 3 mL of venous blood was collected into a plain red-top tube after standard antiseptic preparation. Samples were centrifuged within 30 minutes of collection, and serum was stored at −20°C until analysis. Serum estradiol was measured using a commercial Estradiol ELISA kit (Bioassay Technology Laboratory) according to the manufacturer's instructions.

Briefly, 50 µL of serum or standard was added to the microplate wells, followed by 50 µL of biotinylated antigen and incubation at 37°C for 60 minutes. After five washing cycles, 50 µL of avidin-HRP was added and incubated at 37°C for 60 minutes, followed by another five washing cycles. Substrate Solutions A and B (50 µL each) were then added and incubated at 37°C for 10 minutes in the dark. The reaction was terminated with 50 µL of stop solution. Absorbance was measured at 450 nm within 10 minutes using a microplate reader. Samples were analyzed in duplicate, and estradiol concentrations were calculated from the standard curve and expressed in pg/mL.

2.6 Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 29.0. Continuous variables were assessed for distributional characteristics and summarized as mean ± standard deviation for normally distributed data or median (minimum–maximum) for non-normally distributed data. Categorical variables were presented as frequencies and percentages.

Initial between-group comparisons were performed using the Mann–Whitney U test for non-normally distributed continuous variables and the independent-samples t-test for normally distributed variables. Categorical variables with small expected cell counts were compared using the Fisher–Freeman–Halton exact test. Serum estradiol concentrations across nutritional-status and menstrual cyle phase categories were compared using the Kruskal–Wallis test. Among participants with SLE, differences in estradiol concentrations across disease-activity categories were assessed using one-way analysis of variance when parametric assumptions were satisfied. Associations between estradiol concentration and SLEDAI score were evaluated using Spearman's correlation, whereas Pearson's correlation was used for normally distributed continuous variables.

To evaluate whether serum estradiol concentrations differed between the SLE and non-SLE groups after accounting for factors that may influence estradiol concentrations, analysis of covariance (ANCOVA) was performed. Study group was entered as the main fixed factor, age as a continuous covariate, and menstrual status as a categorical factor. The assumptions for ANCOVA, including normality of residuals, homogeneity of variance, linearity between the continuous covariate and the outcome, and homogeneity of regression slopes, were assessed and considered acceptable. Homogeneity of variance was additionally assessed using Levene's test. Adjusted results were reported as estimated marginal means with standard errors (SE), 95% confidence intervals (CI), F statistics, p values, and partial eta squared (partial η^2). All statistical tests were two-sided, and a p value <0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Participant Characteristics

A total of 44 participants were enrolled in the study, comprising 22 participants with SLE and 22 without SLE. All enrolled participants completed the study procedures and were included in the final analysis. The participant selection and study enrollment process are presented in Figure 1. Based on Table 1, nutritional status did not differ significantly between groups (p=0.106). However, the SLE group was significantly older (p=0.010) and had a significantly different menstrual-cycle distribution (p=0.005) than the non-SLE group. %BW/H was higher in the SLE group, although the between-group difference was not significant (p=0.089). Overall, nutritional status was comparable between groups, whereas age and menstrual status differed significantly between the SLE and non-SLE groups.

3.2 Comparison of Estradiol levels Between Groups

In the unadjusted analysis, serum estradiol concentrations were numerically higher in the SLE group than in the non-SLE group (See Table 2). The median estradiol concentration was 64.67 pg/mL (50.10–107.80) in the SLE group and 56.37 pg/mL (36.50–95.20) in the non-SLE group; however, the between-group difference was not statistically significant (p = 0.105).

Given the significant between-group differences in age and menstrual status , an ANCOVA was performed to assess the between-group difference in serum estradiol after accounting for these variables. After adjustment for age and menstrual status , the estimated marginal mean serum estradiol concentration was 63.35 pg/mL (SE = 4.02; 95% CI, 55.20–71.50) in the SLE group and 59.71 pg/mL (SE = 4.47; 95% CI, 50.65–68.77) in the non-SLE group. The adjusted difference between groups remained statistically nonsignificant (F = 0.370, p = 0.547, partial η^2 = 0.010). Menstrual status was not significantly associated with estradiol concentration in the adjusted model (F = 0.671, p = 0.617, partial η^2 = 0.068). Age was likewise not significantly associated with estradiol concentration (F = 0.019, p = 0.892, partial η^2 = 0.001).

Table 1. Baseline Characteristics of Female Adolescents With and Without Systemic Lupus Erythematosus

Variable	Category	SLE (n=22)	Non-SLE (n=22)	p-value
Age, months		195.50 (97–215)	157.50 (97–201)	**0.010***
Nutritional status	Poor	0 (0.0%)	1 (4.5%)	0.106†
	Underweight	7 (31.8%)	8 (36.4%)	
	Normal	7 (31.8%)	11 (50.0%)	
	Overweight	7 (31.8%)	1 (4.5%)	
	Obesity	1 (4.5%)	1 (4.5%)	
Menstrual-cycle phase	Premenarcheal	4 (18.2%)	10 (45.5%)	**0.005†**
	Menstrual	3 (13.6%)	4 (18.2%)	
	Follicular	3 (13.6%)	7 (31.8%)	
	Luteal	9 (40.9%)	1 (4.5%)	
	Prolonged menstrual	3 (13.6%)	0 (0.0%)	
%BW/H, %		101.41 ± 16.42	93.87 ± 11.86	0.089‡

*Data are presented as n (%), median (minimum–maximum), or mean ± standard deviation, as appropriate. Mann–Whitney U test. † Fisher–Freeman–Halton exact test. ‡ Independent-samples t-test. A p-value <0.05 was considered statistically significant..

Table 2. Unadjusted and Adjusted Comparison of Serum Estradiol Concentrations Between the SLE and Non-SLE Groups

Analysis	SLE	Non-SLE	Between-group difference	p value
Unadjusted	64.67 (50.10–107.80)	56.37 (36.50–95.20)	—	0.105*
Adjusted	63.35 (55.20–71.50)	59.71 (50.65–68.77)	3.65 (−8.50 to 15.79)	0.547**

* Unadjusted values are presented as median (minimum–maximum), and between-group differences were assessed using the Mann–Whitney U test. ** Adjusted values are presented as estimated marginal means with 95% confidence intervals. Between-group differences were assessed using analysis of covariance (ANCOVA), adjusting for age and menstrual status

3.3 Estradiol According to Nutritional Status, Menstrual-Cycle Phase, and Disease Activity

The distribution of serum estradiol concentrations according to nutritional status, menstrual-cycle phase, and disease activity is presented in Table 3. Among all participants, estradiol concentrations did not differ significantly across nutritional-status categories (p=0.292). Descriptively, the highest concentration was observed among participants with obesity, whereas the lowest was observed in the poor nutritional-status category. Similarly, estradiol concentrations did not differ significantly across menstrual-cycle phases (p=0.281). The highest concentration was observed during the luteal phase, while the lowest was observed among participants with prolonged menstrual cycles (Table 2).

Among participants with SLE, estradiol concentrations showed no significant difference across disease-activity categories based on SLEDAI (p=0.204). Nevertheless, a descriptive increase in estradiol concentration was observed with increasing disease activity, from remission to mild and moderate-to-severe activity (Table 3). Overall, neither nutritional status nor menstrual-cycle phase was significantly associated with serum estradiol concentration in the overall study population, and disease activity was not significantly associated with estradiol concentration among participants with SLE.

3.4 Correlation of Estradiol With Disease Activity, Age, and %BW/H

Correlation analyses are presented in Table 4. Among participants with SLE, serum estradiol showed a weak positive correlation with SLEDAI score, but the association was not statistically significant (r=0.213, p=0.341). Across the entire study population, estradiol also showed a weak positive correlation with age, which did not reach statistical significance (r=0.184, p=0.231). No correlation was observed between estradiol and %BW/H (r=−0.003, p=0.987). Overall, serum estradiol was not significantly correlated with disease activity, age, or %BW/H in the study population.

Table 3. Serum Estradiol Concentrations According to Nutritional Status, Menstrual-Cycle Phase, and Disease Activity

Variable	n	Estradiol, pg/mL	p-value
Nutritional status			**0.292***
Poor	44	46.97 (46.97–46.97)	
Underweight		66.63 (36.55–107.82)	
Normal		56.37 (39.43–95.29)	
Overweight		64.00 (52.98–87.55)	
Obesity		69.94 (52.98–86.90)	
Menstrual-cycle phase			**0.281***
Premenarcheal	44	56.37 (39.85–86.90)	
Menstrual		56.79 (36.55–95.29)	
Follicular		61.93 (37.60–84.12)	
Luteal		66.35 (52.98–107.82)	
Prolonged menstrual		54.11 (52.98–68.88)	
Disease activity (SLEDAI)			**0.204†**
Remission	22	58.35 ± 8.25	
Mild		65.64 ± 9.59	
Moderate-to-severe		73.58 ± 24.16	

Data for nutritional status and menstrual-cycle phase were analyzed among all participants (n=44) and are presented as median (minimum–maximum). †Disease activity was assessed among participants with SLE (n=22) and is presented as mean ± standard deviation. *Kruskal–Wallis test. †One-way analysis of variance. A p-value <0.05 was considered statistically significant.

Table 4. Correlations of Serum Estradiol With Disease Activity, Age, and %BW/H

Variable	n	Estradiol	
		r-value	p-value
SLEDAI	22	0.213	0.341*
Age, months	44	0.184	0.231*
%BW/H	44	−0.003	0.987**

Age and %BW/H were analyzed in all participants (n=44), whereas SLEDAI was assessed only in participants with SLE (n=22). *Spearman correlation test. **Pearson correlation test. r = correlation coefficient. A p-value <0.05 was considered statistically significant. %BW/H = percentage of body weight relative to ideal body weight for height.

3.5 Discussion

The present study evaluated the relationship between serum estradiol and SLE in female adolescents, a population in which pubertal hormonal changes may interact with autoimmune mechanisms. The main finding was that serum estradiol did not differ significantly between adolescents with and without SLE in either the unadjusted analysis or adjusted analysis. Although concentrations tended to be higher in the SLE group, this finding suggests that circulating estradiol alone may not distinguish adolescent patients with SLE from their non-SLE counterparts. This is in line with Kim et al. (2022), who reported inconsistent evidence regarding circulating sex hormones in SLE.[5]

The adjusted analysis is particularly relevant because the SLE and non-SLE groups differed significantly in age and menstrual-cycle distribution at baseline. Participants with SLE were older and were more frequently in the luteal phase, whereas the non-SLE group included a greater proportion of premenarcheal and follicular participants. These differences are biologically relevant because circulating estradiol varies with pubertal maturation and menstrual-cycle phase. Kim et al. (2022) emphasized that menstrual phase is an important determinant of circulating estradiol and should be considered when interpreting hormonal

measurements.[5] The greater occurrence of menstrual disturbances in SLE may also reflect disease- or treatment-related effects on the hypothalamic–pituitary–ovarian axis, consistent with Nirouei et al. (2023).[11] Age is similarly relevant because estradiol increases during pubertal maturation, although chronological age does not necessarily reflect pubertal stage.[4]

Despite these baseline differences, neither menstrual status nor age was significantly associated with serum estradiol concentration in the adjusted model. Thus, the absence of a significant between-group difference in estradiol persisted after accounting for these potential sources of variation. The nonsignificant between-group difference should not be interpreted as evidence of equivalence. The adjusted mean difference was 3.65 pg/mL, with a relatively wide 95% confidence interval (−8.50 to 15.79 pg/mL), indicating substantial uncertainty regarding the magnitude and direction of the between-group difference. Therefore, modest differences cannot be excluded, particularly given the relatively small sample size.

The biological effects of estrogen depend not only on circulating concentrations but also on receptor expression, receptor sensitivity, and interaction with other sex hormones. Accordingly, Abdolahpour et al. (2025) demonstrated that combined hormonal and receptor profiles may provide greater information regarding disease activity than individual hormone concentrations.[9]

Nutritional status did not differ significantly between groups, although excess weight was more frequent among participants with SLE. This finding is consistent with Park et al. (2025), who reported that metabolic abnormalities and excess weight are common in juvenile-onset SLE.[2] Pan et al. (2023) similarly noted that nutritional and growth disturbances may reflect chronic inflammation, reduced physical activity, disease severity, and prolonged glucocorticoid exposure.[3]

Estradiol concentrations varied across nutritional categories, although no significant association was demonstrated. This observation is biologically plausible because adipose tissue contributes to peripheral estrogen production through aromatization of androgens.[12] However, conventional nutritional categories may not adequately capture body composition, adipose distribution, or endocrine activity, particularly in adolescents with chronic inflammatory disease. Similarly, the variation in estradiol across menstrual phases is consistent with the physiological dynamics of ovarian estrogen secretion.[12] The occurrence of Prolonged menstrual cycles among participants with SLE may further indicate disruption of reproductive endocrine function, as previously reported by Nirouei et al. (2023).[11]

Within the SLE group, estradiol showed a weak positive tendency with disease activity but no significant association. This finding is consistent with Kim et al. (2022), who reported heterogeneous relationships between estrogen concentrations and clinical disease activity.[5] The lack of a significant association does not exclude a biological role for estradiol, as estrogen signaling can enhance B-cell survival, autoantibody production, and innate and adaptive immune responses through estrogen receptors and Toll-like receptor pathways.[13] Accapezzato et al. (2023) further emphasized that disease activity results from the interaction of multiple immunological pathways, suggesting that a single circulating hormone may not adequately represent the complexity of active disease.[14]

The absence of significant associations between estradiol and age or %BW/H further supports the complexity of hormonal regulation during adolescence. Chronological age is an imperfect marker of pubertal maturation, while anthropometric indices do not directly reflect adipose tissue distribution or estrogenic activity. Ignatiuk et al. (2025) similarly highlighted the complex relationship between adiposity and hormonal regulation.[15]

Overall, these findings indicate that serum estradiol concentrations did not significantly differ between adolescents with and without SLE in this study, and serum estradiol was not significantly associated with SLEDAI-defined disease activity. Nevertheless, its potential immunomodulatory role supports further investigation of estradiol within a broader endocrine–immune framework incorporating reproductive status, estrogen-receptor signaling, and other immunological biomarkers. A strength of this study is its focus on female adolescents with SLE, a population in which data regarding circulating estradiol and disease activity remain limited.

This study has several limitations. First, the cross-sectional design precludes definitive conclusions regarding causality between serum estradiol and disease activity. Second, the relatively small sample size may have limited statistical power to detect modest differences or associations. Third, estradiol was measured at a single time point and may not adequately capture physiological hormonal fluctuations across the menstrual cycle. Fourth, although age and menstrual-cycle status were accounted for in the adjusted analysis, residual confounding from unmeasured reproductive, hormonal, and treatment-related factors may still have influenced serum estradiol concentrations. Fifth, the hospital-based recruitment of non-SLE controls with mild acute conditions

may have introduced selection bias and may limit the generalizability of the findings to healthy community populations. Finally, potentially relevant factors, including medication exposure, vitamin D status, genetic background, and other endocrine or immunological variables, were not assessed and may have influenced the observed associations.

4. CONCLUSION

Among female adolescents with SLE, serum estradiol concentrations were numerically higher than those in the non-SLE group; however, no statistically significant difference was observed in either the unadjusted analysis or after adjustment for age and menstrual status . Serum estradiol also showed a weak positive but nonsignificant correlation with disease activity assessed using SLEDAI. These findings suggest that circulating estradiol concentration alone was not significantly associated with either SLE status or disease activity in this study population. Larger prospective studies incorporating standardized assessment of pubertal and reproductive status, serial hormone measurements, and adjustment for treatment-related and other endocrine factors are warranted to further clarify the role of estrogen in juvenile SLE.

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AUTHOR CONTRIBUTIONS

IM: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, and Project administration. **RDA:** Methodology, Supervision, Validation, and Writing – review and editing. **BF:** Methodology, Investigation, and Validation. **MM:** Supervision, Validation, and Writing – review and editing. **JS:** Investigation, Data curation, and Validation. **MMA:** Investigation, Data curation, and Writing – review and editing.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ETHICS STATEMENT

The study was approved by the Biomedical Research Ethics Committee of the Faculty of Medicine, Hasanuddin University (No. 1130/UN4.6.4.5.31/PP36/2025). Written informed consent was obtained from the parents or legal guardians of all participants before enrollment, and participation was voluntary.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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