Study Of Metaplastic Lesions Of Different Parts Of The Female Genital Tract: A Prospective Study

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Citation

Abstract
Objective: To study the pattern and relative incidence of metaplastic lesions of different parts of the female genital tract and the relationship of different metaplastic lesions with age.
Method: A total of 200 female genital tract samples in the form of hysterectomy specimens, endometrial curettings, pap smears and cervical biopsies were subjected to gross and microscopic examination and the metaplastic changes observed were recorded. Among all the samples, 57.5% were hysterectomy specimens, 20% were pap smears, 15% were endometrial curettings and 2.5% were cervix biopsies. Maximum number of patient (73%) was in the age group of 30-49.
Results: Among 200 patients enrolled in the study, 120 (60%) were found to be positive for different types of metaplasias. Among the cervical metaplasias, 60.2% were showing squamous metaplasia of the cervix, followed by Ciliated and Microglandular metaplasia with a frequency of 25.5% and 20.4% respectively with the highest frequency in the age group of 40-59 years. Among the endometrial metaplasias Ciliated, Mucinous and Eosinophilic metaplasias were found to be the commonest with a frequency of 28.5%, 25.5% and 25.5% respectively. In the study, it was also observed that the metaplastic lesions of the endometrium and that of the cervix co-existed with each other in 74% of the cases
Conclusions: From these observations, squamous metaplasia of the cervix was the commonest metaplastic lesion observed on histological examinations, followed by ciliated and microglandular metaplasia, where as in the endometrium ciliated (tubal) metaplasia was the commonest followed by eosinophilic and mucinous metaplasia.. A large number of metaplastic lesions of the cervix co-existed with each other and also with that of the endometrium.

INTRODUCTION
The adult nulliparous uterus is a hollow, pear shaped organ that weights 40 – 80 grams and measures 7 to 8 cm along its longest axis. It is divided into the corpus and the cervix. The cervix is the lower portion of the uterus and is divided into a portion that protrudes into the vagina (portio vaginalis) and one that lies above the vaginal vault (supravaginal portion). The outer surface of the portio vaginalis is known as the exocervix or ectocervix and the portion related to the endocervical canal corresponds to the endocervix.¹

The endometrium lines the uterine cavity above the level of internal os. During the first half of the menstrual cycle, all the components of the endometrium including glands, stroma and blood vessels, proliferate under the influence of estrogens and during the later half, these elements respond to progesterone with the production of glandular secretions and there are stromal and vascular alterations.²

Most of the exocervix is covered by non-keratinizing squamous epithelium while as the glandular mucosa of the endocervix is formed by a layer of columnar mucous secreting cells. The area where the squamous and glandular epithelia meet is known as the squamo-columnar junction. This is a very unstable region, in which replacement of one epithelium for another repeatedly occurs, a process that Robert Meyer referred to as “the fight of the epithelia”. Today this area is more prosaically known as the transformation zone.³

Metaplasia is a condition in which there is a change of one type of differentiated tissue into another type of similar differentiated tissue⁴ or as the abnormal transformation of an adult, fully differentiated tissue of one kind into a differentiated tissue of another kind.⁵ The mullerian derived epithelium which lines most of the female genital tract is well known for its capacity to differentiate into various types of epithelium such as, ciliated, mucinous, endometrioid, transitional and squamous types.⁶
The metaplasias of the uterine corpus and cervix are the most common sites of metaplasia. Metaplasia occasionally can occur in other parts of the female genital tract such as mucosa of the fallopian tube and the vagina. Mucinous lesions of the fallopian tube mucosa are extremely rare and are of interest because of their association with other mucinous lesions of the female genital tract and with Peutz-Jeghers syndrome.

The abdominal and pelvic peritoneum, part of the secondary mullerian system, can also undergo metaplasia into the various mullerian epithelia. The secondary mullerian system comprises the mesothelium and the adjacent mesenchyme of the pelvis and lower abdomen. Conditions such as endosalpingiosis and endocervicosis are regarded as examples of mullerian metaplasia.

Endometrial epithelial metaplasia is a group of non-neoplastic lesions, often coexisting with endometrial hyperplasia or adenocarcinoma. Endometrial epithelial metaplasia of the female genital tract can be subdivided as per WHO classification into squamous metaplasia with morules, mucinous metaplasia, ciliated or tubal metaplasia, clear cell metaplasia, hobnail cell metaplasia, eosinophilic (oxyphilic, oncocytic) metaplasia, papillary syncytial metaplasia, papillary syncytial changes and arias-stella change. (Figure 1, 2)

**Figure 1**
Figure 1. Endometrium showing combined mucinous and squamous metaplasia. (H&E X 100)

Mesenchymal metaplasia may involve the endometrial stroma. This form of metaplasia is rare and may be in the form of smooth muscle metaplasia, cartilaginous metaplasia, osseous metaplasia, glial metaplasia, adipose metaplasia and extramedullary hematopoiesis.

Cervical squamous metaplasia is extremely common in the cervix. Before full maturation is reached, there are stages of reserve cell hyperplasia and immature squamous metaplasia, both of which may cause diagnostic difficulty. Squamous metaplasia occurring in the squamo-columnar junction (transformation zone) of the cervix begins as a patchy process, the foci of squamous metaplasia enlarging and eventually fusing. The metaplasia involves both the surface epithelium and underlying crypts. Cervical epithelial metaplasia may further be subdivided into: reserve cell hyperplasia, immature and mature squamous metaplasia (Figure-3), transitional metaplasia (Figure-4), tubal metaplasia, tuboendometrial metaplasia endometriosis, cervical microglandular hyperplasia, intestinal metaplasia and oxyphil metaplasia.

**Figure 2**
Figure 2. Arias stella change of the endometrium (H&E x 100)
Metaplasias elsewhere in the female genital tract are relatively very rare and can be transitional and mucinous metaplasia of the fallopian tube. The abdominal and pelvic peritoneum, as part of the secondary Mullerian system, may undergo metaplasia into various Mullerian epithelia. Non-neoplastic secondary Mullerian lesions, which are in many cases a form of metaplasia, comprise endometriosis, endosalpingiosis and endocervicosis. When occurring in combination, they have been termed as mullerianosis. It is recognized that probably most cases of abdominal and pelvic endometriosis are not truly metaplastic but are the result of retrograde menstruation. Endosalpingiosis is characterized by the presence of non-neoplastic glands lined by ciliated tubal type epithelium. It usually involves the peritoneum and sub-peritoneal tissue including the surface of ovaries. Endocervicosis is characterized histologically by the presence of non-neoplastic mucinous glands resembling endocervical glands. This is much less common than endometriosis or endosalpingiosis. Involved sites have included the peritoneum, pelvic lymph nodes, urinary bladder, uterine serosa, cervix and the vagina.

Jammu And Kashmir State differs in many respects from the rest of the country as the population density is the lowest, environmental and climatic conditions vary greatly. Our institution is having satisfactory medical facilities for the diagnosis and treatment of the gynecological problems. Therefore the study of the profile of metaplastic lesions of the female genital tract has been helpful to estimate the relative incidence and age distribution of different types of metaplasias of the female genital tract.

MATERIALS AND METHODS
The present study was carried for a period of one year on hysterectomy specimens, endometrial curettings, cervical biopsies and pap smears, submitted to the Department Of Pathology by the Department of Obstetric & Gynaecology, Acharya Shri Chander College of Medical Sciences and Hospital, Sidhra, Jammu. The processing of histopathological specimens was done as follows:

HYSTERECTOMY SPECIMENS
Hysterectomy specimens were grossed and 3-5 mm thin sections were taken for processing. Endometrial curettings were processed as such. Fixation was done in 10% buffered formol saline. Dehydration was carried out in ascending concentrations of ethanol. Clearing was done in xylene, and impregnation in paraffin wax. Tissue blocks were prepared using leukhart’s ‘L’ pieces. 3-5 micrometer thin sections were cut using rotary microtome and were stained with haematoxylin and eosin.

The staining with Haematoxylin and Eosin was done as follows: Dparaffinization was done in xylene and the sections were treated in descending concentrations of ethanol and then brought to water. Staining was done with Harris haematoxylin for 10-40 minutes. Bluing was done under running tap water. Sections were differentiated in 1% acid alcohol, followed by Washing in water. Counter staining with 1% aqueous eosin for 2-4 minutes followed by dehydration in ascending concentrations of ethanol was done. Sections cleared in xylene and were finally mounted in DPX.

CERVICOVAGINAL SMEARS
Papanicolaou staining method was used. The smears were wet fixed rapidly in 95% ethyl alcohol, before any air drying.

Figure 3
Figure 3. Squamous metaplasia of the cervix (H&E x 40)

Figure 4
Figure 4. Ectocervix showing transitional cell metaplasia (H&E x 100)
occurred. Polyethylene glycol fixative was removed in 50% alcohol (wherever coating fixatives were used). Sections were hydrated in 95% & 70% alcohol for 2 minutes each. Staining was done in Harris haematoxylin for 5 minutes. Slides were differentiated in 0.5% aqueous hydrochloric acid for 10 seconds, followed by rinsing in water for 2 minutes. Bluing was done in Scotts tap water substitute for 2 minutes. Smears were dehydrated in ascending concentrations of ethanol. Staining with OG 6 (orange G 6) was done for 2 minutes followed by rinsing in 95% alcohol for 2 minutes. Staining in EA50 for 3 minutes was done followed by rinsing in 95% alcohol for 1 minute. The nuclei should appear blue/black and cytoplasm of non-keratinizing squamous cells should appear blue/green and that in keratinizing cells, pink/orange. A detailed histopathological examination of haematoxylin & eosin stained sections was carried out & the findings were recorded.

**OBSERVATIONS**

The following observations were made:

The total number of specimens included 200, out of which 125 (62.5%) specimens were obtained from hysterectomy (endometrium, myometrium, cervix, fallopian tubes). Endometrial curettings accounted for 30 (15%) specimens, Pap smears for 40 (20%) specimens and cervical biopsies for 5 (2.5%) specimens. All the above specimens were unremarkable on gross examination. (Table 1)

**Figure 5**

Table 1: Showing the types of sample

<table>
<thead>
<tr>
<th>S.No</th>
<th>Gross</th>
<th>No. of samples</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hysterectomy specimens</td>
<td>125</td>
<td>62.5%</td>
</tr>
<tr>
<td>2</td>
<td>Pap smears</td>
<td>40</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>Endometrial curettings</td>
<td>30</td>
<td>15%</td>
</tr>
<tr>
<td>4</td>
<td>Cervical biopsies</td>
<td>05</td>
<td>2.5%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>200</td>
<td>100%</td>
</tr>
</tbody>
</table>

Out of 200 specimens enrolled in the study 120 (60%) were found positive for different types of metaplasias. Some patients were having more than one type of metaplasia in the same specimen. Out of 120 positive specimens 69 (57%) were hysterectomy specimens (endometrium, myometrium, cervix, fallopian tubes), 28 (23.3%) were pap smears (cervix only), 22 (18.3%) were endometrial curettings (endometrium, myometrium) and 01 (0.12%) specimen was of cervical biopsy (cervix only). (Table 2)

**Figure 6**

Table 2: showing the number and percentage of Positive samples

<table>
<thead>
<tr>
<th>S.No</th>
<th>Gross</th>
<th>No. of samples</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hysterectomy specimens</td>
<td>69</td>
<td>57.5%</td>
</tr>
<tr>
<td>2</td>
<td>Pap smears</td>
<td>28</td>
<td>23.3%</td>
</tr>
<tr>
<td>3</td>
<td>Endometrial curettings</td>
<td>22</td>
<td>18.3%</td>
</tr>
<tr>
<td>4</td>
<td>Cervical biopsies</td>
<td>01</td>
<td>0.12%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>120</td>
<td>100%</td>
</tr>
</tbody>
</table>

Maximum numbers of patients were in the age group of 30-39 yrs i.e 94 (47%) cases followed by the next age group of 40-49 yrs i.e 52 (26%) cases. Clubbing the two age groups together it was found that 146 (73%) cases were in the age group 30-49 yrs with the mean age of 39.5 yrs. The youngest patient in the study was 23 yrs old and the oldest was 67 yrs old. (Table 3)

**Figure 7**

Table 3: Showing the Age Distribution of cases

<table>
<thead>
<tr>
<th>S. no</th>
<th>Age range (in years)</th>
<th>No. of cases</th>
<th>percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29 and less</td>
<td>07</td>
<td>3.5%</td>
</tr>
<tr>
<td>2</td>
<td>30–39</td>
<td>94</td>
<td>47%</td>
</tr>
<tr>
<td>3</td>
<td>40 – 49</td>
<td>52</td>
<td>26%</td>
</tr>
<tr>
<td>4</td>
<td>50-59</td>
<td>38</td>
<td>19%</td>
</tr>
<tr>
<td>5</td>
<td>60 and above</td>
<td>09</td>
<td>4.5%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>200</td>
<td>100%</td>
</tr>
</tbody>
</table>

In the current study a significant number of cases presented with more than one lesion at a time, the 50-59 yr age group demonstrated a maximum number of such cases i.e 34 cases, followed by the age group of 40-49 yrs with 15 cases. (Table 4)

**Figure 8**

Table 4: Showing number of cases with Multiple lesions in various age groups

<table>
<thead>
<tr>
<th>S.no</th>
<th>Age range (in years)</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29 and less</td>
<td>02</td>
</tr>
<tr>
<td>2</td>
<td>30–39</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>40 – 49</td>
<td>04</td>
</tr>
<tr>
<td>4</td>
<td>50-59</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>60 and above</td>
<td>06</td>
</tr>
</tbody>
</table>

Common clinical features encountered in this study were of menstrual complaints which include, Menorrhagia, menometrorrhagia, metrorrhagia, polymenorrhoa, polymenorrhagia, utero vaginal prolapse, dysmenorrhoea in addition to these complaints vaginal discharge and urinary symptoms were also encountered. (Table 5)
Out of 120 patients found positive for metaplasia 93 (77.5\%) had received some sort of hormone replacement therapy while as 27 (22.5\%) were not on any sort of hormone replacement therapy. Out of 80 patients found negative for metaplasia only 15 (18.75\%) had received some sort of hormone replacement therapy while as 65 (81.25\%) were not on any kind of hormone replacement therapy. In the study it was also seen that the relationship between HRT and metaplasia was not significant, as all the types of metaplasias were evenly distributed among the patients taking hormones.

Out of 98 positive specimens of cervical metaplasia, 59 specimens were observed to show squamous metaplasia. The next common presentation was that of ciliated (tubal) metaplasia of the cervix in 25 specimens. Next to follow were microglandular metaplasia of the cervix 20 specimens, tuboendometroid 18 specimens and the least common was Arias Stella change seen in only 05 specimens. (Table 6a)

Out of the total of 91 positive specimens of endometrium/myometrium (hysterectomies, endometrial curettings) 26 were found positive for ciliated metaplasia. The next common presentation was that of mucinous metaplasia and eosinophilic cell change 23 cases each. Next to follow was squamous metaplasia in 03 cases and the least common was Arias Stella change of the endometrium in 01 case only. Other rare forms of metaplasia like hobnail cell metaplasia, clear cell metaplasia, cartilaginous, osseous, glial and smooth muscle metaplasia were not seen in any of the cases. (Table 6b)

Out of the total of 91 positive specimens of endometrium/myometrium (hysterectomies, endometrial curettings) 26 were found positive for ciliated metaplasia. The next common presentation was that of mucinous metaplasia and eosinophilic cell change 23 cases each. Next to follow was squamous metaplasia in 03 cases and the least common was Arias Stella change of the endometrium in 01 case only. Other rare forms of metaplasia like hobnail cell metaplasia, clear cell metaplasia, cartilaginous, osseous, glial and smooth muscle metaplasia were not seen in any of the cases. (Table 6b)

The prevalence of cervical metaplasia was maximum in age group of 50-59 for squamous, equal between 40-49 and 50-59 for ciliated and 50-59 for both microglandular and Tuboendometroid subtypes. (Table 8)
metaplasias. (Table 9)

Figure 14
Table 9: showing the Prevalence of Endometrial metaplasias in different age group.

<table>
<thead>
<tr>
<th>Age groups in years</th>
<th>Ciliated metaplasia</th>
<th>Micinous metaplasia</th>
<th>Eosinophilic metaplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>29 and below</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>30 – 39</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>40 – 49</td>
<td>10</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>50 – 59</td>
<td>13</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>60 and above</td>
<td>0</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

DISCUSSION

Genital metaplasias refer to the replacement of the normal endometrial or cervical glandular epithelium by cells that are either not encountered in the normal endometrium or cervix or, if present, are usually inconspicuous elements. Because these cells appear unusual or “atypical” and because they may line architecturally complex glands, this benign process is frequently confused with adenocarcinoma.

The present study provides an analysis of the metaplastic lesions of 200 patients who were evaluated on the basis of the histopathological findings. Metaplasias of other parts of the female genital tract like the Fallopian tubes and the vagina are very rare and were not encountered in any of the cases enrolled in the study.

Squamous metaplasia is extremely common in the cervix and should be seen as a normal phenomenon rather than an abnormal pathological process. In the present study, squamous metaplasia of the uterine cervix was found to be the commonest with a frequency of 60.2%. Similarly in the study of Auerbach and Pund 1945, this lesion was found to be commonest with the frequency of 72%. The age of presentation of this lesion is mostly in the post-menopausal and peri-menopausal period as described in the studies of Auerbach and Pund 1945, Hendrickson et al 1980 and Longrace et al 1996. In the present study also, the age of presentation of squamous metaplasia of the uterine cervix is mostly in the age group of 50-59 years (post-menopausal) with 22/59 lesions, followed by 40-49 years age group (peri-menopausal) with 16/59 cases.

In pure tubal metaplasia, the endocervical glands are lined by an epithelium that more closely resembles that of the fallopian tube and contains many more ciliated cells that are normally present in the endocervical epithelium. Similarly tuboendometroid metaplasia of the cervix is a type of metaplasia that is histologically similar to the tubal metaplasia. In this type of metaplasia the endocervical glands are lined by pseudo-stratified epithelium composed of columnar cells with a high N:C ratio. Both can be misinterpreted as adenocarcinoma in situ, but the location and shape of the glands and lack of desmoplastic or edematous stroma differentiates them from malignant glands. In the present study the frequency of ciliated (tubal) metaplasia was found to be 25.5% which is almost similar to the study of Jonasson et al 1992, in which the frequency of ciliated (tubal) metaplasia was 31%.

Similarly in this study, tuboendometroid metaplasias were seen in 18.3%, which is in accordance with the study of Ismail 1991, which shows the frequency of tuboendometroid metaplasia to be 26%. Maximum number of patients 15/25 (60%) were seen in the reproductive age group (30-49 years) replicating the studies of Ducatman et al 1993, and Jonasson et al 1992.

Although not a true metaplasia, microglandular metaplasia is best characterized with metaplasias. It is common within the cervix and is usually associated with exogenous hormone use or pregnancy and usually occurs in the reproductive age group. In the present study the frequency of microglandular metaplasia was 20.4% which lies in close range with the study findings of Brown and well 1986, in whose study its frequency was found to be 27%.

Arias Stella reaction that develops in the endocervical glands during pregnancy is identical to that which occurs in the endometrium. The Arias Stella reaction can occasionally be mistaken for clear cell carcinoma or adenocarcinoma in situ of the cervix. The Arias Stella reaction of the endocervix is usually focal and is more commonly present in the proximal portion of the endocervix. In our study we found 5 cases (5.1%) of Arias Stella reaction in the age group of 40-59 years which lie in close proximity to the results of the study of Schneider 1981, having frequency of 9% in the same age group.

Ciliated endometrial epithelial cells are a normal phenomenon, so a diagnosis of ciliated metaplasia should be made only when one or more endometrial glands are lined predominantly by ciliated cells. In our study the relative incidence of ciliated metaplasia was found to be 28.5% out of which 50% were in the reproductive age group of 29-49 years, which lies in close proximity with the studies of
Masterton et al 1975 and Suzuko et al 2005 with the relative incidence of 20% and 31% respectively.19,20

Mucinous endometrial metaplasia should be reserved for cases in which the endometrial epithelial cells are replaced by cells with abundant mucin containing cytoplasm resembling endocervical cells. Normal endometrial epithelial cells contain some intracytoplasmic mucin, so abundant mucin is required for the diagnosis. In our study the relative incidence of mucinous metaplasia of the endometrium was found to be 25.5% in which more than 60% were in the postmenopausal group (50 years and above). The findings were consistent with the studies of Suzuko et al (2005), with 26% of mucinous metaplasia in the post-menopausal group and Nucci et al (1999) in whose study 80% of the patients were in the post menopausal group.21

Eosinophilic cell change is one of the common endometrial metaplasias occurring in both non-neoplastic and neoplastic endometrium. It is characterized by the presence of epithelial cells with abundant eosinophilic cytoplasm. The cytoplasm may be granular in which case the term oncocytic metaplasia has been used. Some degree of cytoplasmic eosinophilia is commonly found in endometrial epithelial cells and does not alone warrant a diagnosis of eosinophilic metaplasia. In the present study the relative incidence of eosinophilic cell change was 25.5% with the maximum number of cases (74%) in the post-menopausal age group of 50 years and above. Suzuko et al (2005) in their study found the relative incidence of this lesion to be 28% and maximum number of cases were in the post-menopausal age group with the mean age of 56 years.

Squamous metaplasia of the endometrium may be a focal finding or it may be widespread and involve most of the endometrium. Microscopically it is composed of bland squamous cells with eosinophilic cytoplasm. Morules differ from mature squamous metaplasia in that they lack keratinization and intercellular bridges. Morules and foci of mature squamous metaplasia often co-exist. The present study found 3 cases (3.2%) of squamous metaplasia of the endometrium within the age groups of 40-49, 50-59, 60 & above years respectively, whereas Suzuko et al 2005, in their study found the frequency of the same lesion to be 7%.

Arias Stella change is almost always seen in pregnancy, trophoblastic diseases and occasionally with hormone therapy rarely there is no relation. The most important diagnostic dilemma is its differentiation from clear cell adenocarcinoma but the diagnosis of Arias Stella change is usually straightforward if there is a history of pregnancy or other morphological features of pregnancy are present. We in our study observed 1 (1.09%) case of Arias Stella change of the endometrium in 40-49 years age group, which is similar to the study findings of Suzuko et al (2005) with the frequency of 1%.

References
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