OS CAMINHOS DE MELHORIA DOS MÉTODOS DE TRATAMENTO DA HIPOSPÁDIAS EM CRIANÇAS: REVISÃO DE LITERATURA**THE WAYS OF IMPROVEMENT OF THE METHODS OF HYPOSPADIAS TREATMENT IN CHILDREN: LITERATURE REVIEW****СОВЕРШЕНСТВОВАНИЕ СПОСОБОВ ЛЕЧЕНИЯ ГИПОСПАДИИ У ДЕТЕЙ: ОБЗОР ЛИТЕРАТУРЫ**

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RESUMO

A relevância do estudo se deve ao fato que a hipospádia é uma malformação congênita do sistema urogenital em meninos. A taxa de incidência de hipospádia varia em diferentes países. O principal fator etiológico no desenvolvimento desse defeito é o desequilíbrio hormonal da mãe que é causado por várias razões. A correção da hipospádia é realizada apenas cirurgicamente. Atualmente, muitos métodos cirúrgicos são utilizados, mas, apesar disso, o número de complicações no pós-operatório permanece alto. O objetivo do artigo foi estudar os resultados do tratamento cirúrgico da hipospádia em crianças após vários métodos de uretroplastia utilizando diferentes enxertos. Foram pesquisados os artigos no único banco de dados eletrônico Pub Med, Elsevier, Scopus, Web of Science de 2007 a 2018. Foram examinados 265 artigos de tratamento da hipospádia usando os seguintes métodos: método TIP (placa incisada tubularizada), Mathieu, GTIP (placa incisada tubularizada de enxerto) e uretroplastia em dois estágios de Bracka. As complicações mais comuns em vários estudos foram seguintes: fístula, estenose da luz neurouretral e deformidade peniana secundária. Assim, os métodos existentes de tratamento cirúrgico desse defeito em crianças não levam à completa eliminação da ocorrência de complicações pós-operatórias. Nesse sentido, o tratamento das hipospádias permanece relevante e requer o desenvolvimento de novos métodos de uretroplastia.

Palavras-chave: *crianças, métodos TIP, GTIP e Bracka, complicações.*

ABSTRACT

The relevance of the study is due to the fact that hypospadias is a congenital defect of the urogenital system in boys. The incidence rate of hypospadias differs in different countries. The main etiological factor of this defect development is a hormonal imbalance of different origin in mothers. Hypospadias can be corrected only surgically. Currently, there are a number of surgical approaches used, but still, the number of complications in the postoperative period remains high. The purpose of the article was to evaluate the outcomes of surgical correction of hypospadias in children observed after different approaches to urethroplasty involving transplanting. The authors performed a search for articles in electronic databases Pub Med, Elsevier, Scopus, Web of Science for the period from 2007 to 2018. The authors reviewed 265 articles dedicated to the correction of hypospadias by the following methods: TIP (tabularized incised plate), Mathieu, GTIP (graft tabularized incised plate) and two-stage Bracka urethroplasty. The most widespread complications mentioned in different studies were fistulas, stenosis of the urethral neo-meatus, and secondary deformation of the penis. Current approaches to surgical correction of hypospadias in children do not provide complete recovery from post-operative complications. Due to this fact, the issues of treatment of hypospadias remain relevant, requiring the development of new approaches to urethroplasty.

Keywords: *children, TIP, GTIP and Bracka methods, complications.*

АННОТАЦИЯ

Актуальность исследования обусловлена тем, что гипоспадия является врожденным пороком развития мочеполовой системы у мальчиков. Показатель частоты встречаемости гипоспадии различается в разных странах. Основным этиологическим фактором развития данного порока является гормональный дисбаланс матери, вызванный различными причинами. Коррекция гипоспадии осуществляется только хирургическим путем. В настоящее время применяются множество оперативных методик, но несмотря на это, количество осложнений в послеоперационном периоде остается высоким. Цель статьи – изучить исходы хирургического лечения гипоспадии у детей после различных методов уретропластик с использованием разных трансплантатов. Проведен поиск статей в единых электронных базах данных Pub Med, Elsevier, Scopus, Web of Science с 2007 года по 2018 год. Рассмотрены 265 статей лечения гипоспадии с применением следующих способов: TIP (tubularized incised plate) метода, Mathieu, GTIP (graft tubularized incised plate) и двухэтапной уретропластики Bracka. Наиболее распространенными осложнениями в различных исследованиях были свищ, стеноз провета неоуретры и вторичная деформация полового члена. Таким образом, существующие методики оперативного лечения данного порока у детей не приводят к полному устранению возникновения послеоперационных осложнений. В связи с этим лечение гипоспадии остается актуальным и требует разработок новых способов уретропластики.

Ключевые слова: дети, TIP, GTIP и Bracka методы, осложнения.

1. INTRODUCTION

Hypospadias is the second widespread congenital anomaly of external male genital organs, giving the leading position to cryptorchism. It is diagnosed in 1 in 200–300 newborn babies. The degree of hypospadias can vary from insignificant to severe, depending on the localization of the urethral meatus (Bouty *et al.*, 2015; Canning, 2016; Aydogmus *et al.*, 2017; Bhat *et al.*, 2017; Dokter *et al.*, 2018).

According to the performed systematic review of 169 original articles, the incidence rate of hypospadias varies significantly in different countries from 4 to 43 cases per 10,000 newborns. Some research data indicates the increase in the incidence rate of hypospadias in China, Australia, USA, and Europe (van der Zanden *et al.*, 2012). Monitoring of congenital anomalies, conducted by the European register by 19 forms, showed that in Moscow, during the past 4 years, hypospadias occupied the 4th place and its incidence rate was 8.86% of the total diagnosed congenital anomalies of the development (Rudin *et al.*, 2013). A major European research that included more than 5.8 million newborns in 23 UEROCAT registers for the period from 2001 to 2010 showed that the general incidence rate of hypospadias was 18.61 per 10,000 of births (Bergman *et al.*, 2015). European Surveillance of Congenital Anomalies (EUROCAT) is a network of registers of congenital anomalies in Europe that is financed by the EU and exists for more than 30 years. It operates according to the standard methodology for registering the data on the cases of congenital anomalies at birth, death of a fetus older than 20

weeks of gestation age and miscarriage, and anomalies of fetus development. EUROCAT surveils three spheres: incidence rate, primary preventive measures, and prenatal screening. In general, in Europe, the performed analysis on the relative risks based on mothers' age showed that teenage mothers have a higher risk of NCA development (non-chromosomal congenital anomalies) as compared to elder mothers aged 35–44, who did not have that risk, and that the age of mothers itself does not contribute to the risk of NCA development (Loane *et al.*, 2009). General incidence rate of hypospadias in Rotterdam is 38 cases per 10,000 of the living population. In Mainz, from 2001 to 2010, the incidence rate was 36.83 per 10,000 births (Pierik *et al.*, 2002; Ayob and Arnold, 2016).

One of the studies, conducted for the analysis of mothers' age, showed that the highest incidence rate of the total hypospadias in six age groups of mothers was in the group of teenage mothers as compared to the mothers aged from 25 to 29 years old (Bergman *et al.*, 2015).

Retrospective analysis of the database ECLAMC the Latin American Collaborative Study of Congenital Malformations (ECLAMC) contained the data on the newborns that were diagnosed with hypospadias from January 1989 to December 2012. The study excluded the countries that lacked or provided incomplete information. The final analysis included 159 hospitals from six counties of South America. The researchers examined 4,020,384 of newborns and diagnosed 4,537 cases of hypospadias, which gave the incidence rate of 11.3 per 10,000 of newborns. The analysis of the tendencies revealed a global increase in the hypospadias

incidence rate by 0.2 cases per 10,000 newborns annually ($h < 0.0001$). This made the increase by 3.3% for the studied period. Totally, 82.2% of cases were diagnosed as isolated hypospadias, the rest 17.8% of hypospadias cases were associated with other anomalies. The most widespread associated anomaly was cryptorchism, which was observed in 15.3% of cases. The present study provides epidemiologic based proof that during the past twenty years, an incidence rate of hypospadias increased in different countries of South America. Reports from other countries show the increase in hypospadias incidence rate from 1 to 4% (Fernández *et al.*, 2017). The study of temporary tendencies and geographical variations of the incidence rate of isolated anomalies, multiple anomalies and general cases in China from 1996 to 2008 showed that the rate were 7.64, 1.39 and 9.03 per 10,000 births, respectively. The highest incidence rate (12.10 per 10,000 births) was registered in the eastern region. Increasing tendencies and differences in the incidence rate of hypospadias by the classification of urban (5.28%) and rural (9.79%) regions and geographical location were the following: in eastern region – 9.08%, in central region – 9.08%, and in western region – 6.57%. These rates indicate the fact that the impact on the environment and mothers' age can play a crucial role in the development of hypospadias (Li *et al.*, 2012). The incidence rate of hypospadias in Poland is 17.9 per 10,000 births (Kowal *et al.*, 2015). According to some researchers, the total incidence rate in the Danish county Funen was 16.9 per 10,000 births. For the period of 1986-1999, as compared to 2000-2009, the incidence rate of hypospadias nearly doubled from 12.2 in the first period to 23.7 in the second one, but in 2008, the incidence rate decreased, especially the rate of simple cases as compared to the severe ones (Nissen *et al.*, 2015).

In the case of extracorporal fertilization, the incidence rate of hypospadias increases by 5 times (Makazhanov, 2012; Badawy *et al.*, 2018). Many studies were conducted for the children who were conceived due to assisted reproductive technology (ART). In the general population, 3% of the survived newborns have one serious congenital anomaly at birth. According to the authors, the main causes of congenital anomalies are genetic factors that also provoke spontaneous preterm abortions in the first trimester (Kermani *et al.*, 2012; Gong and Cheng, 2017). Distal form (glans penis, coronal, or subcoronal) of hypospadias in newborns are registered in 60–65% of cases, mid penile form –

in 20–30% of cases, and proximal (posterior penile, penoscrotal, scrotal, or perineal) form – in 10–15% of cases (Singal *et al.*, 2016; Alsaywid *et al.*, 2017; Ollivier *et al.*, 2018).

2. MATERIALS AND METHODS

The most widespread complication after the urethroplasty is urethrocutaneous fistula. After the primary Duckett urethroplasty with a preputial island flap, successful closure of the fistula was registered in 6.55%, and in 33.5% of cases, recurrent unfavorable outcome was registered. The potential factors for the development of fistulas are patients' age, fistula size, localization and quantity of fistulas after the primary urethroplasty, the duration of the operation time, the length of the neo-urethra, time of the fistula closure and post-operative infections. It was established that the recurrent fistula was observed in patients with ucf diameter of 2 mm and more. The authors also believe that the application of caudal regional anesthesia does not prevent the development of urethrocutaneous fistula (Menon *et al.*, 2017; Kreysing and Höhne, 2016; Seleim *et al.*, 2017; Han *et al.*, 2018; Kagantsov and Surov, 2018).

W. Snodgrass and N. Bush in their study made a review of widely used surgical methods of restoration for distal and proximal hypospadias, their complications, functions of urinary tracts and esthetic results. The obtained data indicate that the tip is more preferable than Mathieu. In all the cases of primary hypospadias, only two methods were used: tip and two-step preputial grafts (Snodgrass and Bush, 2016; Snodgrass and Bush, 2017). To compare the complications after the urethroplasty for the distal hypospadias, the authors performed a systematic review of the information in the databases Medline, Embase, and Cochrane from 1990 to 2009. According to the data obtained in 23 publications, 15 series of reports and 1,892 cases of tip method operations and 10 series of reports on 1,496 cases of Mathieu method operations, the following complication rates were revealed: meatus stenosis, neo-urethra strictures, and fistulas were observed in 6.9% of cases after tip urethroplasty (tabularized incised plate) and 6.7% after Mathieu urethroplasty (Snodgrass and Bush, 2016; Chandrasekharam, 2016).

One of the studies was focused on the comparison of the treatment outcomes of hypospadias by the methods of tip and urethroplasty without urethral plate incision. The general rate of urethrocutaneous fistula after tip

was 36%, and after urethroplasty without urethral plate incision – 32%. The second complication in the rating was meatus stenosis – 27.4%. Penis edema was registered in 7.55% of cases, hematoma – in 1.9% of cases, infection of urinary tracts – in 1.9% of cases in both groups (Wilkinson *et al.*, 2012).

The authors show the results of two-step urethroplasty with buccal mucous graft. In 1/3 of patients, graft fibrosis developed after the first step. Complications after the second step of the surgery were registered in 34% of patients: urethral stenosis, glandular split, fistula, balatinis xerotica obliterans (Leslie *et al.*, 2011; Faure *et al.*, 2016). Thus, general complications registered after the correction of hypospadias included urethrocuteaneous fistula, meatus stenosis, neo-urethra stenosis, urethra diverticula or urethrocele, which can lead to the development of infection, esthetic defects, hair growth in the urethra, splattering or abnormal urine flow, erectile dysfunction, balatinis xerotica obliterans leading to the strictures. In the majority of cases, postoperative complications are usually revealed at the early stage within the first months after the surgery, but some complications such as fistula, neo-urethral stenosis, and recurrent deformation of the penis can be registered at later stages (Kendigelen *et al.*, 2016; Keays and Dave, 2017; Faasse and Liu, 2017). The average time of the diagnostics of complications such as glans penis deformation was 2 months, of urethral fistula, meatostenosis, stricture and diverticula of the urethra – 6 months. Control examination of the patients in the post-operative period was performed in 1.2 weeks and 1.3 and 6 months, and further one time a year until the completion of penis growth (Tiryaki *et al.*, 2016).

In the majority of cases, hypospadias has isolated character, but it can also be associated with other anomalies, especially those that are located in the urogenital tract (Bouty *et al.*, 2015). Hypospadias is one of the most widespread congenital anomalies. However, its etiology remains understudied. The study on the role of genetic and ecologic factors in the development of familial aggregation of hypospadias was conducted. Monogenic mode of inheritance of hypospadias in families and association with genetic defects in the biosynthesis of androgens indicates on the genetic background (Schnack *et al.*, 2007). Heritability of hypospadias is high, around 65–75%, and the risk of its development is estimated as elevated (12–20-fold in the first degree of family relatives) (Schnack *et al.*, 2007). The results of the conducted cohort study of the

familial aggregation of hypospadias within the couples of male twins and first, second and third-degree relatives showed that the genetic inheritance is observed equally often patrilineally and matrilineally, and the risks of hypospadias recurrence for brothers and sons are similar. The main role in familial hypospadias can be played by genetic factors and not by general environmental ones (Schnack *et al.*, 2007; Li *et al.*, 2016; Kim *et al.*, 2016; Kozyrev *et al.*, 2017).

Other causes of hypospadias in children include genetic polymorphisms, identified in FGF8 and FGFR2 genes, that were observed in a minor share of cases. Since the development of male reproductive organs is an AR-dependent process, it can be suggested that polymorphisms, identified in FGF8 and FGFR2 genes in boys with hypospadias, can prevent AR-responses during the development of the urethra (Beleza-Meireles *et al.*, 2007; Sadeghi *et al.*, 2017).

A longitudinal study that included vegetarian women showed that the influence of phytoestrogens on the development of a male reproductive system and confirmed that the incidence rate of hypospadias in newborn boys was higher (North and Golding, 2000). Urogenital anomalies, including hypospadias, are met in 22% of cases in newborns with Ellis-van Creveld syndrome (EVC) (Kowal *et al.*, 2015). Hypospadias was described in more than 200 other syndromes, like WAGR, (Wilms tumor, Aniridia, Genitourinary defect, mental Retardation complex), Denys-Drash syndrome (genitourinary defects and susceptibility to WT) and Smith-Lemli-Opitz syndrome (congenital anomaly of heart, lungs, kidneys, gastrointestinal tract and genitals). The genetic basis of these syndromes is the mutation in the genes, like C31 in children with Denys-Drash syndrome or DHCR7 in children with Smith-Lemli-Opitz syndrome (Bouty *et al.*, 2015; Nakamura *et al.*, 2018).

The group of chemical substances that were studied in terms of influence on hypospadias development is pesticides. Some of them can be destructive for the endocrine system. A major study in Australia, based on professional data of newborns registration, reported on the elevated risk associated with heavy metals but not with other chemical groups of substances. Prospective cohort study conducted in Denmark gave some limited proof that professional impact of such endocrine destructive substances, such as phthalate ester ethers, alkyl-phenols, and bis-phenols, on future mothers, in general, elevated the risk of hypospadias development (Morales-Suárez-

Varela *et al.*, 2011). Urethral closure depends on the transformation of testosterone into dihydrotestosterone (DHT) (anabolic steroid of 5 α -reductase type II), binding of DHT ligand with nuclear apparatus of androgen and the following respective androgen receptors activities (AR). The last two studies highlighted the influence of progesterone on the increase in the risk of hypospadias development (Carmichael *et al.*, 2012; de Andrade *et al.*, 2017; Wilkinson *et al.*, 2017; Wong *et al.*, 2018; Wu *et al.*, 2018).

Hypospadias develops as a result of the anomalous or incomplete formation of the urethra during the first weeks of embryonal development. There are two stages in the development of exterior reproductive organs in humans: early hormone-independent stage (5–8 weeks of the gestation) and hormone-dependent stage (8–12 weeks) (Blaschko *et al.*, 2012). Embryogenesis: Primary gonads are formed between the 4th and 5th weeks of the fetus development. The presence of Y-chromosome provides the development of the testicles. The formation of the posterior urethra by splitting of the primary cloaca into the primitive rectum and urogenital sinus occurs between the 30th and 40th day of the embryo life. Urogenital sinus or vesicourethral channel develops into the bladder and posterior urethra. By the 43–45th day (the length from the coccyx to the crown of head is 15 mm), the posterior urethra is completely formed and opens as ostium urogenitale. The development of the anterior urethra starts at the beginning of the 3rd month. On the 5th week of gestation, genital eminence develops in a form of tissue cranially to cloaca; on the 6th week, urethral folds and scrotal rolls appear. It is suggested that Y-chromosome encodes the synthesis of protein Y-antigen that contributes to the conversion of indifferent gonad into testicular tissue. Embryogenic phenotypic differences develop in two directions: differentiation of inner ducts and outer genitals. At the early stages of development, an embryo contains both female (paramesonephric) and male (mesonephric) ducts.

Internal genital organs develop from Wolffian and Mullerian ducts that are located nearby each other in an embryo at the early stages of development. During the development of a male embryo, Mullerian ducts begin to degenerate at the 6th week, which indicates on even earlier differentiation of germinal epithelium and activation of hormonal activity of the formed gonad. In male embryos, Wolffian ducts develop into epididymis, seminal ducts, and seminal vesicles, while Mullerian ducts disappear. Female

embryos have Mullerian ducts develop into fallopian tubes, uterus and upper part of the vagina and Wolffian ducts regress. Outer genitals and urethra in embryos of any sex develop from urogenital sinus and genital eminence, genital folds, and hills. Development of the urethra from the urethral plate is described in the works of different authors. According to Herzog and Howard, quick growth of urethral duct from urethral plate coincides with the intensive development of Wolffian bodies on the 6th – 10th week of gestation. The closure of urethral ducts begins around the meatus of the urogenital sinus, gradually spreading upwards to the glans penis strictly by the median line. This process begins from the 10th – 11th week of the embryo life and completes by the end of the 14th week. By this time, when the length of an embryo from the coccyx to the crown of head reaches 80mm, the outer urethral meatus opens on the volar surface of the penis under its glans. Glandular section is formed independently from the isolated urethral plate. The migration of the outer urethral meatus to the top of the glans penis is observed from the 15th to the 20th week of gestation. Herzog used to identify outer urethral meatus in a fetus located on the lower surface of the glans penis at the 4th month of the gestation.

Fetal testicles can synthesize a protein called anti-Mullerian factor that reduces paramesonephric ducts in male embryos. On the 8th week of gestation, when the gonads differentiated into testicles on males (XY), a hormone-dependent phase of differentiation begins. Besides, starting on the 10th week of gestation, first, under the influence of chorion gonadotrophic hormone (CGH), and then, under the influence of luteinizing hormone (LH), fetal testicles begin to synthesize a lot of testosterone that affects undifferentiated outer genitals leading to their masculinization. During the 5th week of pregnancy, mesodermal cells spread on the cloaca membrane and form a couple of cloaca folds. These folds are located along the line anterior to the cloaca membrane to form genital tubercle. At the end of the 2nd month, the tubercle is 1.5 mm high. However, at this stage, it is still impossible to identify visually a male embryo from a female one. The differences in the exterior structure of the genitals appear by the end of the 3rd month (50–55 mm) when in female embryos this tubercle begins to bend down and in male embryos, it remains straight. By this time, male embryos have closure of the urethral duct started from the bottom to the top. The formation of genital tubercle completes by the 6th week. A week later, scrotum folds and urethral plate

appear in the bottom of the tubercle. Genital tubercle is growing, transforming into a penis, urogenital sinus develops into a prostate and prostatic part of the urethra, and genital folds merge forming a male urethra. The meatus is formed by the retraction of epithelial tissue inside the glans penis and merges with the distal end of the forming urethra in the area of fossa navicularis. The fusion of urethral folds is the key stage in the formation of a penis. Penile skin, including the foreskin, develops from ectodermal tissue that covers the whole penis. According to other authors, the formation of the urethra coincides with the formation of the foreskin and frenulum that are the two formations that are also deformed in males with hypospadias. The development of the foreskin coincides with the completion of urethral duct closure under the glans penis. On the 3rd month of gestation, there is a focus of epithelization on the top of the glans penis is observed. It is a plastic material for the formation of inner and outer layers of the foreskin. It is believed that epithelial layers, that cover the glans, fuse with the epithelial cover of the closed urethral duct and form the frenulum. By the end of the 1st trimester, the genitals get formed completely. It should be noted that inner male genitals (genital ducts) are formed under a direct action of testosterone, while the external genitals develop under the influence of the active metabolite T-DHT (dihydrotestosterone), which is produced in cells in the presence of a specific enzyme – 5 α -reductase (Bouty *et al.*, 2015; Shirazi *et al.*, 2016).

3. RESULTS AND DISCUSSION:

As a rule, hypospadias is an isolated anomaly, but it can represent one of the peculiarities of more than 200 different syndromes. The diagnostics includes the collection of anamnesis, clinical examination, evaluation of local status, laboratory analyses and diagnostic instrumental methods. The associated anomalies in the development of urogenital ducts are widespread in newborns with proximal hypospadias. The most common anomalies are groin hernia, cryptorchism, and renal agenesis. For this reason, proximal hypospadias requires thorough evaluation. The presence of one or both testicles can indicate such a condition as an androgenetic syndrome or combined gonad dysgenesis. In this case, it is necessary to investigate the karyotype and perform ultrasound scanning of urinary tracts and inner genitals. Besides, endoscopic examination of the urethra and bladder during the surgery to

exclude the urogenital sinus. If hypospadias is associated with kidney and renal tract anomalies, it is necessary to perform advanced clinical examination using urodynamic tests, X-ray imaging (excretory urography, urethrocytography), radioisotope and endoscopic methods of diagnostics (Manzoni *et al.*, 2004).

Based on the results of the life and diseases anamnesis, local status, and laboratory and instrumental data, the form of hypospadias is identified. But precise diagnostics of the hypospadias form, degree of cavernous bodies deformity, and quality of the urethra are possible to perform only under general anesthesia, which often results in the change of initially indicated surgical treatment plan.

The study of outcomes of surgical treatment of different forms of hypospadias in children, based on the data obtained by foreign and Russian researchers, showed that the problem of this anomaly correction remains acute because different complications are observed in both early and late postoperative period. Surgical treatment for hypospadias targets the restoration of penis function and anatomy. The main task of the treatment is to reconstruct a direct, esthetically normal penis with the urethral meatus located in the proper place (Ziada *et al.*, 2011).

One of the main aspects of hypospadias treatment is the age of a patient. It is still disputable when the correction of the anomaly should be more feasible. Earlier, foreign authors had a different opinion on the age when the treatment should start. Some authors recommended starting the radical correction at the age of six months, others recommended to wait until one year of age. Presently, the American Academy of Pediatrics and European experts recommend that the correction of hypospadias has to be performed at the age of 6 – 12 months. When it is not possible to perform it earlier for any reason, the treatment can be started at the age of 3-4 years old (Manzoni *et al.*, 2004).

Surgical treatment of different forms of hypospadias has its peculiarities. Currently, for the formation of the glanular part of the urethra and urethral duct, different methods are used, like the methods of Duplay, Snodgrass, Mathieu, Duckett and two-phase methods. According to the research data, normally formed spongy tissue in the glans never involves urethra and the ends of the corona do not touch each other. Urethral duct is “suspended” in the ventral surface of the

glans penis. Often, glanuloplasty is performed as follows: the formed urethral duct is encircled by the ends of the glans, creating a continuous sleeve around the distal part of the artificial urethra, which may cause complications. Due to this, an important role plays the formation of glanular part of the urethra that influences the effectiveness of the urinal flow. Insignificant resistance to the urinal flow in glanular part of the urethra leads to the increase in micturation pressure in the proximal part of the neo-urethra and, as a result, the risk of urinary fistula (Staroverov and Kazanskaya, 2016). The main drawback of the Mathieu technique is a round shape of the meatus instead of a slot-like one (Yesildag *et al.*, 2004) which, probably, leads to the development of stenosis and fistula. This fact also proves that the conducted randomized study on the primary hypospadias with distal forms (glanular, subglanular, midshaft) that was corrected with two methods of urethroplasty: conventional TIP Snodgrass and combined Mathieu-IP (urethra incised-plate). As a result, meatus stenosis and urethral fistula developed as a complication in 21.8% of cases after TIP Snodgrass and in 2.9% of cases after Mathieu-IP. Thus, the combined method with urethral plate incision reduces the rate of complications and improves the esthetic effect (Khalil *et al.*, 2017). To correct moderate and severe torsion of a penis with a distal form of hypospadias, some authors propose to perform a decutanization with the excision of fibrous remnants. If the torsion remains completely or partially, it is recommended to fix a flap of fibrous tunic of the penis to the periosteum of the pubic bone, which is considered a more reliable and efficient method of the torsion correction. Torsion of a penis is a rotation of cavernous bodies around the radial axis. It is identified by the displacement of the "median raphe" from the central line going along the ventral surface of a penis from the corona to the scrotum and perineum. These authors believe that vast mobilization of the urethra to the perineum does not lead to the correction of torsion and only minimally improves the angle of penis rotation. Further studies are needed for the deep and detailed understanding of the pathogenesis of a congenital torsion of a penis (Elbakry *et al.*, 2013).

Urethroplasty, which is a method of surgical correction for hypospadias, is performed by the method of tabularized incised plate (TIP), application of cutaneous flaps and transplants. From the mid 90's, the TIP method became widespread in the correction of distal, proximal and re-operational hypospadias. According to the

author, TIP potentially simplifies surgical solutions and techniques, has a low rate of complications and better esthetic effect. However, to achieve optimal results, it is necessary to pay special attention to the surgical details and understand the counter-indications to the procedure (Snodgrass, 2005).

Formation of the neo-urethra using buccal mucosa was first proposed by Humby in 1941 (Humby, 1941; Elsheikh and Fayad, 2011) and Mirabet in 1964 (Mirabet-Ippolito, 1964; Stein *et al.*, 2006). In 1993, el-Kasaby *et al.* (el-Kasaby *et al.*, 1993) were the first to report about the application of a buccal mucosa transplant in the restoration of penile and bulbar structures in 20 adult men without hypospadias. In 2001, Asopa *et al.* (Asopa *et al.*, 2001) described the technique of dorsal implantation of a buccal flap for the restoration of front urethral strictures. In 1995, severe forms of hypospadias were corrected with two-stage Bracka urethroplasty (Bracka, 1995).

Application of buccal mucosa as a transplant for urethra replacement was a revolutionary method in the management of serious cases of hypospadias (Manzoni *et al.*, 2004). According to the authors, the skin defect on the ventral surface of a penis is replaced by the buccal mucosa flap with further formation of artificial urethra or buccal mucosa can be used as a graft into a narrow urethral path (Snodgraft), which allows for the formation of the urethra with a diameter that is suitable for the patient's age. Such operations became widespread from the beginning of the 2000's in adult and pediatric patients. Thus, the patients, who were operated using this technique, were mainly children, and some authors believe that it is difficult to evaluate the final results. This provokes some concerns about the application of this method. In this case, the urethra is formed from a tissue that is not homologous to the tissue of a penis, and the experience of hypospadias treatment shows that all the cases of the registered penis cancer development were caused by the application of non-homologous tissues. The buccal mucosa flap is tightly sutured to the cavernous bodies, which is an obligatory condition for its engraftment. Thus, the formed urethral duct in a child remains fixed to the cavernous bodies and the urethra loses mobility, which is necessary for its elongation during the erection. In adult patients with the formed penis, this does not lead to serious complications, but in children, it is not known yet, how this surgery will influence on their sexual life. During the plastics with unattached

flaps, there is a risk of trophic failure in the graft, which leads to its necrosis (Staroverov and Kazanskaya, 2016). Some authors believe that the method of grafting with the inner layer of the foreskin for the straightening of a penis remains underestimated. This approach was offered in the 1960's by A.M. Cloutier but did not become widespread (Cloutier, 1962).

One of the most widespread problems in hypospadias is the development of fistulas. To reduce the risk of fistula development, it is necessary to follow some rules: optimal choice of glanuloplasty based on anatomic peculiarities, use of the optic tools, quickly degrading suture material, protection of sutures with the dartos fascia, slight penis compression to avoid hematomas and allow for the revascularization, immobilization of the penis and proper urine diversion in postoperative period. Although the TIP is a simple and popular method of urethroplasty, the rate of post-operational complications varies from 11.1 to 33.3%, on average, 21.8% (Van Putte and De Win, 2016). The drawbacks of TIP urethroplasty are high rate of urethral-cutaneous fistula (0–33%) and meatus stenosis that requires regular dilation. These complications are more serious as compared to other complications because of narrow urethral duct and flat, shallow glans (Elbakry *et al.*, 2016).

According to Grosos *et al.* (Grosos *et al.*, 2014), urethral fistula developed after Duplay urethroplasty in 9.1% of cases. According to Sharma data, it developed in 20% of cases after TIP urethroplasty (Sharma *et al.*, 2013). The authors of the study compared the outcome of urethroplasty for the correction of distal hypospadias by the conventional TIP method and modified TIP method with the use of intact and laterally enlarged plate. General rate of the complications was 16.8% and 5.6%, respectively. These conclusions confirm that the most widespread post-operational complication is urethral-cutaneous fistula (Van Putte and De Win, 2016).

Other authors use the PAWGs method of urethroplasty that involves post-auricular Wolfe grafts. Such grafts are thicker than the inner layer of the foreskin, but of the same thickness or thinner than the buccal flap taken from the oral cavity. Significant drawbacks of PAWGs method are keloid scars that sometimes develop on the donor part. Sometimes, synechias developed in the reconstructed urethral duct, which required the replacement of post-auricular skin with the mucous. If the donor's skin was taken closer to the mastoid bone, the treated child may have hair

growing in the meatus of neo-urethra (Bracka, 2008).

For objective functional and esthetic evaluation of the urethroplasty outcome for the correction of hypospadias by different methods, Holland *et al.* in 2001 proposed the system of HOSE scoring (Hypospadias Objective Scoring Evaluation System). For the evaluation of the functional outcome of the treatment, five objective elements are used: position and forms of the meatus, evaluation of the urine flow, straightness of the penis, absence of fistula and any other complications (van der Toorn *et al.*, 2013; Holland *et al.*, 2001). The proposed system of the evaluation is simple and can be measured clinically when the written consent from parents is obtained and in the presence of a qualified clinician that will perform the evaluation procedure. The total score for the evaluation equal to 14 was recommended as an acceptable result (Al-Adl *et al.*, 2014).

Prospective study was conducted for the evaluation of the esthetic and functional outcome of the correction of primary hypospadias with two methods of urethroplasty: MIUP (midline incision of the urethral plate) and TIP (tabularized incised plate) with the grafting of unattached flap of the foreskin, performed from 2012 to 2015. The method of G-TIP included standard steps of Snodgrass urethroplasty. The result was estimated by the HOSE system (Hypospadias Objective Scoring Evaluation System). Despite the fact that esthetic results were acceptable (>14 points in 96% of patients), the most often complications after the urethroplasty were urethrocutaneous fistula, suture scars and transplant on the edge of slot-like meatus, neo-urethra stricture in the place of incision after MIUP and in the graft area after G-TIP, as well as penis angulation by 10–30 degrees (Gupta *et al.*, 2016). Traditionally, the methods of choice for the correction of proximal forms of hypospadias are two-step Bracka operations with the use of buccal mucous graft, post-auricular graft and double isle flap urethroplasty (Sakr *et al.*, 2017).

The prospective study conducted in 2013–2015 focused on the evaluation of esthetic and functional treatment results after the two-step urethroplasty with buccal and tongue mucous grafts. After the first step, the following complications were revealed: infection, penis edema, skin ecchymosis, residual chord, graft rejection or contracture. In the area of donor skin flap, wet dressing was observed and patients complained about the pain that required pain management in 69% of cases. After the second

step of urethroplasty, the complications were skin ecchymoses, penis edema, bleeding, fistulas, and meatus stenosis. Thus, general complications rate was 23% (Gupta *et al.*, 2016).

In one of conducted studies on urethroplasty with buccal and tongue mucous for the correction of front strictures of the urethra, Kumar A., Das S.K. *et al.* highlight earlier post-operational complications in the lingual donor area as compared to buccal area, and in later post-operational period such complications as tightness, discomfort and numbness were observed only in the group, where a buccal flap was used (Kumar *et al.*, 2010). Similar results were presented in the report by Pal D.K., Gupta D.K. *et al.* in the group, where lingual flap was used. In early post-operational period, the patients had scrambled speech, in the group with BMG (buccal mucosal graft), salivary changes were observed, tightness, pain in the donor area and numbness, difficulties with mouth opening, recurrent urethral stenosis (Pal *et al.*, 2016). According to Sharma A.K *et al.*, the preparation of lingual graft took less time than buccal graft (Sharma *et al.*, 2013).

Despite the application of different methods of urethroplasty and unattached grafts and pedicle flaps, the rate of postoperative complications remains high. The right choice of the method of operation provides good functional and esthetic result and reduces the risk of post-operational complications. The analysis of the published information on the treatment outcomes in patients with hypospadias and the search results in the databases of the scientific journals proved the necessity in the development of optimal methods of correction for the urethroplasty in children with hypospadias.

4. CONCLUSIONS:

The review of numerous studies allowed the authors to suggest that the incidence rate of hypospadias, in general, in different countries tends to increase annually. The authors established that the main cause of hypospadias was a failure of endogen stimulation of the penis development, which results in the malformation of the urethra and the adjoining structures. There are a number of different methods of urethroplasty and unattached grafts or pedicle flaps used, but still, the number of complications in post-operative period remains high. The right choice of the surgery provides good functional and esthetic results and reduces the risk of the development of post-operative complications.

The analysis of the data on the outcomes of the treatment for hypospadias, based on the data obtained from the databases of the published journals, proved the need in the development of optimal variants of urethroplasty in children with hypospadias. The maximum risk factors for the development of complications after urethroplasty grafting include the wrong choice of glanduloplasty (the urethra is placed unacceptably deep), suture material, insufficient inversion of the epithelial edges of a wound, insufficient coverage of the urethroplasty area with the second layer of the tissue, unattached grafts, insufficient hemostasis, ischemic necrosis of tissues, method and duration of the urine deprivation in the post-operative period. For this reason, long-term observation of patients is required.

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ANEX 1 - LIST OF ABBREVIATIONS

TIP – tubularized incised plate

GTIP – graft tubularized incised plate

NCA – non-chromosomal congenital anomalies

ECLAMC – the Latin American Collaborative Study of Congenital Malformations

DHT – dihydrotestosterone

AR – androgen receptor

LH – luteinizing hormone

HOSE – Hypospadias Objective Scoring Evaluation system

UCF – urethrocutaneous fistula

MIUP – the midline incision of the urethral plate

PAWGs – post-auricular Wolfe grafts