ISSN 1062-3604, Russian Journal of Developmental Biology, 2018, Vol. 49, No. 2, pp. 101–107. © Pleiades Publishing, Inc., 2018.
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MORPHOGENESIS

Sex-Related Differences in Urethra Development in Human Embryos

T. V. Khmara, M. A. Riznichuk*, and L. A. Strizhakovskaya

Bukovinian State Medical University, Chernovtsy, 58001 Ukraine

**e-mail: rysnichuk@mail.ru*

Received February 3, 2017

Abstract—Virtually no information on the chronology of prenatal development of the human urinary tract and the sex-related differences in the emergence of urinary tract topography during embryonic development is presently available. The aim of our work was to study sex-related differences in urethra development in human embryos and early fetuses. Forty-nine preparations of human embryos and early fetuses without external signs of anatomical abnormalities were studied in order to achieve the aim and fulfill the objectives of the study. Embryos and early fetuses were divided into six groups according to gestational age and parietococcygeal length. The complex of adequate methods of morphological research used in the study included preparation and microscopy of serial histological and anatomical sections of human embryos, including female and male urinary tracts, preparation of 3D-reconstruction models, and morphometry. The formation of prostatic urethra, a derivative of the urogenital sinus, was shown to occur at the beginning of the ninth week of embryogenesis, and the primordium of the internal sphincter of the urinary tract was formed at the end of the tenth week. Formation of the terminal part of spongy urethra took place during weeks 10–11 and involved funnel-like protrusion of the ectoderm from the top of the balanus towards the urethra lumen. The secondary ventral displacement of the urethral opening does not occur in female fetuses, and, therefore, only the prostatic urethra is a homolog of the female urinary tract. The pelvic part of the urogenital sinus was transformed into the prostatic urethra and the membranous urethra of the male at the end of the first stage of fetal development. Elongation of the genital tubercle (a penis primordium) and formation of the urethral ridge walls that involved the urogenital folds occurred at the same time.

Keywords: early fetuses, urinary tract, 3D-reconstruction, morphogenesis

DOI: 10.1134/S1062360418020042

INTRODUCTION

Virtually no information on the chronology of prenatal development of the human urinary tract and the sex-related differences in the emergence of urinary tract topography during embryonic development is presently available. However, in perinatology an exact knowledge on the time of formation of specific structures is important for the monitoring of normal development of the fetal urogenital system (Akhtemiichuk, 2012). A comprehensive and systematic anatomical description of the chronological sequence of organ morphogenesis, including male and female urinary tract morphogenesis, during the prenatal period is not available so far. The studies performed are isolated, and the complex relationships between the developing urinary tract and the adjacent urinary and genital system remain uncharacterized, as do the distinctive features of organ syntopy at different stages of the prenatal period of human ontogeny. We believe that these questions are of decisive importance for the elucidation of regularities and major features of urinary tract normogenesis and for the assessment of the reason for variation in the structure and topography of the male and female urinary tract, congenital anomalies (CAs) of this system, and the time when the changes emerge. Moreover, the recently accumulated knowledge on surgical treatment of various CAs of genitalia demonstrates the key role of information on prenatal anatomy for the selection of treatment approach and prognosis of the patient's quality of life. Certain clinical variants of anomalies are difficult to interpret, and some observations do not agree with the universally accepted theory of embryogenesis (Vysotskii et al., 2009).

Therefore, elucidation of sex-related differences in urinary tract normogenesis and syntopy in human embryos and early fetuses was the aim of the present study.

MATERIALS AND METHODS

Forty-nine human embryo preparations without apparent anatomical abnormalities or developmental disorders were studied in order to achieve the aim and fulfill the objectives of the study. All embryos and early fetuses were divided into six groups according to gestation age and parietococcygeal length (PCL) (Table 1).

The age of the study objects was determined according to the tables published by Patten (1959), the

Table 1. Gestation age of the embryos

Gestation time	Parietococcygeal length, mm	Number
7 weeks	14.0–20.0	7
8 weeks	21.0–30.0	8
9 weeks	31.0–41.0	9
10 weeks	42.0–53.0	7
11 weeks	54.0–66.0	8
12 weeks	67.0–80.0	10

criteria proposed by B.P. Khvatov and Yu.N. Shapovalov (Khvatov and Shapovalov, 1969), and PCL measurements. The Guidelines for the Assessment of Perinatal Period Criteria, Live-birth, and Stillbirth Stipulated by Order no. 179 of the Healthcare Ministry of Ukraine (of March 29, 2006) were taken into account. The studies conformed to the major bioethical requirements of the EC Convention on human rights and biomedicine (of March 4, 1997), the Helsinki Declaration of the World Medical Association on the ethical principle of medical research on humans (1964–2013), and Order no. 690 (of September 23, 2009) of the Healthcare Ministry of Ukraine.

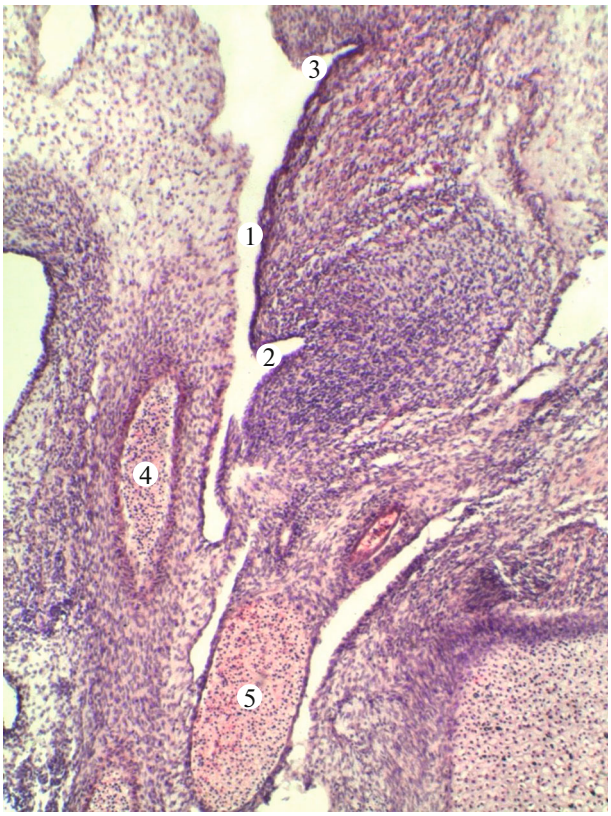

Fig. 1. Sagittal section of the urogenital sinus of an embryo (18.0 mm PCL). Microslide. Hematoxylin-eosin staining. Obj. 8, Oc. 7: 1—urogenital sinus; 2—mesonephric duct; 3—ureter; 4—pubic bone primordium; 5—ischial bone primordium.

Other materials used in the study included serial histological and topographic anatomical sections of human embryos and serial histological sections of the prostate and penis from the museum of the Turkevich Department of Human Anatomy, Bukovinian State Medical University (Ukraine).

The complex of adequate methods of morphological research used in the study included preparation and microscopy of serial histological and anatomical sections of human embryos, including female and male urinary tracts, preparation of 3D-reconstruction models, and morphometry (Akhtemiichuk et al., 1985; Sapin, 2000; Aleksina and Rudkevich, 2002).

Three-dimensional computer reconstructions were produced from each set of serial histotopographical sections in order to analyze the spatial structure and topography of the urinary tract. The approaches proposed earlier (Akhtemiichuk et al., 2006; Akhtemiichuk and Tsigikalo, 2009; Tsigikalo, 2012) were used for three-dimensional reconstruction and morphometry.

RESULTS

The urogenital sinus (UGS) of embryos has the appearance of a slightly curved tube with the curvature directed dorsally during the early seventh week of intrauterine development (embryos, 14.0–17.0 mm PCL). The UGS cavity is not divided into the urinary bladder and urinary tract at this developmental stage.

The UGS shape at the level of the mesonephric duct (MD) opening is nearly oval in 17.0–18.0 mm PCL embryos. The UGS walls consist of epithelial lining surrounded by a relatively thin layer of undifferentiated mesenchyme. The mucosal epithelium of the major part of UGS consists of 3–4 layers of cubic cells with elongated nuclei. The epithelium of the upper UGS is slightly thinner: it consists of 2–3 layers of cells. UGS wall thickness is 158 ± 8 μm. The MD openings are located on the posterior UGS wall (0.8 ± 0.15 mm above the lower end of the sinus). Expansion of the upper part of the UGS and compression of the sinus in the ventrodorsal direction are observed at this stage of embryogenesis (Fig. 1). The UGS cavity caudal to the MD openings has a size of 86 × 220 μm, and the transverse dimensions of the cranial part of the cavity are 230 × 375 μm.

The UGS of 18.5–19.0 mm PCL embryos is 1.9 ± 0.1 mm long. Three parts of the UGS—the upper part, the proximal (pelvic) part, and the distal (phallic) part—can be discerned at this stage. The large upper part of the UGS forms the urinary bladder, and the pelvic part of the UGS is a narrow canal that further gives rise to prostatic and membranous urethra in male fetuses. The phallic UGS part is elongated sagitally, connected to the genital tubercle, and separated by the urogenital partition. Notably, the phallic UGS part is

shifted ventrally along with genital tubercle growth. The subsequent breakage of the posterior part of the urogenital partition leads to the formation of the primary urogenital opening lined by two genital folds that emerge on the lower surface of the genital tubercle. Paramesoneprhic ducts (PMDs) fuse at the level of ureteral openings and form a common opening at the posterior UGS wall. Thus, a Muller tubercle is formed. This tubercle has thick walls and consists of an epithelial protrusion of the distal PMD part that bulges into the UGS lumen. The proximal ends of PMDs remain separated. Embryonic MDs are separated over the entire length, and the caudal ends of these ducts bend forward and slightly upwards to form arch-like shapes. MDs are tightly connected to the posterior UGS wall, and the openings of these ducts are located laterally to the opening of the fused PMDs. Human embryos with the PMD lumen width considerably larger than the MD lumen width can be expected to develop into females. The PMDs of male embryos are gradually reduced in the craniocaudal direction.

The arches of the caudal MD ends are somewhat evened out during further development (embryos, 22.0–28.0 mm PCL). These ducts are perpendicular to the posterior UGS wall in 7-week embryos, but the direction of the ducts becomes downward and angular by the end of week eight of intrauterine development. The distal PMD parts are located anteriorly to the MD, and then the longitudinal direction of these ducts is changed to oblique and a medial shift occurs. UGS extension in the cranial direction and uniform narrowing in the caudal direction occurs at this stage of embryogenesis. UGS length is 2.4 ± 0.2 mm, and its cavity is lined by stratified cubic epithelium.

MDs of male fetuses (27.5–28.5 mm PCL) are in tight correlative interactions with the posterior UGS wall. The openings of these ducts are located on both sides of the PMD duct opening. The PMDs fuse at the level of ureter openings and form a single opening at the posterior UGS wall.

An almost inconspicuous isthmus appears in embryos of 29.0–32.0 mm PCL due to the convex shape of the posterior UGS wall, and the bladder neck is formed in this area at the subsequent developmental stages.

The proximal UGS part located above the isthmus gives rise to the urinary bladder in fetuses of 33.0–35.0 mm PCL, and the distal part of the UGS gives rise to the urinary tract (Fig. 2). The bladder neck, a constricted part of urinary bladder cavity, becomes conspicuous caudally to the ureters due to the divergence of ureter and MD openings, but there is no distinct boundary at the site of bladder and UGS joining.

Epithelium proliferation occurs at the lower part of the pelvic UGS, so that the UGS lumen becomes narrower and gradually acquires a stellate shape on transverse sections of this area. The UGS cavity cranial to the MD openings is slightly larger. The UGS wall consists of mesenchyme and mucosa lined by stratified cubic epithelium. UGS wall thickness ranges from 205 to 230 μm in different parts of the sinus. A small protrusion of 18 ± 2 μm in height is formed due to intensive proliferation of mesenchyme cells along the anterior surface of the posterior UGS wall starting from the bladder neck, and, thus, the urethral crest starts to form. Division of the UGS into urinary bladder and urinary tract primordia continues at this stage, but the mesenchymal cells of the latter do not differentiate.

Notably, the division of the UGS cavity into the urinary bladder and the urinary tract becomes more distinct during week nine of embryogenesis (early fetuses, 31.0–41.0 mm PCL). Ventrodorsal constriction of the anterior part of the urinary tract occurs due to seminal tubule enlargement. The pelvic part of the UGS has a crescent-like shape on transverse sections.

An elongated accumulation of mesenchymal cells separated from the anterior UGS wall can be discerned in front of the distal UGS part (pars phallica) at this developmental stage. This structure can be regarded as the penis primordium.

The urethral groove is discernible on the caudal surface of the penis. This groove extends proximally into a slit-like opening on the UGS wall. The urethral groove closes due to urogenital fold fusion at the subsequent stages of development, and, thus, the proximal part of the urinary tract is formed.

A common uterovaginal canal is formed in 38.0–43.0 mm PCL female fetuses due to the fusion of caudal PMD parts near the posterior wall of the UGS, and mesenchyme cells are accumulated around this canal. A mesenchymal partition divides the uterovaginal canal into left and right cavities that have a slit-like appearance. Formation of a Y-shaped uterovaginal canal is followed by fusion of its caudal end to the dorsal UGS wall and formation of a protrusion (the Muller tubercle). The formation of vestibular bulbs starts near the distal part of the Muller tubercle. The vestibular bulbs are paired endodermal protrusions that extend as strands from the UGS to the caudal parts of the uterovaginal canal and participate in the formation of vaginal structures. Vaginal wall structures and vestibular bulbs divide the UGS all the way to the perineum level. This transformation determines the anatomical position of the female urinary tract.

Isolated arteries 20 ± 4 μm in diameter (primordia of the branches of internal iliac arteries) are found in the mesenchyme around the UGS, MD, and PMDs during the early tenth week of embryogenesis (early fetuses, 42.0–46.0 mm PCL), but these structures remain undiscernible inside the walls of these structures. A common uterovaginal canal is formed in female fetuses at this developmental stage.

Primordia of cavernous and spongy bodies of the penis can be distinguished in male fetuses at 44.0–49.0 mm PCL. Penis peduncles are in tight contact with pubic bone primordia. Blood vessels located in

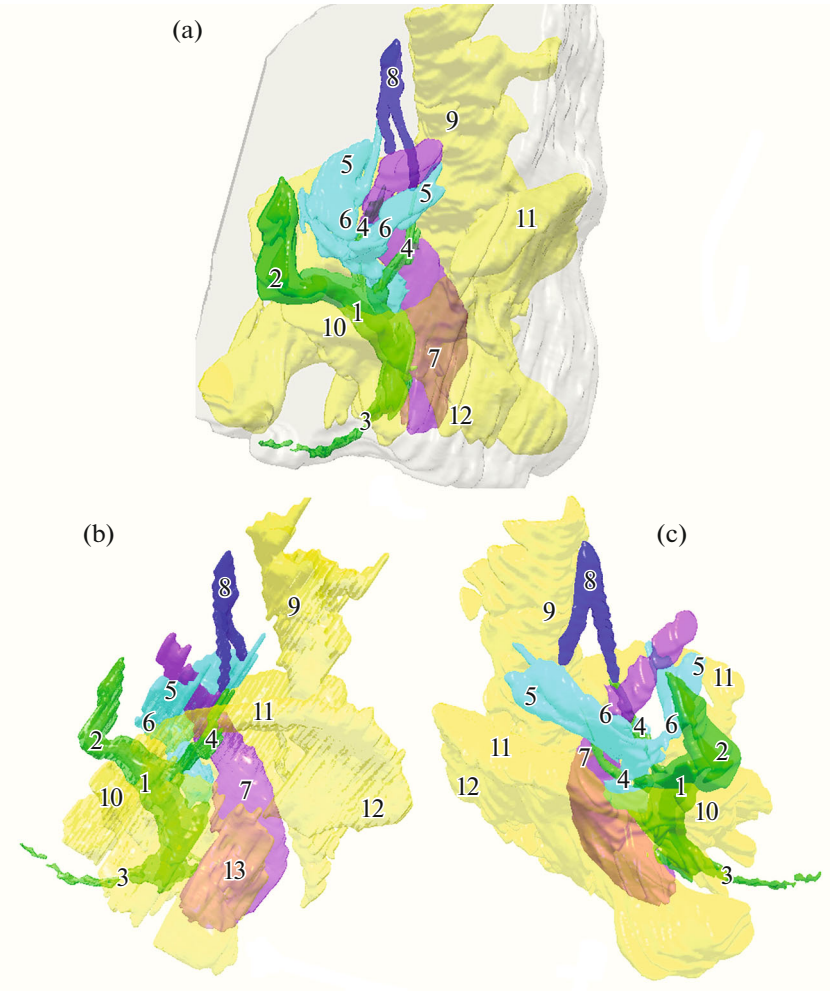

Fig. 2. Three-dimensional computer reconstruction of the urogenital sinus and adjacent structures in an embryo, 21.0 mm PCL. (a) Left frontolateral, (b) left and (c) right anterosuperior projections. Magn. 7: 1—urogenital sinus; 2—urinary bladder primordium; 3—urinary tract primordium; 4—ureters; 5—mesonephric kidneys; 6—metanephrons; 7—rectum; 8—common iliac vein; 9—vertebral column; 10—pubic symphysis; 11—iliac crest; 12—tuber ischii; 13—levator ani.

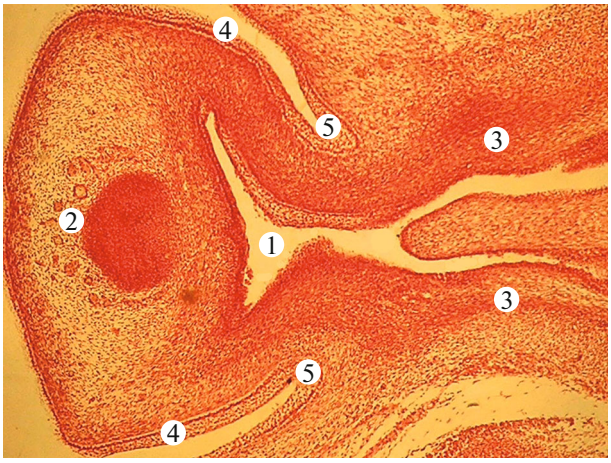

Fig. 3. Horizontal section of a fetal penis (47.0 mm PCL). Microslide. Hematoxylin-eosin staining. Obj. 3.5, Oc. 10: 1—lumen of spongy urethra; 2—balanus, 3—cavernous body primordia; 4—foreskin primordium; 5—genital ridges.

pubic bone primordia are detected laterally from the medial sagittal plane. An accumulation of vessels of various diameters is discernible in the balanus area. A lumen with irregular contours (diameter 84 ± 4 μm) lined with simple cubic (and locally, prismatic) epithelium is discernible in the spongy urethra (Fig. 3).

The distalmost part of the male urinary tract is formed by the end of the third month of intrauterine development as a strand of ectodermal cells that extends from the balanus to the proximal part of the spongy urethra. A canal is formed in this strand at the subsequent developmental stages, and the external opening of the urinary tract is thus formed.

The primordium of the internal sphincter of the urinary tract is discernible on frontal sections of the urinary tract from 48.0–50.0 mm PCL fetuses as an accumulation of elongated mesenchyme cells corresponding to the spherical shape of the urinary tract.

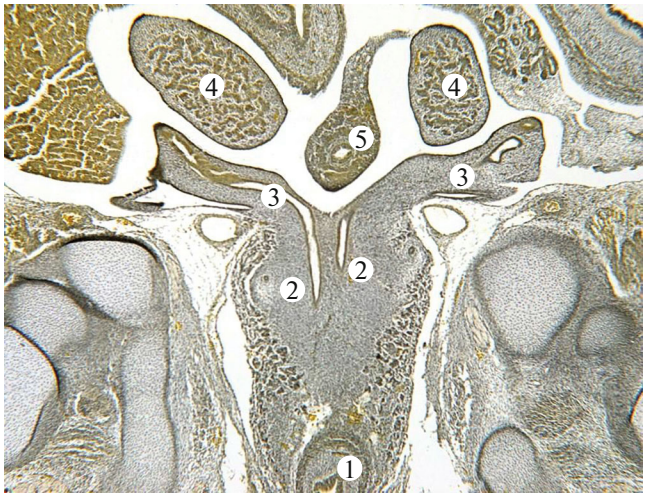

Fig. 4. Frontal section of a fetus, 58.0 mm PCL. Van Gieson staining. Microslide. Obj. 8, Oc. 7: 1—urinary tract lumen; 2—paramesonephric ducts; 3—mesonephric ducts; 4—ovaries; 5—rectum.

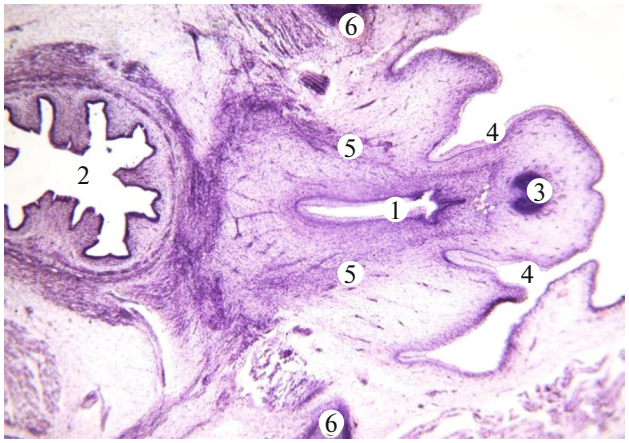

Fig. 5. Horizontal section of a male fetus, 65.0 mm PCL. Microslide. Hematoxylin-eosin staining. Obj. 3.5, Oc. 10: 1—lumen of spongy urethra; 2—urinary bladder; 3—balanus; 4—foreskin primordium; 5—cavernous body primordia; 6—pubic bone primordia.

However, some of the mesenchyme cells are arranged in a helical pattern.

Degradation of the mesenchyme partition of the uterovaginal canal starts in 44.0–53.0 mm PCL female fetuses. The medial part of the partition is thinned, and complete destruction of the partition occurs at the subsequent developmental stages (early fetuses, 55.0–58.0 mm PCL) (Fig. 4).

The uterovaginal canal is lined by pseudostratified cylindrical epithelium surrounded by a conspicuous layer of closely apposed mesenchymal cells.

Analysis of serial histological sections from 11-week male fetuses (54.0–56.0 mm PCL) and plastic reconstruction models based on these fetuses showed that MD diameter above and below the bladder neck increases at this stage. PMDs, with the exception of the conjoined caudal part, are reduced in examined fetuses, since the caudal part is the morphological substrate for the development of the prostatic utricle, which does not form a conspicuous connection to the urinary tract yet. The MD lumen becomes slightly constricted in both cranial and caudal directions to attain a diameter of 40 ± 2 μm. The division of the urinary bladder and urinary tract becomes more conspicuous at this developmental stage, and the bladder neck is formed.

The terminal part of spongy urethra forms during weeks 10–11 of intrauterine development (fetuses, 42.0–66.0 mm PCL) as a funnel-like protrusion of the ectoderm from the top of the balanus towards the urinary tract lumen.

Sequential fusion of urethral groove edges from the center to the periphery occurs in male fetuses at this stage of intrauterine development, and, therefore, the urinary tract lumen is shifted slightly in the ventral direction, from the perineum area towards the coronal sulcus of the penis (Fig. 5).

The diameter of the urinary bladder cavity is almost three times larger than that of the urinary tract lumen in 60.0–76.0 mm PCL fetuses. The transverse dimensions of the medial part of the urinary bladder in a 65.0 mm PCL male fetus were 1.65×2.3 mm, whereas the respective dimensions of the urinary tract lumen were 540×940 μm. The bladder neck extends laterally in a funnel-like manner to acquire an "hourglass" shape.

It is necessary to emphasize that the urethral groove of female fetuses is neither deepened nor closed upon the formation of the urinary tract, which corresponds to the spongy urethra of males, on the clitoris. Genital fold parts that extend to the lower surface of the clitoris remain rudimentary and disappear at the subsequent stages of development. Secondary ventral displacement of the urinary tract opening does not occur in female fetuses, and, therefore, only the prostatic urethra is a homologue of the female urinary tract.

Bulbourethral gland primordia are formed from epithelial protrusions of the proximal part of spongy urethra in male fetuses (70.0–79.0 mm PCL). Primordia of the greater vestibular glands are formed from the epithelial lining of the UGS in female fetuses of this age group. Mesonephros reduction is observed at the end of the early fetal period of ontogeny. Notably, the MD lumen diameter decreases to 5.8 ± 0.2 μm in female fetuses. The pelvic part of the UGS is transformed into the prostate urethra and the membranous urethra in male fetuses (74.0–79.0 mm PCL). Elongation of the genital tubercle (a penis primordium) occurs at the same time, and urinary tract folds contribute to the formation of the lateral walls of the ure-

thral groove. The latter stretches along the caudal part of the elongated penis. The prostatic urethra lumen in males is narrowed considerably in the caudal direction to attain a width of 64 μm at the boundary of the membranous urethra.

DISCUSSION

Urinary and genital organs are developmentally related and tightly connected with regard to topographic anatomy and certain functional features. The ejaculatory ducts of males open into the prostatic urethra, and the urinary tract of females opens into the vestibule of the vagina (Pikalyuk and Osmanov, 2011). The question of sources and time of emergence of urinary tract primordia has attracted the attention of many scientists from different fields of research. Different research methods were used, and this led to discrepancies, especially in the reported timing of urinary tract primordia formation and urinary tract development at early stages of human ontogeny. Some researchers (Pechriggl et al., 2013) noted that the mechanisms of urinary tract development require further analysis for the characterization of the sequence of stages in urethra formation, understanding of hypospadia pathogenesis, and development of new procedures for hypospadia treatment in neonates. Scattered reports on the stages of spongy urethra formation based on a histochemical study of 15 human embryos at weeks 6 to 14 of intrauterine development are available (Hadidi et al., 2014).

Information on the sources of the female urinary tract and certain parts of the male urinary tract formation, the distinctive features of the topography establishment, and the dynamics of urinary tract length changes during the prenatal period of human ontogeny has not been systematized to date. Published studies (Khmara and Marchuk, 2003; Marchuk, 2006; P'yatnits'ka, 2009) contain fragmentary data on structural changes of Wolff MDs and Muller PMDs and emergence of correlations between UGS derivatives in human embryos.

CONCLUSIONS

Thus, the prostatic urethra is formed as the urogenital sinus derivative early during the 9th week of embryogenesis. The intensity of differentiation in urinary tract wall layers is increased during the 10th week of embryogenesis. Cell differentiation is intensified along with cell proliferation, especially in the surface layers of the epithelium.

Caudal parts of the paramesonephric ducts fuse near the posterior wall of the urogenital sinus to form a single uterovaginal canal in female fetuses during the late 9th and the early 10th week of gestation. The primordium of the intrinsic sphincter of the urinary tract is formed at the end of the 10th week of embryogenesis.

The terminal part of spongy urethra forms during weeks 10–11 of intrauterine development as a funnel-like protrusion of the ectoderm from the top of the balanus towards the urinary tract lumen. Sequential fusion of urethral groove edges from the center to the periphery occurs in male fetuses of this age group, and, therefore, urinary tract lumen is shifted slightly in the ventral direction, from the perineum area towards the coronal sulcus of the penis. Secondary ventral displacement of the urinary tract opening does not occur in female fetuses, and, therefore, only prostatic urethra is a homologue of the female urinary tract.

The pelvic part of the urogenital sinus is transformed into the prostatic urethra and the membranous urethra at the end of the early period of fetal development. Elongation of the genital tubercle, a penis primordium, and the transformation of urinary tract folds into the lateral walls of the urethral groove occur at the same time.

Conflict of interests. The authors report no conflict of interests.

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Translated by S. Semenova