ISSN 2377-1542

GYNECOLOGY AND OBSTETRICS RESEARCH

OpenJournal

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Original Research

Systemic Lupus Erythematosus as a Risk Factor for Cervical Cancer and its Precursor Conditions: Assessment Using Pap Smear and Histopathology

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Article information
Received: January 8th, 2021; **Revised:** April 20th, 2021; **Accepted:** April 28th, 2021; **Published:** January 3rd, 2022

Cite this article
Gobran MA, El-Ghoneimey S, Ibrahim SAS, Mohamedhanafy S. Systemic lupus erythematosus as a risk factor for cervical cancer and its precursor conditions: assessment using pap smear and histopathology. *Gynecol Obstet Res Open J.* 2022; 8(1): 1-7. doi: 10.17140/GOROJ-8-155

ABSTRACT

Background
Cancer of the cervix is a common cause of malignancy. Its association with systemic lupus erythematosus (SLE) is debatable.

Objective
Early detection of cervical pre-neoplastic lesion in SLE patients.

Method
A case control study was performed on 64 SLE group and 64 control group using a colposcopy, pap smear and histopathological examination.

Conclusion
This study revealed that preneoplastic and neoplastic lesions of the cervix were higher in the SLE group.

Keywords
Systemic lupus erythematosus (SLE); Cancer; Cervix; Low grade squamous intra-epithelial lesions; High grade squamous-intra-epithelial lesions; Cervical; Intraepithelial neoplasia; Squamous cell carcinoma.

Abbreviations
ASCUS: Atypical squamous cells of undetermined significance; LGSIL: Low grade squamous intra-epithelial lesions; HGSIL: High grade squamous-intra-epithelial lesions; CIN: Cervical intraepithelial neoplasia; SQCC: Squamous cell carcinoma; SLE: Systemic lupus erythematosus.

INTRODUCTION

While overall mortality of patients with cervical carcinoma has declined over the years due to the widespread availability of successful screening programs, cervical cancer remains the second most prevalent malignancy in women and a significant cause of morbidity and mortality, with nearly 510,000 newly diagnosed cases and 288,000 associated deaths. Overall, the 5-year survival rate was stated to be 73% but the prognosis was unsatisfactory.[1]

Cervical cancer has been recognized as a sexually transmitted disease for decades, and sexually transmitted human papillomavirus (HPV) infection has been implicated in its pathogenesis. In the mid-1970s, Meisel and Fortin recognized, on morphological grounds, that cervical HPV infection often occurred with histological characteristics of mild cervical intraepithelial neoplasia (CIN).[2]

Systemic lupus erythematosus (SLE) is a chronic systemic, autoimmune disease that affects multiple organ systems with a wide variety of symptoms, clinical and laboratory manifestations.[3]

A significant complication of SLE is the increased occurrence of malignancy, including cervical cancer, autoimmune system failure, and chronic infections. Further, exposure to immunosuppressive drugs may offer reasons that indicate an increased incidence of malignancy in SLE.[4]

Cytology is used to detect HPV diseases of the cervix using the Pap test which is named after pathologist George Papanicolaou, who discovered this test. It is a screening tool for abnormal changes in cervical cells. CIN 1 coresponds to low-grade squamous intra-epithelial lesions (LGSIL) in cytology that refers to dysplastic change with nuclear pleomorphism and hyperchromatism involves about one-third of the thickness of the epithelium. CIN 2; corresponding to high-grade squamous-intra-epithelial lesions (HGSIL) in cytology refers to abnormal changes in about one-third to two-thirds of the epithelial layer. CIN 3 (the most severe form; corresponding to HGSIL in cytology) describes dysplastic changes that affects more than two-thirds of the epithelium.[5]

Patients with SLE have a greater incidence of cervical dysplasia than the general population. It has been proposed that epidemiological monitoring in this category of patients should be more vigilant, with pap dysplasia earlier in existence and possibly performed every 6-months.[6]

Irregular cervico-vaginal dandruff is documented by some studies in SLE patients. Cervico-vaginal smearing is an easy, economic, safe, repeatable and noninvasive technique for screening and early detection of cervical neoplastic lesions in SLE.[7,8]

AIM OF THE STUDY

The aim of this study is to determine the relationship between SLE, premalignant and malignant changes of the cervix.

SUBJECTS AND METHODS

The Subjects

A cross sectional case control study was conducted on 128 patients during the period (from June 2019 to February 2020) including 64 SLE patients and 64 healthy volunteers as a control group.

Inclusion Criteria

1. Sexually active female patients.
2. Females not pregnant at the time of the Pap smear intake.
3. Females consenting to be included in the study.
4. The age of the cases ranged from 22 to 43-years.
5. SLE patients with disease duration ranged from 1.5 to 16-years.

Exclusion Criteria

1. Patients with bleeding.
2. Pregnant ladies.
3. Patients refusing examination or participation in the study.
4. Virgins.

Design of the Study

All patients were subjected to the followings:

1. Complete history information collection.
2. General examination.
3. Local and bimanual examination.
4. Speculum examination with Pap smear intake.
5. Colposcopy examination of those who had abnormal pap smear, multiple biopsies were taken from patient's suspicious area by colposcopy for histopathological examination.

Written informed consents were obtained from each patient participating in this study after informing them about the steps of study.

Each participant was subjected to test according to the guidelines in 2013: Patient is positioned on an exam table in lithotomy position and a speculum is gently inserted to open the vagina and to reveal the cervix and upper vagina.

The cervix was examined the and pap smear taken by Ayer's spatula applied on ectocervix including TZ and rotated 360°. A cytobrush applied inside the endocervical canal, rotated and collected ectocervical and endocervical smears rapidly spread over glass slide and immediately fixed the smear in 95% ethyl alcohol.

Three-step colposcopic examination was done to cervix: Firstly wash cervix with saline technique and examination of abnormal blood vessel pattern (Punctuation-, Mosaicism-Sharply demarcated borders).

Apply 5% acetic acid with a cotton ball held in a ring forceps, and then gently apply vinegar. Repeat the application every 5-minutes to show aceto-white areas and to detect the depth of the lesion. Those with sharp geographic boarders and roughness are likely to be histologically severe. Vessel atypia in the lesions indicates dysplasia.

Lugol' siodine (Schiller's test) to show negative iodine area: Multiple biopsies taken from the patients with suspicious areas by colposcopy were fixed in 10% buffered formalin and embedded in paraffin block, cut at 3-4 micro section and stained with hematoxylin and eosin (H and E) stain for histopathological examination.[9]

Careful post-procedure instructions were provided. These instructions include: no douching, intercourse, or tampons until spotting subsides. Patients are advised to revisit for foul vaginal discharge, pelvic pain and or fever. Tylenol and ibuprofen may be used for cramps. Follow-up was usually done 1 to 3-weeks to discuss histopathology results.[10,11]

Statistical Analysis

Data entry and statistical analyses were done using SPSS (statistical package of social sciences) version 21 (SPSS Inc., Chicago, IL, USA). Categorical data are expressed in number and percent-

age, while continuous normally distributed data are expressed in mean and standard deviation. Kolmogrov Smirnov test is used to examine the normality of the quantitative data. When probability ($p \leq 0.05$), the data is considered statistically significant.

For continuous normally distributed data, Student *t*-test was used. Chi square (χ) test or fisher exact test was used to compare the risk of the cervical lesions in SLE patients *versus* in the control group. Analysis of variance (ANOVA) is used to compare between continuous data with various types of cervical lesions.

RESULTS

A case control study was conducted on 64 SLE female patients as well as 64 females as control group. Regarding the demographic characteristics, there is no statistically significant difference between SLE and control group. In our study we found that, there is a significant association between cervical cancer and SLE patients (p=0.034). A significant association between atypical squamous cells of undetermined significance (ASCUS), younger age of marriage (p=0.019) and shorter duration of SLE was detected in this study (0.014) (Tables 1 and 2) (Figures 1, 2 and 3).

Table 1. *Association between SLE and Dysplastic Changes of Cervix by Histopathology and Pap Smear*

Cervical Cancer	SLE N=64	Control N=64	*p* value
Positive	10(15.6)	0(0)	0.034*
Negative	54(84.4)	64(100)	
ASCU	4(6.3)	--	
CIN I/LGSIL	2(3.15)	--	
CIN II/III/HGSIL	2(3.15)	--	
SQCC	2(3.15)	--	

**p<0.05 is significant*

Table 2. *Association between Premalignant Changes of Cervix and Clinical Characteristics of SLE Patients*

Pathological Changes Association with Clinical Characteristics Result							*p* value
		Normal	ASCUS	CIN I/LGSIL	CCN II/III/HGSIL	SQCC	
Age of marriage mean±SD		29.8±5.8	18.5±0.7	32	34	30	0.019*
Duration of SLE mean±SD		11.9±3.9	3.5±0.7	12	13	10	0.014*
Oral Contraception	-ve	52	4	2	2	2	0.151
		96.3	100	100	100	100	
	+ve	2	0	0	0	0	
		3.7	0	0	0	0	
Parity	Multi	48	4	2	2	2	0.483
		88.9	100	100	100	100	
	Nully	6	0	0	0	0	
		11.1	0	0	0	0	
Coital Bleeding	-ve	50	0	0	0	0	0.003*
		92.6	0	0	0	0	
	+ve	4	4	2	2	2	
		7.4	100	100	100	100	
Marriage	Once	48	4	2	2	2	0.521
		88.9	100	100	100	100	
		6	0	0	0	0	
		11.1	0	0	0	0	
Smoking	-ve	50	4	2	2	2	0.573
		92.6	100	100	100	100	
	+ve	4	0	0	0	0	
		7.4	0	0	0	0	
History of Cervical Lesion	-ve	50	0	0	0	0	0.003*
		92.6	0	0	0	0	
	+ve	4	4	2	2	2	
		7.4	100	100	100	100	

*1. *p<0.05 is significant; 2.**p<0.0001 is highly significant.*

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Figure 1. *Microscopic Picture of LGSIL, Low Grade Squamousintraepithelial Cells, with Scattered Atypical Squamous Cells among Normal Cervical Epithelial Cells, (Pap smear*100)*

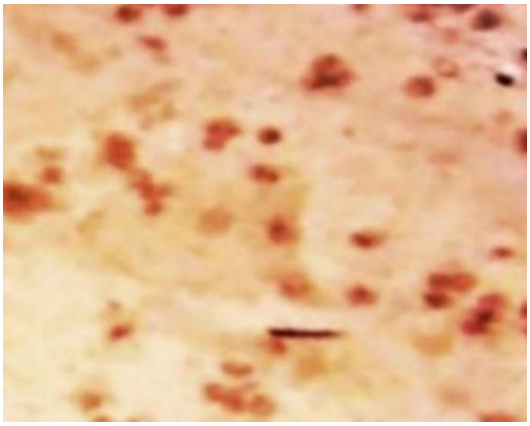

Figure 2. *Microscopic Picture of HGSIL, with Moderate Increase in Number of Dysplastic Cells, (Pap smear*100)*

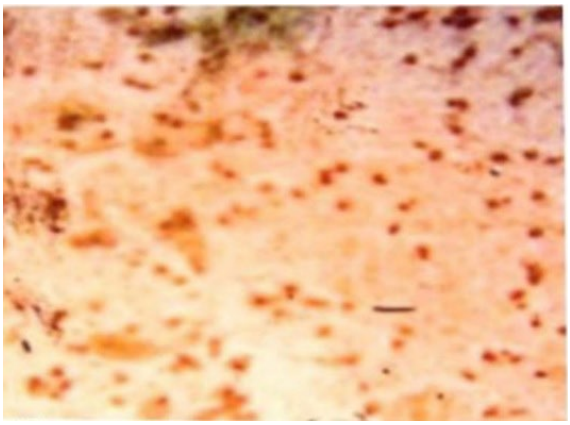

Figure 3. *Microscopic Picture of High Grade CIN; with Severe Dysplastic Cells Involving more than Lower Two Third of Epithelium (100×H&E)*

There is a significant association between cervical cancer, coital bleeding and history of cervical lesion (p=0.003). There is a highly significant association between passive smoking and cervical cancer (especially ASCUS and HGSIL/CIN II). However, other studied risk factors are not significantly associated with cervical lesions in SLE patients as revealed in this study (p>0.05).

In our study, we investigated the performance values of Pap smear and colposcopy in comparison with histopathology results. Pap smear had 60%sensitivity, 100%specificity, 100% positive predictive value, 93.1% negative predictive value while colposcopy showed higher results 80% sensitivity, 100% specificity, 100% positive predictive value, 96.4% negative predictive value.

DISCUSSION

Cervical cancer is the second most prevalent cancer in women and is responsible for up to 300,000 annual deaths.[12] Overall, the 5-year survival rate has been reported to be 73%, but the prognosis is unsatisfactory.[5]

The causes of cervical cancer include early sexual intercourse, multiple sexual partners, HPV infection, genital warts, sexually transmitted infections, genital defects, smoking, passive smoking, inadequate diet, immunodeficiency and malnutrition.[4]

Systemic lupus erythematosus is a multi-organic, autoimmune condition with various immunological and clinical symptoms. It is believed to grow as a result of the dysregulation of the immune system, which contributes to clinical features of inflammation.[13] A correlation between immunological dysfunction and cervical premalignant and malignant anomalies has also been identified.[14,15]

In addition to the clinical symptoms of SLE itself, female patients are at high-risk of developing abnormal cervical smears and squamous intra-epithelial lesions of the cervix and other cancers.[16] Involved studies have shown that SLE syndrome is a permissive effect of immunosuppression on increased host vulnerability to high-risk cancers, pathogens, CIN and cervical cancers.[17] Our study was performed to determine the prevalence of abnormal cervical lesions using colposcopy, Pap smear and histopathology in SLE patients. Our study included 64 SLE female patients and 64 healthy female participants as control groups.

In this research, there is a substantial correlation between

cervical cancer and SLE (p=0.034) patients. Four (4) patients (6.3%) of SLE had ASCUS with scattered abnormal cells with irregular membrane and enlarged nuclei in Pap smears, 2 patients (3.1%) had CIN 1 with dysplastic changes in the lower one third of epithelium in H and E stained slides and LGSIL with mildly enlarged nuclei and mild dyskeratosis in Pap smear slides, 2 patients (3.1%) had CIN II/III HGSIL with severe dysplasia and dyskeratosis in Pap smear stained slides, and 2 patients (3.1%) had SQCC with nests of malignant squamous epithelial cells with pleomorphic hyperchromatic nuclei in H and E stained slides and sheets of dysplastic cells and coarse chromatin in Pap smear slides.

Cao et al[16] in 2015 detected a high degree of correlation between cervical cancer and SLE patientsand reported that cervical cancer is one of the most prevalent cancers among SLE patients.

We are also in line with earlier worldwide findings of Bernatsky et al.[18] 2015 who demonstrated cervical neoplasm among prevalent cancers on top of SLE disease.

In addition, we agree with the broad meta-analysis study carried out by Liu et al[19] that there is a large gap between case and control groups with an elevated risk of cervical neoplasm with SLE. Consensus in the literature shows that immunosuppressive therapy is likely to lead to the growth of cervical disease in patients with SLE as well as the effect of the disease itself.

We also agree with the previous research that SLE, along with ≥2 sexual partners, was identified as an independent risk factor for high-risk HPV infection among Korean women. High-risk HPV infection and cervical cytological defects were more frequent than controls in Korean women with SLE. They concluded that SLE itself may be a risk factor for HPV infection among Korean women, indicating the significance of close monitoring of cervical cytology in SLE.[20]

Also, they have detected epithelial dysplasia in 8 patients, atypical squamous cells of undetermined significance (ASCUS) in 7 patients, and carcinoma *in situ* (CIN) in 7 patients.

We also agree with the most recent study conducted in April 2017 by Wadström et al[21] that is based on 121 cervical neoplasm events in 23,136 person-years among SLE patients, there was an increased risk of cervical neoplasm compared to the general population, but not invasive cervical cancer. The sub-cohort treated with other immunosuppressant were at the greatest risk of cervical neoplasm.

While we were unable to determine the function of immunosuppressive therapy in the occurrence of cervical cancer due to short time of study and lack of follow-up period, we however found a disparity between various researches on the function of immunosuppressive drugs as a predisposing factor for these cervical anomalies. On one hand, the majority of research found little correlation between the use of immunosuppressive agents and increased incidence of cervical anomalies, although the participation of intravenous cyclophosphamide in the production of this cervical complication is indicated by two others.

In our research, as analyzed with respect to clinical characteristics and type of cervical cancer, there is a significant association between ASCUS with younger age of marriage (p=0.019) and shorter duration of SLE (p=0.014) while, other studies did not show any significant association.[22]

We are in disharmony with a report that did not detect any meaningful correlation between the length of SLE and the occurrence of cancer, although they had a lengthy follow-up time.[23]

There was no substantial correlation between any form of cervical cancer and oral contraceptives in SLE patients that disagrees with Bernatsky et al[24] 2004 who identified oral contraceptive pills as a potential risk factor for cervical cancer. This disagreement may be due to variations in the number of research participants and higher number of cervical cancer SLE patients in the later study.

In this research, there is a significant association between cervical cancer (especially ASCUS and CIN II/HGSIL) and passive smoking. This finding was not associated with earlier malignancy findings at the top of the SLE; which highlighted smoking as a high-risk factor for lung cancer rather than cervical cancer.[25] We also disagreed with Dey et al[26] 2013 who observed smoking in a comparable ratio between SLE patients and the control group with no substantial difference.

Previous studies have reported an elevated incidence of atypical cervical dandruff in patients with SLE and asymptomatic patients, increasing from 24 to 36%, compared with a prevalence of ≤5-15% in controls.[27]

Pap examination anomalies in female patients with autoimmune disease have been historically investigated. SLE, rheumatoid arthritis and systemic sclerosis were conducted for the autoimmune community as opposed to usual counterparts.[15]

Both groups were matched for ages and identified risk factors for cervical malignancy. The incidence of irregular Pap tests in the case group was slightly greater than in the controls. The incidence of irregular Pap tests was higher in patients with SLE compared to controls.[15]

In our analysis, the Pap and colposcopy output values relative to histopathology findings were 60% sensitive and 100% specificity, 100% positive predictive value, 96.4% negative predictive value.

This is consistent with the findings of Girbash et al[28] which detected sensitivity in 60% of Pap Dmitry, 87% precision, 43% positive predictive value, 93% negative predictive value with higher colposcopy values. It had 75% sensitivity, 99% accuracy, 94% positive predictive value, 96% negative predictive value.

Mortality and morbidity are higher in SLE patients due to high cancer incidence with long standing SLE. Routine screen-

ing tests should be performed for all SLE patients, including those with potential risk factors. Colposcopy has a greater accuracy and sensitivity.

CONCLUSION

The caesarean section (CS) rate in Lumbini Zonal Hospital was far higher than the suggested optimum CS levels. Evidence of the high prevalence of CS and the concentration of CS in certain obstetric populations, as identified by this study, should be taken into consideration while formulating initiatives to direct public policies for the management of CSs. This study suggests further research be undertaken such as a retrospective analysis of CS rates for multiple years to identify trends. Developing risk profiles of women at high-risk of CS serves to provide evidence for devising timely interventions to limit CS rates for medically unwarranted conditions.

LIMITATIONS

• Long time follow-up is recommended to detect the relation between long standing SLE and cervical abnormalities
• Long time follow-up for immunosuppressive treatment is also recommended to detect any role of immunosuppressive therapy in induction of cervical cancer.
• Extended study is recommended to be applied in large number of SLE patients to detect various type of cervical changes.
• Variable degree of SLE activity should be enrolled in the study to evaluate the relation between SLE disease activity and type of cervical cancer.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Gakidou E, Nordhagen S, Obermeyer Z. Coverage of cervical cancer screening in 57 countries: Low average levels and large inequalities. *PLoS Med.* 2008; 5(6): e132. doi: 10.1371/journal.pmed.0050132

2. Howley PM, Lowy DR. Papillomaviruses and their replication. In: Knipe DM, Howley PM, eds. *Fields Virology*. 4th ed. IL, USA: Wolters Kluwer; 2012: 2197-2229.

3. Ault A. Epidemiology and natural history of human papillomavirus infections in the female genital tract. *J Infect Dis Obstet Gynecol.* 2006; 2006 Suppl: 40470. doi: 10.1155/IDOG/2006/40470

4. Ishida WS, Singto Y, Kanjanavirojkul N, Chatchawan U, Yuenyao P, Settheetham D, et al. Co-risk factors for HPV infection in northeastern Thai women with cervical carcinoma. *Asian Pac J Cancer Prev.* 2004; 5: 383-386.

5. Jones MH, Jerkins D, Singer A. Regular audit of colposcopic biopsies in women with a mildly dyskaryotic or borderline cervical smear results in fewer cases of CIN III. *Cytopathology.* 2006; 7(1): 17-24. doi: 10.1046/j.1365-2303.1996.37582375.x

6. Kjaer SK, Chackerian B, van den Brule AJC, Svare EI, Paull G, Walbomers JM, Schiller JT, et al. High-risk human papillomavirus is sexually transmitted: evidence from a follow up study of virgins starting sexual activity (intercourse). *Cancer Epidemiol Biomarkers Prev.* 2010; 10: 101-106.

7. Al-Sherbeni H, Fahmy A, Sherif N. Predisposition to cervical atypia in SLE: A clinical and cytopathological study. *Autoimmune Dis.* 2015; 2015: 751853. doi: 10.1155/2015/751853

8. ACOG Practice Bulletin. ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists. Number 45, August 2003. Cervical cytology screening (replaces committee opinion 152, March 1995). *Obstet Gynecol.* 2013; 102(2): 417-427. doi: 10.1016/s0029-7844(03)00745-2

9. Harris RWC, Brinton LA, Cowdell RH, Skegg DC, Smith PG, Vessey MP, et al. Characteristics of women with dfysplasia or carcinoma in situ of the cervix uteri. *Br J Cancer.* 1980; 42: 359-369. doi: 10.1038/bjc.1980.246

10. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Coc Psychol.* 1986; 51(6): 1173-1182. doi: 10.1037//0022-3514.51.6.1173

11. Dean OF. statistical methods in scientific research. *Eur J Sci Res.* 2006; 14(3).

12. Cantor SB, Atkinson EN, Cardenas-Turanzas M, Benedet JL, Follen M, MacAulay C. Natural history of cervical intraepithelial neoplasia: A meta-analysis. *Acta Cytol.* 2005; 49: 405-415. doi: 10.1159/000326174

13. Ben-Menachem E. Review article: Systemic lupus erythematosus: A review for anesthesiologists. *Anesth Analg.* 2010; 111: 665-676. doi: 10.1213/ANE.0b013e3181e8138e

14. Dobkin PL, Da Costa D, Fortin PR, Edworthy S, Barr S, Esdaile JM, et al. Living with lupus: A prospective pan-Canadian study. *J Rheumatol.* 2001; 28: 2442-2448.

15. Esmaeili H, Ghahremanzadeh K. Association of pap smear abnormalities with autoimmune disorder. *Pak J Biol Sci.* 2011; 14(10): 600-604. doi: 10.3923/pjbs.2011.600.604

16. Cao L, Tong H, Xu G, Liu P, Meng H, Wang J, et al. Systemic lupus erythematous and malignancy risk: A meta-analysis. *PLoS One.* 2015; 10(4): e0122964. doi: 10.1371/journal.pone.0122964

17. Bao YP, Li N, Smith JS, Y-L Qiao, ACCPAB members. Human papillomavirus type distribution in women from Asia: A meta-analysis. *Int J Gynecol Cancer.* 2008; 18: 71-79. doi: 10.1111/j.1525-1438.2007.00959.x

18. Bernatsky S, Clarke A, Labreque J, Boivin J-F, Costenbader KH, Urowitz MB, et al. Lymphoma risk in systemic lupus: Effects of disease activity *versus* treatment. *Arthritis Rheum Dis.* 2014; 73(1):

138-142. doi: 10.1136/annrheumdis-2012-202099

19. Liu H, Ding Q, Yang K, Zhang T, Li G, Wu G. Meta-analysis of SLE and the risk of cervical neoplasia. *Rheumatology.* 2011; 50(2): 343-348. doi: 10.1093/rheumatology/keq304

20. Lee Y-H, Choe J-Y, Park S-H, Park Y-W, Lee S-S, Kang Y-M, et al. Prevalence of human papilloma virus infections and cervical cytological abnormalities among Korean women with SLE. *J Korean Med Sci.* 2010; 25: 1431-1437. doi: 10.3346/jkms.2010.25.10.1431

21. Wadström H, Elizabeth V, Sjöwall C, Askling J, Simard JF. Cervical neoplasia in systemic lupus erythematosus: A nationwide study. *Rheumatology (Oxford).* 2017; 56(4): 613-619. doi: 10.1093/rheumatology/kew459

22. Nath R, Mant C, Luxton J, Hughes G, Raju KS, Shepherd P, et al. High risk of human papillomavirus type 16 infections and of development of cervical squamous intraepithelial lesions in systemic lupus erythematosus patients. *Arthritis Rheum.* 2007; 57: 619-625. doi: 10.1002/art.22667

23. Dresang LT. Cervical cancer with a normal Pap. *WMJ.* 2003; 102(5): 4.

24. Bernatsky S, Joseph L, Boivin J-F, Gordon C, Urowitz M, Gladman D, et al. The relationship between cancer and medication exposures in systemic lupus erythaematosus: A case–cohort study. *Ann Rheum Dis.* 2008; 67: 74-79. doi: 10.1136/ard.2006.069039

25. Kale M, Ramsey-Goldman R, Gordon C, Clarke AE, Bernatsky S. Malignancies in SLE. *Autoimmun Rev.* 2010; 9(4): doi: 10.1016/j.autrev.2009.07.004

26. Dey D, Kenu E, Isenberg DA. Cancer complicating SLE – a dichotomy emerging from a nested case-control study. *Lupus.* 2013; 22(9): 919-927. doi: 10.1177/0961203313497118

27. Dhar JP, Kmak D, Bhan R, Pishorodi L, Ager J, Sokol RJ. Abnormal cervicovaginal cytology in women with lupus: A retrospective cohort study. *Gynecol Oncol.* 2001; 82: 4-6. doi: 10.1006/gyno.2001.6207

28. Girbash EF, Atta DS, Fahmy DS, Abdelwahab SM, Therwat I. Abnormal Pap tests in systemic lupus erythematosis: A cytopathological and human papillomavirus testing study. *Int J Adv Res.* 2016; 4(5): 1707-1715. doi: 10.21474/IJAR01/355