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Research Article

CELLULAR RENEWAL OF THE INTESTINAL EPITHELIUM IN ARTIFICAL VAGINA IN WOMEN UNDERGOING VAGINOPLASTY

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ABSTRACT

Vaginal agenesis is a congenital disorder commonly associated with Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome, which is characterized by failure to develop the Müllerian duct and vaginal agenesis. This syndrome occurs in approximately 1 case in 4000-10,000 births [1].

KEYWORDS

Non-operative methods, the bladder, Vecchietti, Abbe-McIndoe and Davydov.

INTRODUCTION

In adolescence, it is quite common for girls to complain of amenorrhea, and about 15% of them suffer from MRKH syndrome [5, 9, 10]. This syndrome is one of the main medical indications for neovaginoplasty. In addition, other indications for vaginal reconstruction include cloaca, intersex disorders, and cases where the vagina has been lost due to pelvic exenteration due to gynecologic cancer or postpartum necrosis. There are many surgical and conservative methods for vaginal restoration. Among non-operative methods, such as the Frank technique, serial dilatation is used to create a rudimentary vagina. The mucous membrane of the bladder, amnion and synthetic materials are also used to form the neovagina [9, 10, 11].

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These approaches require prolonged dilatation and stenting to prevent closure of the canal. Research has shown that the use of isolated intestinal segments provides excellent results, bypassing the need for regular dilatation and providing natural lubrication [3, 16, 17]. Numerous proposed treatment methods, which are even more diverse when taking into account their modifications, reflect the complexity of solving this problem. Nevertheless, the relevance of this problem remains, and for gynecologists it will always be an important issue to adequately solve it. Conservative and surgical treatment methods have been developed and used for a long time with possible modifications. Surgical methods can be divided into traction and transplantation. Methods such as Vecchietti, Abbe-McIndoe and Davydov are considered among the most commonly used and recognized in the world.

Intestinal vaginoplasty is a well-studied procedure that uses a pedunculated segment of the large or small intestine. This method is often used for vaginal agenesis, male-to-female sex reassignment surgery in cases of lack of phallic skin, and for revision after unsuccessful primary reconstruction. In our study, we describe the use of a pedunculated colon segment for vaginal reconstruction after serious complications of the initial surgery [8, 21, 22].

Currently, operations to reconstruct an artificial vagina are becoming increasingly common. However, histological analysis of the morphofunctional changes occurring in the functionally leading tissue of the formed bioprosthesis - the intestinal epithelium - remains insufficiently studied. Clinical specialists are naturally focused on the clinical and functional changes occurring both in the artificial vagina and in the patient as a whole. Thus, it is necessary to recognize that these changes are a consequence of reactive compensatory transformations in the mucous membrane, which interacts with an unusual microenvironment. Based on clinical biopsy material obtained from 15 to 40 months after surgery, two-phase changes in the epithelium were identified: first, a mosaic loss of microvilli by enterocytes was observed, and then the appearance of signs of transitional cellular metaplasia [18]. Additionally, some researchers, based on short-term observations of morphology, identify a period of three years during which the intestinal epithelium fully adapts to new conditions [12, 14]. However, such studies remain isolated, usually lacking theoretical justification and focused on solving specific clinical problems [13]. It was previously discovered that reactive compensatory processes in the mucous membrane of the urinary reservoirs, especially in the epithelium, develop in accordance with well-known classical patterns [4,20]. Traditionally, the reactive change process is thought to involve three main phases. The first of them is “emergency mobilization,” characterized by the activation of morphofunctional reserves in response to a sharp change in influencing factors. Then comes the “plateau” phase, when the system reaches relative stability at a new level of

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functioning. With prolonged exposure to extreme factors, a phase of "failure" or decompensation may occur, characterized by a violation of the structural and functional organization. [15, 19]. It is clear that the duration of these phases depends not only on the characteristics of the influencing factor, but also on the histogenetic properties of the tissue on which it affects. Consequently, this also influences the choice of diagnostic and treatment strategies in the follow-up care of these patients after surgery. In addition, it is known that such an adaptation process covers all levels of the structural organization of matter, which are analyzed by a histologist, including subcellular, cellular, cellular-tissue and structural-functional units [4, 15].Transformations of the intestinal epithelium in the structure of the artificial vagina have not been fully considered from the point of view of the described general patterns of pathology. The epithelium of the intestinal type interacts with the connective tissue, forming the morphofunctional complex "crypt-villus" in the intestine. This complex is a self-regulating system characterized by constant renewal of enterocytes due to the proliferation of undifferentiated cells in the crypt [2]. In the lower part of the crypts there are intestinal epithelial stem cells that can differentiate into various cell types. This differentiation occurs in several directions, leading to the formation of prismatic enterocytes (villous epithelial cells), goblet exocrine cells, Paneth cells (with acidophilic granules) and enteroendocrine cells (gastrointestinal endocrinocytes) [6]. Under normal conditions, the cellular components that make up a particular tissue should maintain a standard ratio. This ratio ensures the full functioning of the tissue, including its ability for physiological regeneration and cell renewal [7]. It is assumed that under changed environmental conditions these ratios can change in order to maintain the initial state of the tissue, which indicates their adaptive nature [4]. Tissue reactivity is a term that is used to denote the individual ability of tissues to make compensatory-adaptive morphofunctional changes in response to various superphysiological influences [7].

The purpose of the study is to determine the patterns of changes in the cellular renewal of the intestinal epithelium in the vagina formed from the sigmoid colon.

Materials and methods of research. The material was biopsy samples obtained during vaginoplasty after prolapse in women undergoing surgery to create an artificial vagina. At the same time, material obtained from different patients within a period of 6 months to 10 years after reconstructive surgery was available for study. Biopsies were taken from several areas of the artificial vagina, usually from the anterior, left and right walls, as well as from the posterior wall.

The obtained samples for histological examination were taken from 38 patients with congenital anomalies of the vagina. These specimens were fixed in 10% neutral formalin for 24–48 hours and subjected to

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histological processing, including paraffin embedding and sectioning at 5–6 µm thickness. For morphological analysis of sections, hematoxylin and eosin staining methods, the Van Gieson method, and the Weigert method were used.

Histochemical study. To identify the process of mucus formation, more precisely the formation of mucopolysaccharides in the goblet cells of the mucous membrane and glands of the submucosal layer, a histochemical study was performed using Alcian blue staining. To identify glycol or aminohydroxyl groups that form dialdehyde, a PIR reaction (Schiff reagent staining) was performed.

In addition, using the PAS reaction, it is possible to analyze the accumulation of mucin, glycogen, flu-like lesions, as well as lymphoproliferative processes in neovagina tissue. The results were assessed semi-quantitatively (in points).

A total of 76 blocks were processed, from which 208 drugs were manufactured and studied. When studying micropreparations, histological and histomorphometric analyzes were performed. Histomorphometric analysis was carried out using a scanner on a NanoZoomer microscope (REF C13140-21.S/N000198/HAMAMATSU PHOTONICS/431-3196JAPAN), using the NDP.VIEV2.0.,QuPath.0.4.0.url program.

To obtain statistically reliable results, at least 20 objects were analyzed in several fields of view. A morphometric study was carried out with the calculation of the following parameters: average villi height (µm); average crypt depth (µm); average height of epithelial cells (µm); proportion of Paneth cells in relation to all crypt epithelial cells (%).

Statistical data processing. Since a normal distribution of signs was not identified and taking into account the need to evaluate indicators before and after surgery, non-parametric methods were subsequently used to compare related groups based on quantitative characteristics.

The statistical significance of the differences between each indicator before and after surgery at different times was assessed using the Wilcoxon test at $P < 0.05$, the interpretation of the results was formalized with the exact p values.

For comparison, the results obtained were compared with the data identified during the study of biopsy specimens of the native sigmoid colon.

Results of our own research. It has been established that in the initial months of the functioning of the intestinal epithelium, reactive changes occur at all levels of its structural organization. This is especially true for the crypt-villus system and the cellular composition of the epithelial lining. Already in the first half of the year of exposure, significant structural changes are observed compared to the control. For example, after 6-12 months, a variety of sizes of intestinal villi is detected; their length varies even within one biopsy from 140 to 230 micrometers, while in a normal sigmoid colon this figure is approximately

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357.5 ± 15.8 micrometers. Villi located close to each other differ in size, shape and structure, therefore the average values of villi height are arbitrary and not statistically significant. Most villi have a non-standard shape, with various bends and local thinning. The structure of the crypts remains constant and does not differ significantly from the normal mucosa; their depth ranges from 135.8 to 263.7 micrometers, while in normal intestine it is approximately 186 ± 4.0 micrometers. These changes persist for 6-12 months. Further, an increase in the variety of shapes and sizes of villi is observed. They are located at unequal distances from each other, have different heights and shapes, with numerous bends between them. The villi themselves have an irregular, curved shape, and in some areas are absent for significant lengths. The crypts have a tortuous course, which leads to the presence of a large number of transverse and longitudinal sections of the crypts, and polymorphism is manifested in their different diameters. At 36 months, extensive areas without villi were observed, and the crypts had a shallow depth of 170–220 micrometers (Fig. 1).

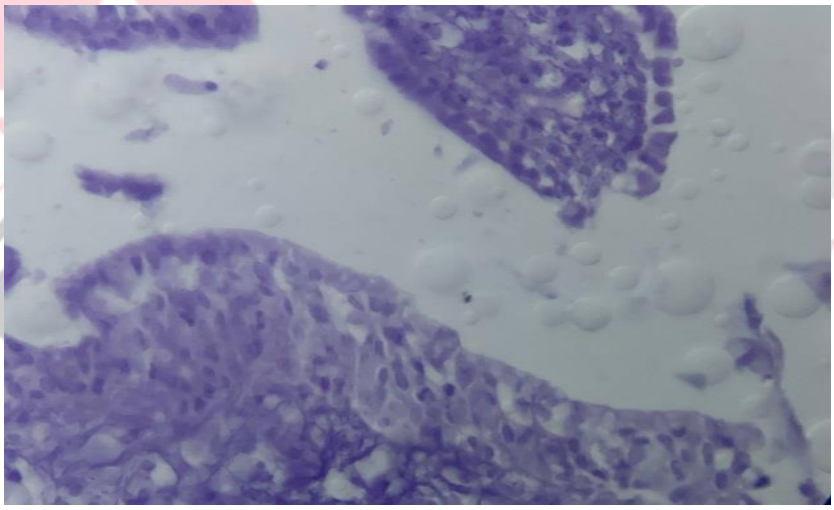

Fig. 1. Single-row cubic epithelium of the villi of the mucous membrane of the neovagina. Hematoxylin and eosin staining. Increased 400.

These crypts were separated from each other and had some fibrotic structure, and were also infiltrated with lymphocytes and eosinophils. The remaining villi had an atypical shape with terminal extensions in the form of pins. At the level of cellular differentiation, a pronounced hyperplasia of cells that produce mucus was observed, and goblet cells became dominant among them. Under normal conditions of the sigmoid colon, the proportion of goblet cells among all epithelial cells usually does not exceed 12%, and they are found mainly in the upper third of the crypts.

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However, already 6 months after reconstructive surgery, the proportion of goblet mucocytes sharply increases to 32.5%, and on the surface of the villus, half of all cells in which nuclei could be visualized are mucocytes.

Subsequently, changes in the proportion of goblet mucocytes were insignificant and remained stable until late follow-up, ranging from 18–30%, which is twice the usual values for the sigmoid colon. These cells were located deep in the crypts and in some cases could be found even at the 6–7 cell position. The dynamics of the proportion of Paneth cells showed significant fluctuations, however, the detected trends indicate that immediately after the onset of exposure to sexual contact - during the first 6-8 months - their proportion among all crypt cells increased sharply compared to the norm. Subsequently, this indicator stabilized at the level of 5-8%, which in most cases significantly exceeded the level in the sigmoid colon under normal conditions (3±0.14%). The synthetic activity of enterocytes remained at a typical level until 18-26 months.

The results of histological examination showed that the neovaginal mucosa was completely re-epithelialized and began to produce glycogen within approximately 6 months in all cases. Vaginoscopic demonstrations using Schiller staining also confirmed this fact. They showed that the transformation of the single-layer epithelium of the sigmoid colon into a stratified epithelium secreting glycogen occurred due to the expansion of the initial epithelial beams originating from the entrance of the hymen upward to the apex of the vagina.

After 32-36 months, the mucous membrane showed significant disturbances in the architecture of the crypt-villus system. Typical villi were absent from the biopsies, replaced by widened and short stromal protrusions covered by single-layer intestinal epithelium.

In some cases, the initial sections of convoluted crypts were found inside these protrusions, infiltrated with lymphocytes. In the period from 36 to 48 months, single polymorphic villi were observed on the surface of the mucous membrane, some of which reached a significant length - from 160 to 210 µm. In some areas, local polyp-like growths of the epithelium were also noted, which could be identified as anastomosing villi. Paneth cells were located at positions from 1 to 5 cells, exceeding their natural niche (1-3 cells). 48 months after the operation, subtotal villous atrophy and a decrease in the number of crypts are noted, in some cases their presence is reduced to single ones; the stroma becomes fibrotic. In a specimen obtained 76 months after surgery, villi of various lengths were found, with one long (150 µm) and 3-4 short (60-100 µm). The crypts become subatrophic, resembling intervillous folds, and can only be identified as crypts due to the presence of Paneth cells.

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After 90 months, no villi are visible; there are only local elevations covered with polymorphic intestinal epithelium. Crypts become rare; Paneth cells are found only sporadically in them. The subepithelial layer of the stroma is sclerotic, and deeper there is the development of fibrous connective tissue with powerful collagen fibers. A similar picture persists after 94 months.

At later stages, after 7-10 years, the proportion of goblet cells decreased, and in some cases they could no longer be identified morphologically. A statistically significant change in cell height was observed after 94 months. Along with the elongation of the cells, they became significantly thinner, especially on the lateral surfaces of the villi or in the villous areas.

Consequently, by this moment there is a gradual increase in dysplastic processes, which indicates the beginning of the third phase of compensatory changes - decompensation. The most pronounced dysplasia was found in the biopsy specimen of a patient with a history of 8 years after surgery. Most epithelial cells were polymorphic spindle cells. When sections are stained with Alcian blue, different colors of goblet cells and submucosal gland cells are observed, from light and transparent to dark. Mucus formation persisted until late follow-up. Compared with the period of 1-3 years of observation, after 8-10 years of reconstructive surgery, a significant decrease in mucus formation was found in the mucous membrane of the neovagina. This is confirmed by the fact that at this stage dysplastic processes increased in favor of stratified squamous epithelium.

Single crypts turned out to be small, almost equal in depth to the height of epithelial cells and reached sizes of 90–95 μm. The underlying stroma consisted of compacted fibrous connective tissue with strong collagen fibers. The apical apparatus of enterocytes was characterized by sharply atrophied microvilli, which sometimes resembled membrane vesicles separated from the cell surface. The basal bodies were larger than the villi themselves. The differentiation of cells into different types of enterocytes was opaque, and in most cases the cells were filled with discrete vesicles with mucus-like contents. There were cells with a “mixed phenotype”, expressing characteristics of both bordered and goblet cells. The basolateral domain of cells was characterized by excessive tortuosity, and observation of the course of the basement membrane was difficult.

An unexpected finding was that binucleate enterocytes were clearly visible, which is considered a clear sign of intestinal epithelial dysplasia. In no case were there signs directly or indirectly indicating squamous metaplasia (Fig. 2), which probably corresponds to the determination of the epithelium of the endodermal type.

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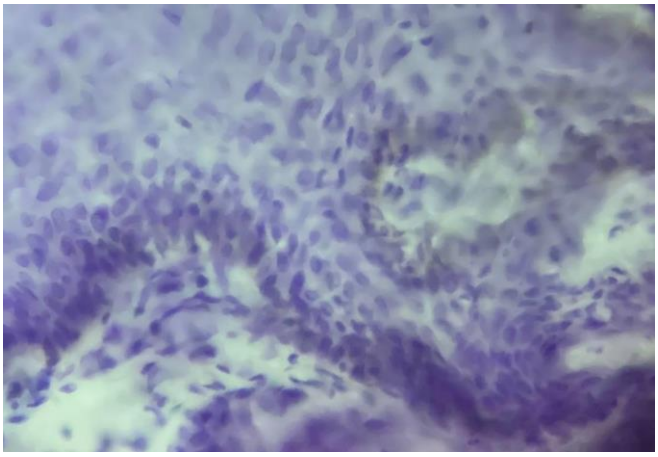

Fig. 2. Hyperplasia of the basal cells of the stratified squamous non-keratinizing epithelium of the neovaginal mucosa. 8 years after surgery. Hematoxylin and eosin staining. Increased 400.

The conducted research allows us to conclude that there are significant structural and functional changes at the considered levels of organization: at the level of structural and functional units, the cellular differentiated level and their synthetic activity. However, changes do not occur at all these levels simultaneously. Regardless of the level of manifestation of reactive changes, they are all realized during a three-phase process, ending with dysplasia of the intestinal epithelium (Fig. 3).

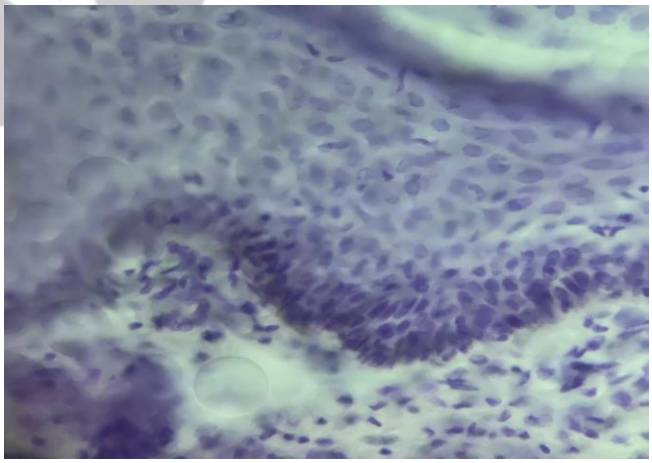

Fig. 3. Focal dysplasia of stratified squamous epithelium and moderate lymphocytic infiltration of the lamina propria. 10 years of observation. Hematoxylin and eosin staining. Increased 400.

Such changes in the walls of the neovagina confirm the adaptive-transforming mechanisms of the artificial vagina and post-transplant accommodation of the sigmoid colon. This circumstance, despite the stability of the histogenetic type and the stable determination of the intestinal epithelium of the

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sigmoid colon, requires certain oncological attention in the later stages of the functioning of the artificial vagina.

CONCLUSION

Thus, this study indicates the success of surgery to create a neovagina in women with MRKH syndrome, as demonstrated by complete re-epithelialization of the mucous membrane and the onset of adaptive-transforming processes 6-12 months after surgery.

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