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A three-dimensional study of human fetal endocervix with special reference to its epithelium

F. Barberini[1], S. Makabe[2] and P.M. Motta[1]

[1]Department of Human Anatomy, University of Rome «La Sapienza», Rome, Italy and

[2]Department of Obstetrics and Gynecology, Toho University, Tokyo, Japan

Summary. The development of human fetal cervix has been systematically studied by SEM, obtaining a detailed map of its fine structure, particularly concerning the differentiation and maturation of the endocervical epithelium, including its "eversion" and "squamous metaplasia", normally occurring in postnatal life, but not yet observed in detail by electron microscopy in the fetus. Cervices from spontaneous abortion at 12, 15, 18, 20, 21 and 22 weeks and from intrauterine fetal death (hydrocephalus) at 31 weeks of development have been examined. At 12-15 weeks, as the canalization of the cervix proceeded, the endocervical epithelium consisted of high polyhedral cells, with regularly flattened or concave apices exhibiting scarce microvilli and often single primary cilia. Some narrow intercellular infoldings probably corresponded to primordial tubular glands. At the 18th week the epithelium was made up of a mosaic of flat or slightly raised polygonal cells, whose apical surface showed thin microplicae. At the 20th week a pseudostratified epithelium with many apically convex cells lined the cervical canal and the tubular glands. At 21 and 22 weeks "*plicae palmatae*" developed, covered by cells, often showing a smooth central area surrounded by microvilli, provided with a primary cilium and swollen by secretory material. This also formed rounded masses on the epithelium. In the lower part of the endocervix some very elongated cells showed short microplicae resulting from fusion of microvilli. At the 31st week secretion increased and its products spreading from the bottom of the glands contacted isolated ciliated cells at their openings and diffusely covered the surface epithelium. Most of the ectocervix exhibited squamous elements, with well-developed labyrinthine microplicae. These cells could overlap each other and also desquamate. The zone of the *portio vaginalis* around the os of the cervical canal appeared infolded and hypertrophic. Here, an indented squamo-columnar junction between the ectocervical and endocervical epithelium, caused by tongue-like prolongations of squamous epithelium directed toward the endocervix, was found. Their tips consisted of elongated cells, rich only in short microvilli.

Our data indicate that the features of the microvillous cells are an expression of a hormone-dependent differentiative process. Thus, their secretion might be stimulated by progesterone. Similarly microplicae on the ectocervical epithelium (a sign of squamous maturation) might be promoted by estrogens. Furthemore, two aspects were significative: 1) the finding - in an early phase only (18th week) - of endocervically-located squamous cells, although devoid of microplicae; and 2) the occurrence - in the latest phase (31st week) - of an indented squamo-columnar junction on the surface of the portio. These features are in agreement with the caudal shift of the squamo-columnar junction near the uterine cavity to the ectocervix after cervico-vaginal demarcation; the squamous metaplasia of this everted endocervical epithelium has been reported by some authors. It is likely that these processes, occurring in fetal life as well as in pregnant women, are related to a common hormonal background, arising from the mother to her fetus.

Key words: Uterine Cervix, Human Fetus, Epithelium, Ultrastructure

Offprint requests to: Prof. Fabrizio Barberini. Department of Human Anatomy, via Alfonso Borelli, 50 - 00161, Rome, Italy. FAX: 39-6-4452349. e-mail: MOTTA@AXRMA.UNIROMA1.IT

Introduction

Ultrastructural features of development and differentiation of the epithelium of the Mullerian-derived organs in humans have not been completely studied so far. Nevertheless, in some reports by transmission or scanning electron microscopy (TEM and SEM) the occurrence of ciliogenesis (Stegner, 1962; Patek and Nilsson, 1973; Konishi et al., 1987) and microvillous cells (Patek et al., 1972) in fetal Fallopian tube have been described. Furthermore, secretory cells were occasionally described in fetal endometrium and endocervix (Konishi et al., 1985).

In order to clarify this complex differentiative process and possibly to obtain a chronological map of

the progressive ultrastructural modifications related to these phenomena, we have recently undertaken a series of systematic three-dimensional observations on the human female genital ducts at increasing fetal ages (Barberini et al., 1994). The data here provided are part of this extensive study and describe in the fetus the maturative steps of the uterine cervix, as seen three-dimensionally by SEM, with special reference to the epithelium lining the cervical canal.

Furthermore, in this study the so-called "eversion" or "ectropion" of the endocervical epithelium out of the external os of the cervical canal was specifically investigated, including the consequent caudal displacement of the squamo-columnar junction, that normally occurs in postnatal life. The phenomenon produces a squamous metaplasia of this everted epithelium, which can give rise to a "squamous metaplastic transformation zone", variably extending onto the vaginal surface of the portio (Williams et al., 1975; Ferenczy, 1987). These aspects, occasionally reported also in fetal life (Pixley, 1976; Hafez, 1986; Ferenczy, 1987), to our knowledge, have never been examined in detail by electron microscopy.

Materials and methods

Female genital ducts were collected from necroscopy of human fetuses aborted spontaneously at the 12th, 15th, 18th, 20th, 21st and 22nd week of development and which died because of hydrocephalus at the 31st week. These ages have been calculated from the dates of tha last menstruation of the mothers. The ducts were cut in cross sections at various levels throughout their length. The fragments were then immersed in 2.5% glutaraldehyde in sodium cacodylate buffer 0.1M, pH 7.35, for 24 hours at 4 °C. After rinsing in the same buffer, the pieces were dehydrated in acetone, dried in a CPD 020 critical point dryer (Balzers), mounted on aluminium stubs, shadowed with gold in an S 150 high-vacuum sputter coater (Edwards) and observed by a S 450 Hitachi Electron Microscope, operating at 8-20 KV. All patients gave their written consent to participate in this study.

Results

12th week

At this stage of development the epithelial lining of the human fetal endocervix was formed by a layer of cells, that apically appeared somewhat regularly flattened or scarcely concave. The luminal surface of each cell exhibited numerous, short microvilli and a single primary cilium arising from the center of the apex of the cell (Figs. 1-3). Some intercellular openings (about 2-6 μm wide), scattered on the luminal surface, were also observed (Fig. 2). In particular, their luminal wall was covered with microvilli and/or cilia, apparently coming out from their bottom (Fig. 3). These structures probably corresponded to the lumen of primordial tubular glands.

15th week

Overall SEM observations revealed that at this stage the endocervix already possessed well developed walls and its interior was fully canalized (Fig. 4). Higher magnification of longitudinal sections showed a clear cervical canal lined with a tall epithelium, made up of columnar cells (Fig. 5).

18th week

In this phase the cervical walls swelled luminally in

Fig. 1. Endocervix. The wall is lined by a layer of apically-flattened or scarcely concave microvillous cells. Many of these show luminally a single primary cilium (ci and arrow). 12th wk, x 4,000

Fig. 2. Endocervix. On the luminal surface, some intercellular holes (*), probably corresponding to primordial cervical glands, scattered among the epithelial cells, are seen; cells with primary cilia (ci and arrows) are frequent. 12th wk, x 5,000

Fig. 3. Endocervix. From the bottom of the intercellular holes, microvilli and/or cilia are sprouting out (arrow); primary cilia (ci and arrows) are numerous. 12th wk, x 10,000

Fig. 4. Longitudinal section of the cervix. It appears to be well developed and internally canalized. 15th wk; x 60

Fig. 5. Higher magnification of Fig. 4. The cervical canal (cc) is lined by a tall epithelium (ep), made up of columnar cells. BL: basal lamina; s: stroma of the mucosa. 15th wk, x 280

Fig. 6. Longitudinal section of the cervix. The endocervical wall (en) is raised in prominent folds, outlined by deep furrows. Other folds occur on the wall of the ectocervix (ec). os: external os of the cervical canal. 18th wk, x 30

Fig. 7. Star-like shaped ectocervical folds diverge from the external os (os) of the cervical canal. 18th wk, x 70

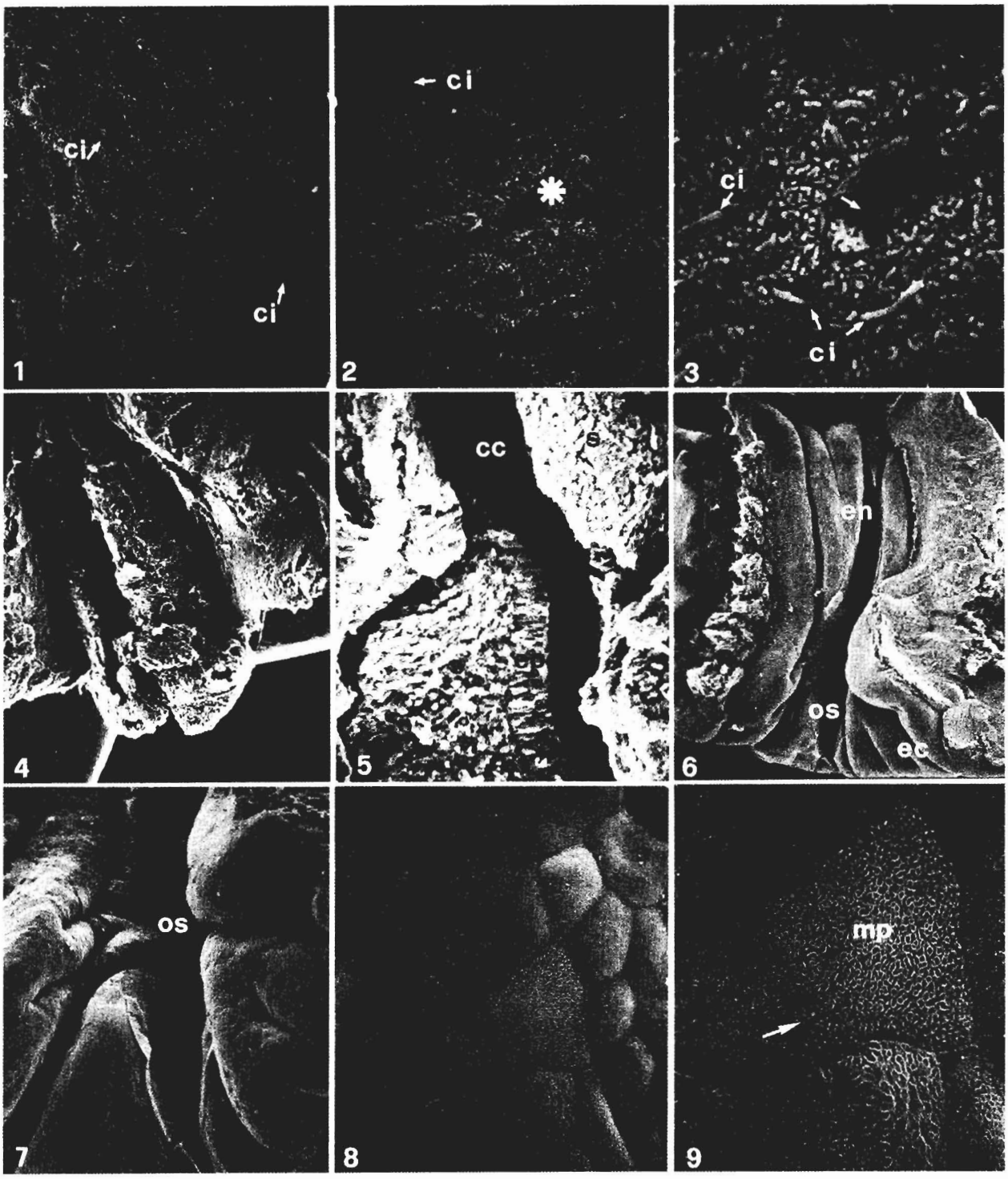
Fig. 8. Endocervical epithelial cells appear in a mosaic pattern, formed by flat or slightly raised polygonal elements. 18th wk, x 1,000

Fig. 9. Higher magnification of Fig. 8. The flat polygonal endocervical cells are outlined by evident edges (arrows) and many of these show a network of thin surface microplicae (mp). Neither microvilli, nor cilia are visible. 18th wk, x 2,000

prominent folds separated by deep furrows.

The mucosal folds converged toward the external os of the cervical canal (Fig. 6), from which they diverged in a star-like fashion on the external (vaginal) surface of the portio (Fig. 7).

The epithelial cells lining the parietal folds of the endocervix were arranged in an elegant mosaic of flattened or only slightly raised cells with polygonal contours (Fig. 8). At higher magnification, these appeared as tiles with evident edges, and many elements showed a network of thin surface microplicae, variable in number and design (Fig. 9). However, the microplical



networks never reached a great complexity. Neither microvilli, nor cilia were observed (Fig. 9).

20th week

The endocervical epithelium appeared columnar, consisting of high cells (Fig. 10). In particular, it was typically pseudostratified. In fact, many cells extended throughout its entire thickness and jutted into the cervical canal with their convex apices, whereas others were shorter, and not far from the basal lamina (basal cells) (Fig. 11). In addition, some tubular invaginations of the epithelium into the cervical wall were detected. Very likely they corresponded to cervical glands (Fig. 12).

21st week

The columnar cells of the lower part of the endocervix were somewhat polymorphic (Fig. 13). In the same zones, many of these appeared globose and were provided with short, stubby microvilli (Fig. 14), while others were more elongated and their luminal surface exhibited short microplicae (Fig. 15). At higher magnification these microplicae appeared to arise from the fusion of early microvilli. In fact, they consisted of thick portions delimited by microthrottlings, assuming a rosary chain appearance (Fig. 16).

22nd week

The endocervical wall was arranged in radiate formations, recalling the future shallow "*plicae palmatae*" of the adult. These upward diverging folds occurred in the distal part of the endocervix (Fig. 17). The "*plicae*" were separated by furrows and covered by polyhedral and cylindrical cells with convex apices (Fig. 18). As a rule these cells were rich in microvilli, but many others showed a stretched central area, on their luminal surface, swollen by secretory material, and surrounded by a characteristic crown of peripheral microvilli. In addition, single primary cilia were often observed arising from the surfaces of these microvillous cells (Fig. 19). Such features are likely to be related to an apocrine process, because secretory material was often observed in form of globose masses on the luminal surface of these cells (Fig. 20).

31st week

At this stage of development the secretory processes of the columnar endocervical epithelium were more abundant than those observed at the 22nd week. In fact, secretory droplets were clearly extruded also from the bottom of cervical glands, spreading over the endocervical wall and diffusely covering the surface of microvillous cells. The cervical glands appeared as deep parietal invaginations bordered by ciliary bundles (Fig. 21). Ciliated cells, scattered among microvillous cells often in contact with secretory droplets, were also observed. However, the number of ciliated cells in the endocervical wall was very scarce if compared to that of microvillous cells (Fig. 22). The ectocervical epithelium was made up of flat and squamous elements. Their apical faces showed polygonal contours and well-defined, labyrinthine microplicae. Some squamous cells appeared partially overlapped and also detaching from the underlying cell layer (Fig. 23). At higher magnification the free surface of squamous cells revealed a complex, convoluted pattern of microplicae and prominent boundaries between flattened adjacent cells. The latter formations ran as double parallel contours and

Fig. 10 . Longitudinal section of the cervical canal. The epithelium (ep) bordering the lumen (L) is columnar, consisting of high cells. BL: basal lamina; s: stroma. 20th wk, x 500

Fig. 11. Higher magnification of columnar endocervical epithelium. This appears pseudostratified, possessing both tall cells extending from the basal lamina (BL) to the cervical canal with convex apices (arrows), and shorter, basal cells (bc). 20th wk, x 2,000

Fig. 12. Invagination of columnar endocervical epithelium into the cervical wall, probably corresponding to an early glandular formation. BL: basal lamina; s: stroma. 20th wk, x 1,000

Fig. 13. Lower part of the endocervix. Polymorphism of some epithelial cells is apparent (arrows). 21st wk, x 1,000

Fig. 14. Lower part of the endocervix. Many epithelial cells are globose and their luminal surface exhibits short, stubby microvilli (mi). 21st wk, x 10,000

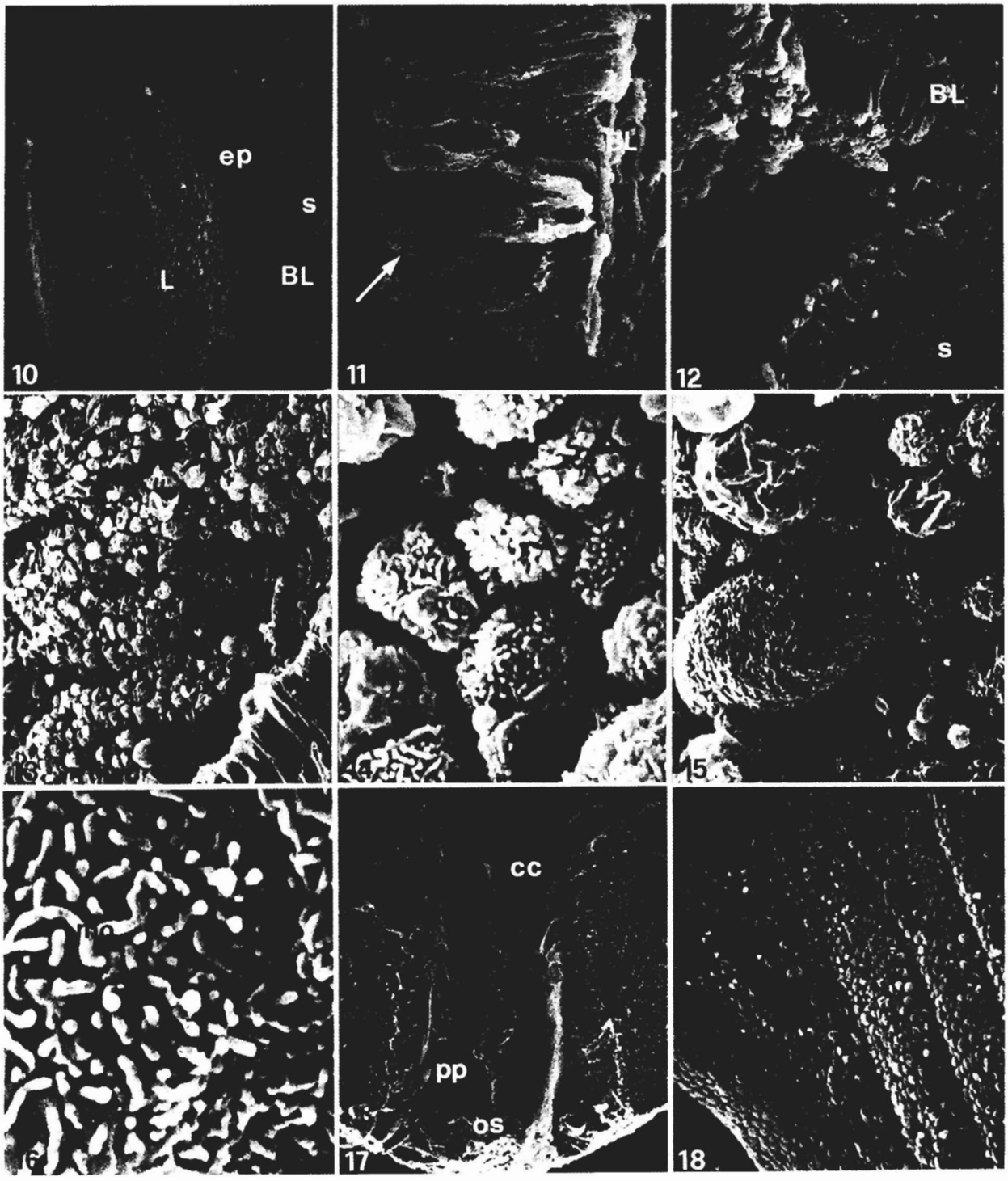
Fig. 15 . Lower part of the endocervix. Some epithelial cells appear larger and more elongated if compared to others around them. The large elements are probably metaplastic cells and are covered by small microplicae (mp). 21st wk, x 5,000

Fig. 16. Higher magnification of an elongated epithelial endocervical cell (metaplastic cell). Microplicae (mp) are formed by microvilli fused together, thus assuming a rosary chain appearance. 21st wk, x 20,000

Fig. 17. Longitudinal section of the cervix. In the lower part of the cervical canal (cc), some radiate "*plicae palmatae*" (pp) in the form of upward diverging folds, are detected. os: external os of the cervical canal. 22nd wk, x 60

Fig. 18. Higher magnification of "*plicae palmatae*". These are folds separated by interposed furrows and covered by cells with convex apices. 22nd wk, x 500

this feature was due to the side-by-side juxtaposition of the luminal cell membranes (Fig. 24). In older fetuses (31 weeks of age) the ectocervical mucosa bent onto the vaginal "portio" toward the external os of the cervical canal. This reflection consisted in irregularly parallel and prominent mucosal folds, with occasional signs of hypertrophy. Such an aspect was in contrast with the smoother mucosa covering the endocervical wall, so that the boundary between these two morphologically different parts of the uterine cervix was easily recognizable (Fig. 25). At higher magnification under the SEM, this ecto-endocervical contact zone probably



corresponded to the "*squamo-columnar junction*" (Fig. 26). However, the boundary between the microvillous endocervical cells and the squamous ectocervical cells was not sharp, but rather indented, in that these latter cells invaded the endocervical epithelium as flat digitations or small "tongues". In addition, the tips of these squamous "tongues" consisted of elongated cells, showing only short microvilli (Fig. 27). The different cell types of the cervical epithelium as revealed by SEM in the above developmental stages are summarized in a series of illustrated diagrams (Figs. 28-35).

Discussion

To our knowledge, the fine morphological details of cervical epithelium in human fetuses during various developmental stages have not been studied so far. Therefore, the present systematic SEM observations allowed the elucidation of some ultrastructural aspects related to the complex morphodynamic processes responsible for the differentiation of the human uterine cervix.

Particularly, cell differentiation of Mullerian endocervical epithelium, examined in specimens of different ages, resulted typically pseudostratified and columnar, i.e. provided with both tall and short (basal) cells. This arrangement was similar to that occurring in the adult, and previously described for the human fetal cervix (Davies and Kusama, 1962; Forsberg, 1976) and oviduct (Barberini et al., 1994). A common general feature in the fetuses of different ages was the presence in this type of epithelium of microvillous cells. These were the most abundant elements lining the cervical canal; their aspect, however, could differ in the various developmental phases. In fact, in the earliest stages (12th week) the majority of these cells showed a surface provided with a uniform carpet of regularly-arranged microvilli, while in more advanced phases (22nd week) (involved in secretory processes) microvilli were found only peripherally, their central area appearing relatively "bare". Furthermore, microvillous cells of both ages often exhibited single isolated (primary) cilia rising among microvilli or from the smooth central area, respectively. Another cell type detected in the Mullerian endocervical epithelium was highly ciliated. Elements provided with many cilia, however, have been noted only in the older fetuses (31st week), but these cells were less numerous than those with microvilli. This might indicate that the quantity of ciliated cells in human endocervix is rather scarce also in fetal life, according to that referred to endocervix in adult woman (about 5% of all epithelial endocervical cells). This is a very low percentage, indeed, if compared with that of other mammals, such as the rabbit (about 50%) (Moghissi, 1972). Therefore, on the basis of a surface morphological evaluation of the endocervical columnar cells, it may be postulated that the Mullerian epithelium lining the cervical canal of human fetal uterus is mainly formed by numerous microvillous and scarce ciliated cells. Furthermore, the arrangement in number, size and location of the microvillous population, including those with single cilia and secretory cells was highly variable. Therefore, it is likely that the different appearance of microvillous elements basically reflects a different functional behaviour of the same cell type, depending upon estrogenic and/or progestational influence, during the various phases of cervical development. In addition, especially in early fetuses, rather small intercellular infoldings in the epithelial luminal surface were observed. These were rich in microvillous cells, and

Fig. 19. Many cells covering the "*plicae palmatae*" show a crown of peripheral microvilli on their luminal surface (mi and arrows) encircling a stretched central area, swollen by secretory material (*). From the surface of these microvillous cells single primary cilia (ci and arrows) often arise. 22nd wk, x 4,000

Fig. 20. Apocrine-like secretion of some microvillous cells (mc) in the form of globose masses (arrows) on their surface. 22nd wk, x4,000

Fig. 21. Small masses of secretory material (arrows) released from the cervical glands. This material also appears spread on the microvillous cells (mc) of the endocervical luminal surface. Some ciliated cells (cc and arrows) occur at the mouth of the cervical glands. 31st wk, 2,000

Fig. 22. Scattered ciliated cells (cc), often contacting secretory masses (arrows), on the endocervical wall. These are less numerous than the adjacent microvillous cells (mc). 31st wk, x 2,000

Fig. 23. Ectocervical epithelium made up of flat squamous cells. These are outlined by irregular contours (arrows) and possess well-defined, labyrinthine microplicae (mp). Some overlapping and detaching cells (*) are also observed. 31st wk, x 1,000

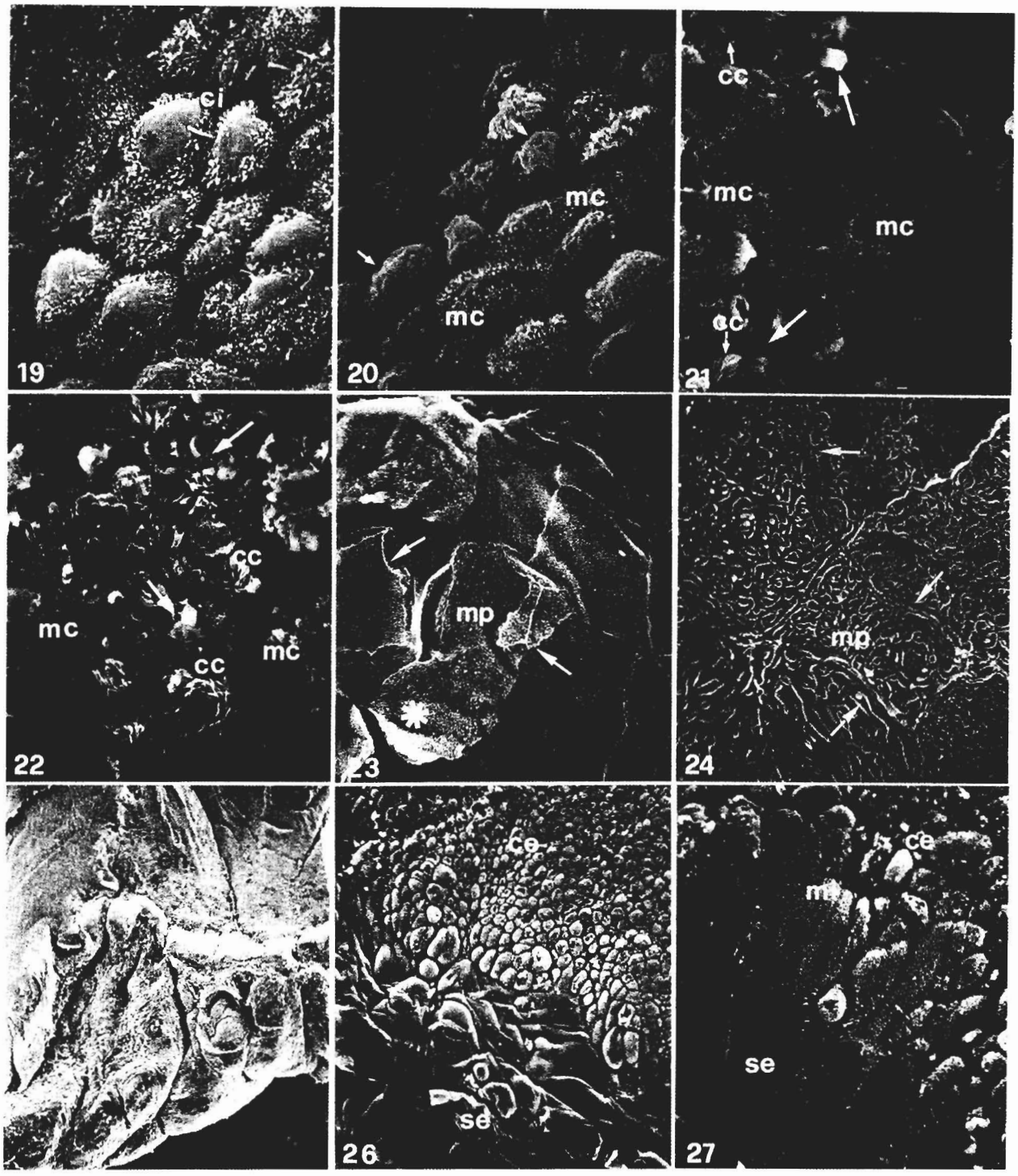
Fig. 24 . Higher magnification of squamous ectocervical cells. Note the complex, convoluted pattern of the microplicae (mp), and the double prominent ridges (arrows) that indicate facing plasmalemmas of two adjacent cells. 31st wk, x 4,000

Fig. 25. External os of the cervical canal. Ectocervix (ec) is raised in hypertrophic folds; by contrast, endocervix (en) is smoother, so that the boundary between them is apparent. 31st wk, x 20

Fig. 26. Higher magnification of the ecto-endocervical boundary. This zone appears as a squamo-columnar junction, between the squamous ectocervical (se) and columnar endocervical (ce) epithelium. 31st wk, x 400

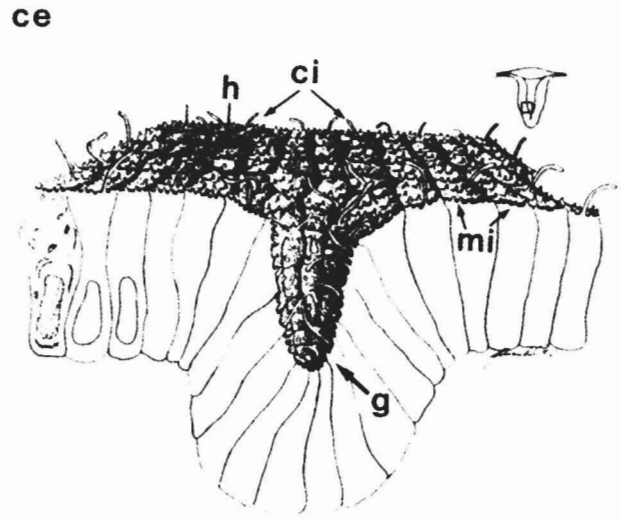
Fig. 27. At the squamo-columnar junction, flat tongue-like extensions of squamous ectocervical (se) epithelium are directed toward the columnar endocervical (ce) epithelium. The cells forming the tips of these extensions are elongated and covered by short microvilli (mi). 31st wk, x 1,000

were also provided with a few or single cilia. Similar features were reported by SEM in oviductal epithelium of human fetus (Barberini et al., 1994), and have been compared morphologically and functionally to surface invaginations in the Mullerian epithelium of postnatal Mongolian gerbil vagina (Kress et al., 1989). Certainly according to the general pattern of the fetal or adult female genital tract, these aspects are an expression of morphodynamic processes of cell differentiation, and/or renewal in actively remodelling epithelia. Nevertheless, the possibility that these infoldings represent primordial cervical glands should not be ruled out especially if they

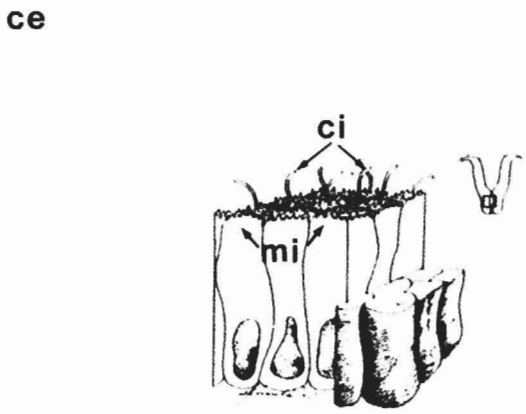


are compared with the tubular glandular invaginations of the subsequent phases. Thus, it is likely that the small infoldings, which in our study occurred at the 12th week of development, might indicate the first morphological sign of glandular anlage; that is, the initial formation of simple tubular glands. Therefore, our microtopographical SEM ultrastructural observations might have detected the first appearance of the cervical glands in an earlier stage (12th week) than those previously reported (15th or 16th week) in human fetuses (Hoang-Ngoc Minh et al., 1989a). In the present study we also noted progressive differentiation of ectocervical epithelium, resulting from the ultrastructural evaluation of the luminal side of the squamous cells lining the vaginal portio. In particular, a gradual complexity of surface microplicae, according to the fetal development, a likely sign of cell maturation, has been detected. It must be added that these squamous elements, which partially overlapped each other, were often raised above the epithelial surface, detaching from the underlying cell layers. Therefore, these features can be a morphological expression of a complete cell cycle, whose desquamative aspects represent the normal occurrence of apoptosis. Therefore, by means of our SEM investigation, vitality and dynamics of endocervical- as well as ectocervical-developing epithelium of human fetus were on the whole apparent.

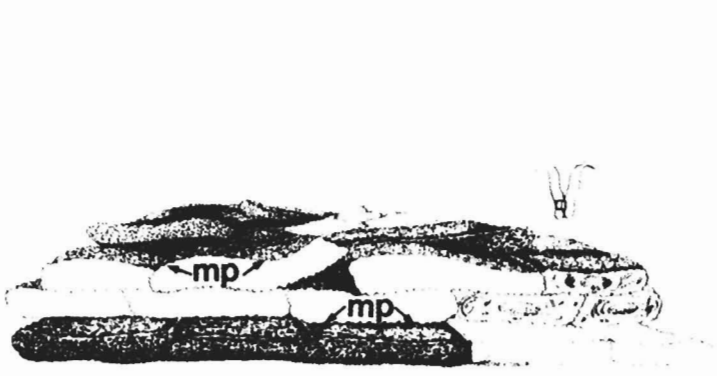
Another worthwhile aspect we observed in the cervix was the presence of a mosaic of flattened or slightly raised cells, lining the wall of the cervical canal



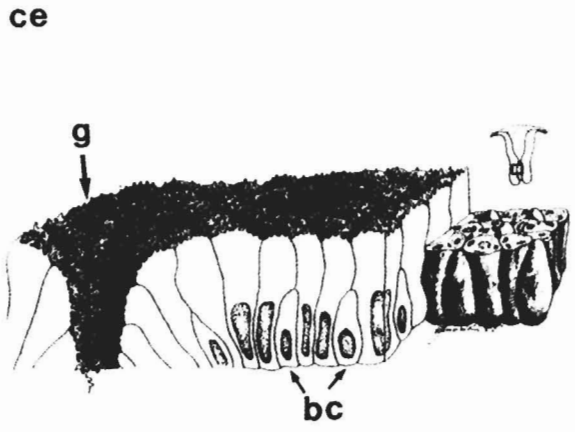
28 12wk



29 15wk



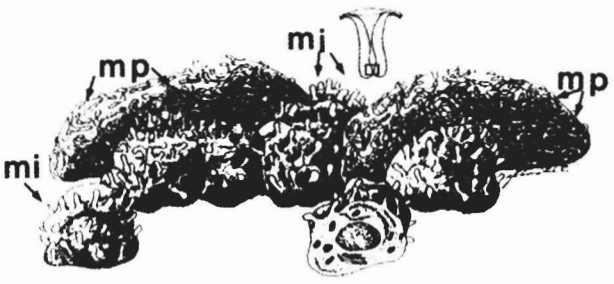
30 18wk



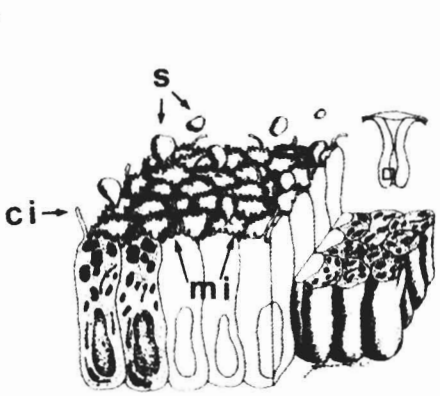
31 20wk

Figs. 28-35. Diagrams summarizing the main 3-D dynamic features of the endo- and ectocervical epithelium in the stages of development studied by SEM. ci: cilia; mi: microvilli; mp: microplicae; bc: basal cell; mpc: metaplastic cell; h: (intercellular) hole; s: secretory products; ce: columnar (endocervical) epithelium; se: squamous (ectocervical) epithelium; g: glandular-like infoldings.

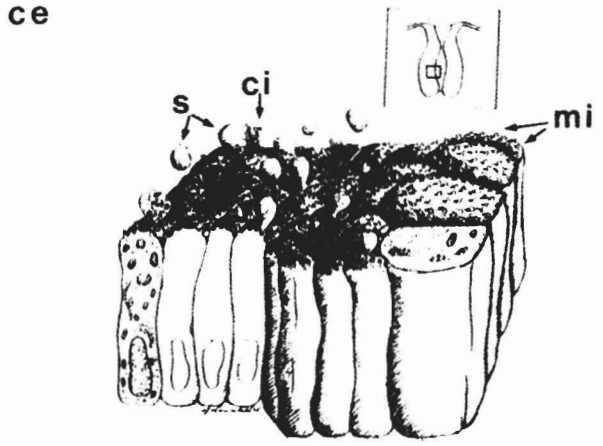
in the 18 week old fetuses. These elements were morphologically squamous, showing evident edges and a network of thin, delicate surface microplicae. Such a SEM report may constitute the ultrastructural demonstration of what was previously described in early human fetus, whose squamo-columnar junction has been said to reside in the upper part of the cervical canal, closer to the uterus than to the vagina (Meyer, 1910; Fluhmann, 1960). In particular, progression of sinusal pluristratified epithelium from the ectocervix into the endocervix, toward the internal orifice of the cervical canal, with subsequent withdrawal of the Mullerian columnar epithelium, has been observed by light microscopy in 20-week-old fetus (Hoang-Ngoc Minh et al., 1989b; Hoang-Ngoc Minh and Smadja, 1992). After the 20th week of development - following the demarcation of the cervix from the vagina - the interface between the endocervical columnar epithelium (of Mullerian origin) and the squamous one (from the uro-genital sinus) extends down, to the external (vaginal) surface of the portio, causing endocervical ectropion (Davies and Kusama, 1962; Hoang-Ngoc Minh and Smadja, 1992). This process has been thought to be dependent on the action of sexual hormones, especially estrogens, because in human fetus it is associated with massive hypertrophy and keratinization of the vaginal epithelium (Davies, 1967). Furthermore, it is morphologically similar to the endocervical eversion occurring in postnatal life, at the time of puberty and during the reproductive age, when hormonal stimulation physiologically increases (Hafez, 1986; Ferenczy, 1987). In our observations the absence of squamous cells and the occurrence of all columnar cells in the fetal cervix following the 18th week, might represent the ultrastructural finding of the above mentioned "descent" of the squamo-columnar junction. In our study this phenomenon seems to be established earlier than that reported to occur after the 20th week. In older fetuses (31 weeks) we also found a hypertrophic zone of the vaginal portio around the external os of the cervical canal. Such a picture was similar to the surface



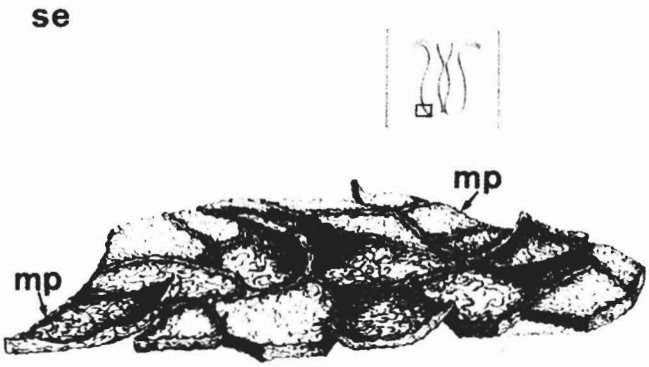
32 21wk



33 22 wk



34 31wk



35 31wk

protrusions formed by the columnar endocervical epithelium in the same zone in adult woman. These features are visible colposcopically as roundish, grape-like structures, undergoing squamous metaplasia in the form of flat processes, which, like small tongues, are directed toward the cervical canal, making the boundary between squamous ectocervical and columnar endocervical epithelium indented (Singer, 1975; Williams et al., 1975; Kenemans et al., 1982). Specifically, presence of microvillous cells, larger and more flattened than the other columnar cells, has been reported by SEM in human adult endocervical epithelium near the squamo-columnar junction. These elements have been regarded as a columnar epithelium undergoing squamous metaplasia in the so-called "transformation zone" (Kenemans et al., 1982), probably influenced by the vaginal acidity (Singer, 1975; Ferenczy, 1987). Multifocal nature of squamous metaplasia has been demonstrated to occur in the human adult endocervical columnar epithelium, becoming ectopic, after eversion onto the ectocervix in the form of grape-like villous bumps (endocervical ectropion or ectopy). In these formations many large cells, showing surface microvilli, and interspersed among the otherwise regular columnar elements, have been detected by SEM. This metaplastic process gave rise to numerous tongue-like protrusions of squamous epithelium extending across the columnar zone (Williams et al., 1975).

Both flat tongue-like processes overlapping columnar cells, becoming elongated squamous cells, with short microvilli and poorly developed microplicae were also observed by SEM and TEM in the transformation zone of adult cervix. These findings have been supposed to be signs of squamous metaplasia (Barberini et al., 1991). Large, elongated microvillous cells, similar to those showing features of squamous metaplasia in adult woman, such as cell shape and volume and surface microvillous pattern, were also found in fetal endocervical epithelium. In particular, in 21-week-old fetuses, some epithelial endocervical cells, more elongated than the surrounding ones, exhibited luminally short microplicae. These surface microstructures clearly resulted from fusion of chains of microvilli as revealed under more detailed SEM examination by their irregular thickness, thus assuming a rosary chain appearance. Furthermore, the present SEM observations revealed that in older fetuses (31 weeks of development) the squamo-columnar junction was indented like in the adult. This fetal ecto-endocervical aspect was apparently caused by squamous metaplasia of columnar cells. In fact, many elongated endocervical cells, close to the squamous cells, showed only short microvilli. In our investigation these particular microvillous cells were found in the tips of the tongue-like formations made-up of squamous elements. The general appearance of such a finding was the occurrence of an ectocervical invasion into the endocervical epithelium. With regard to this it has been reported in a light microscopy study that in the majority (about 70%) of human mature fetuses (after 36 weeks of development) the ectocervix is covered by three types of epithelia: mature squamous, metaplastic squamous and columnar. The last two may appear variably intermingled (Pixley, 1976). The transformation zone from columnar to squamous metaplastic epithelium has also been reported in pregnant women, as well as the eversion of the columnar endocervical epithelium out of the cervical canal onto the ectocervix with the consequent more caudal location of the squamo-columnar junction (Singer and Jordan, 1976; Ferenczy, 1987). Therefore, it might be suggested that these processes are promoted by the special condition of pregnancy. In fact, this linking of the mother to the fetus, might create in a way a sort of common hormonal background, able to induce similar histological changes on both the maternal and fetal uterine cervix. Moreover, concerning the influence of sex steroid hormones on the development of the fetal female genital organs, it must be stressed that these substances increase in the maternal and fetal plasma during gestation (Tulchinsky et al., 1972; Tulchinsky, 1973), and estrogen and progesterone receptors have been found in fetal guinea-pig uterus (Pasqualini and Nguyen, 1980; Pasqualini et al., 1984; Sumida et al., 1987). Recently, in the same animal, a study of the metabolism of tritiated estrone, estradiol and estrone sulfate in isolated fetal uterine and vaginal cells has clarified that the enzymatic mechanisms of the bioavailability of the estradiol for the biological responses of the hormone occur in the target tissue (Urabe et al., 1993). More specifically, in the human fetal uterine cells, gene expression for the epidermal (EGF), fibroblast (FGF), insulin, and insulin-like growth factor receptors has been detected. These receptors may act on uterine maturation and cell differentiation (Shifren et al., 1993; Glatstein et al., 1994).

In conclusion, our 3-dimensional ultrastructural data shed some light on the nature of these continuously evolving and re-modelling differentiative cellular processes, that reveal a great complexity as early as in fetal life.

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