Received 24 February 2020
Revised 8 August 2020
18 August 2020
Accepted 19 August 2020

Influence of estrogen exposure on systemic lupus erythematosus in Bangladeshi women: a case-control study scenario

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Abstract

Purpose – This study was conducted to find out the association between estrogen exposure and systemic lupus erythematosus (SLE) in Bangladeshi women.

Design/methodology/approach – A case-control study was carried out from January to December 2015 among 128 intervention cases and 128 age-matched control group participants to find out the association with estrogen exposure and development of SLE.

Findings – Case group participants were five times (OR 5.14, 95% CI 2.14–12.33), three times (OR 3.40, 95% CI 1.25–9.21) and four times (OR 4.00, 95% CI 1.45–11.00) more likely to receive different higher levels of education compared to the control group. Exposure to estrogen showed a positive association with the development of SLE. The case group (12.63 ± 1.61 years) had a lower age at menarche than that of the control group (13.31 ± 1.47 years; $p < 0.001$) and their proportion (62.6%) of using oral contraceptive pills were more than that of the control group (45.6%; $p < 0.01$). After controlling the effect of the positively associated variables, SLE patients were found two times (adjusted OR 2.26; 95% CI 1.29–3.95) more likely to use oral contraceptive pills than the control group. The case group was more (adjusted OR 0.771; 95% CI 0.642–0.927) prone to have an earlier age at menarche compared to the control group.

Originality/value – This study identified the association between estrogen exposure and SLE. Contraceptive pills should be used cautiously and both consumers and service providers need to be aware of their effects.

Keywords Systemic lupus erythematosus (SLE), Estrogen exposure, Autoimmune disease, Bangladesh

Paper type Research paper

Introduction

Systemic lupus erythematosus (SLE) is a wide spectrum of chronic multisystem autoimmune disease with effects ranging from minor skin involvement to severe organ damage [1]. Although endogenous hormones and genetic factors play an important role in the development of SLE, many other risk factors such as estrogen exposure, drugs containing

Journal of Health Research
Vol. 36 No. 1, 2022
pp. 68-76
Emerald Publishing Limited
e-ISSN: 2586-940X
p-ISSN: 0857-4421
DOI 10.1108/JHR-01-2020-0025

aromatic amines, tobacco, sunlight exposure and hair coloring agents also trigger the disease process [2]. According to the American College of Rheumatology (ACR) definition, the age-standardized prevalence and incidence rates of SLE were 62.2 and 4.6 per 100,000 person-years [3].

Autoimmune disease is regarded as one of the top ten causes of death in women under 65 years of age with a women having about 9 times higher rate than a man for prevalence (107.4 versus 12.5) and incidence (7.9 versus1.0) [4–6]. Overall, the female immune system shows an increased reactivity by producing enhanced antibodies, increased activity of monocyte by more antigen presentation, a stronger type I interferon (IFN) response, and a higher rate of homograft rejection [7, 8].

The two main factors that play a key role in such reactivity are the estrogen hormone and genetics [8, 9]. Many studies have shown that SLE patients have increased concentrations of serum 16- hydroxyestrone. SLE patients also showed increased alpha hydroxylation of estrogen, producing more estrogen metabolites which were responsible for activation of the T-cell and thus an increased differentiation of the B cell [10, 11].

Increased risk has been associated with higher levels of estrogen exposure in a lifetime. This exposure can be natural or artificial. Prolonged exposure to estrogen in the form of early menarche, late menopause and uses of contraceptive pills play a role in the development of SLE [10, 11]. Participants with early menarche at an age below 10 years and late menopause are exposed to estrogen for a prolonged period of their life. Manipulations of the estrogen hormone both by using oral contraceptive pills and taking postmenopausal estrogen replacement therapy may influence the incidence and activity of SLE [12]. Age at menarche is influenced by genetic factors, ethnicity, nutritional conditions and secular trends [13–15]. In Bangladesh, the average age of menarche and menopause were found to be 11.6 ± 3.6 years and 51.14 years [16, 17]. Regarding this exposure to estrogen, socio-demographic characteristics and some clinical attributes play a role as background variables. No studies on risk factors of SLE were found so far in literature reviews from the perspective of Bangladesh. To fill up the data gap, initiatives were taken to conduct this case-control study.

Methods

A case-control study was conducted from 01 January to 31 December 2015 to find out the association between estrogen exposure and SLE in females. Cases enrolled in the study were diagnosed by physicians according to the American College of Rheumatology (ACR) guideline criteria for the diagnosis of SLE [18]. Patients who did not fulfill the criteria of ACR guideline as SLE patients made up the control group. They were matched with cases by ±2 years of age and type of hospital. Patients who refused to participate or were unable to give an interview because of aphasia, reduced consciousness or other reasons were excluded from the study.

Cases were selected from SLE clinics and indoor medicine units of three tertiary level hospitals of Bangladesh (Bangabandhu Sheikh Mujib Medical University, Dhaka Medical College Hospital, and Shaheed Suhrawardy Medical College Hospital).

Controls were selected from the indoor medicine units and rheumatology clinics of the same hospitals. Considering the current utilization rate of oral pills in Bangladesh which is 27% or 0.27 [19] as exposure proportion in controls and predicted odds ratio 2.1 [20]; the calculated sample size was 128 cases and 128 controls.

Study places were selected purposively for data collection. Cases and controls were collected conveniently. A pre-tested structured interview administered questionnaire and checklist were used for data collection. The questionnaire was pre-tested on 2 phases over 20 respondents and was finalized after necessary modifications. To measure estrogen exposure,

age at menarche, age at menopause, uses of oral contraceptive pills and history of hormone replacement therapy was asked of the respondents. The total duration of taking each type of pill was also noted.

Data were collected by face-to-face interviews and by reviewing the medical records. The data were entered, cleaned and edited with Statistical Package for the Social Sciences version 16.

Chi-square test and Fisher's exact test were carried out to assess the association of categorical variables. To compare the mean differences between the two groups, student *t*-tests were done. Odds ratio (OR) and their corresponding 95% confidence interval (CI) were calculated to assess the strength of association. Binary logistic regression analyses were carried out to find out the adjusted odds ratio. Statistical significance was defined as $p < 0.05$. The effect of the other variables was removed and finally, after identifying the significant variables, the best predictor was determined. Due to the smaller sample size and restricted time for data collection, SLE patients were not classified based on pathophysiology and immunological parameters. Therefore, a subset analysis was not done.

Ethical approval

The Ethical Review Committee of the National Institute of Preventive and Social Medicine (NIPSOM) gave ethical approval with the IRB Code: NIPSOM/IRB/2015

Results

Socio-demographic variables

Table 1, out of 128 case group participants and 128 (age-matched ± 2 years) control group participants, the mean age (29.02 ± 10.11 years and 29.02 ± 10.16 years) of participants were almost equal without normal distribution. The proportion of respondents of less than 20 years of age was insignificantly ($p > 0.05$) higher in the control group (18.8%) than in the case group (15.6%). The proportion of Muslims was higher in the case group (98.4%) than in the control group (93.8%). The case group participants (75.8%) were more commonly married than the control group participants (67.2%), but this difference was not statistically significant ($p > 0.05$). SLE patients had significantly higher educational status than the control group ($p < 0.001$). A binary logistic regression model was constructed, and the effect of other significant variables was adjusted (Table 3).

Background variables

Exposure to sunlight, a personal habit of using tobacco (both smoking and smokeless), alcohol and hair coloring agents, some clinical attributes (blood group, blood transfusion, rhesus factor, history of allergy, history of asthma, some specific drug use, previous history of hypertension), family history of the disease were included in the study as background variables. Out of 31 smokeless tobacco users, the number of gul, jorda and sadapata (different products) users were 9, 19 and 3, respectively, in the case group and 2, 16 and 2, respectively, in the control group. The case group participants were about 5 times (OR 4.77; 95% CI 1.01–22.51) more likely to use gul than the control group. After removing the effect of other significant variables, SLE patients were about 8 times (adjusted OR 7.83; 95% 1.40–43.71) more likely to use gul than that of the control group. But due to the small number of users, further analysis was not performed. A significantly higher proportion of case group participants (18%) had a previous history of asthma than the control group (6.2%). By removing the effect of age at menarche, oral contraceptive pills (OCP), educational status and uses of gul, the case group were found to be more likely to have a history of asthma almost

Characteristics	Control group (n = 128) n	%	Case group (n = 128) n	%	χ^2	p	OR (95%CI)
Age (yrs)							
<20	24	18.8	20	15.6			
20-24	24	18.8	27	21.1			
25-29	23	18.0	27	21.1			
30-34	18	14.1	15	11.7	1.41	0.97	
35-39	17	13.3	18	14.1			
40-44	11	8.5	9	7.0			
>44	11	8.5	12	9.4			
Mean ± SD	27.36 ± 10.16		27.38 ± 10.11			0.98	
Religion							
Muslim	120	93.8	126	98.4	3.75	0.051	
Others	8	6.2	2	1.6			
Marital status							
Unmarried	26	20.3	23	18.0			
Married	86	67.2	97	75.8	3.51	0.173	
Widowed/Divorce	16	12.5	8	6.2			
Education							
Never went to school	30	23.4	15	11.7			
Up to primary	22	17.2	11	8.5			1.00 (0.38–2.59)
6–9	43	33.6	31	24.3			1.44 (0.67–3.12)
Secondary school certificate (SSC)	14	10.9	36	28.1	25.11	<0.001	5.14 (2.1412.33)
Higher secondary certificate (HSC)	10	7.9	17	13.3			3.40 (1.25–9.21)
Graduate and others	9	7.0	18	14.1			4.00 (1.45–11.0)
Occupation							
Housewife	79	61.6	88	68.7			
Student	20	15.6	23	18.0			
Business	3	2.3	0	0.0			
Service holder	6	4.7	6	4.7	9.08	0.11	
Worker	10	7.9	2	1.6			
Unemployed	10	7.9	9	7.0			
Residence							
Rural	44	34.4	41	32.0			
Urban	61	47.6	53	41.4	2.79	0.25	
Semi urban	23	18.0	34	26.6			
Average monthly family income							
<5000	13	10.2	4	3.1			
5000–15000	83	64.8	86	67.2	5.33	0.07	
>15000	32	25.0	38	29.7			
Mean ± SD	14300 ± 20056.94		15890 ± 13697		−2.27	0.02	

Table 1.
Socio-demographic characteristics of the case and control groups

three times (adjusted OR 2.96; 95% CI 1.16–7.54) more than that of the control group. Among all the respondents, 14 were hypertensive and under medication. A higher proportion of respondents were diagnosed as hypertensive before the development of SLE (6.2% vs 4.7%). But it was not statistically significant ($p > 0.05$). On average, the case group (124.38 ± 86.03 months) was hypertensive for a longer period than the control group (34.17 ± 36.54 months) and it was statistically significant ($p < 0.05$).

Exposure to sunlight for the respondents was measured using the sunlight exposure measurement questionnaire (SEM-Q) developed by Aga Khan University of Karachi [21].

No significant association was found with the use of alcohol and hair coloring agents, some clinical attributes and family history of the disease.

Estrogen exposure

SLE patients had significantly earlier menarche (12.66 ± 1.61years) than the control group (13.31 ± 1.47 years, $p < 0.01$). A binary logistic regression model was constructed. After removing the effect of other significant variables, age at menarche on SLE remained significant ($p < 0.05$). A total of 20 menopausal respondents were included in this study, of whom 11 were case group participants. Age at menopause, on average, was higher amongst the control group (47.11 ± 4.76 years) than in the case group (42.73 ± 8.28 years, $p > 0.05$). Among all the respondents, 97 cases and 86 controls were married. Out of the married women, 67 case group participants and 47 control group participants took oral contraceptive pills. A significantly higher proportion of SLE patients (62.6%) took oral contraceptives than the control group (45.6%, $p < 0.05$). SLE patients were two times (OR 1.99; 95% CI 1.15–3.46) more likely to use oral contraceptive pills than the control group. Table 2, after adjusting the effect of other significant variables use of OCP remains significant (adjusted OR 2.41; 95% CI 1.36–4.26). The

Table 2. Uses of oral contraceptives pills

Characteristics	Control group (n = 128) n	%	Case group (n = 128) n	%	χ^2	p-value	OR (95%CI)
OCP							
No	56	54.4	40	37.4	6.10	0.01	1.99 (1.15–3.46)
Yes	47	45.6	67	62.6			
Emergency contraceptive pills							
No	123	96.1	118	92.2	1.77	0.18	
Yes	5	3.9	10	7.8			
Uses of OCP more than one year							
No	15	31.9	22	32.8	0.01	0.92	
Yes	32	68.1	45	67.2			
	Mean ± SD		*Mean ± SD*				
Age of starting OCP	20.71 ± 4.99		20.29 ± 6.26		0.41	0.68	
Duration of OCP use	25.08 ± 50.98		22.38 ± 58.53		0.53	0.59	
Total no of i-pill use	3.10 ± 3.03		2.90 ± 3.26		−1.21	0.22	

Table 3. Adjusted odds ratio of the significant variables (after removing the effect of other variables)

Characteristics	p-value	Adjusted OR (95% CI)
Educational status		
Up to primary	>0.05	0.21 (0.07–0.65)
6–9	>0.05	0.27 (0.08–0.89)
SSC	<0.001	0.48 (0.18–1.3)
HSC	<0.01	1.42 (0.48–4.18)
Graduate and others	<0.01	1.05 (0.32–3.46)
Age at menarche	<0.001	0.771 (0.624–0.927)
Uses of OCP	<0.01	2.41 (1.36–4.26)
History of asthma	<0.01	2.96 (1.16–7.54)
Uses of gul	<0.05	7.83 (1.40–43.71)

number of respondents who took emergency contraceptive pills was 15, of whom 10 were case group participants and 5 were from the control group. Out of 12 respondents with problems related to menstruation, a higher proportion was in the case group (6.2%) than in the controls group (3.1%) which were not statistically significant ($p > 0.05$). There was only a single case who took hormone replacement therapy for three months.

Best predictor determination

The variables that remained significant after removing the effect of other variables were put together and forward LR was done to identify the best predictor (Table 4). The full model containing all variables was statistically significant ($\chi^2 = 11.256, p = 0.001$). Age at menarche was the best predictor followed by the presence of asthma and OCP use.

Discussion

The cases in our study were diagnosed with SLE by physicians. A further classification was not done as most of the patients were chronic cases and interviewed during follow-up visits. Proper documentation of their treatment process was absent. The current study found SLE cases were significantly more educated than the control group ($p < 0.001$) and had a higher average monthly family income ($p < 0.05$). Although we expected to find equal participation from all the financial classes, the case group had a higher income than the control group. This is mostly due to the complex pathogenicity of the disease, different outcomes of the same treatment in different patients, and the lack of reliable biomarkers which has made the treatment process lengthy and expensive [22]. It requires patience, awareness, social support and financial security to deal with this disease. This might cause the loss of the patient from the weaker economic condition from the SLE clinics. The data were collected from tertiary centers where most patients came for a follow-up check, were educated, conscious and financially solvent to carry out this huge burden of the disease. Higher family income also helps to attain a higher level of education. Educated people are more aware of SLE and consequently more concerned about their treatment. This finding supports the study conducted in Primary Health Care Clinics at KAMC in Riyadh [23] that found that a person's knowledge and attitude toward SLE was dependent on the education level where the higher the level of education the higher the knowledge about the disease.

A major proportion of case group participants were married, and OCP is a popular method of contraception in Bangladesh. The duration of OCP use was higher in the control group (25.08 ± 50.98 years) than among the case group (22.38 ± 58.63 years). When a female of reproductive age is diagnosed with SLE, physicians advise them to stop using estrogen-containing oral contraceptive pills. In this study, the current age of the case and control groups was matched. So there was a gap in using OCP in cases from their date of diagnosis of

Steps	Variables	*p*-value	Adjusted OR (95% CI)
Step 1			
	Age at menarche	0.001	0.756 (0.637–0.897)
Step 2			
	History of asthma	0.004	3.583 (1.506–8.524)
	Age at menarche	0.001	0.745 (0.626–0.886)
Step 3			
	History of asthma	0.002	3.962 (1.645–9.548)
	Age at menarche	0.001	0.749 (0.628–0.894)
	OCP	0.01	1.99 (1.180–3.358)

Table 4. Best predictor determination for the development of systemic lupus erythematosus in females

disease to the date of data collection. But the use of OCP is strongly associated with the development of SLE.

Case group participants were almost two times more likely to use oral contraceptive pills than control group participants (OR 1.99, 95% CI 1.15–3.46) and more cases were married. In the last 40 years, the country has experienced a sevenfold increase in the use of contraceptive methods, from 8% to 62% and the use of oral contraceptive pills is the most widely practiced method among married women [19, 24]. This result is similar to Bernier *et al.*'s study and other studies, which reported use of combined oral contraceptive was associated with an increased risk of SLE [10, 11]. Grimaldi *et al.*, found that sex hormones estrogen and prolactin may play a role in the development of SLE which also contributes to the gender bias of the disease. Another important mechanism is the involvement of the quinone-semiquinone redox cycling of estrogen that produces free radicals which can damage the deoxyribonucleic acid (DNA). This would probably alter the antigenicity of the DNA leading to the induction and increased level of SLE autoantibodies that somehow cross-reacting with the native one [25, 26].

This study found an association between early menarche and the development of SLE ($p < 0.01$). SLE patients (12.66 ± 1.61 years) had an earlier age at menarche than the control group (13.31 ± 1.47 years). This association remains strongly significant after removing the effect of other significant variables such as educational status, use of OCP, use of gul and history of asthma. It was also identified as the best predictor in forwarding the LR model. So early menarche was associated with a prolonged period of exposure to estrogen in females. Costenbader *et al.* also found similar results regarding early menarche among the cases of SLE and suggested that the duration rather than the timing of exposure to estrogen may be related to the risk of SLE [11].

Aromatic amine is present in both kinds of tobacco which were reported to be a factor for the development of SLE and smokers are at a greater risk of developing diseases than non-smokers [2, 27]. Our study found an association with smokeless tobacco users. But the number of cases was less.

A higher proportion of the case group (6.8%) was diagnosed as hypertensive compared to the control group (4.7%) before the diagnosis of SLE which was statistically insignificant. This might be the consequence of the undiagnosed SLE because the date of hypertension diagnosis could not be cross-checked with the date of diagnosis of SLE due to lack of data. SLE causes vascular damage and endothelial cell dysfunction, contributing to hypertension [28]. Hypertension might be a manifestation of the disease, not the risk factor.

A higher proportion of case group participants (18%) had a previous history of asthma than in the control group (6.2%, $p < 0.05$). Asthma is an atopic disease. The etiologies of both the atopic diseases and SLE are multi-factorial and heterogeneous. The dysregulation of the immune system with the activation of B-cells leading to the production of immunoglobulins and autoantibodies plays an important role in SLE and atopic diseases. Again atopic disease increases immunoglobulin E (IgE) which may play an important role in the development of lupus [29]. However, we did not assess the study participant's immunoglobulins.

Conclusion

Exposure to estrogen is associated with SLE in females. This exposure occurs as early menarche and by using oral contraceptive pills. This study further established that among all the estrogen exposure sources, early age at menarche is the most important factor for the development of the disease. Therefore, females with early menarche should be under regular follow-up to search for the presence of other factors in them. Estrogen-containing pills should be used after proper counseling and with the regular supervision of the experts.

Conflict of interest: There is no conflict of interest.

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