Background: In the life of a woman, after 40 years of age, onset of menopause occurs during which hormonal imbalances take place. The present study is aimed at finding out cytopathological changes in the cervical epithelium associated with this hormonal disturbance. Materials and Methods: Cervical cancer screening program is in progress under auspices of Era’s Lucknow Medical College and Hospital, Lucknow, since May 2013, in the villages of Lucknow West through camp approach. Till September 2017, 140 camps have been organized and 2440 women attending the camp have been cytologically examined. Out of these, 1534 women were perimenopausal, 165 premenopausal, and 441 postmenopausal. The cytopathological changes have been studied in these three categories of women in relation to different predisposing factors to the cervical carcinogenesis. Results: The squamous intraepithelial lesion (SIL) rate was higher with onset of menopause in the premenopausal women. The SIL rate was higher with nulliparity in these women as well as in the postmenopausal women and also with different gynecological symptoms and clinical lesions of the cervix. The SIL changes associated with HPV and HSV were also higher in them. Conclusion: A high SIL rate found with onset of menopause may be the outcome of gradual estrogen withdrawal in the premenopausal women. Hence, cytological evaluation is mandatory in women between 41 and 45 years of age to rule out any occurrence of cervical cytopathology.

Keywords: Menopausal onset, premenopausal women, squamous intraepithelial lesion

INTRODUCTION

The life of a woman after attainment of puberty is broadly divided into reproductive and menopausal phases. The reproductive cycle is normal till 40 years of age with regular occurrence of menstruation. Between 40 and 45 years, premenopausal phase begins when the ovaries gradually produce less estrogen, and in the postmenopause, sustained lower estrogen level occurs and the progesterone level is higher resulting in the atrophic changes in the lower female genital tract.

During ongoing cervical cancer screening program in Rural Lucknow West which is being conducted under the auspices of Era’s Lucknow Medical College and Hospital, Lucknow, since May 2013, a total of 2440 women have been cytologically examined till September 2017 through camp approach. Of these 2440 women, 1534 women were perimenopausal, 165 premenopausal, and 441 were postmenopausal (beyond 45 years). Since we have detailed information regarding the cytological findings in these three categories of women and also predisposing factors related to the cervical carcinogenesis, we thought it interesting to compare the squamous intraepithelial lesion (SIL) findings in relation to the different parameters in the three phases of women life to find out any impact of onset of menopause on the cervical cytology. The findings obtained are presented in this paper.

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Materials and Methods

Cervical cancer screening program is in progress in the villages of Kakori and Malihabad blocks of Lucknow since May 2013 and 140 camps have been organized till September 2017. Pap smears have been collected in 2440 women attending these camps. The cervical smears were stained according to the Papanicolaou’s technique, and the cytological findings were graded according to the revised Bethesda system of reporting cytological changes in the cervical smears (2002).[1]

The 2440 registered women at the camps were divided into three groups depending on the reproductive phase of the women – perimenopausal (1834) with normal menstrual cycle, premenopausal (165) between 41 and 45 years in whom the transition to menopause takes place, and postmenstrual women (441) beyond 45 years who have attained menopause. Informed consent has been obtained in all these women before collection of Pap smear in the form of signature or thumb impression. The incidence of SIL and atypical squamous cells of undetermined significance (ASCUS) in these three groups of women and the predisposing factors of cervical carcinogenesis such as age, parity, gynecological symptoms, and clinical lesions have been analyzed in detail and presented in this paper. The incidences of different sexually transmitted diseases (STDs) have also been investigated in these three categories of women.

All the data have been statistically analyzed applying Chi-square test and P value was obtained to show the significance. The ethical clearance was obtained from the Ethical Committee of Era’s Medical College and Hospital Lucknow before the commencement of the screening program.

Results

The incidences of ASCUS and SIL in the three categories of women were as follows.

| Category          | ASCUS | SIL  |
|-------------------|-------|------|
| Perimenopausal    | 9.7%  | 18.1%|
| Premenopausal     | 9.1%  | 21.2%|
| Postmenopausal    | 4.1%  | 17.2%|

The ASCUS incidence was highest (9.7%) in the normal menstruating women and showed decline in the remaining two groups –9.1% in the premenopausal and 4.1% in the postmenopausal women. The difference in the ASCUS incidence in the three groups was highly significant ($\chi^2 = -14.6; P < 0.001$). The SIL incidence was almost identical in peri- and postmenopausal women (18.1% and 17.2%, respectively) and was statistically insignificant ($\chi^2 = 1.30; P = 0.521$) but was higher in the premenopausal women (21.2%) and was highly statistically significant ($\chi^2 = 9.26; P < 0.009$). It may be that the hormonal disturbances occurring during the 5 years (41–45 years), during the cessation of the menstrual cycle, might be the reason for the high SIL rate in the premenopausal women. The details of these findings are presented in Table 1.

The number of women in all parity groups and the SIL incidence are given in Table 2 in the three categories of women. The number of cases showed a rise from nulliparity to multiparity in all the three groups of women, and the number of multiparous women was higher in all the three categories of women. The incidence of SIL was very high with nulliparity in the pre- and postmenopausal women and was highly statistically significant ($\chi^2 = 23.4; P < 0.001$). There was no significant difference in the SIL rate in parity 1 and 2 ($\chi^2 = 0.414; P = 0.913$ and $\chi^2 = 0.105; P = 0.949$, respectively). However, the SIL rate was higher in multiparity (With three or more children) and the difference was statistically significant ($\chi^2 = 8.60; P = 0.04$).

The number of cases showing the different gynaecological symptoms and SIL incidence seen with these symptoms was also investigated in the three categories of women [Table 3]. The vaginal discharge was the most common symptom seen in all the three groups of women and showed rising trend from perimenopausal to pre- and postmenopausal women. However, the number of patients was almost identical in the three groups with other symptoms such as pain in abdomen and different type of menstrual disorders. Six cases of postmenopausal bleeding were seen in the postmenopausal women. The SIL incidence was found to be higher in the pre- and postmenopausal phases with vaginal discharge and pain in lower abdomen, while this was less than half in the perimenopausal women. The difference was highly significant in both vaginal discharge and pain in lower abdomen cases ($\chi^2 = 20.1; P < 0.001$ and $\chi^2 = 11.6; P < 0.004$, respectively). The hormonal disturbances due to withdrawal of estrogen might be responsible for a high SIL incidence in pre- and postmenopausal women. However, there was no significant difference with menstrual disorder between peri- and premenopausal women ($\chi^2 = 0.519; P = 0.471$). The SIL was diagnosed in the two of the six women showing postmenopausal bleeding.

The number of women showing different clinical lesions of cervix and SIL rate found with these lesions in three categories of women is shown in Table 4. The erosion cervix was the most common finding in all the phases. The SIL rate showed rising trend from
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| Table 1: Incidence of atypical squamous cells of undetermined significance and squamous intraepithelial lesion in three groups of women |
|---------------------------------------------------------------|
| Cytopathological lesion | Perimenopausal (1834 cases) (%) | Premenopausal (165 cases) (%) | Postmenopausal (441 cases) (%) |
| ASCUS | 179 (9.7) | 15 (9.1) | 18 (4.1) |
| SIL | 331 (18.1) | 35 (21.2) | 76 (17.2) |

ASCUS: Atypical squamous cells of undetermined significance, SIL: Squamous intraepithelial lesion

| Table 2: Incidence squamous intraepithelial lesion in relation to parity in three groups of women |
|---------------------------------------------------------------|
| Parity | Perimenopausal (1834 cases) (%) | Premenopausal (165 cases) (%) | Postmenopausal (441 cases) (%) |
| | Number of cases | SIL incidence | Number of cases | SIL incidence | Number of cases | SIL incidence |
| Nulliparous | 141 (7.6) | 7 (4.9) | 2 (1.2) | 1 (50) | 3 (0.6) | 2 (66.6) |
| Parity 1 | 195 (10.6) | 32 (16.4) | 8 (4.8) | 2 (25) | 17 (3.8) | 3 (17.6) |
| Parity 2 | 356 (19.4) | 59 (16.5) | 8 (4.8) | 1 (12.5) | 29 (6.5) | 5 (17.2) |
| Parity>3 | 1086 (59.2) | 264 (21.5) | 144 (87.2) | 31 (21.5) | 381 (86.3) | 65 (17.6) |

SIL: Squamous intraepithelial lesion

| Table 3: Different gynaecological symptoms and squamous intraepithelial lesion incidence in three groups of women |
|---------------------------------------------------------------|
| Gynaecological symptoms | Perimenopausal (1834 cases) (%) | Premenopausal (165 cases) (%) | Postmenopausal (441 cases) (%) |
| | Number of cases | SIL incidence | Number of cases | SIL incidence | Number of cases | SIL incidence |
| Vaginal discharge | 743 (40.5) | 106 (14.2) | 44 (26.1) | 13 (29.5) | 56 (12.6) | 19 (33.9) |
| Pain in lower abdomen | 520 (28.3) | 82 (15.7) | 44 (26.1) | 13 (29.5) | 87 (19.2) | 24 (28.2) |
| Menstrual disorders | 188 (10.2) | 23 (12.2) | 10 (6.1) | 2 (26) | - | - |
| Postmenopausal bleeding | - | - | - | - | 6 (1.3) | 2 (33.3) |

SIL: Squamous intraepithelial lesion

| Table 4: Clinical lesions of the cervix and squamous intraepithelial lesion incidence in three categories of women |
|---------------------------------------------------------------|
| Clinical lesions of cervix | Perimenopausal (1834 cases) (%) | Premenopausal (165 cases) (%) | Postmenopausal (441 cases) (%) |
| | Number of cases | SIL incidence | Number of cases | SIL incidence | Number of cases | SIL incidence |
| Erosion cervix | 168 (9.1) | 35 (20.8) | 9 (5.4) | 3 (33.3) | 17 (3.8) | 8 (47.1) |
| Hypertrophied cervix | 32 (1.7) | 9 (28.1) | 1 (0.6) | - | 3 (0.6) | - |
| Cervix bleeds on touch | 17 (0.9) | 5 (29.4) | 2 (1.2) | 1 (50) | 2 (0.4) | - |
| Others | 89 (4.8) | 13 (14.6) | 7 (4.2) | 2 (28.5) | 20 (4.5) | 5 (25) |

SIL: Squamous intraepithelial lesion

The incidence of different STDs, nonviral (Candida albicans and Trichomonas vaginalis), and viral (HPV and HSV) have also been investigated in the three categories of women and the findings are shown in Table 5. The incidence of all the four STD’s was seen higher in normal perimenopausal women and it is obvious because these are sexually active group and chances of STD transition is higher in them. However, the SIL incidence was higher with Candida but was lower with trichomonal infection, but the difference was insignificant ($\chi^2 = 0.424; P = 0.809$ with Candida and $\chi^2 = 0.151; P = 0.171$ for T. vaginalis infection). The SIL incidence was higher with HPV in all the three groups of women, but the difference was insignificant ($\chi^2 = 1.73; P = 0.420$). The SIL rate with HSV was higher only in the premenopausal group and was highly significant ($\chi^2 = 0.333; P = 0.521$ using Fisher’s Exact Test).

The ASCUS incidence was seen higher in the perimenopausal women (9.7%) and showed decline in the pre- (9.1%) and postmenopausal women (4.1%). This has also been reported by Iavazzo et al.[2] A low
incidence of ASCUS was also found in the rural postmenopausal women of Chennai by Ambedkar et al.\[^3\]

The incidence of SIL was, however, higher in the premenopausal women (21.2%) than in the peri- (18.1%) and postmenopausal women (17.2%). The hormonal imbalance caused by the gradual decline in the estrogen level may be the reason for high SIL rate seen in the premenopausal women. However, in a comparison of cytological findings in the pre- and postmenopausal women, Moore et al. have seen that incidence of cervical intraepithelial neoplasia (CIN) was significantly higher in the premenopausal women than in the perimenopausal women (41% as against 29%). This was also true for cervical malignancy.\[^4\]

Gyllensten et al. in a HPV screening study in the postmenopausal women have found that the high-risk HPV was found in 6.2% of the women and in the 22% of the higher CIN + 2 lesions based on biopsy. The Pap smear taken in conjunction with HPV test was abnormal in 9.7% of HPV-positive women.\[^5\]

Tokmak et al. also found preinvasive lesions significantly higher in the premenopausal women than postmenopausal and low-grade CIN was seen in 23.2% of the perimenopausal women than 12.2% of the postmenopausal women. Similarly, high-grade CIN was seen in 4.9% of the perimenopausal than 1.8% with postmenopausal women.\[^6\]

Giuliano et al. found both oncogenic and nononcogenic HPV genotypes in the premenopausal women, while in the postmenopausal women, the positivity was predominantly oncogenic genotype. They opined that the prevalence of HPV infection may have a second peak among the postmenopausal women.\[^7\]

Misra et al. have also found a high incidence of condyloma (HPV) in the postmenopausal women and suggested that the HPV infection appears to remain latent in such cases and becomes evident only after the menopause.\[^8\]

The SIL rate showed progressive rise with increasing parity and majority of women screened were in the high-parity group in all the three categories of women. Similar findings have also been reported by Rajput et al.\[^9\]

Vaginal discharge and pain in the lower abdomen were the most common gynaecological symptoms complained by the three categories of women. Similar findings have also been reported by Srivastava et al.\[^10\] and Nikumbh et al.\[^11\] The SIL incidence was higher with all symptoms in three groups of women, but that SIL rate was very high in the pre- and postmenopausal women and this may be related to the estrogen withdrawal.

Erosion cervix was the most common clinical lesion observed in all the three categories of women. Nikumbh et al. and Rajput et al. have reported a high incidence of erosion cervix in rural women. The SIL rate was higher with all lesions and showed progressive rise from premenopausal to postmenopausal women. Hormonal imbalance may be the reason for this rise in the SIL rate.

In the present study, Candida infection was found to be most prevalent in the rural women. However, Srivastava et al., Nikumbh et al., and Arora et al.\[^12\] found trichomonal infection more common than Candida in their series of rural women. The nonviral STDs were seen higher in the perimenopausal women, while the viral STDs were seen maximum in premenopausal women. The SIL rates in the nonviral STDs were higher in the perimenopausal women and showed decline with increasing age. The SIL rate with viral STDs was alarmingly higher in all three groups of women. However, the association of HSV with SIL rate was very high in the premenopausal women.

### Conclusion

A high SIL rate has been found in the premenopausal women than in the peri- and postmenopausal women and was largely associated with predisposing factors of cervical cancer like high parity, gynaecological symptoms like vaginal discharge and clinical lesions like erosion cervix. A high abnormal findings in premenopausal women may be due to gradual estrogen withdrawal during this period of onset of menopause and hence cytological surveillance is essential in women between 41-45 year to rule out any onset of premalignancy.

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**Table 5: Different sexually transmitted diseases and squamous intraepithelial lesion incidence in the three categories of women**

| STD                | Perimenopausal (1834 cases) (%) | Premenopausal (165 cases) (%) | Postmenopausal (441 cases) (%) |
|--------------------|--------------------------------|------------------------------|-------------------------------|
|                    | Number of cases | SIL incidence | Number of cases | SIL incidence | Number of cases | SIL incidence |
| Candida albicans    | 108 (5.8)  | 24 (22.2)  | 8 (4.9)  | 1 (12.5)  | 5 (1.1)  | 1 (25)  |
| Trichomonas vaginalis | 26 (1.4)  | 4 (15.3)   | -        | -        | 1 (0.8)  | -        |
| HPV                | 8 (0.6)    | 4 (50)     | 2 (1.2)  | 2 (100)  | 3 (0.2)  | 2 (66.6) |
| HSV                | 2 (0.1)    | -          | 1 (0.6)  | 1 (100)  | -        | -        |

SIL: Squamous intraepithelial lesion, STD: Sexually transmitted disease, HPV: Human papillomavirus, HSV: Herpes simplex virus
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**Conflicts of interest**
There are no conflicts of interest.

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