Menstrual and Gonadal Function Alterations in Women with Systemic Lupus Erythematosus

Debasmita Mandal¹, Geetabali Sircar², Archana Pandey³, Saroj Mandal⁴, Dipanwita Banerjee⁵, Alokendu Ghosh⁶, Manotosh Panja⁷

Abstract

Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disorder and may affect the reproductive health status of the women. Objective is to analyze the types, incidence of various menstrual disturbances in these women, to identify risk factors and to assess the gonadal function.

Methods: The prospective cohort study was conducted in the SLE clinic of the Rheumatology Department of IPGMEandR, Kolkata from April 2010 to April 2011. Out of 152 females attending clinic, 110 patients fulfilling criteria were included in the study.

Results: Mean age of the study population was 27.25±3.4 years. Sixty six cases had menstrual abnormalities (12.72% amenorrhea, 44.45% oligomenorrhea, 2.7% premature ovarian failure, 10.9% menorrhagia). When comparative analysis of demographic, hormonal, ovarian Doppler and therapeutic variables of normal and abnormal cycles was carried out, following parameters were significantly more related to patients with abnormal cycle ; SLEDAI score (12.48±5.53 vs 8.69±4.9; p=0.00), disease duration (6.46±3.08 vs 4.3±1.36; p<0.05), TSH (7.73±8.64 vs 3.07±2.06; p=0.00), LH (6.55±4.38 vs 4.56±3.29; p=0.02), a high normal prolactin (12.57±7.75 vs 8.73±3.07; p=0.02), peak systolic velocity (6.53±2.17 vs 9.12±2.1; p=0.00), end-diastolic volume (4.21±2.32 vs 9.35±2.32; p=0.00) and cumulative dose of steroid (24.02±41.44 vs 9.32±9.96; p=0.01).

Cyclophosphamide with cumulative dose ≥10 gm was related to amenorrhea and affected gonadal function. Gonadal insufficiency was evident in 33.63% and 2.72% had ovarian failure.

Conclusion: Reduced menstruation is a major health concern in women with SLE as it is frequent and can result in depressed and failed gonadal function later. Doppler study of ovaries is a novel way of depiction of gonadal status in these women. Certain risk factors and revolving treatment part can be preventable.

Introduction

Systemic lupus erythematosus (SLE) is chronic inflammatory disease of autoimmune in origin, predominantly affecting women in the reproductive age group (female: male= 10:1).¹,² It is characterized by several circulating autoantibodies and immune complexes which lead to various disease manifestations. Thus reproductive health issue starting from menstruation to fertility and pregnancy become challenging milestones for these women. One of the major issue is the menstrual cycle disturbances, resulting mostly due to temporary or permanent gonadal failure.³ These menstrual alterations starts from menorrhagia, oligomenorrhea, temporary amenorrhea to premature menopause certain times.² Several authors have tried to analyze this health issue of SLE and found various causal factors i.e. SLE disease activity, anti-ovarian antibody, altered thyroid status, hyperprolactinemia, steroid therapy and chemotherapy etc.³,⁴ These all have been associated with depressed gonadal function in some or other way and result in altered menstruation.

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literature and first reporting from our geographical location, Eastern India. Till date no study has impacted on ultrasound Doppler assessment of ovarian function in SLE patients, which is a very easily accessible and noninvasive way of depiction. Objective of the present study is to assess the prevalence and pattern of this abnormality among our SLE affected population. At the same time exploration of associated causal factors and gonadal function assessment have been carried out.

**Material and Methods**

This prospective cohort study was held in the SLE Clinic of Rheumatology Department at IPGMEandR, Kolkata. All women coming for treatment from April 2010 to April 2011 were consecutively included in the study. A total of 152 women with SLE were screened out and of which 110 cases were selected as subjects. The inclusion criteria were; signing of written informed consent, patients aged between 19 and 40 years who had menarche in due time and who fulfilled 1982 American College of Rheumatology (ACR) criteria for diagnosing SLE.\(^9\) Exclusion criteria were primary amenorrhea, cases with known cause of secondary amenorrhea, cases with organic cause of bleeding, women on any hormonal therapy, women undergoing any gynecological interventions that can alter their gonadal function and SLE patients associated with other medical problems not resulting from the disease itself.

Questionnaires included data regarding age, marital status, education, personal habits, clinical data of SLE (disease duration, scoring of disease activity according to SLE disease activity index [SLEDAI] criteria, clinical manifestations, previous autoimmune diseases and treatment information) and gynecological data (age of menarche, previous and present menstrual pattern, fertility status and detail obstetric history) etc.

The diagnosis of altered uterine bleeding was made according to the criteria led by Sens et al.\(^9\) Normal and regular menstrual pattern or eumenorrhea was characterized by bleeding between 24 and 32 days, amount of bleeding was about 80 ml and duration existed between two and seven days. Menarche was defined as day of initiation of first menstruation in a woman’s life. Menorrhagia termed as cyclical increased amount (>80 ml) and duration of bleeding (>7 days). Oligomenorrhea understood as reduction in the frequency of menstruation where menstrual intervals might vary between six weeks and six months. Menorrhagia was complete absence or cessation of menstruation for more than six months.

All patients were investigated for routine hemogram and few special tests concerned to rule out the cause of menstrual changes as well as to assess the gonadal function i.e. thyroid function test, serum prolactin, serum estradiol, serum LH and serum FSH in the follicular phase. Anti-TPO antibody and antimullerian hormone assessment could not be carried for most of cases because of affordability and unavailability issues in nearest centers.

Ultrasoundography (USG) with Doppler velocimetry of ovaries was carried out postmenstrually with least intra-observer variation. The parameters mainly considered were PI (pulsatility index), RI (resistance index), PSV (peak systolic velocity), EDV (end-diastolic volume) and ovarian volume of both ovaries. Sign of ovulation was considered as presence of dominant follicle (normal diameter 20-24 mm). Sign of ovarian failure was diagnosed with increased S/D ratio of ovarian artery with decreased size and volume of ovaries (normal= 8-10 cm\(^3\)) and presence of decreased vascularity of ovarian stroma.

Normal gonadal function was considered when the cases had normal menstrual cycles with normal hormonal pattern (serum LH, FSH and estradiol) in both phases of cycle, normal ovarian vascularity as well as normal follicular status in USG.

Ovarian insufficiency was defined according to clinical parameters like presence of amenorrhea ≥4 months or oligomenorrhea with the abnormal hormonal and USG findings. Premature menopause (PMP) was defined as amenorrhea for ≥1 year before 35 years of age with estrogen deficiency and elevated serum LH and FSH.

This study was ethically approved from Institutional Ethical Committee, IPGME and R, Kolkata. Statistical analysis used software Graph Pad Prism version (San Diego, California: GraphPad SoftWare Inc. 2005). Comparison of numerical variables between all four groups was done by Kruskal-Wallis ANOVA and multiple group comparison test to locate differences between groups in pairs was carried out by Dunn’s multiple comparison test. A p value of < 0.05 was considered as significant.

**Results**

For analysis purpose allotment groups were carried out according to their pattern of menstruation. Group 1 was with normal cycle (n=24) while Group 2, 3 and 4 included in abnormal cycle pattern [2- amenorrhea including three PMP patients (n=17), 3-oligomenorrhea (n=57), 4-menorrhagia (n=12)].

Demography data (Table 1) showed the subjects with normal cycle had mean age of 26.65±8.45 years and who had abnormal cycle presented with a mean age of 27.86±7.46 years. All attained menarche at 12.08±0.9 years. The SLEDAI score was significantly high in amenorrheic group (p value= 0.003). Table 2 compares the hormonal assays among all groups.
Table 1: Demographic data in various menstrual patterns

<table>
<thead>
<tr>
<th>Types of menstrual pattern</th>
<th>Age (yrs)</th>
<th>Age at menarche (yrs)</th>
<th>SLEDAI score</th>
<th>Disease duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr1 (n=24) (Regular)</td>
<td>26.65±8.45</td>
<td>12.08±0.9</td>
<td>8.69±4.903</td>
<td>4.30±1.363</td>
</tr>
<tr>
<td>Gr2 (n=17) (Amenorrhea)</td>
<td>28.41±8.26</td>
<td>12.41±1.06</td>
<td>17±3.72</td>
<td></td>
</tr>
<tr>
<td>Gr3 (n=57) (Oligomenorrhea)</td>
<td>27.08±7.10</td>
<td>12.49±0.86</td>
<td>12.63±5.82</td>
<td>6.46±3.082</td>
</tr>
<tr>
<td>Gr4 (n=12) (Menorrhagia)</td>
<td>27.33±8.58</td>
<td>12.5±0.9</td>
<td>8.75±4.65</td>
<td></td>
</tr>
</tbody>
</table>

P value 0.091 0.943 0.00 0.00 0.00

Table 2: Biochemical analysis and menstrual patterns

<table>
<thead>
<tr>
<th>Types of menstrual pattern</th>
<th>Serum LH (mIU/ml)</th>
<th>Serum FSH (mIU/ml)</th>
<th>Serum prolactin (ng/ml)</th>
<th>Free T4 (ng/dl)</th>
<th>Serum TSH (µIU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr1 (n=24) (Regular)</td>
<td>4.56±3.29</td>
<td>6.54±4.86</td>
<td>8.73±3.07</td>
<td>2.58±6.45</td>
<td>3.07±2.06</td>
</tr>
<tr>
<td>Gr2 (n=17) (Amenorrhea)</td>
<td>5.8±4.43</td>
<td>22.96±25.8</td>
<td>12.81±7.72</td>
<td>1.6±0.84</td>
<td>7.88±5.34</td>
</tr>
<tr>
<td>Gr3 (n=57) (Oligomenorrhea)</td>
<td>7.06±4.55</td>
<td>7.72±6.11</td>
<td>12.76±7.9</td>
<td>1.05±0.47</td>
<td>8.12±10.15</td>
</tr>
<tr>
<td>Gr4 (n=12) (Menorrhagia)</td>
<td>5.21±3.19</td>
<td>4.51±1.18</td>
<td>11.34±7.59</td>
<td>0.83±0.039</td>
<td>5.65±2.37</td>
</tr>
</tbody>
</table>

P value 0.724 0.399 0.003 0.0005

Table 3: USG Doppler parameters and menstrual patterns

<table>
<thead>
<tr>
<th>Types of menstrual pattern</th>
<th>PI (cm/sec)</th>
<th>RI (cm/sec)</th>
<th>PSV (cm/sec)</th>
<th>EDV (cm/sec)</th>
<th>OV volume (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr1 (n=24) (Regular)</td>
<td>0.95±0.18</td>
<td>0.59±0.06</td>
<td>9.12±2.16</td>
<td>9.35±11.1</td>
<td>6.68±1.31</td>
</tr>
<tr>
<td>Gr2 (n=17) (Amenorrhea)</td>
<td>0.91±0.16</td>
<td>0.87±1.24</td>
<td>4.86±1.47</td>
<td>2.91±0.69</td>
<td>3.11±1.73</td>
</tr>
<tr>
<td>Gr3 (n=57) (Oligomenorrhea)</td>
<td>1.07±0.26</td>
<td>0.65±0.4</td>
<td>6.35±1.5</td>
<td>3.35±1.66</td>
<td>5.94±2.66</td>
</tr>
<tr>
<td>Gr4 (n=12) (Menorrhagia)</td>
<td>0.97±0.17</td>
<td>0.59±0.07</td>
<td>9.73±2.47</td>
<td>10.14±2.35</td>
<td>7.68±1.97</td>
</tr>
</tbody>
</table>

P value 0.0602 0.0015 0.1053 0.0006 0.001

Table 4: Therapeutic associations with menstrual patterns

<table>
<thead>
<tr>
<th>Types of menstrual pattern</th>
<th>CYP (gm)</th>
<th>Mycophenolate (mg)</th>
<th>AZ (gm)</th>
<th>Steroid (mg)</th>
<th>HCQ (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr1 (n=24) (Regular)</td>
<td>CYP (n=3)</td>
<td>Mycophenolate (n=2)</td>
<td>AZ (n=1)</td>
<td>Steroid (n=17)</td>
<td>HCQ (n=16)</td>
</tr>
<tr>
<td>Gr2 (n=17) (Amenorrhea)</td>
<td>CYP (n=9)</td>
<td>Mycophenolate (n=2)</td>
<td>AZ (n=5)</td>
<td>Steroid (n=7)</td>
<td>HCQ (n=8)</td>
</tr>
<tr>
<td>Gr3 (n=57) (Oligomenorrhea)</td>
<td>CYP (n=15)</td>
<td>Mycophenolate (n=4)</td>
<td>AZ (n=4)</td>
<td>Steroid (n=31)</td>
<td>HCQ (n=36)</td>
</tr>
<tr>
<td>Gr4 (n=12) (Menorrhagia)</td>
<td>CYP (n=4)</td>
<td>Mycophenolate (n=3)</td>
<td>AZ (n=1)</td>
<td>Steroid (n=7)</td>
<td>HCQ (n=7)</td>
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</tbody>
</table>

P value 0.125 0.369 0.426 0.013 0.104

and revealed normal serum LH and FSH level in both phases of cycle in women with regular or normal menstrual cycle. While serum FSH and TSH were statistically significant showing their mean values at 22.96±25.18 mIU/ml and 7.88±5.34 mIU/ml, respectively in the patients with amenorrhea. Women with oligomenorrhea also revealed a high TSH level (normal range 0.39-4.16 mIU/ml) with a mean value at 8.12±10.15 mIU/ml. Serum LH (6.55±3.38 ng/dl vs 4.56±3.29 mIU/ml; p=0.02) was high in patients with abnormal cycles (n=86) when compared to women with regular cycles (n=24). Though prolactin level (12.57±7.75 ng/dl vs 8.73±3.07 mIU ; p= 0.025) was not as high as other hormonal parameters, it was at moderately higher normal range than patients with regular cycle (normal range 2.5-14.5 ng/ml).

Table 3 reveals the comparative analysis of USG Doppler parameters among four groups. Here PSV, EDV, ovarian volume were significantly different. Patients with amenorrhea had PSV, EDV and ovarian volume at 4.86±1.47 cm/sec, 2.91±0.69 cm/sec, 3.11±1.73 cc, respectively. While those with regular cycle had abovementioned parameters at 9.12±2.16 cm/sec, 9.35±11.1 cm/sec and 6.68±7.31 cc, respectively.

Table 4 depicts the therapeutic association with menstrual pattern. Total number of subjects treated with IV cyclophosphamide (CYP), oral mycophenolate acetate, azathioprine (AZ), methotrexate, oral steroid and oral hydroxychloroquine (HCQ) were 31,16,11, 4, 62 and 67 respectively. A strong association of abnormal menstrual cycle was noted with steroid. Mean dose of steroid was at 27.85±34.23 mg in patients with amenorrhea.

Table 5 explains the comparative analysis of all parameters between women with regular cycle (n=24) and that with abnormal cycle (n=86). The major related factors with abnormal cycle were SLEDAI score, TSH, LH, a high normal prolactin, PSV, EDV, ovarian volume and cumulative dose of steroid.

Discussion

The reproductive health status of women with SLE became stressful from the beginning with menstrual alteration. In this study, 2345 women with SLE approached for treatment. Women with menstrual...
irregularity accounted 36.6 per 1000 women with SLE. Oligomenorrhea represented more than the half of the study population, followed by amenorrhea (15.45%) and menorrhagia (10.9%). Women with regular cycle consisted 21.81% of the total study population. Some literature mentioned menarchia and amenorrhoea to be the frequent menstrual alteration in patients with SLE.\textsuperscript{10,11} Pasoto et al observed normal menstruation in 47% of the patients and detected no specific pattern of cycle and Silva et al also agreed to this finding.\textsuperscript{11,12} The mean age of subjects ranged between 12.08±0.9 and 12.5±0.9 years, which referred to a normal age of attaining menarche in our geographical population. Other study had noticed delayed menarche (13.5±1.4 years) in women with SLE.\textsuperscript{12}

Except type of menstruation, some other parameters are also helpful to determine gonadal status. Silva et al explored cervical mucus length, urinary hormonal cytology, serum estradiol, serum progesterone, serum FSH, serum LH and USG to detect dominant follicle, endometrial thickness and ovarian volume in women with SLE.\textsuperscript{13} They observed normal gonadal function in 70% and abnormal gonadal function in 30%.\textsuperscript{12} Another study found 15.49% of ovarian insufficiency as per clinical criteria of 4 months of amenorrhoea.\textsuperscript{3} Mean serum estradiol in our SLE women with regular cycle was 108±117.7 pg/ml and those with reduced and amenorrheic cycle had 9.2±10.2 pg/ml stating a very hypoestrogenic profile in 37.33% of subjects.

In the present analysis Doppler velocimetry revealed reduced PSV and EDV of ovarian arteries and also a reduced ovarian volume in 25.45% of the study population in all patients with amenorrhoea and some with oligomenorrhea. Pelliziarie et al confirmed the role of color and pulsed Doppler analysis in evaluating functional state of the reproductive organs and observed a decreased PSV and EDV inamenorrhoeic subjects.\textsuperscript{13}

After correlating clinical, hormonal and USG findings, present study noticed ovarian insufficiency in 33.63% and premature ovarian failure in 2.72% of SLE women.

While exploring causal factors for this above issue, some observed high TSH (>5 µIU) in 11.9% women with SLE and out of whom 20% were positive for autoantibodies\textsuperscript{3} and also an associated hyperprolactinemia.\textsuperscript{3} While another author contradicted and noticed a normal prolactin level in their SLE subjects.\textsuperscript{14} The present series observation concord with the above study showing a normal prolactin level in all cases with SLE, but the mean level was at higher normal side in patients with abnormal cycle in comparison to those with regular cycle (8.73±3.07 ng/ml vs 12.57±7.75 ng/ml; p<0.05). Clinical hypothyroidism was observed in 16.36% and subclinical hypothyroidism in 39.09% of total study population. Majority (67.56%) patients with reduced cycle and ovarian insufficiency had high TSH level (8.12±10.15 µIU/ml). Thyroid peroxidase antibody was positive in 3.63%.

It has been analysed that corticoids have immunosuppressive action and inhibitory effect on gonads at hypothalamo-pituitary axis level by interfering in production of gonadotropins which stimulates follicular development and further hormone production for endometrial proliferation.\textsuperscript{1,15} Nonato et al had observed 26.4% of the menstrual alteration, in patients receiving some type of corticoid.\textsuperscript{1} All SLE patients in this study received therapy as per ACR guidelines. Sixty two out of total subjects (56.36%) received steroid in various doses. Twenty nine patients had a cumulative dose ≥10 mg/day and while 16 received ≥25 mg/day. Here a high correlation of menstrual abnormalities (oligomenorrhea and amenorrhoea) and ovarian insufficiency with steroid was observed. Thirty-one patients (28.18%) were treated with

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Variables & Normal cycle & Abnormal cycle & P value \\
& (Gr1) (n=24) & (Gr 2, 3 and 4) (n=86) & \\
\hline
Age & 26.65±8.45 & 27.86±7.46 & 0.288 \\
Menarche & 12.08±0.92 & 12.47±0.9 & 0.125 \\
SLEDAI score & 8.69±4.9 & 12.48±5.53 & 0.002 \\
TSH & 3.07±0.6 & 7.73±8.64 & 0.00 \\
T4 & 2.58±4.65 & 1.14±0.61 & 0.08 \\
LH & 4.56±3.29 & 6.55±4.38 & 0.02 \\
FSH & 6.54±4.88 & 10.28±13.61 & 0.284 \\
Prolactin & 8.73±3.07 & 12.57±7.75 & 0.025 \\
PL & 0.95±0.18 & 1.02±0.24 & 0.193 \\
RI & 0.59±0.06 & 0.6±0.63 & 0.78 \\
PSV & 9.12±2.1 & 6.53±2.17 & 0.00 \\
EDV & 9.35±2.32 & 4.21±2.9 & 0.00 \\
Ov vol & 6.68±1.31 & 5.63±2.77 & 0.07 \\
CYP (gm) & (n=3) & (n=28) & 0.616 \\
Mycophenolate (mg) & 301.93±336.67 & 702.85±329.2 & 0.153 \\
AZ (gm) & (n=1) & (n=10) & 1.00 \\
Steroid (mg) & 72.0 & 28.91±19.26 & 0.001 \\
HCQ (mg) & 9.32±9.96 & 24.02±41.44 & 0.07 \\
& (n=51) & (n=28) & 0.01 \\
& 325±100 & 419.6±170.9 & 0.088 \\
All values: Mean ± SD \hline
\end{tabular}
\caption{Comparative analysis of demographic, hormonal, USG and therapeutic variables of normal and abnormal cycles.}
\end{table}
CYP. All patients with amenorrhea and PMP (64.51%, 20/31) had cumulative dose of CYP ≥10 gm. Fantoon NNA et al also revealed that SLE patients treated with cumulative dose more than 10 gm had 3.2 times higher risk of developing ovarian insufficiency than who received less than 10 gm.16

Disease duration was significantly associated with abnormal menstruation when compared. Whereas literature from Singapore explained disease duration to be an insignificant risk factor.16

Another major related factor for menstrual abnormality was SLE disease activity, a high SLEDAI score (≥8) had been observed with menstrual alterations.13 In this analysis, all amenorrheic patients had SLEDAI scored at 17±3.72, whereas patients with oligomenorrhea and regular cycles had mean SLEDAI score at 12.63±5.82 and 8.69±4.903 respectively. SLEDAI score ≥12 was well correlated with presence of menstrual alteration and gonadal function abnormalities. Contradicting to the above finding few authors found a high SLEDAI score among normally menstruating patients also, so they concluded that disease activity might not have a role in amenorrhea even gonadal function.3,12,16

Amenorrhea and oligomenorrhea presented as major abnormal menstrual pattern in this study population. The health issue was not only restricted to altered menstruation but also was associated with depressed and failure of gonadal function. Factors related to the above morbidities were clinical and subclinical hypothyroidism, high SLEDAI score ≥12, disease duration and steroid therapy ≥25 mg/day. All patients instituted with CYP ≥10 gm had amenorrhea, ovarian insufficiency and few had ovarian failure. This alarms a revision of regular treatment schedule of SLE patients. Doppler velocimetry found to be a predictive way of expressing ovarian function in SLE patients and it can be considered as a regular follow up tool during the treatment of SLE with drugs which depress the gonadal function. Initial diagnosis and treatment is desirable of this health issue in SLE patients to get a better reproductive performance ahead.

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References