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Microplicae-like structures of the fallopian tube in postmenopausal women as shown by electron microscopy

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Summary. Female reproductive aging is associated with several morphological changes of the genital tract with a subsequent decline in fertility; however, ultrastructural changes occurring after menopause have still not been well illustrated. Our aim was to characterize the three-dimensional microanatomy of the luminal surface of the human fallopian tube in perimenopause and postmenopause. Twenty bioptic samples of fallopian tubes were obtained after surgery under the informed consent of the patients. Samples were processed for transmission electron microscopy (TEM) and field-emission scanning electron microscopy (FE-SEM). As age increases the surface epithelium of the fallopian tube appeared somewhat flattened. Correlated TEM/FE-SEM observations showed gradual shortening of microvilli and deciliation. The most interesting finding was the gradual formation of microplicae-like structures on the surface epithelium, particularly from late perimenopause to postmenopause. Microplicae-like structures, associated with other regressive changes, represent an important adaptation of the epithelium of the fallopian tube; these are likely induced by the physiological process of aging, thus better withstanding hormonal changes associated with the advent of the menopause.

Key words: Endosalpinx, Fallopian tube, Menopause, Electron microscopy, Microplicae

Introduction

The life of a woman is invariably bound to reproductive milestones, one of which is represented by menopause. Studies on the microarchitecture of the human fallopian tube generally focus on the fertile period and are carried out using mostly two dimensional techniques such as light microscopy and transmission electron microscopy (TEM) with respect to three-dimensional approaches such as scanning electron microscopy (SEM). Ultrastructural changes of the human fallopian tube after menopause are still poorly understood and correlated TEM-SEM studies are scarce (Gaddum-Rosse et al., 1975; Orlandini and Pacini, 1978; Amso et al., 1994; Crow et al., 1994). Lately, with the pioneering leadership of Pietro M. Motta (1942-2002), our group has been involved in the analysis of the morphological changes of the female reproductive tract after menopause using field-emission SEM (FE-SEM) and TEM (Makabe et al., 1998; Motta et al., 2002; Motta and Makabe, 2003; Heyn et al., 2005). This report evaluates systematically the ultrastructural and three dimensional (3-D) changes that take place in the epithelium of the human fallopian tube during perimenopause and postmenopause with the aid of correlated FE-SEM and TEM. In particular, our original study illustrates in detail the formation of microplicae-like structures on the surface of the endosalpinx.

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Material and methods

Samples of fallopian tubes, mostly from the ampullae, belonging to 10 perimenopausal and postmenopausal women (48 to 69 years old), with no history of pelvic inflammatory disease, obtained at the time of surgery (hysterosalpingectomy or salpingectomy), were used for this study after the informed consent of the patients. Patients were not submitted to any hormonal therapy and were classified according to Soules et al. (2001) in early perimenopause (n=2); late perimenopause (n=2); early postmenopause (n= 3) or late postmenopause (n=3). Table 1 shows the distribution, age and histopathological findings of the patients. This study has been approved by the local

Ethics Committee of the Department of Anatomy, University of Rome "La Sapienza".

Specimens were fixed by immersion in a solution of 2.5% glutaraldehyde in 0.1M phosphate buffer saline (PBS, pH 7.4), and stored at 4°C for a minimum of 48 h. Samples were conductive stained with 1% tannic acid, postfixed in 1% osmium tetroxide in 0.1M PBS (pH 7.4), then dehydrated in increasing concentrations of ethanol and divided in pieces that were processed for TEM and FE-SEM.

Samples processed for TEM were embedded in Epon. Semi-thin (1 µm in thickness) and thin (0.12 µm in thickness) sections were obtained by means of an ultramicrotome (Reichert-Jung Ultracut E, Vienna, Austria). The former were stained with methylene blue and then checked for their general histological conditions. Ultrathin sections were mounted on copper grids, contrasted with lead citrate and uranyl acetate and finally observed with a Zeiss M10 TEM.

Specimens prepared for FE-SEM were critical point dried with carbon dioxide (EMITECH K850 Critical Point Dryer, Ashford, UK or Balzers Union CPD 020, Liechtenstein), mounted on aluminum stubs and metal coated with 3 nm of platinum (EMITECH K550 Sputter Coater, Ashford, UK or Ion-Sputter Coater E-1030 Hitachi, Japan). Samples were finally observed with either a Hitachi S-4000 FE-SEM or a Hitachi S-4500 FE-SEM, both operating at accelerating voltages of 7-15 kV.

The following ultrastructural parameters were considered for the analysis of the fallopian tube: general surface microanatomy (presence and shape of microvilli and cilia; presence of apical protrusions, blebs or any sign of secretion; definition of the intercellular limits); epithelial features (continuity; general cell height; cytoplasmic features; nuclear shape and electron density).

Results

Taking into consideration that distinct surface morphologies usually appear within adjacent tissue areas of a single sample, our findings are described according to the most representative pattern for each reproductive stage.

Early perimenopause

At low magnification by FE-SEM and TEM the lining epithelium is simple columnar and is composed of dome-shaped cells of which there are rather scarce ciliated cells and numerous non ciliated cells (Figs. 1, 2A). The latter exhibit somewhat shortened microvilli (Figs. 1, 2A) and occasionally show a central and single cilium. Cell limits are well identified through surface overviews performed by FE-SEM (Fig. 1). When seen by TEM the epithelial cells' nuclei are pale and often show prominent nucleoli (Fig. 2A). The cytoplasm of both ciliated and microvillous cells contains electron lucid vesicles (Fig. 2A) usually in a supranuclear location. In addition pleomorphic mitochondria, short cisternae of the rough endoplasmic reticulum and some electron dense granules were also observed (Fig. 2B). Ciliated cells evidence mature cilia with striated rootlets (Fig. 2B) composed only of the striated conical parts.

In some samples, a gradual process of deciliation begins to be evident. Apoptotic and degenerated cells are rarely observed among epithelial cells; these are mainly recognized by their more condensed nuclei and by the presence of myelin figures or membrane whorls in the cytoplasm.

Late perimenopause

Non ciliated epithelial cells with a smooth, rather concave surface, are sometimes observed in the endosalpinx by FE-SEM (Fig. 3). If seen at a higher magnification almost nude apical cell areas correspond to transitional cell apexes that contain scattered and stubbed microvilli on one side and knobby microvilli on the other side (Fig. 3). Cell outlines are generally cobblestoned or polyhedral. The epithelium of the endosalpinx may sometimes appear disarranged when observed by TEM: columnar cells arrange tightly packed in a way that compresses both the cytoplasm and nucleus of adjacent cells, thus dislocating them to different levels within the epithelium, giving the appearance of pseudostratification (Fig. 4). The cytoplasm of epithelial cells contain mostly the same organelles (Fig. 4) already described in the previous stage. By TEM the most apical parts of some epithelial cells appear bulging into the lumen, a feature that probably precedes cellular extrusion into the lumen (Fig. 4). In fact, fragments of cytoplasm, likely belonging to ciliated cells, may sometimes appear within the tube lumen.

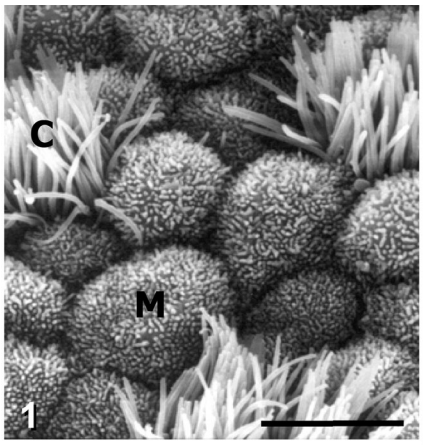
Early postmenopause

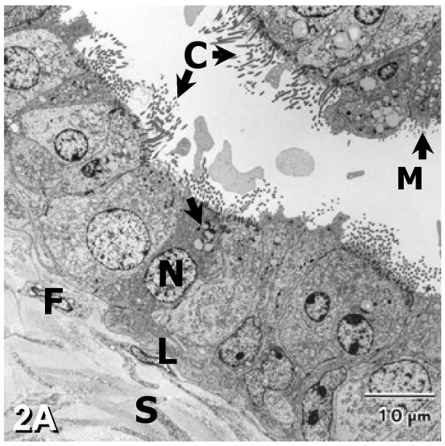
A higher degree of morphological heterogeneity of the endosalpinx epithelium is revealed during this stage.

Table 1. Patients information.

AGE (y)	REPRODUCTIVE STAGE*	HISTOPATHOLOGY
48	Early perimenopause	Uterine fibroma
49	Early perimenopause	Uterine fibroma
50	Late perimenopause	Uterine fibroma
53	Late perimenopause	Endometrial hyperplasia
55	Early postmenopause	n.d.
55	Early postmenopause	Uterine fibroma
56	Early postmenopause	n.d.
61	Late postmenopause	Uterine carcinoma
67	Late postmenopause	n.d.
69	Late postmenopause	Uterine fibroma

* On the basis of Soules et al. (2001). n.d.: unknown





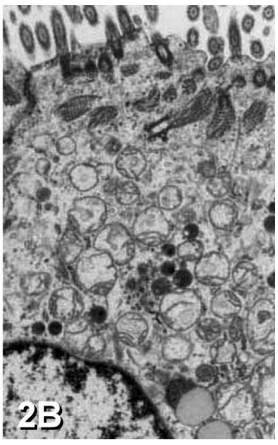
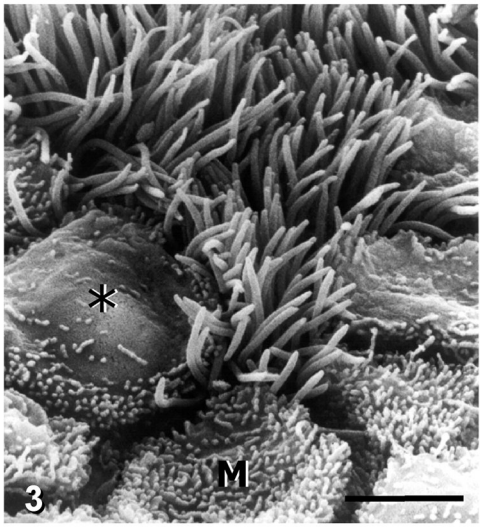


Fig. 1. Early perimenopause. The endosalpinx is composed of ciliated (C) and microvillous (M) cells. The latter show shortened microvilli. SEM, original magnification, x 2,500. Bar: 7.20 µm.



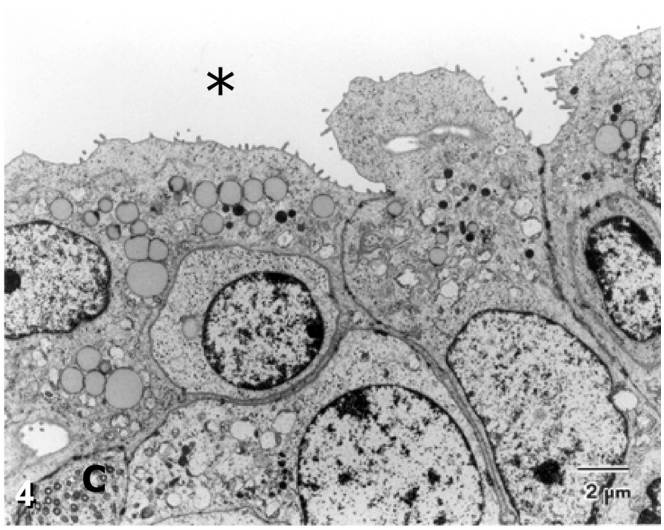
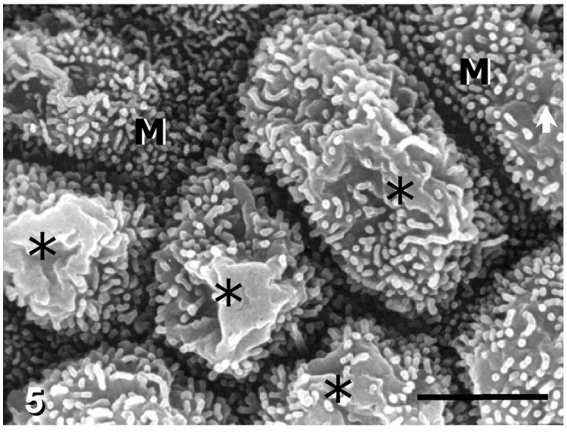


Fig. 2. Early perimenopause. **A.** The surface epithelium of the fallopian tube shows ciliated (C plus arrows) and microvillous cells. Shortened microvilli are clearly seen in some areas (M plus arrow). Note pale nuclei (N) with usually prominent nucleoli. The arrow indicates supranuclear electron lucent vesicles. The basal lamina (L) appears somewhat irregular but continuous. The stroma (S) shows mainly fibrocytes (F) and collagen fibers. TEM. Bar: 10.00 µm. **B.** A higher magnification shows the apical portion of the cytoplasm of a ciliated cell. Pleomorphic mitochondria, free ribosomes and supranuclear electron dense granules are observed. Note the striated rootlets of the cilia. TEM, x 4,000.



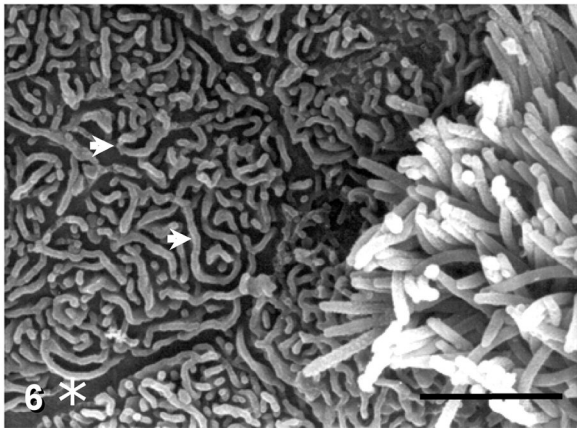


Fig. 3. Late perimenopause. Morphological heterogeneity is illustrated. Some epithelial cells of the tube are in a transitional stage with their surface covered by cilia and irregular knobby microvilli (M); others reveal apical areas covered by knobby microvilli or appear rather nude, almost smooth surfaced (asterisk). SEM, original magnification, x 4,000. Bar: 4.50 µm.

Fig. 4. Late perimenopause. Note the presence of few ciliated cells (cross-sectioned, C). The surface epithelium appears somewhat disarranged and the apical portions of some epithelial cells protrude into the tubal lumen (asterisk). The latter feature corresponds to the incipient formation of microplicae-like structures. TEM. Bar: 2.00 µm.

Fig. 5. Early postmenopause. Incipient formation of microplicae-like structures. Large cell expansions (asterisks) as well as curved and short microvilli (M) are confluent to form the new structures. The absence of ciliated cells in this area of tissue and the presence of shortened microvilli make cellular limits clearer. SEM, original magnification, x 5,000. Bar: 3.60 µm.

Fig. 6. Early postmenopause. Microvilli tend to adopt twisted or bent shapes, exposing typical areas on the surface of the epithelial cells with incipient formation of microplicae-like structures (arrows), giving the cell surface a labirynthine shape. Some ciliated cells are still present (right). The asterisk indicates intercellular limits. SEM, original magnification, x 3,000. Bar: 3.00 µm.

Areas of the mucosa devoid of cilia show epithelial cells covered by knobby and bent microvilli which appear by FE-SEM as fused to form thick and irregular apical membrane specializations (Fig. 5). The main morphological feature is undoubtedly represented by the conspicuous presence of incipient microplicae-like structures on the cell surface (Fig. 6). These originate from gradual bending, twisting, massive fusion and subsequent remodeling of apical surface specializations such as knobby microvilli, blebs and large cytoplasmic extensions, giving the whole surface a typical convoluted shape (Fig. 6). The surface epithelium is simple columnar to cuboidal. No mitotic activity is observed. The cytoplasm of epithelial cells contains electron lucent vesicles, small electron dense granules, few mitochondria and rare cisternae of the endoplasmic reticulum. The nuclei appear pale and sometimes show central nucleoli. Junction complex areas are seen in between adjacent cells (Fig. 7).

Late postmenopause

Membrane specializations, corresponding to microplicae-like structures, are generally widely identified by FE-SEM on the apical surface of the epithelial cells. Few ciliated cells and cells with rare knobby microvilli still remain in some areas of the mucosa (Fig. 8). Microplicae-like structures show by FE-SEM different and characteristic patterns of arrangement: labirynthic, parallel arrays or irregular and dense profiles (Figs. 9-11). The epithelium appears by TEM mainly consisting of cuboidal cells and rarely shows knobby microvilli. The nuclei are pale and occasionally show a dense nucleolus (Fig. 12). Cell membranes of neighboring cells interdigitate (Fig. 12).

As also occurs in preceding stages, the epithelial basal lamina is continuous with a somewhat loopy course.

Discussion

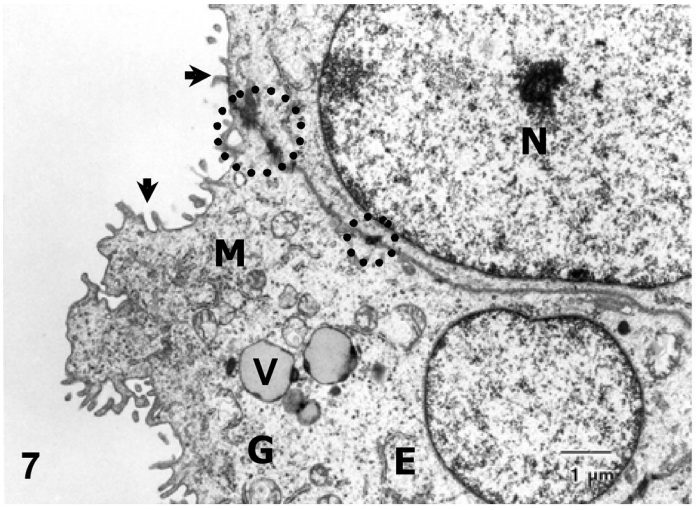
General TEM and FE-SEM results

To our knowledge, this is the first systematic study that approaches the ultrastructural analysis of the human endosalpinx cell surface in perimenopause and postmenopause by both TEM and FE-SEM.

The FE-SEM analysis of the human fallopian tube epithelium shows general morphological features of age-related changes such as shortening of microvilli and gradual deciliation if compared with cells of the epithelium in fertile age (Verhage et al., 1979; Jansen, 1984; Motta and Makabe, 2003). These phenomena imply an impairment of secretory activity as a consequence of the aging processes. Although similar changes have been reported in the bitch (Myers et al., 1984) and in the woman (Ferenczy et al., 1972; Gaddum-Rosse et al., 1975; Orlandini and Pacini, 1978; Crow et al., 1994) using SEM, most studies do not offer any information on the presence of microplicae-like structures. This discrepancy may be attributed to differences in the clinical setting of the patients and to the heterogeneity of surface features in single samples. In particular, Orlandini and Pacini (1978) observed just one perimenopausal and two postmenopausal patients so it is possible that they did not include advanced stages and, consequently, there was probably no chance to observe microplicae-like structures. In a similar way, Gaddum-Rosse et al. (1975) observed only two untreated perimenopausal patients and showed a decrease in surface ciliated cells. Crow et al. (1994), in turn, observed only one patient who was in an inactive histological phase of the cycle (classified by them as perimenopause). This single sample showed a predominance of non-ciliated cells with short and sparse microvilli and absence of secretory granules. According to what was observed at this stage of perimenopause, our FE-SEM observations demonstrate a prevalence of microvillous cells and deciliation, whereas microplicae-like structure are rarely found. Ferenczy et al. (1972) did not refer to the total number of postmenopausal patients observed, simply limiting their description to "patients aged 30 years or more" and illustrated only one by low magnification SEM image.

Our most striking and original finding is undoubtedly the microplicae-like structures that are gradually formed on the mucosal surface of the tube from the perimenopause on. Figure 13 illustrates our hypothesis on the dynamics of microplicae-like structures' formation in the epithelium of the human endosalpinx: presence of ciliated and microvillous cells in perimenopause; transitional stages and partial deciliation in early postmenopause; and complete deciliation, with irregular surface arrays and loopy basal lamina in late postmenopause.

The TEM analysis shows general age-related features such as slight epithelial flattening and regressive cytoplasmic changes, some of which already reported in the literature (Amso et al., 1994; Crow et al., 1994). In particular, the perimenopausal cases studied by Crow et al. (1994) showed little evidence of secretory activity such as the presence of a lower number of flattened domes. Ribosomes, Golgi apparatus and glycogen particles, in turn, are interpreted by these authors as indicative of continued cellular activity. Our observations are in agreement with the above features detected in perimenopause but also support a progressive dedifferentiation of both nuclear and cytoplasmic patterns towards the transition from the stage of perimenopause to early postmenopause and late postmenopause. In addition, in our studies it is interesting to note that, even if perimenopausal and postmenopausal ovaries may show epithelial cells with evident morphological signs of apoptosis (Motta et al., 2002; Motta and Makabe, 2003), this phenomenon was not frequently observed in the tube. In our opinion, the general epithelial microstructural pattern may be rather interpreted to be more similar to a dedifferentiation



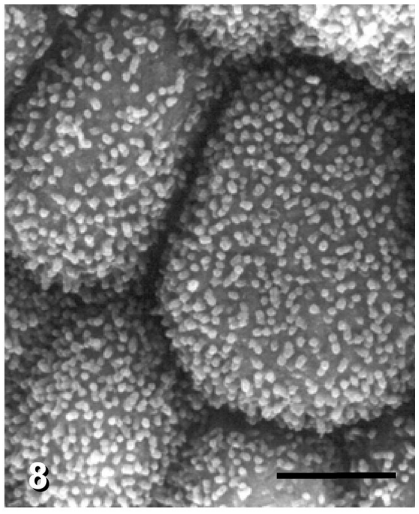
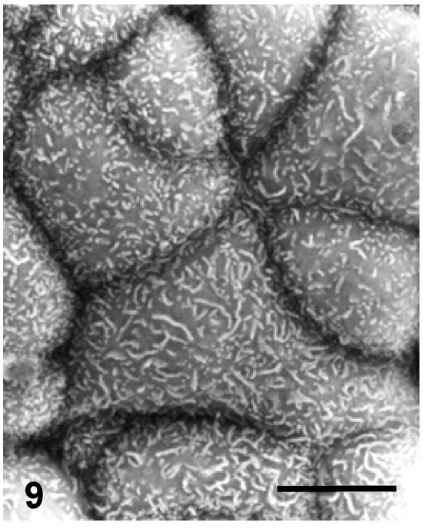


Fig. 7. Early postmenopause. High magnification of two epithelial cells with rare shortened microvilli (arrows) and the incipient formation of microplicae-like structures. The cytoplasm contains electron lucent vesicles (V), electron dense granules (G), few mitochondria (M) and rare cisternae of the endoplasmic reticulum (E). The nuclei appear pale and one of them shows a central nucleolus (N). Junction complex areas are seen in between both cells (dotted areas). TEM. Bar: 1.00 µm.



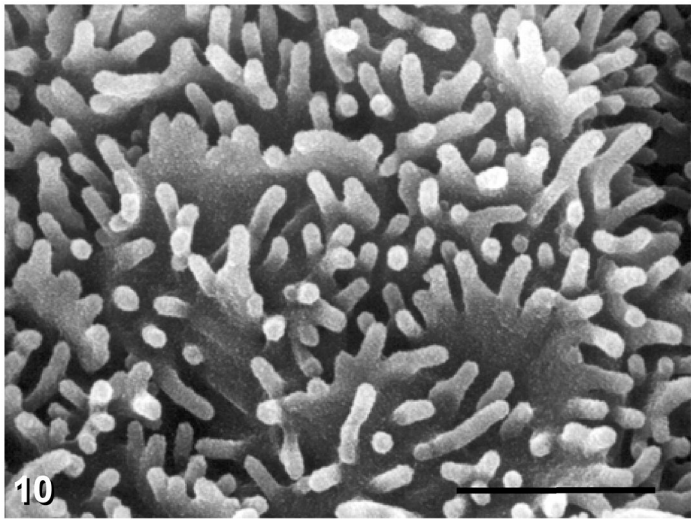
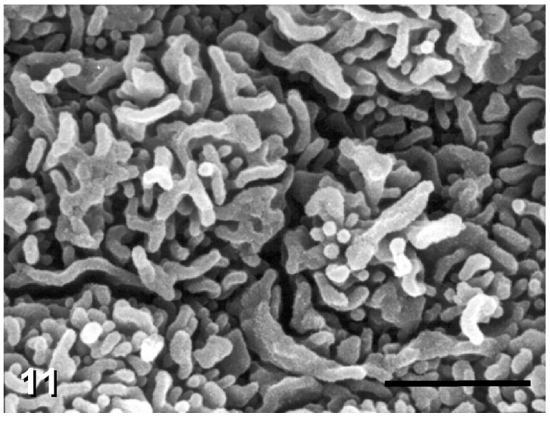


Fig. 8. Late postmenopause. Epithelial cells are covered only by knobby microvilli. Cellular limits are well defined. SEM, original magnification, x 5,000. Bar: 4.50 µm.

Fig. 9. Late postmenopause. The surface of the endosalpinx shows a labirynthine pattern. Microvilli or cilia are not identified anymore. Cellular outlines are polyhedral. SEM, original magnification, x 5,000. Bar: 10.00 µm.



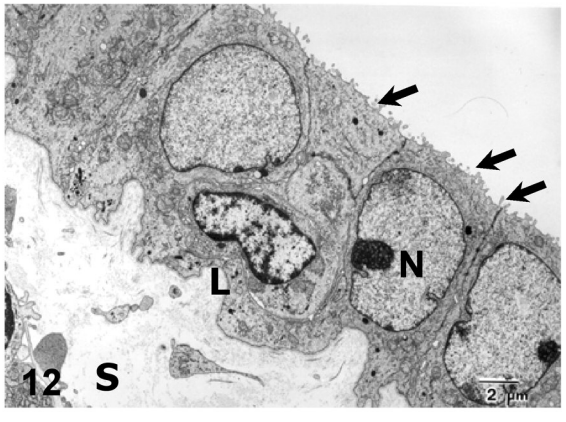


Fig. 10. Late postmenopause. Typical microplicae-like structures form due to twisting, bending and fusion of microvilli and/or other wide cell surface extensions. SEM, original magnification, x 13,000. Bar: 1.38 µm.

Fig. 11. Late postmenopause. Note the absence of cilia; only distorted cell surface extensions fuse to form microplicae-like structures (advanced stage). The apical parts of the epithelial cells show very irregular and dense arrays that do not allow identification of clear cellular limits. SEM, original magnification, x 7,000. Bar: 1.80 µm.

Fig. 12. Late postmenopause. The epithelium appears cubic and shows rare knobby microvilli (arrows). The nuclei are pale; one of them shows a dense nucleolus (N). Cell membranes of neighboring cells interdigitate. The basal lamina (L) is continuous and has a loopy shape that allows portions of the cytoplasm of epithelial cells to make prominence into the subjacent stroma (S). TEM. Bar: 2.00 µm.

process. In addition, the occasional finding of pseudostratification of the epithelium in perimenopause has also been reported by Crow et al. (1994) in a patient two years after menopause and under hormonal replacement therapy, and reminds us the morphodynamics of the fallopian tube differentiation during human fetal development (Barberini et al., 1994), further supporting the idea of regressing or dedifferentiating changes.

Surface microplicae: their significance

Our group is the first one that describes the formation of microplicae-like structures in the woman's genital tract after menopause (Makabe et al., 1998; Motta and Makabe, 2003; Heyn et al., 2005). Microplicae, also termed microridges, microvillar ridges or cytoplasmic folds, are membrane specializations that follow straight or winding paths, often thick and branched, and exhibit a wide variety of characteristic patterns over the apical surfaces of epithelial cells (Andrews, 1976). Typical microplicae generally appear on the surface of differentiated cells that are exposed to the external environment and to periodic abrasive effects (Motta et al., 1977) such as stratified squamous epithelia, i.e. cornea, pharynx, esophagus, ectocervix, vagina and vulva (Andrews, 1976; Sperry and Wassersug, 1976; Motta et al., 1977; Barberini et al., 1991, 1994, 1998; Sargeant et al., 1996). Andrews (1976), when referring to typical microplicae, suggested that they may represent the modified remodeled expression of microvillous like extensions. It is very interesting to note that the above epithelia are generally stratified and squamous and that microplicae are a surface specialization of more superficial and very flattened cells. Similar structures have been also described in quite different anatomical places such as intercalated cells of the kidney (Fawcett, 1994) and gill chloride cells of fishes (Perry, 1997; Stoffel et al., 2000). Microplicae in general enhance epithelial cell cohesion (Saito and Ito, 1993; Stoffel et al., 2000), contribute to increase the overall cell surface and junctional area and may be an indicator of the degree of squamous maturation of the epithelial cells (Miles, 1982).

Our comparative FE-SEM and TEM observations show that in human menopausal endosalpinx, microplicae are associated with columnar or cuboidal epithelial cells with cytoplasmic features of stem cells. In our opinion, microplicae-like structures, such as those observed in the fallopian tube, may be involved in a dedifferentiation process associated with cytoplasmic changes comprised within the physiological and morphological adaptation of epithelial cells to aging. Therefore, their presence should not be misinterpreted as a sign of inflammation or neoplasia. We have noted that these structures generally appear as patches in areas of the mucosa that show normal epithelial features. Whether the remarkable remodeling of the surface microanatomy of the tube after menopause will lead to

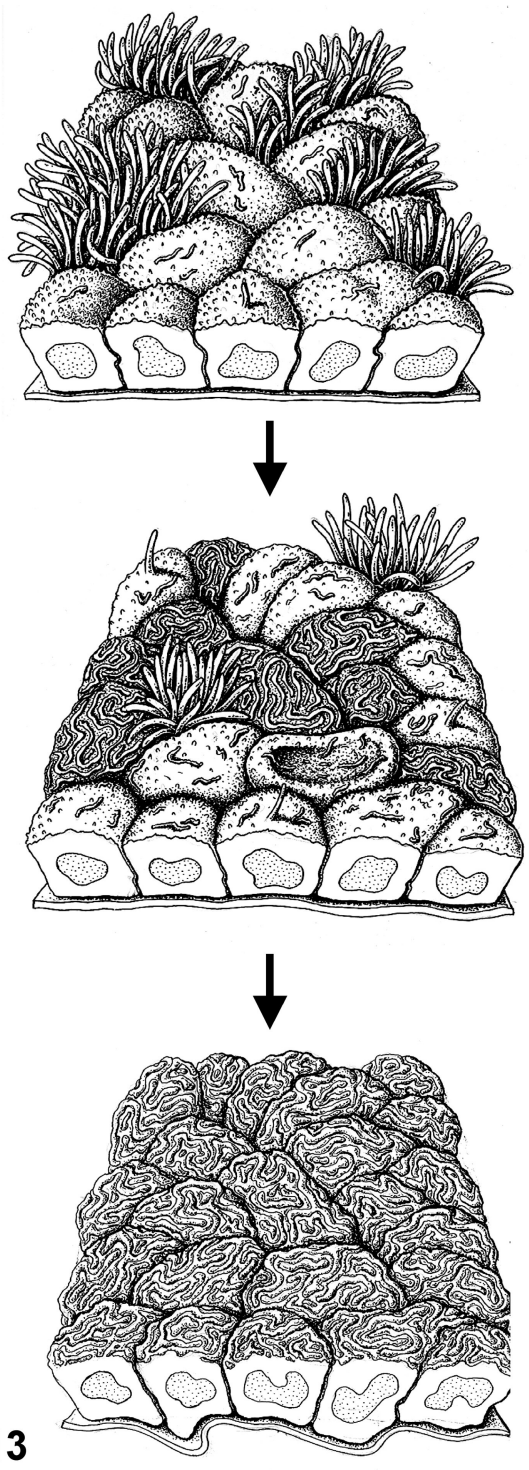


Fig. 13. Schematic representation of microplicae-like structures formation in the human endosalpinx surface. Perimenopause (top); early postmenopause (center); late postmenopause (bottom). There is a gradual process of deciliation. Microvilli shorten and other wide cell surface extensions twist, bend and finally fuse with each other thus forming irregular arrays of structures with complex parallel/labirynthine patterns like microplicae structure. Note the typical loopy shape of the basal lamina in the last stage (bottom).

metaplastic, dysplastic or neoplastic phenomena as reported in other tissues (Vijayakumar et al., 1999; Slak, 2000), up until now is not known. The occasional presence of rather concave, almost nude and smoother surfaces in some epithelial cell apexes likely argues towards transitional morphological stages between shortening of microvilli and the formation of microplicae-like structures.

Ultrastructural morphology and aging

During the reproductive life cyclic changes are observed in both ciliated (ciliation and ciliar activity) and non ciliated secretory cells of the tubal epithelium and these are strictly related to steroidogenesis (Donnez et al., 1983, 1985; Jansen, 1984). Similarly, differences in the microanatomy of the endosalpinx epithelium during perimenopause and postmenopause should also be attributed to qualitative and quantitative changes in hormonal profiles, particularly steroids (Gaddum-Rosse et al., 1975; Donnez et al., 1983; Crow et al., 1994). Interestingly, a sort of dysynchrony appears to exist between steroid receptor profiles in the tube, detected several years after the final menstrual period, and the presence of a morphologically atrophied tube (Punnonen and Lukola, 1981). In fact, signs of cellular metabolic activity, as deduced by the organelles present in the cytoplasm, may still remain in some postmenopausal women. It is likely that the aging process initially affects more the uterus and the tube if compared to the ovary (Kurjak and Kupesic, 1995). Shortening of microvilli and reduction in number of ciliated cells until complete deciliation and microplicae-like structure formation are all involutional processes, varying from one woman to another, that can last even twenty or thirty years after the final menstrual period. Moreover, the fine morphodynamic changes taking place in the remodeling of the human endosalpinx epithelium after menopause are to be considered a gradual and very dynamic process (Orlandini and Pacini, 1978; Crow et al., 1994). We can even think about endosalpingeal subcellular domains that adopt different cell patterns according to the new microenvironment therein established, as has been proposed by Hodges (1992) and Ameen et al. (2000) for some other cell types. Considering that the apical and basolateral domains of epithelial cells contain different sets of membrane proteins and cytoskeletal elements (Yeaman et al., 1999), many interesting fields to further highlight in future research concern the role played by the cytoskeleton in the rearrangement of the epithelial surface that leads to the formation and maintenance of microplicae-like structures after menopause.

Our findings evidence a sort of morphological heterogeneity of the endosalpinx in both perimenopause and postmenopause, according to the zone of the sample that is analyzed. This fact may simply reflect the passage from a normal epithelium, i.e. fixed proportions of ciliated and microvillous (actively secreting) cells, to a mucosa that is responding to the several processes of deciliation, microvilli shortening and absence of secretion. Nikas et al. (1999) reported the necessity of analyzing many tissue pieces of the endometrium from each single biopsy since it may show more advanced or retarded morphology from one area to another. In our opinion, this latter situation may also be applied to the tube. On the other hand, morphological differences observed among patients of the same age group can be explained by the fact that reproductive aging is associated with large interindividual variability of hormonal profiles, especially in postmenopause (Burger, 1999; Kraemer et al., 2003).

In conclusion, the present systematic observations revealed the complex ultrastructural changes underlying ageing of the human endosalpinx. Microplicae-like structures, associated with other regressive changes, are an outstanding adaptation of the fallopian tube cytoarchitecture, in particular, of the surface epithelium. These modifications probably reflect the hormonal changes occurring after menopause.

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