

## Tubal metaplasia and use of contraceptive methods

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### Abstract

To determine the frequency of detecting tubal metaplasia of the endocervix (TME) in cervico-vaginal cytological smears, we retrospectively reviewed 450 out of 2,371 cervico-vaginal Pap smears, selected by chance, with no glandular abnormality at the first examination [150 from women using intrauterine contraceptive device (IUD), 150 from sterilized women by bilateral tubal ligation (BTL); and 150 from women using no or other contraceptive methods]. TME was seen in 16.7% of the patients using IUD; 70.1% of the patients submitted to BTL; and 49.0% of the patients from the last group. Atypical glandular cells on cervical cytology are a problem for clinicians and pathologists alike. The differential diagnosis of endocervical glandular abnormalities including TME is discussed.

**Keywords:** Tubal metaplasia. Cervix. Cervico-vaginal smear.

### INTRODUCTION

The Bethesda System for reporting cervico-vaginal smears introduced in 1988 the diagnostic category *atypical glandular cells of undetermined significance* (AGUS) to denote a broad morphologic spectrum of cytological changes in glandular cells that exceed those typical of reactive changes but are quantitatively and/or qualitatively not diagnostic of adenocarcinoma (CHHIENG et al., 2001), including atypical endocervical repair, micro glandular endocervical hyperplasia, tubal metaplasia and adenocarcinoma *in situ* (AIS) (SELVAGGI; HAEFNER, 1997). It recommends qualifying atypical glandular cells

with regard to their possible anatomic origin: endocervical versus endometrial (KURMAN; SOLOMON, 1994). However, Papanicolaou (Pap) smear sensitivity for glandular abnormalities is not well established, ranging from 48-91% (BODDINGTON; SPRIGGS; COWDELL, 1976; COSTA; KENNY; NAIB, 1991; HURT et al., 1977; SAIGO et al., 1985). Moreover, the relative contributions to falsely positive or negative diagnoses of sampling, screening, and interpretive errors are uncertain.

Tubal metaplasia of the endocervix (TME) is a benign endocervical lesion frequently found in cone or hysterectomy specimens, but there may be confusion on Papanicolaou smears, in distinguishing tubal metaplasia from endocer-

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vical gland dysplasia. It may be even confused morphologically with glandular neoplasia in some cases. Published series and our own experience lead us to suggest that these smears will continue to present diagnostic difficulties.

The purpose of this study was to determine the frequency of detecting TME in cytological smears from women using intrauterine contraceptive device (IUD) and from sterilized women by bilateral tubal ligation (BTL).

## MATERIAL AND METHODS

To determine the frequency of detecting TME in cervico-vaginal cytological smears, in the files of the Sociedade Baiana de Citopatologia (Sobaci) collected from Paripe, Salvador, Bahia, between 1999 and 2001, we retrospectively reviewed the data bank and 450 out of 2,371 cervico-vaginal Pap smears selected by chance (150 from sterilized women by BTL; 150 from women using IUD; and 150 from women using no or other contraceptive methods). All the selected Pap smears showed no glandular abnormality at the first examination. Cytology specimens were prepared as alcohol-fixed, Pap-stained smears.

The smears were all re-screened by one cytopathologist (NMCR). The smears were scrutinized for architectural arrangement (flat sheets vs. three-dimensional clusters vs. single cells), nuclear shape (round vs. oval vs. elongate), nuclear position (basal or central), chromatin pattern (fine or coarse), the presence or absence of nucleoli, cytoplasmic features (pale vacuolated or dark granular) and the presence and frequency of ciliated cells.

Our criteria for TME were the presence of three from the following aspects: ciliar plate and ciliated cells, anisonucleosis, nuclear pleomorphism, hyperchromasy, irregular chromatin pattern, and cell superimposition.

## RESULTS

The Pap screening history was obtained from all the patients. Women who had a bilateral tubal ligation (BTL) were compared with those who did not have this form of birth control.

### Clinical features

The age of the patients were 54.8% between 31-45 years old; 42% between 16-30; 11.8% >50; and 0.9% <15. Sixty three percent of the patients were asymptomatic. The most common complaint was dyspareunia. Thirty-four patients were postmenopausal (55%), and 5 patients were in hormonal replacement therapy. The number of pregnancies related by the patients were: 0 in 6%; 1-3 in 55%; 4-6 in 27%, more than 6 in 10% (ignored in 2%).

The contraceptive methods used were: BTL in 36% of the patients; IUD in 25% of the patients; other methods in 25% of the patients; and ignored in 11% of the patients. No follow-up was available. None had repeated cervico-vaginal smears or had undergone biopsy.

### Cytological findings

Of the smears reviewed, a number of 85 (18.9%) cases were excluded because no endocervical cells were noted in the smears. Of the 365 cases analyzed, none showed squamous abnormalities, but 169 (46%) showed cytological features consistent with TME.

TME in smears showed groups and strips of glandular cells with nuclear pseudo-stratification. Cervical cytology smears exhibited (TABLE 1; FIGURES 1, 2) low to high overall glandular cellularity. Crowded sheets of columnar cells were frequently observed. The cells edges of these tissue fragments usually retained their cytoplasm, yielding a relatively smooth border to the edges of the sheets. Cytoplasm was thin or moderately dense and uniformly cyanophilic as compared to the pale cytoplasmic stain-

ing of normal mucinous endocervical cells. Nuclei were moderately enlarged, round to oval and broad, and were typically polarized to the basal portions of the cells, with regular contours. Nuclei also occasionally exhibited slight to moderate anisonucleosis with increased N/C ratios, particularly when glandular groups were viewed en face. Chromatin was finely to moderately granular. Tiny inconspicuous nucleoli were seen in some cases. Apical terminal bars with cilia were characteristically present. Cilia were identified in many cases. They were frequently observed in planes of focus above or below those of the nuclei of the same cells. In cases where cilia were poorly preserved as a result of artifactual drying or clumping, the cells consistently retained a sharp, flat, somewhat thickened apical border, and the nuclei maintained a basilar location in the cells. Flat, honeycombed sheets with relatively evenly spaced nuclei were frequently seen in tubal metaplasia. Isolated strips of cells were infrequent, and rosettes were rare. Single cells were relatively numerous in several cases. Grooves and haloes were absent.

TME was seen in 21 (16.7%) out of 126 patients using IUD; 103 (70.1%) out of 147 patients submitted to BTL; and 45 (49.0%) out of 92 patients using no or other contraceptive methods.

## DISCUSSION

Glandular abnormalities of the uterine cervix are well known to be a particularly challenging area in cervical cytology. New patterns of cellular presentation on cervical smears have become more frequent since the introduction of new sampling devices, which provide increased material from the upper portions of the endocervical canal. The normal histologic variability of the endocervical canal, as well as the presence of TME, infectious and inflammatory reactions, squamous lesions involving endocervical glands, and true endocervical neoplastic lesions in these areas, have presented the cytol-

Table 1- Summary of cytology features for TME

Cytologic feature	Tubal metaplasia
Feathered edges	Infrequent, focal
Isolated strips	Absent to few
Single cells	Few to many
Terminal bars/cilia	Present
Cell shapes	Columnar
Cytoplasmic features	Thin or moderately dense, uniform, cyanophilic Abundant, pale, vacuolated to dark: 98.8%
Nuclei	Enlarged, oval and broad, evenly spaced, polarized to cell base Slight to moderate anisonucleosis in 93.1% Nuclear pleomorphism in 95.8%
Chromatin pattern	Fine to moderate, even granularity Irregular: finely-coarsely granular in 11.1% Hyperchromatic: finely-coarsely granular in 76.7%
Ciliar plate	In 78.3%
Ciliated cells	In 29.1%

gist with a variety of cellular appearances which may cause difficulties in differential diagnosis, sometimes turning the assessment of neoplastic disease in gynaecological histopathology a difficult task (COMER et al., 1999). Recognition of these entities, their cytologic manifestations and the effects of increased high endocervical sampling will allow the cytologist to begin the process of gaining the experience necessary to assess these new cellular patterns.

TME refers to the replacement of endometrial or endocervical glandular epithelium by benign ciliated columnar epithelium resembling normal fallopian tube epithelium. However, recapitulating normal uterine tube epithelium, two cell types should be also considered in addition to ciliated cells

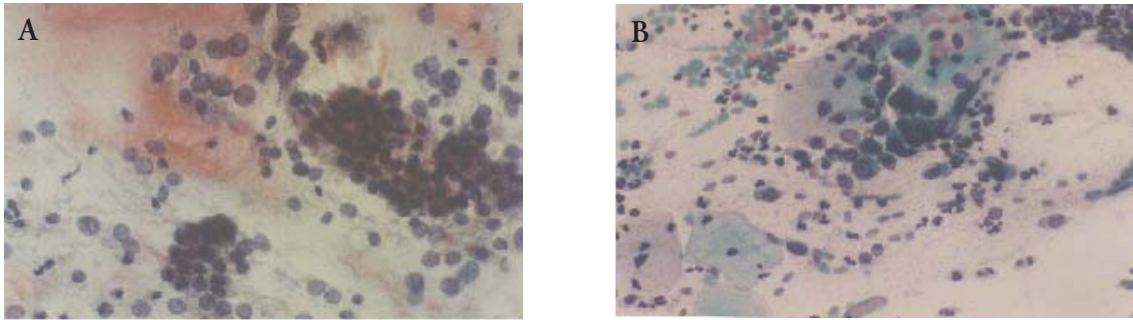


Figure 1 - Tubal metaplasia

- (A) Fragment of crowded columnar cells exhibiting slightly enlarged, relatively uniform, moderately hyperchromatic nuclei (Papanicolaou stain, x500).  
 (B) Group of glandular cells containing enlarged and hyperchromatic nuclei with moderately granular chromatin and inconspicuous nucleoli. Some cells show ciliar plate (Papanicolaou stain, x400).

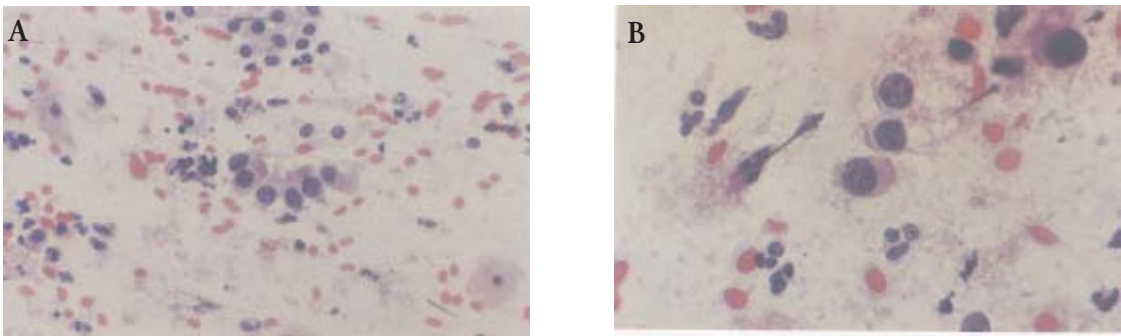


Figure 2 - Tubal metaplasia

- (A) Cluster of tubal metaplasia showing cells with poorly preserved cilia, but the cells have retained their cytoplasm and have basilar nuclei (Papanicolaou stain, x500).  
 (B) Individual dispersed cells of tubal metaplasia containing oval, broad nuclei that are polarized to the bases of the cells. Chromatin is finely to moderately granular. Nucleoli are inconspicuous. Note the well-preserved apical terminal bars and cilia (Papanicolaou stain, x800).

(MARQUES; ANDRADE, 1997), endocervical secretory (non-ciliated) cells, and peg (intercalary) cells (cells with dark and granular scanty cytoplasm and dark-staining, elongate or triangular-shaped nuclei). Ciliated cells are infrequent in normal endocervical epithelium but common in TME (COLEMAN; EVANS, 1988). Secretory cells in TME have a more granular cytoplasm and variably placed nuclei than normal endocervical cells. Peg cells are found only in TME (DUCATMAN et al., 1993). When all three types of cells were observed, some authors considered TME to be present. TME also includes cohesive groups of streaming spindle nuclei with haloes, grooves, tapered ends, and wrinkled contours.

TME may be confused with endocervical gland dysplasia (EGD) and with AIS on Pap

smears. In spite of being observed in the higher parts of the endocervix, TM was also detected in the lower segment, where the differential diagnosis with AIS is important (MARQUES; ANDRADE, 1997). In spite of that, it possibly has no malignant potential (SCHLESINGER; SILVERBERG, 1999). With a better understanding of the diagnostic criteria for TME, EGD may be distinguished from these entities, thus preventing unnecessary intervention (VAN LE; NOVOTNY; DOTTERS, 1991). Terminal bars and cilia are the most helpful features in the cytologic recognition of TME and its distinction from EGD and AIS (TRANBALOC, 2002). Other cytologic criteria include a paucity of rosettes and crowded cellular sheets with frayed edges, the presence of relatively evenly spaced oval broad nuclei with less distinct and less

densely dispersed chromatin, and absent or rare mitoses (NOVOTNY et al., 1992). In recent years, an increasing number of cases in which TME not only coexists with AIS, but also possesses atypia with transitions between ordinary TME, atypical TME, and AIS with residual tubal morphology have been largely reviewed by the authors in consultation materials. It cannot be assumed that all ciliated tubal epithelium in the cervix is benign and possesses no premalignant potential. The relationship of atypical TME (dysplasia) to tubal-type AIS must be defined, and the latter pattern should be added to the known types of differentiation of cervical AIS (SCHLESINGER; SILVERBERG, 1999). In retrospect, differential diagnosis with AIS is possible in most cases if diagnostic criteria are strictly applied. Indeed, contrary to AIS, feathering is often restricted to one end of the crowded sheets. Moreover, none of these crowded sheets contain glandular openings, and strips and rosettes with pseudostratification are absent (DRIJKONINGEN; MEERTENS; LAUWERYNS, 1996).

There is a need to identify specific tissue markers for TME, which can be applied in routine histopathological practice. Immunohistochemically, TME is positive for vimentin in 78% of cases, and only in 39% for CEA (MARQUES; ANDRADE; VASSALLO, 1996). The clinical potential of a monoclonal antibody LhS28 was demonstrated (COMER et al., 1999) for identifying metaplasia of tubal type and in distinguishing TME from low-grade cervical glandular intraepithelial neoplasia.

In addition to the diagnostic problems inherently associated with TME, our findings showed that the use of IUD caused less TME than the use of other contraceptive methods. On the contrary, the patients submitted to BTL showed in this study a high frequency of TME.

Clinicians and cytologists incompletely or inaccurately know the cytological modifications due to IUDs. IUDs of all types bring about a modification of the maturation index, and particularly of the estrogenic index, which, throughout the cycle, appears to be lower than that of a control group. Presently, there is no

sign of any carcinogenic role played by IUDs (SAUREL et al., 1982). Moreover, the use of an IUD does not increase the incidence of squamous intraepithelial lesions, but inflammatory alterations have been seen more frequently in women with IUD than in the controls. Any abnormal Pap smear in an IUD user should be first repeated after local vaginal treatment, if only to temporarily palliate the inflammatory cellular reaction, which impedes unequivocal interpretation of the routine Pap smear (KAPLAN et al., 1998).

BTL has become one of the most frequently performed surgical procedures, and estimates suggest that over 50 percent of all women will undergo surgical sterilization by age 45 (COHEN; ROOS, 1986). Preventive health procedures such as Pap tests are often performed when women visit physicians for family planning and obstetric care. Since women do not visit physicians for these reasons following BTL, the proportion of women receiving Pap tests fell in the years after surgery for the BTL women. The reasons for this decline in testing were a decline in the number of visits for gynecologic and obstetric reasons and a decline in testing because of high rates of "screening" prior to surgery (COHEN; ROOS, 1986). Women who have had a BTL should be considered at high risk because of poor screening compliance (WINKLER et al., 1999), in spite of that a small decrease in risk is observed during the first 5 postoperative years (LI; THOMAS, 2000). BTL probably provides an opportunity for secondary prevention of cervical cancer. Anyway, it is recommendable continued annual Pap screening for women who are submitted to BTL.

Familiarity with the cytologic criteria for the diagnosis of TME on cervical smears and features of AIS and EGD that distinguish these lesions from TME and other potential mimics is essential. It can, therefore, be concluded that atypical glandular cells on cervical cytology are a problem for clinicians and pathologists alike, but the responsibility for the diagnosis of these lesions lies on surgical pathologists and cytopathologists.

## *Metaplasia tubária e uso de métodos contraceptivos*

### **Resumo**

*Para determinar a frequência de detecção de metaplasia tubária endocervical (MTE) em esfregaços citológicos cérvico-vaginais, foram revistos retrospectivamente 450 escolhidos ao acaso de 2.371 esfregaços cérvico-vaginais Pap, sem anormalidades glandulares no primeiro exame — 150 de mulheres usando dispositivo intra-uterino (DIU); 150 de mulheres esterilizadas por laqueadura tubária bilateral (LTB); e 150 de mulheres usando nenhum ou outros métodos contraceptivos. MTE foi constatada em 16,7% das pacientes usando DIU; 70,1% das pacientes submetidas a LTB; e 49,0% das pacientes do último grupo. Células glandulares atípicas em citologia cervical são um problema tanto para clínicos quanto para patologistas. O diagnóstico diferencial de anormalidades glandulares endocervicais, incluindo MTE, é discutido.*

**Palavras-chave:** *Metaplasia tubária. Cérvix. Esfregaço cérvico-vaginal.*

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