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RESEARCH ARTICLE

Fertility and Pregnancy Outcomes in Systemic Lupus Erythematosus Patients: A Study Using Antimullerian Hormone

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ABSTRACT:

Background: Systemic lupus Erthymatosus (SLE) affects predominantly women of reproductive age, and can lead to both negative effect on their fertility and adverse pregnancy outcomes. Antimullerian hormone (AMH) serum levels have been found to be a reliable marker of ovarian reserve.

Objectives: This research aimed to assess ovarian reserve by measuring AMH level in premenopausal SLE patients and to study different factors that can have an effect on it, and also to evaluate pregnancy outcomes in SLE patients.

Methods: The study was performed on 60 subjects divided into 2 groups; (I): 30 SLE female patients and (II): control group which includes 30 healthy female subjects. Full history taking and examination were carried out including assessment of disease activity by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) score and damage index by Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage index (SLICC/ACR) on SLE patients, pregnancy questionnaire were used for taking history of the pregnancy outcomes. AMH levels were measured in both groups using AMH Gen II ELISA kits.

Results: There was no statistically significant difference between both groups as regard to median AMH levels and there was no statistically significant correlation between AMH and disease duration, BMI, SLEDAI-2K activity score, damage index and the immunosuppressive drugs such as cyclophosphamide, mycophenolate mofetil and azathioprine. There was statistically significant difference between both groups as regards to occurrence of miscarriage ($P<0.0166$) and hypertension in pregnancy ($P<0.04$).

Conclusion: From these results we can conclude that AMH values did not differ between SLE patients and healthy subjects, and the disease duration and/or activity did not affect its level. Moreover, the study reflected that immunosuppressive agents such as cyclophosphamide, azathioprine and mycophenolate mofetil did not affect the fertility in SLE patients. However, it was noted that adverse pregnancy outcomes were relatively more common in SLE patients, namely hypertension in pregnancy and miscarriages.

Introduction:

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the presence of a variety of circulating autoantibodies leading to diverse clinical manifestations and target tissue damage. This is more prevalent in fertile age women [1].

Anti–mullerian hormone (AMH) is expressed by the granulosa cells of growing follicles. Its level is relatively stable throughout the menstrual cycle, and its measurement thus does not require timing with menstruation [2].

Cyclophosphamide (CYC) is a cytotoxic agent which reacts with DNA bases and damages DNA repair mechanisms, thus inhibits cellular replication[3]. Menstrual disorders are reported to be common complications of intravenous cyclophosphamide (IV CYC) therapy in SLE women, and it is known to cause amenorrhea and premature ovarian failure [4]. In CYC therapy, longer period of treatment, and high cumulative dose of IV CYC are reported to be the major risk factors for ovarian failure [5]. Moreover, Previous use of CYC predisposes SLE women to lower fertility, and adverse pregnancy outcomes particularly increased preterm deliveries [3].

The AMH levels of female patients treated with mycophenolate mofetil (MFM) for lupus were almost the same to that of the control population. However, birth outcomes of SLE mothers on this drug included cases of malformation of the CNS, skull, limbs, intrauterine growth retardation and cardiomyopathy [6].

Infants of mothers taking Azathioprine (AZA) in early pregnancy are at higher risk of developing congenital malformations, specifically ventricular/atrial septal defects, in addition to the increased risk of growth restrictions and preterm deliveries [7].

In spite of these congenital anomalies, SLE patients on Azathioprine had a similar number of pregnancies compared to that of the control group [8].

Objectives:

- To asses ovarian reserve in SLE patients reflected by measuring antimullerian hormone level.
- To evaluate pregnancy outcomes in SLE patients in correlation to AMH hormone level.

Methods:

❖ **Subjects:**

-Sample size was calculated by Stata Corp. 2021.

-The null hypothesis was considered with possible absence of a difference between SLE cases compared to healthy controls regarding the AMH level. The expected mean (± SD) of AMH in SLE group is 1.69 (± 1.35), while in control group, the expected mean (± SD) of AMH is 2.98 (± 1.50).

- The required minimal sample size is 24 subjects per group (total 48 subjects) using α error 5% and a power of 80%. The sample size was increased to 30 in each group to increase the power of the study.

Subjects were divided into two groups:

- **Group I (SLE Group):**

-The patients were attending the rheumatology clinics in Zagazig University Hospitals

-30 female patients with systemic lupus erythematosus (SLE), fulfilling the ACR/ SLICC revised criteria for classification of SLE [9].

-Ages ranged from 19-48 years with a mean of 32.23 ± 8.846 years. Disease duration ranged from 1 – 15 years with a mean (6.87 ± 4.313) years.

- **Group II (Control Group):**

-30 healthy female volunteers. Their ages ranged from 18 - 42 years with a mean of 29.03 ± 7.837 years.

➢ **Exclusion criteria:**

1- Patients with other autoimmune diseases.

2-Patients with previously diagnosed gynecological problems affecting fertility.

❖ **Methodological Execution**

-Case-control study.

-Patients were subjected to the following:

1. Full History Taking:

- It was conducted a full clinical record of all patients, including the type of immunosuppressive drugs (azathioprine- hydroxycholoquine- mycophenolate mofetil –cyclophosphamide) and the duration of the intake and the dose of these drugs.

2. General and Muscloskeletal examination.

3. Assessment of disease activity in SLE patients:

Patients were assessed by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K score), this index measures disease activity within the last 10 days. It is a global index including 24 weighted objective clinical and laboratory variables. Disease activity can range from 0 to 105, [6].

Activity categories defined on the basis of SLEDAI scores, [9]

- No activity (SLEDAI; 0),
- Mild activity (SLEDAI; 1–5),

- Moderate activity (SLEDAI; 6–10),
- High activity (SLEDAI; 11–19),
- Very high activity (SLEDAI≥ 20).

5. Damage index:
Assessment of Systemic lupus International Collaborating Clinics/ American Collage of Rheumatology (SLICC/ACR) Damage Index for Systemic lupus erythromatosus [10].
A damage index for SLE was developed by the SLICC and endorsed by the ACR, where 12 systems are assessed by 42 items for damage, and present for at least 6 months [10].

6. Pregnancy in SLE questionnaire [11]:
- This questionnaire was designed to cover the socio-demographics, pregnancy history and outcome in SLE patients.
- It Contains 43 questions that was approved by the Health Sciences Research Ethics Board of the University of Western Ontario, London, Ontario, Canada

9- Antimullerian hormone measurement:

❖ **Principle** [12]:

The AMH Gen II ELISA is an enzymatically amplified two-site immunoassay. In the assay, calibrators, controls and samples are incubated in microtitration wells which have been coated with anti-AMH antibody. After incubation and washing, anti-AMH detection antibody labeled with biotin is added to each well. After a second incubation and washing step, streptavidin-horseradish peroxidase (HRP) is added to the wells. After a third incubation and washing step, the substrate tetramethylbenzidine (TMB) is added to the wells. Lastly, an acidic stopping solution is added. The degree of enzymatic turnover of the substrate is determined by dual wave length absorbance measurement at 450 nm and between 600 and 630 nm. The absorbance measured is directly proportional to the concentration of AMH in the samples. A set of AMH calibrators is used to plot a calibration curve of absorbance versus AMH concentration. The AMH concentrations in the samples can then be calculated from this calibration curve.

❖ **Statistical analysis:**
The data were coded, entered and processed on computer using *Statistical package for social science (SPSS)* (version 18).The results were represented in tabular and diagrammatic forms then interpreted. Mean, standard deviation, median, range, frequency, and percentage were use as descriptive statistics. **Chi-Square test X^2** was used to test the association variables for categorical data. **Student's t-test** was used to assess the statistical significance of the difference between two population means in a study. **Mann Whitney U test** was used to compare non-parametric data. **Pearson & Spearman's correlation** were used to evaluate the linear association between 2 quantitative variables: Pearson for parametric data and Spearman for nonparametric data. **P value was considered significant as the following:** $P > 0.05$: Non significant; $P \leq 0.05$: Significant.

Results:

Table (1): Comparison between both groups regarding serum AMH level:

	Group I (No= 30)	**Group Π (No= 30)**	**MW test**	**P. value**
AMH *Median (Range)*	2.7 (0.1-9.7)	3.07 (0.3 – 20)	388.0	0.359
	SLE Group (No= 30)	**Control Group (No= 30)**	**X2**	**P**
Low AMH *No (%)*	2 (6.7%)	1(3.3%)	0.351	0.554
Normal AMH *No (%)*	28 (93.3%)	29 (96.7%)		

Normal range: (0.3-20) ng/ml

Table (1): shows that there was no statistically significant difference between the two groups regarding mean AMH values (P>0.05).

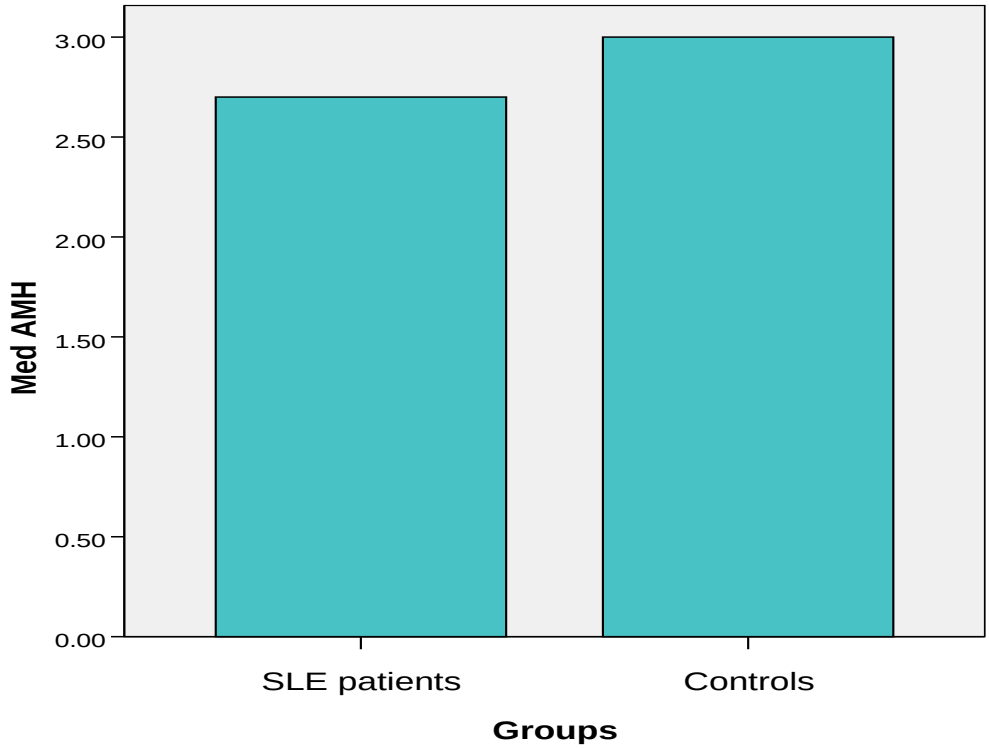
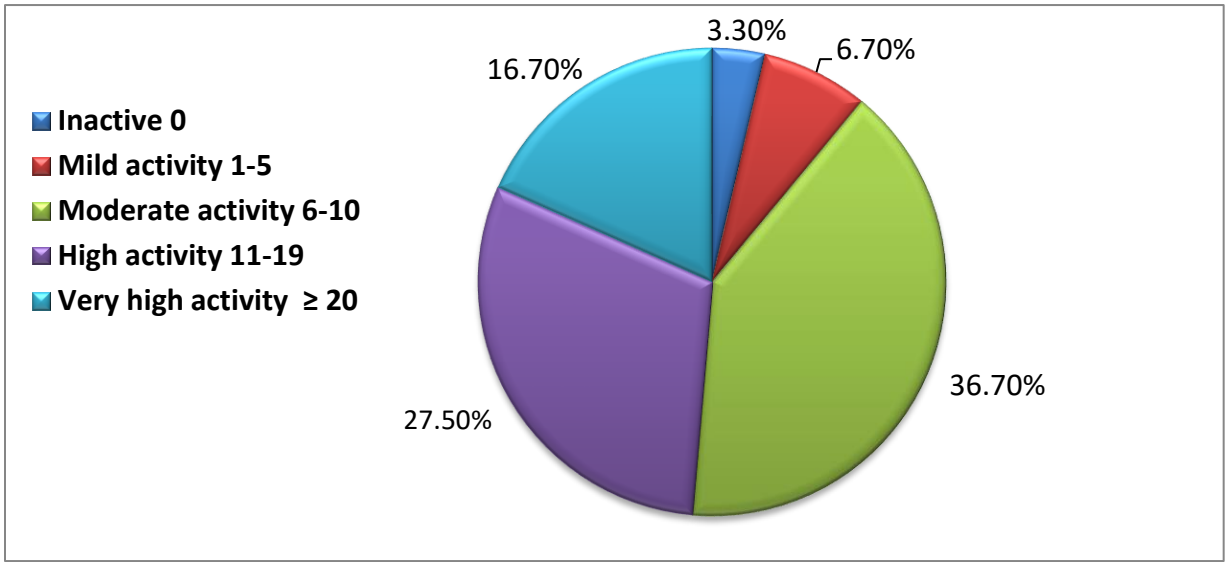


Figure (1): shows the comparison between the median of AMH level between the two groups.



SLEDAI activity score among cases. :Figure (2)

This figure shows the frequencies of inactive, mild, moderate, high, very high activity categories, they were 3.3%, 6.7%, 36.7%, 27.5%, 16.7% respectively. The majority of our patients had moderate disease activity.

Table (2): Damage index among studied Group I:

Organ involved	No	%
Ocular	0	0
Neuropsychiatric	2	6.6
Renal	3	10
Pulmonary	0	0
Cardiovascular	0	0
Peripheral vascular	1	3.3
Gastrointestinal	0	0
Musculoskeletal	1	3.3
Skin	0	0
Premature gonadal failure	1	3.3
Diabetes	0	0
Malignancy	0	0
Total No. with damage	6	20

This table shows that 20% of our patients developed a disease related organ damage, the most common was renal damage 10%.

Table (3): Correlation between Serum AMH level and disease-related variables:

Variables	correlation with AMH	
	R	P
Age	0.443	0.07
BMI	0.390	0.08
Disease duration	0.031	0.140
SLEDAI score	0.16	0.68
Damage index	-0.254	0.094

OCP oral contraceptive pills, BMI: body mass index, SLEDAI Systemic Lupus Erythematosus, AMH anti-mullerian hormone

Table (3) shows that there was no statistically significant correlation between AMH level and other variables including age, BMI, disease duration, SLEDAI and Damage index (P>0.05)

Table (4): Comparison between AMH levels in relation to different drugs (Cyclophosphamide, Azathioprine and Mycophenolate Mofetil):

	AMH *Median (Range)*	**MW**	**P value**
Azathiprine			
Non-Users (n=11) Users (n=19)	2.7 (0.1- 6.5) 2.7 (0.1- 9.7)	98	0.78
Mycophenolate Mofetil			
Non-Users (n=22) Users (n=8)	3.3 (0.1-9.7) 2.4 (0.6-3.5)	59	0.174
Cyclophosphamide			
Non-users (n=22) Users (n=8)	2.6 (0.25-9.7) 3.95 (0.1-6.5)	64.5	0.270

Table (4): shows the difference in AMH levels among different drug users. No significant difference was found.

Table (5): The correlation of serum AMH levels with the duration of use and cumulative doses of different medications:

Variables	Mean ± SD	Correlation with AMH	
		R	P
Cyclophosphamide			
Duration (years) Cumulative dose (Grams)	0.71± 1.36 8. 38 ±2.38	0.63 0.30	0.09 0.46
Azathioprine			
Duration (years) Cumulative dose (Grams)	4.6 ± 2.4 3.2 ± 1.7	0.15 0.13	0.59 0.64
Mycophenolate mofeil			
Duration (years) Cumulative dose (Grams)	6.4±1.14 1120.2 ± 483.6	0.22 0.3	0.62 0.50

Table (5) shows the duration of usage of immunosuppressive therapies (cyclophosphamide, azathioprine and mycophenolate mofetil) and the cumulative doses among SLE patients.

Table (6): Comparison between both groups regarding adverse pregnancy outcomes:

Pregnancy Outcomes (Out of those pregnant)	**Group I (No= 24)**	**Group Π (No= 25)**	**X2**	**P. value**
Miscarriage (at least one) *No (%)*	6(25%)	1(4%)	2.86	**0.03(S)**
Therapeutic abortion *No (%)*	2 (8.3%)	0(0%)	1.79	0.191
Still birth *No (%)*	0(0%)	0(0%)	0	1
Neonate death *No (%)*	3(12.5%)	1(4%)	0.31	0.572
Preterm *No (%)*	4(16.6%)	0(0%)	2.72	0.068
Out of those married	**Group I (No= 26)**	**Group Π (No= 25)**	**MW**	**P. value**
Number of pregnancies/ woman *Median (range)*	3 (0 – 6)	3 (1 – 6)	258	0.919
Number of children/ woman *Median (range)*	2 (0 – 5)	3 (1 – 6)	174.5	**0.04 (S)**

(HS) highly significant, (S) significant

There was statistically significant difference between both groups regarding miscarriage (at least one) and number of children.

Table (7): Comparison between both groups regarding maternal complications of pregnancy:

Out of those pregnant		**Group I (No.= 24)**	**Group Π (No.= 25)**	**X2**	**P. value**
Gest.DM	**No.(%)**	0(0%)	0(0%)	0	1
HTN in pregnancy	**No.(%)**	5(20.83%)	0(0%)	2.71	0.03
SLE flare in pregnancy	**No.(%)**	8(33.3%)	-	-	-

Gest.DM:gestational diabetes, HTN:hypertension

There was statistically significant difference between both groups regarding hypertension in pregnancy and gestational diabetes.

Table (8): Comparison between both groups regarding adverse pregnancy outcomes:

Pregnancy Outcomes (Out of those pregnant)	**Group I (No= 24)**	**Group Π (No= 25)**	**X2**	**P. value**
Miscarriage (at least one) *No (%)*	6(25%)	1(4%)	2.86	**0.03(S)**
Therapeutic abortion *No (%)*	2 (8.3%)	0(0%)	1.79	0.191
Still birth *No (%)*	0(0%)	0(0%)	0	1
Neonate death *No (%)*	3(12.5%)	1(4%)	0.31	0.572
Preterm *No (%)*	4(16.6%)	0(0%)	2.72	0.068
Out of those married	**Group I (No= 26)**	**Group Π (No= 25)**	**MW**	**P. value**
Number of pregnancies/ woman *Median (range)*	3 (0 – 6)	3 (1 – 6)	258	0.919
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(HS) highly significant, (S) significant

There was statistically significant difference between both groups regarding miscarriage (at least one) and number of children.

Table (9): Comparison between both groups regarding maternal complications of pregnancy:

Out of those pregnant		**Group I (No.= 24)**	**Group Π (No.= 25)**	**X2**	**P. value**
Gest.DM	**No.(%)**	0(0%)	0(0%)	0	1
HTN in pregnancy	**No.(%)**	5(20.83%)	0(0%)	2.71	0.03
SLE flare in pregnancy	**No.(%)**	8(33.3%)	-	-	-

Gest.DM:gestational diabetes, HTN:hypertension

There was statistically significant difference between both groups regarding hypertension in pregnancy and gestational diabetes.

Table (10): Comparison between both groups regarding obstetric history:

Obstetric History	**GroupI (No.= 30)**	**GroupΠ (No.= 30)**	**X2**	**P. value**
Ever pregnant *No (%)*	24(63.3%)	25(83.3%)	3.06	0.080
Had child(ren) (out of those pregnant) *No (%)*	23(76.6%)	25(83.3%)	2.54	0.0166 (S)
Had no children (out of those pregnant) *No (%)*	1(3.3%)	0(0%)	2.54	0.0166 (S)

(HS) highly significant, (S) significant

This table shows that there was statistically significant difference between both groups regarding having children or not.

Discussion:

SLE affects predominantly women in reproductive age, whose fertility can be negatively affected by both, the disease activity and the required medical treatment as well [13].

Ovarian function can be reduced by autoimmune oophoritis, which may lead to premature ovarian failure. Evidence of the gonadotoxic effect of cyclophosphamide has already been reported in the literature [14].

Antimullerian hormone (AMH) is a dimeric glycoprotein belonging to the transforming growth factor-β family (TGFβ). In the ovary, AMH is secreted by the granulosa cells of growing follicles, and its serum levels have been found to be a reliable marker of ovarian reserve. AMH levels also remain relatively stable over the course of the menstrual cycle, which is an advantage over other measures of ovarian reserve [15].

This research aimed to assess ovarian reserve by measuring AMH levels in premenopausal SLE patients and to study their pregnancy outcomes. Studies of AMH levels have produced conflicting results regarding the reduction in ovarian reserve in women with SLE [16].

This was a case control study, which included 60 female subjects divided into two equal groups, SLE female patients and healthy control group.

As regard to AMH levels, there was no statistically significant difference between both groups (3.2±2.35 ng/ml in Group I vs 4.19 ±4.128 ng/ml in Group Π). This agrees with **Di Mario** who found no significant correlation in AMH levels between patients and controls (4.2 ± 3.1 ng/ml vs. 5.0 ± 3.1 ng/ml) [17].

This agrees also with **Gasparin** who aimed to investigate the ovarian reserve of patients with SLE by measuring AMH levels, and compare it to that of healthy controls.The study was performed on 80 premenopausal SLE patients. They found mean AMH concentration was (22.79± 17.32 ng/ml) in patients with SLE and (21.41± 16.22 ng/ml) in the control group and the difference between these values was not significant [18]. However, **Martins' et al.** study demonstrated different results; average AMH value in the SLE group was significantly lower than that in the non-SLE control group after adjusting for age (median 0.7 vs 2.7 ng/ml, $p < 0.0001$) [19].

This study showed that the prevalence of low AMH in SLE group was 6.7%. This percentage is very low compared to that documented by **Martins' et al.** study which was 38%, [19].

SLEDAI-2K of our SLE patients ranged between inactive 3.3%, mild 6.7%, moderate 36.7%, high 27.5% and very high activity 16.7%. Another study involving 59 SLE Egyptian patients and 20 healthy controls found 51% of the SLE patients had mild activity and 27.2% had moderate to severe activity. No activity was present in 13%, while 16% had from moderate to severe activity[20].

Notably, there were not significant statically correlation between AMH levels and SLEDAI-2K score in this research. **Martins et al.** have also reported the same finding in their study, in which AMH serum levels were assessed in 52 SLE female patients with regular menstrual cycle compared with 20 aged matched healthy controls. They found that no association was found between AMH serum levels and SLEDAI score ($p = 0.087$) [19]. **Di Mario et al.** reported the same finding in their cohort study on 86 SLE patients, where no association was found between SLEDAI score and AMH level ($P = 0.80$) [17].

Our study showed no significant correlation between AMH value and damage index. This is in agreement with **Gasparin** who did not find an association between AMH level and SLE damage[18]. **Di Mario et** also did not find a significant difference in his study in AMH level in patients with minor organ involvement; mainly articular or cutaneous; (4.5 ± 3.4 ng/ml) and control subjects ($p = 0.33$) [17]. However, lower AMH values in SLE patients with major organ involvement; mainly renal and neurological; were detected in their study (3.8 ± 2.7 ng/ml, $p = 0.08$).

This study showed that there were no statistically significant correlations between AMH with BMI and age. The literature on the topic has produced conflicting results. **Gasparin and Martins** found no influence of BMI on the ovarian reserve of patients with SLE [18,19]. Concurrently, some authors have found inverse associations between BMI and AMH levels [21,22].

According to another study, the association between BMI and AMH may be mediated by age, since both of these variables change significantly over time [15]. Moreover, **Di Mario** found inverse correlation between current age and AMH serum concentration in SLE patients ($p < 0.001$)[17].

In addition to the previous findings, this study showed that there was no statistically significant correlation between AMH levels and cyclophosphamide (Cyc), azathioprine (AZA) and mycophenolate mofotil (MMF).This agrees with **Gasparin** who found that AMH levels did not differ between patients who received Cyc

14.8(8.23-26.69), MMF 19.1(2.29-158) or AZA 15.6(10.09-24.12) [18].This finding disagrees with that of **Yang** who found on his study on 45 SLE patients that AMH level significantly decreased after 6 months of cyclophosphamide, but remains relatively the same after the same period of treatment with MMF and azathioprine [23].

The percentage of miscarriage (at least one) was highly statistically significant higher among SLE group than control group (20% vs. 3.3%).This disagrees with **Yuen** who found miscarriage, did not differ between SLE group (31%) and control group(30%) [24]. Also **Di Mario** found that, there was no statistically significant difference between SLE patients and controls regarding miscarriage (p =0.14) [17].

This study showed that, the percentage of preterm births was statistically insignificant higher among SLE group than control group (10% vs. 0%) (P=0.07). This is in agreement with **Di Mario** who found that there was no statistically significant difference between SLE patients and control regarding percentage of preterm (p = 0.85) [17]. **Abdwani** who aimed to determine the neonatal and maternal outcomes of pregnancies in SLE patients compared to pregnancies in healthy controls. They analyzed 147 pregnancies and compared 56 (38.0%) pregnancies in women with SLE with 91 (61.9%) pregnancies in healthy control women. They found the neonates born to mothers with SLE were more likely to be preterm (28.5% vs. 1.0%; p < 0.001), have a low birth weight (< 2500 g) (32.1% vs. 1.0%; p < 0.001), and were associated with stillbirth (7.1% vs. 0.0) when compared to neonates born to healthy control mothers[25].

This present study shows that the reduction in the number of children compared to that of the controls was due to adverse pregnancy outcomes; particularly miscarriage; rather than reduced ovarian reserve as a complication of the disease or the medication.

This study showed that the percentage of SLE flare in pregnancy was present in (26.7%) among SLE group. This agrees with **Smyth** research which showed that SLE flare in pregnancy was estimated at 25.6% among SLE cases [26].

One of the limitations of our study was the small number of cases. In addition to the lack of previous AMH level measurements in SLE patients before receiving the previously mentioned medication, to clarify if they decreased from the baseline or remained within the normal values.

Our results suggest that AMH, as a measurement of ovarian reserve, did not differ between patients and controls, and was not affected by the disease activity, damage index or immunosuppressive medications. However, patients had significantly less offsprings than that of the controls as a consequence of adverse pregnancy outcomes.

Conclusion:

It can be concluded that the reduction in the number of children compared to that of the controls was due to adverse pregnancy outcomes; particularly miscarriage; rather than reduced ovarian reserve as a complication of the disease or the medication.

Finally our results suggest that AMH, as a measurement of ovarian reserve, did not differ between patients and controls, and was not affected by the disease activity, damage index or medications. However, patients had significantly less offsprings than controls as a consequence of adverse pregnancy outcomes.

Recommendations:

On the light of results of the present study, we can recommend the following:

1. This study may help rheumatologists make the decision of cyclophosphamide therapy to young SLE patients less worrying regarding its impact on fertility, especially when it's the best option for treatment. New regimens with less doses are also present with similar efficacy.
2. A baseline AMH level monitoring once the disease is diagnosed can help detect changes in its level by the disease or the medications, as a useful follow up tool.
3. Patient education regarding strict control of activity and follow up before and during conception is necessary to avoid adverse pregnancy outcomes.
4. Future research should compare between AMH level in SLE patient from different races, as AMH level is documented to vary among races, which may guide treatment choices.

Conflicts of Interest Statement:

- The author reports no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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