

The Current State of the Problem of Diagnosis and Correction of Dysbiosis of the Artificial Vagina after Sigmoid Colpopoiesis

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Abstract Vaginal and uterine aplasia is a congenital malformation characterized by the absence of a vagina. This condition can be caused by various pathologies, including the Mayer–Rokitansky–Kuster–Hauser syndrome (SMRCX). This pathology is diagnosed in one of 4,500-5,000 newborn girls [4,10], it occurs as a result of impaired intrauterine development of the Muller ducts. Additional clinical manifestations may be malformations of the urinary system, malformations of the musculoskeletal system [4,10]. Currently, there is no single approach to the treatment of this pathology.

Keywords Newborn girls, Bloodless colpopoiesis, Neovagina microbiota

1. Introduction

The main methods include colpoelongation (bloodless colpopoiesis) and surgical intervention, which allow patients to lead a full sexual life. Surgical techniques are divided into traction (Vecchietty, Wallwiener method) and transplantation. Among the latter, the methods of Abbe – McIndoe, Davydov, intestinal vaginoplasty, Williams in the Creast modification are distinguished [4,10,21]. The first-line therapy is colpoelongation, and surgical techniques are used if it is ineffective. Currently, the creation of an artificial vagina from the sigmoid colon is an operation of choice and can be used in any variant of the anatomical structure of the perineum [4,10,21,23].

To fully understand the essence of the change in the neovagina microbiota after sigmoid colpopoiesis, it is necessary to give an idea of the intestinal microbiome. About 90% of the total microbiota consists of bacteria of the types Firmicutes and Bacteroidetes, mainly represented by hard-to-cultivate obligate anaerobes. Single% of the intestinal microbiota of adults consists of bacteria of the types Actinobacteria and Proteobacteria, an even smaller part is Fusobacteria, Verrucomicrobia, as well as methanogenic archaea of the type Euryarchaeota. Researchers identify three main enterotypes: Bacteroides, Prevotella and Ruminococcaceae, respectively [4,10,17]. Despite the active use of the term "dysbiosis" in the literature as a link in the pathogenesis of various diseases, the concept of the "normal" composition of the human intestinal microbiota is still not clearly defined, the microbiome is called a "virtual endocrine organ" [10,11,21].

The end products of carbohydrate catabolism are short-chain fatty acids produced by microorganisms in anaerobic intestinal conditions - acetic, propionic and butyric acids; they cause proliferation of intestinal goblet cells and increase mucin production. Another important role of the intestinal microbiota is the formation of colonization resistance, which prevents its colonization by pathogenic microorganisms [10,21,23]. Anatomical and physiological aspects of sigmoid colpopoiesis. To date, the creation of a neovagina from the sigmoid colon can be used in any variant of the anatomical structure of the perineum [4,10,21,23]. The sigmoid colon (Latin colon sigmoideum) is the final section of the human large intestine, resembling the letter "Sigma" (Σ) of the Greek alphabet, its further continuation is the rectum (lat. rectum) [1], the average length is about 40 cm, the wall has a powerful muscular musculature that ensures the movement of contents forward through the intestine, forms folds called a haustrum; the main function is the active absorption of water and the formation of fecal masses; the mucosa consists of a single-layer cylindrical epithelium, which provides a high absorption surface and participates in processes absorption of moisture and electrolytes from the contents of the intestine, as well as protection from the effects of various substances passing through the intestine. [4,10,21,23]. Sigmoid colpopoiesis.

2. Materials and Methods

The anatomical and physiological study of the changes occurring in sigmoid colpopoiesis is important for understanding the consequences of this surgical procedure. In sigmoid colpopoiesis, changes occur in the epithelial wall of the sigmoid colon, since its segment is used to create a vagina: during surgery, a segment of the sigmoid colon is extracted

and used to create a new structure - the vagina [4,10]; it is taken with preservation of blood supply and innervation; An important step is the reconstruction of the vascular system of the segment to ensure its blood supply. After transplantation of a segment of the sigmoid colon, it finds itself in a new environment different from the intestinal one, this includes changes in humidity, temperature and chemical composition; epithelial cells begin to adapt to new conditions; After surgery, regeneration and healing processes begin, epithelial cells of the sigmoid colon wall may undergo changes in structure and function, as they are exposed to the effect of new physiological factors [21,23]. After sigmoid colpopoiesis, monitoring of changes in the postoperative period is important: In the postoperative period, it is important to carefully monitor changes in the sigmoid colon wall in order to prevent possible complications and ensure effective healing. All these steps of intervention in the structure of the sigmoid colon in sigmoid colpopoiesis can affect the function and adaptation of the epithelium, which emphasizes the importance of a multifaceted approach and long-term follow-up in postoperative care [10,23]. Microbiocenosis of the vagina. The collection of microorganisms colonizing the vagina is called the microbiota or microbiocenosis of the vagina. Most of the microbial biomass in the vagina is made up of bacteria. At reproductive age, 1 ml of vaginal discharge may contain up to 10⁸ bacteria, which is explained by the presence of an available nutrient substrate – glucose, formed as a result of glycogen hydrolysis, which in turn is synthesized by epithelial cells after estrogenic stimulation [5,8]. When talking about the contribution of the vaginal microbiota to maintaining the health of the female reproductive system, attention is usually focused on the role of lactoflora, which is considered the normal microflora of the vagina [5,8]. Lactobacilli provide colonization resistance of the vagina, thereby reducing the risk of developing STIs and BV. By colonizing the vaginal epithelium, they can block the adhesion of various urogenital pathogens: group B streptococcus, *Staphylococcus aureus*, *G. vaginalis*, *Neisseria gonorrhoeae*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* [2,5,8,28]. The ability of lactobacilli to produce lactic acid is another important protective factor that suppresses the growth of the causative agent of gonorrhea and acid-sensitive microorganisms associated with BV [8,9,28]. In addition, lactobacilli also produce hydrogen peroxide, bacteriocins, or can modulate the local immune response and maintain the barrier function of the epithelium [8,9,13]. A decrease in the number or complete absence of peroxide-producing lactobacilli is associated with the development of BV and vaginal infections, an increased content of *Escherichia coli*, endometritis, and premature birth [8,9,13]. Certain types of lactobacilli are detected with different frequency in healthy women and patients with BV. The *L. crispatus* species is often detected in healthy women, and extremely rarely in patients with BV [13], while the *L. iners* species is often detected in high quantities in both categories of women [13,15,28]. Women with *L. iners* are more likely to be colonized by bacteria of the genera *Leptotrichia* and

Megasphaera, *Eggerthella*-like and BV- associated bacteria. Currently, most researchers point to the clear dominance of the *L. crispatus* species in the vaginal biotope of healthy women (32%), *L. crispatus* is a favorable prognostic factor, whereas the dominance of other species should be regarded as a less favorable indicator in prognostic terms [8,9,13,15,28]. Dysbiosis of the artificial vagina. Vaginal dysbiosis after sigmoid colpopoiesis can manifest itself in an imbalance of microorganisms, which in turn can lead to an increased risk of infections and inflammatory processes [12,16,20,22,24]. There are isolated literature data on neovaginal dysbiosis after sigmoid colpopoiesis, as the authors describe that the epithelium of the sigmoid colon is also very different from the epithelium of the EDV (estrogen of the dominant vagina) and penis. It is a single-layered columnar epithelium expressing a pair of cytokeratin K8/K18 and containing highly specialized epithelial cells such as goblet cells (producing mucus) and Paneta cells (producing antimicrobial peptides) and others [12,16,20,22,24,27]. Studies by foreign authors emphasize that dysbiosis in the artificial vagina can cause various pathologies, such as inflammation, discomfort and changes in the microflora, and can significantly affect the quality of life of patients after surgery. A systematic review of the neovaginal microbiome was conducted in accordance with PRISMA recommendations until October 2021. 13 articles were included, covering a total of 458 patients. Neovaginal designs were most often performed using penile and scrotum skin grafts, sigmoid segments, and peritoneal grafts. The revealed neovaginal microflora, as a rule, was polymicrobial and had similarities with native tissue. Nine studies have identified *Lactobacillus*: 5 out of 6 for the skin of the penis, 1 out of 3 for the sigmoid colon, 1 out of 1 for the peritoneum and 2 out of 3 for other types of transplants, which suggests that neovagina can support *Lactobacillus* either innately, through rectal migration or oral administration of probiotics [12,16,20,22,24,27]. A polymicrobial environment similar to bacterial vaginosis was found in 9 studies. Inflammatory markers were also described: 2 out of 6 for the skin of the penis, 2 out of 3 for the sigmoid colon, 0 out of 1 for the peritoneum and 1 out of 3 for other types of grafts. There was scant data on the effect of the duration of the postoperative period, oral hormones, dilatations, sexual practices or douching on the neovaginal microbiome. Understanding and optimizing the polymicrobial neovaginal microenvironment can improve surgical outcomes, especially inflammatory, painful, and infectious ones [12,16,20,22,24,27].

Data on the transformation of the microbiocenoses of the neovalage are very scarce, they mainly concern transgender women [12,16,20,22,24,27]. It is also necessary to study the issue of the development of the biotope of the neovagium after sigmoid colpopoiesis and the pathological processes that occur in it. Very little is known about the effect of surgical invagination and exogenous estrogen on the character of epithelial cell differentiation in neovagin. Although vaginal epithelial cells have the ability to differentiate into corneocytes in response to hormonal or mechanical signals, due to their expression of both K4/K13 (typical for non-horny multilayer

epithelium) and K1/K10, epithelial cells derived from the skin and sigmoid colon contain low levels of glycogen and do not express K4/K13. Although the neovagina, built entirely from the skin of the penis, and the neovagina, including the sigmoid colon, may be exposed to the same environmental effects (oxygen levels, estrogen levels, etc. Factors such as residual keratinization or the presence of goblet cells producing mucus can determine which bacteria colonize the neovagina. microenvironment and which bacteria are beneficial and which are pathogenic [12,16,20,22,24,27]. Thus, people suffering from neovaginal symptoms may need different courses of treatment, depending on the tissue used to create the neovaginal canal. In general, knowledge of the epithelium used for vaginoplasty does not support the view that the optimal neovaginal microenvironment would include *Lactobacillus* spp. and acidic pH [12,16,20,22,24,27]. The neovaginal microbiome. Despite the enormous impact of the vaginal microbiome on the sexual and reproductive health of MV, there have been few reports of a microbiota colonizing neovagina, and there is no data on which microbiota is optimal and which is associated with inflammation, symptoms, and STI risk. Until recently, data on the microbiota colonizing neovagina were limited to case reports and small studies that used limited culture-based detection methods or targeted PCR to detect the presence of specific species of interest. In addition, there is evidence that representatives of the lactobacillar microflora are isolated in 75% of cases from an artificially formed microecosystem - neovagines of transsexual women (male-to-female). At the same time, the species *L. gasseri* and *L. crispatus* were most often isolated. The authors believe that the main source of lactoflora in the absence of glycogen-enriched epithelium may be the intestinal microbiota [12,16,20,22,24,27]. Recently, one study by Birse et al. (2020) used a combination of proteomics and 16S rRNA gene sequencing to study the neovaginal microbiome in five tF patients, four of whom underwent penile inversion vaginoplasty and one patient underwent sigmoid vaginoplasty (median 10 years after vaginoplasty, range 4-36 years). Although the small sample size limits the ability to draw conclusions, this important study is the first study of the neovaginal microbiome and hints at interesting hypotheses [12]. It is interesting to note that the neovaginal microbiome of the only participant who underwent sigmoid vaginoplasty was clearly expressed, completely absent *Prevotella* and was instead determined by taxa common in the intestinal microbiota, *Bacteroidaceae* and *Enterobacteriaceae* [12]. These data suggest that even many years after vaginoplasty, the origin of the tissue used determines the colonizing microbiota. Therefore, it is extremely important that all future studies of the neovaginal microenvironment take into account the source of tissues and ideally ensure stratification by the source of tissues.

3. Results and Discussions

Researchers and doctors in this field should be aware that, depending on the tissue used for neovaginal construction, different treatment standards and clinical recommendations

may be required [12,16,20,22,24,27]. There are several important knowledge gaps in understanding the neovaginal microbiome that urgently need to be filled to improve neovaginal healthcare. Preliminary data from Trans Pulse Canada (n = 2873), a national survey of the THD population in Canada, show that almost half of the participants who underwent vaginoplasty had experienced gynecological symptoms in the past, including unpleasant odor, abnormal or disturbing discharge and itching. Such symptoms are often associated with BV in EDV; however, the main cause of these symptoms in neovagin remains unidentified [12]. Neovaginal swabs sent for clinical diagnosis often give the results of "altered vaginal flora incompatible with bacterial vaginosis", and treatment developed for estrogen-dominant vagina (EDV) (metronidazole) often proves ineffective [12,16,20,22,24,27]. Candidiasis is another common cause of vaginal itching in EDV; One series of cases was published in which neovaginal candidiasis was reported in five people [16], which requires further characterization of the types of neovaginal candidiasis and the development of clinical recommendations for prevention and treatment. The cause of the neovaginal odor also requires further investigation. The unpleasant odor in EDV is associated with the production of biogenic amines by bacteria associated with BV [16,17]. To determine treatment options, more extensive studies using omic approaches are urgently needed, including metagenomics, metatranscriptomics and metabolomics to characterize the neovaginal microenvironment in individuals with symptoms [16,17,20]. It is equally important to determine what the optimal neovaginal microbiota is after sigmoid vaginoplasty. This information is important for determining treatment options, because what a treatment leaves intact may be just as important as what it removes. Part of the effectiveness of metronidazole in the treatment of BV caused by EDV is that it selectively preserves lactobacilli and thus helps maintain an optimal microbiome resistant to re-colonization by inflammatory / pathogenic anaerobes [16,17,20]. Additional information on the microstructure of the neovaginal epithelium after penile inversion or sigmoid vaginoplasty will help determine which type of bacterial commensals can contribute to the creation of an optimal, low-inflammatory and protective microenvironment of neovagin [16,17,20]. Methods of diagnosis of dysbiosis. To date, several approaches can be used to evaluate the vaginal microbiota in clinical practice. The microscopic method is traditionally the most affordable and cheapest method and allows you to identify up to 10 morphotypes of microorganisms living in the vagina, including *Lactobacillus* spp., *Gardnerella vaginalis*, *Bacteroides* spp., *Mobiluncus* spp., *Leptotrichia* spp., *Fusobacterium* spp., *Veillonella* spp., *Candida* spp., gram-positive and gram-negative cocci, gram-negative rods [2,3]. The microscopic method has a number of limitations: microscopy makes it impossible to identify a number of pathogens significant in pathology, which is due either to their small size (*Chlamydia trachomatis*), or the absence of a cell wall (*Mycoplasma* spp. and *Ureaplasma* spp.) or pronounced studies in the diagnosis of BV (identification of "key cells") ranges from 40 to 90%,

The specificity is about 80% [2,3,9]. The bacteriological (or cultural) method still remains the "gold" standard in the diagnosis of many infectious diseases, as it allows not only to isolate pathogenic microorganisms from the patient's material, but also to identify them to the type (strain), estimate their approximate number and determine sensitivity to antimicrobial agents. At the same time, it should be remembered that in accordance with modern ideas about the composition of the vaginal microflora, some reproductively significant obligate pathogens (*Chlamydia trachomatis*, *Mycoplasma genitalium*) and most opportunistic microorganisms inhabiting the vagina are difficult to cultivate or uncultivated. The sensitivity of this research method in the diagnosis of BV is 25-60%, the specificity is about 90% [2,3,9]. BV is a clinical and laboratory syndrome characterized by a decrease in the number of lactobacilli and an increase in the number of opportunistic pathogens (including *G. vaginalis* and *A. vaginae*), which can lead to the appearance of vaginal discharge, often accompanied by odor, and an increase in vaginal pH. To date, the diagnosis of BV can be divided into clinical (Amsel method), microscopic ("Bedside" – microscopy, Nugent method, Ison-Hay method), cultural, chromatographic and molecular biological. In clinical diagnosis, the Amsel method is the leading one. Its implementation is based on the identification of any three criteria out of four possible [9-12,19,3]: the presence of specific vaginal secretions; the pH of the vaginal discharge is above 4.5; a positive amine test; identification of "key" cells during microscopic examination of the native drug. The sensitivity and specificity of this test do not exceed 85% [2,3,9]. In addition, BV can be diagnosed based on the results of smear microscopy: for this purpose, the Nugent scale is used, which takes into account the nature of the vaginal microflora. The advantages of Nugent's method are relatively high sensitivity and specificity, but the method is time-consuming to perform [2,3,9,15]. The bacteriological method is practically not used, since the cultivation of anaerobic microorganisms causes significant difficulties, and the identified ones are components of the normal vaginal microflora. The gas-liquid chromatography method allows comparing the content of the main metabolic products of lactobacilli and *Gardnerella vaginalis* in the vaginal discharge. In BV, the concentration of succinic acid increases, and the amount of lactic acid decreases, which is used as a positive diagnostic criterion. In practice, this method is rarely used due to the high degree of complexity and cost [2,3,9]. The method of qualitative polymerase chain reaction (PCR). It allows you to identify the nucleic acid of a microorganism, which allows you to identify microorganisms that cannot be cultured in the laboratory. [2,3,9]. The quantitative PCR method allows to identify with high accuracy the majority of participants in vaginal microbiocenosis, as well as to determine their absolute number in the shortest possible time. To date, there is an available set of reagents for a comprehensive assessment of the vaginal microbiota by PCR-RV ("Femoflor" produced by DNA technology), and criteria for interpreting the results have been developed [2,3,9,14], which allows

this method to be implemented in clinical practice. Methods of nucleic acid amplification (MANC) in the presence of a minimum initial amount of a microorganism, fragments of the pathogen genome are isolated as a result of the amplification reaction. The diagnostic sensitivity is 85-98%, and the specificity is 100%. The technology of quantitative assessment of microorganisms (real-time PCR/NASBA) is one of the most informative methods for diagnosing BV, nonspecific colpitis and mycotic vulvovaginitis to date. [3,9,19]. Methods for correcting dysbiosis of the pathogenetic component of chronic and often recurrent forms of BV are the ability of microorganisms to form bacterial biofilms [3]. It should be noted that biofilm formation is characteristic of both symbiotic bacteria (including *Lactobacillus* spp.) and pathogenic microorganisms. Biofilms formed during BV [2,3] provide a 5-fold increase in the resistance of bacteria to high concentrations of hydrogen peroxide and 4-8-fold to lactic acid, respectively, compared with planktonic forms of microorganisms [2,3,6]. It was found that biofilms in BV are mainly represented by the species *G. Vaginalis* - up to 60-95% of the film weight, and the species *A. vaginae*, which make up 1-40% of the biofilm, respectively; up to 5% of biofilms in BV are species *Lactobacillus* spp. [6,28]. Treatment of dysbiosis may include the use of probiotics, prebiotics, antimicrobials, and others. The therapeutic approach to correcting the imbalance of the vaginal microbiota includes measures aimed at eliminating opportunistic microflora with the help of antibacterial drugs. Repeated use of antibacterial drugs in the treatment of recurrent BV is itself a risk factor for the development of microbial imbalance [6,7], which closes the pathological circle: "antibiotics-dysbiosis-antibiotics" [7]. Given the role of LPS gram-negative bacteria in the pathogenesis of BV, it is advisable to include drugs aimed at neutralizing and eliminating LPS in the scheme of correction of this syndrome. For this purpose, after the completion of antibacterial therapy, additional use of drugs with sorption-detoxification effect (enterosgel sorbent) was proposed [1,26]. Local detoxification in BV with the use of enterosgel sorbent increased the effectiveness of treatment, characterized by a decrease in the frequency of relapses of the disease by 5 times compared with standard therapy [1,9]. Another modern trend in the pathogenetic treatment of BV aimed at inhibiting LPS is replacement therapy with probiotics, which are living microorganisms of microbial origin that have positive effects on the physiological, biochemical and immune responses of the body through stabilization and optimization of the function of normal microflora [2,3,9,11,14,26]. An important pathogenetic justification for the use of probiotic cultures of lactobacilli to correct microbial imbalance in the vaginal biotope is the property of lactobacilli to destroy cells of opportunistic microorganisms with antimicrobial peptides [11,18,19,26]. In later in vitro studies, it was found that the metabolites of the probiotic strains *L.rhamnosus* GR-1 and *L.reuteri* RC-14 are able to suppress biofilms formed by *G. vaginalis* and *A. vaginae*, and in combination with metronidazole cause the destruction of biofilms and act bactericidal on these microorganisms [6]. The authors also describe the

results of BV treatment using bacteriophages [11,18,19]. However, the issue of translocation of lactobacilli from the intestine to the vagina remains open and controversial, since how such a transition is carried out has not yet been fully clarified [11,18]. One of the probiotics designed to restore the vaginal microflora is the biologically active food additive ecofemin floravag for oral administration, containing viable bacterial cells *L. crispatus* (60%), *L. brevis* (20%) and *L. acidophilus* (20%). The advantages of using the oral form of ecofemin-floravag include the unique composition of this probiotic drug, however, further study of the mechanism of action of probiotic preparations of lactobacilli is required in accordance with the principles of evidence-based medicine [17,22]. There is insufficient data on methods that contribute to the creation of an optimal neovaginal microenvironment both in the immediate postoperative period and for long-term hygiene and care. Due to the lack of evidence-based guidelines, recommendations for neovaginal care vary significantly from center to center [25]. After surgery, frequent dilation is necessary to prevent stenosis of the neovaginal canal [25,27], the authors recommend abundant water-based lubrication to facilitate dilation and protect the integrity of surgical dilators [25,27].

4. Conclusions

Douching and the use of soap or lubricants may contribute to molecular BV, but their effect on the neovaginal microbiota is unknown. Regular use of hygiene products and boric acid is also often reported to reduce pH, colonize with lactobacilli, and treat vaginal yeast infections [16,17,22]. A review of the literature data emphasizes that sigmoid colpopoiesis can lead to various changes in the anatomy and physiology of the vagina, which requires additional study to optimize the results of this surgical procedure and reduce possible negative consequences. Summarizing the existing data and highlighting the main trends in research on dysbiosis of the artificial vagina after sigmoid colpopoiesis emphasizes the importance of further research and development of effective methods for standardization of testing, development of classification systems and treatment of neovaginal dysbiosis.

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