Research Article

CORRELATION BETWEEN SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX SCORE AND ANTI-MULLERIAN HORMONE LEVEL IN PEDIATRICS SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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ABSTRACT

Background: Systemic lupus erythematosus disease activity index **(**SLEDAI) is a scoring system to assess the activity of systemic lupus erythematosus (SLE) disease. SLE patients are at risk of amenorrhea, which may lead to infertility. The anti-Müllerian hormone is used as a marker for infertility risk in females.

Aim: To analyze the correlation between systemic lupus erythematosus disease activity index score and the level of anti-Müllerian hormone (AMH) as a marker for infertility risk in pediatric SLE patients.

Methods: A cross-sectional study was conducted in 6-18 years old female patients with SLE admitted to the pediatric ward of dr. Moewardi General Hospital, Surakarta between December 2018–October 2019. The diagnosis of SLE was established based on systemic lupus international collaborating clinics (SLICC 2012) criteria. All subjects received SLEDAI scoring and anti-Müllerian hormone examination. The correlation between variables was analyzed using the Spearman rank test to determine the correlation coefficient and the p value of ≤ 0.05 was considered significant.

Results: Twenty-one female pediatric SLE patients were included in the study. The mean age of the subjects was 14 years old. There was a significant negative correlation between SLEDAI score and AMH level in pediatric SLE patients ($r = -0.841$; p-value < 0.0001).

Conclusion: In pediatric SLE patients SLEDAI score has a negative correlation with AMH level.

Keywords: SLE**,** SLEDAI, AMH, Pediatrics.

INTRODUCTION

For Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune disease characterized by periods of increased disease activity caused by inflammation of blood vessels and connective tissue. Pediatric patients with SLE have a more severe clinical course in comparison with their adult counterparts. Patients typically present with rash, fever, and arthritis. The World Health Organization (WHO) recorded an estimate of 5 million people affected by systemic lupus erythematosus. Around 5% of the cases occurred in children, especially during puberty. The overall prevalence of SLE in children was 10 to 25 cases per 100,000 children.[1, 2, 3]

There is a scoring system used to assess the activity of SLE by combining clinical condition and laboratory results, known as the systemic lupus erythematosus disease activity index (SLEDAI). The SLEDAI score was first introduced in 1995 in Toronto University to determine the disease activity of systemic lupus erythematosus. The SLEDAI score is easy to use, even for a beginner observer. This score contains a relatively few and simple variables, thus it can be completed quickly.[4]

SLE patients have a risk of amenorrhea, which may lead to infertility. Anti-Müllerian hormone (AMH) level in SLE patients was lower than the AMH level found in normal individuals. AMH level examination can be used as a parameter of ovarian reserve, whereas low level can be a sign of infertility risk in female individuals.[5]

A study to determine the risk of infertility in pediatric SLE patients is needed. One of which is by determining the correlations of SLEDAI score and AMH level in pediatric systemic lupus erythematosus patients.

METHODS

This is a cross-sectional study conducted on pediatric patients with underlying systemic lupus erythematosus admitted in the pediatric ward of Dr. Moewardi General Hospital, Surakarta, Indonesia between December 2018–October 2019. The target population was female children aged between 6 and 18 years old. The samples were taken by using a consecutive sampling technique. The inclusion criteria were 6-18 years old female SLE patient and willing to participate in the study by signing the informed consent. We excluded patients with a history of ovarian surgery and endometriosis. We used numerical data, the data were presented in mean and standard deviation. Shapiro Wilk was used to test data normality. The correlation of SLEDAI to AMH level was analyzed with Spearman Rank test. All data were analyzed with SPSS 22 and p value of ≤ 0.05 was considered significant statistically.

RESULTS

Table 1. Baseline Data

Variable	Number (%)	Mean ± SD (years)
Age	21 (100%)	14.5 ± 2.3
Menstrual Cycle		
Regular	7 (33%)	
Irregular	8 (38%)	
Had not menstruated	6 (29%)	
Age at first menstruation	15 (71%)	12.7 + 1
Diagnosis		
Mild SLE	4 (19%)	
Severe SLE	17 (81%)	
Treatment		
Without Cyclophosphamide	4 (19.0%)	
With Cyclophosphamide	17 (81.0%)	

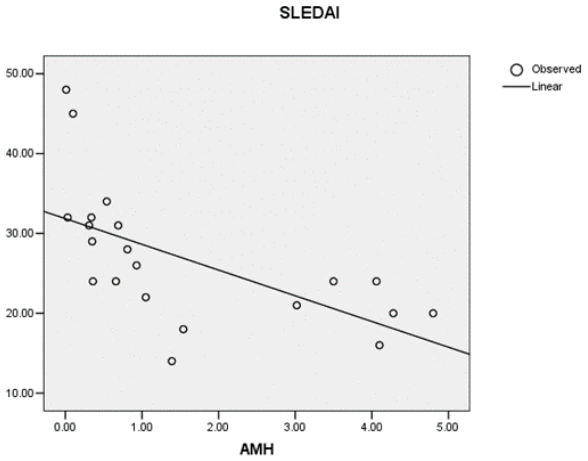
Most subjects had irregular menstruation (38%). Fifteen subjects (71%) had their first menstruation at the average age of 12.7 + 1 years old. Eighty one percent of subjects were diagnosed with severe SLE. The subjects were mostly treated with cyclophosphamide (81%). Table1

Shapiro Wilk test obtained that SLEDAI had normal distribution (p = 0.109), while AMH level was not normally distributed (p = 0.001).

Table 2. The Correlation between SLEDAI Score and AMH Level in Pediatric Systemic Lupus Erythematosus Patients

Variable	AMH	
	R	p-value
SLEDAI	-0.841	< 0.0001

Spearman Rank test revealed a strong negative correlation between SLEDAI score and AMH level (r = - 0.841). However the correlation between SLEDAI score and AMH level was statistically significant (p = < 0.0001). Table 2



Scatter plot of the correlation between SLEDAI score and AMH level in pediatric SLE patients

Scatter plot demonstrated that increase in SLEDAI score correlated with decreased AMH level significantly. Figure 1

DISCUSSION

This study obtained 21 female pediatric SLE patients with the mean age of 14.5 ± 2.3 years old and the mean age of first menstruation period was 12.7 + 1 years old. In this study the subjects experienced regular menstruation (33%), irregular menstruation (38%) and even did not have menstruation at all (29%). These findings demonstrate that the disturbance in the menstrual cycle of pediatric SLE patients is relatively high. This is in line with a previous study whereas the prevalence of menstrual disturbance in SLE patients was around 15-40%.[6]

In SLE, there is an antibody mechanism that causes premature ovarian failure, lack of follicle, and follicle dysfunctions are the primary etiology. The mutation of the follicle stimulating hormone (FSH) receptor and improper luteinization is the cause of follicle dysfunction. This is underlined by an anti-ovarium antibody aimed at the ovarium tissue. Cellular immunities such as macrophages and dendritic cells, changes in the CD4+ or CD8+ ratio and major histocompability complex (MHC) class II antigen expression by granulose cells are found in premature ovarian failure.[7]

Antibodies fight against steroid-forming cells in the endocrine gland. Theca cells in the ovarium are part of the endocrine gland. This antibody is known as steroid cell antibody (StCA), which is a polyclonal antibody from IgG. The main antigenic target of StCA is P450-17α-hydroxylase (17α-OH), P450 side-chain cleavage (P450scc). This autoimmune mechanism demonstrates an estrogen increase with inadequate androgen activity, which leads to immune system dysregulation. Estrogen activates polyclonal B cells, causing excessive production of auto-antibodies and attacks theca cells. On the other hand, MHC class II antigen expression in the granulose cells results in a decrease in androgen production by theca cells. The absence of luteinizing hormone (LH) surge leads to no ovulation, thus disrupts the menstrual cycle and causes amenorrhea.[7]

Cyclophosphamide chemotherapy for SLE patients causes premature ovarian failure, in which chemotherapy induces the apoptosis of pre-granulose cells changes resulting in loss of follicles. Therefore, the theca cell and granulose cell surrounding the ovarian cell and oocyte are disrupted, causing a decrease in androgen hormone production, leading to a disruption in androgen changes to estrogen stimulated by FSH. Finally, the production of estrogen hormone, ovum, and oocyte decreases. This is the cause of premature ovarian failure in SLE patients. SLE patients receiving cyclophosphamide with a cumulative dose of more than 10 grams are three times at risk of premature ovarian failure. Previous study reported that the percentage of premature ovarian failure in SLE patients who received cyclophosphamide was 35%.[8]

AMH is the ideal marker for ovarian reserve because this hormone is only formed by the primary follicle with a potential of maturation. AMH level reflects the number of the preantral follicle, therefore it can be a particularly good marker for the oocyte pool. Plasma AMH level assessment is more specific than FSH and inhibin because AMH does not involve in the feedback mechanism of the hypothalamus-hypophysis-ovarium axis. In female patients, AMH can be used to screen fertility. Female individuals with low AMH level tend to produce fewer ovum during *in vitro* fertilization compared to female individuals with high AMH level.[9]

Premature ovarian failure is one of the causes of amenorrhea and infertility, presented as a decrease of ovarium function, ovarium response to FSH, and estrogen decrease. Decreased AMH level in premature ovarian failure patients is caused by follicular atresia and disruption in the theca cells, which decrease AMH production. The benefit of AMH serum level measurement is to identify patients with risk factors of premature ovarian failure such as a history of chemotherapy, radiation, and autoimmune disease.[23]The mean AMH level is significantly lower in SLE patients previously exposed to cyclophosphamide. AMH diagnostic test to predict ovarian reserve has 97% sensitivity and 100% specificity. The risk factors of decreased AMH in SLE are the administration of cyclophosphamide chemotherapy and history of ovarian surgery.[5, 10, 11, 12]

The systemic lupus erythematosus disease activity index (SLEDAI) is a scoring used to assess SLE activity by combining clinical conditions and laboratory findings. In SLEDAI, each variable is clearly defined, thus producing minimum perception difference during form filling. SLEDAI score is also sensitive to changes in disease activity. SLEDAI score observation is performed every 6 months or when there is a change of SLE disease activity. This scoring system describes 8 organ systems. A SLEDAI score of more than 8 show that there is a correlation between menstrual cycle disturbance and high SLEDAI score, which is related to ovarium dysfunction. AMH level can describe ovarium function decrease, which can be seen from a decrease in the hypothalamus-hypophysis-gonad axis.[11, 13]

Our findings revealed that there was a significant correlation between increased SLEDAI score and decreased AMH level in pediatric SLE patients ($r = -0{,}841$; $p < 0.0001$). This study also showed that the higher the SLEDAI score, the lower the AMH level was in SLE patients. Decreased AMH level is commonly observed in patients with premature ovarian failure (POF), which is due to follicular Artesia and disturbances in the ovarium theca cells, causing a decline in AMH production. AMH serum level measurement can identify patients with risk factors of premature ovarian failure, such as the history of chemotherapy, radiation, and autoimmune disease.[5] SLE patients with SLEDAI score of > 8 have a higher risk of developing menstrual disturbance compared to patients with SLEDAI score < 8. This is due to an increased risk of POF and amenorrhea in SLE patients and high infertility.[14]

CONCLUSION

There is a significant correlation between increased SLEDAI score and decreased AMH level in pediatric SLE patients. Therefore pediatricians should be aware that high SLEDAI score shows the risk of infertility in pediatric patients with SLE.

CONFLICT OF INTEREST

None declared.

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