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## PECULIARITIES OF MORPHOGENESIS OF THE COMMON BILE DUCT SPHINCTERS IN HUMAN PRENATAL ONTOGENESIS

## ОСОБЛИВОСТІ МОРФОГЕНЕЗУ СФІНКТЕРІВ СПІЛЬНОЇ ЖОВЧНОЇ ПРОТОКИ У ПРЕНАТАЛЬНОМУ ОНТОГЕНЕЗІ ЛЮДИНИ

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**Abstract.** In order to find out specific peculiarities of prenatal morphogenesis of the common bile duct (CBD) sphincters, the morphologic research of 62 series of sequential histologic sections of human embryos and 50 cadavers of human fetuses have been performed by using of preparation, microscopy and morphometry methods. Statistical analysis of the results of research was carried out with calculation t-test. The complex sphincter of Oddi was detected for the first time in prefetuses beginning from 52,0 mm of the parietal coccygeal length. The asynchronous changes of CBD sphincter's size were established during fetal period of the human ontogenesis. A maximal increase of hepatopancreatic ampulla

sphincter's length was revealed in 8th month fetuses. A maximal augmentation of CBD sphincter's length was detected in 9th month fetuses. In newborns a definitive structure of the sphincter of Oddi is forming with the reliable decrease in the thickness of hepatopancreatic ampulla sphincter ( $P < 0,001$ ).

**Key words:** common bile duct, sphincters, fetus, newborn, human being.

**Резюме.** З метою виявлення особливостей пренатального морфогенезу сфінктерів спільної жовчної протоки (СЖП) проведено морфологічне дослідження 62 послідовних гістологічних зрізів зародків та 50 трупів плодів людини за допомогою методів мікропрепарування, мікроскопії й морфометрії. Статистичний аналіз результатів дослідження проведений з вирахуванням t-критерію Ст'юдента. Комплексний сфінктер Одді виявлений вперше у передплодів 52,0 мм ТҚД. Установлено асинхронні зміни розмірів сфінктерів СЖП упродовж плодового періоду онтогенезу. Максимальний приріст довжини сфінктера печінково-підшлункової ампули виявлений у 8-и місячних плодів, а максимальний приріст довжини сфінктера СЖП виявлений у 9-и місячних плодів. У новонароджених відбувається становлення дефінітивної будови сфінктера Одді з вірогідним зменшенням товщини сфінктера печінково-підшлункової ампули ( $P < 0,001$ ).

**Ключові слова:** спільна жовчна протока, сфінктери, плід, новонароджений, людина.

**Introduction.** Pathology of muscular sphincters of common bile duct (CBD) are in the basis of many diseases of the hepatobiliary system, both organic and functional genesis [5, 10]. Disturbances of the normal function of bile ducts sphincters in 10-15% of cases is due to defects in their prenatal development [7, 8]. Despite the abundant data about the structural and functional organization of CBD sphincters in adults, details of their morphogenesis during the intrauterine period of human development (IUHD) have not been fully elucidated [1, 2]. No common opinion what is considered the anlage of CBD sphincter [3]. Consequently, the terms of appearance of this one are quite controversial highlighted in well-known researches [4]. The sequential chronological patterns of the formation of CBD sphincters during whole prenatal period till the birth have not been disclosed [9]. Specific critical periods of the development of separate components of sphincter of Oddi during prenatal ontogenesis have not been described [6]. Thus, the continuing study of the peculiarities of normal prenatal morphogenesis of CBD sphincters is actual for understanding the morphological preconditions for the occurrence of pathology of the hepatobiliary system in children and adults.

**The aim of research:** to find out the peculiarities of morphogenesis of muscular sphincters of common bile duct during the early period of human ontogenesis.

**Material and methods.** The investigation has been performed on 62 series of consistent histologic sections of embryos and 50 corpses of human fetuses from 11,0 mm to 396,0 mm in parietal-coccygeal length (PCL) by using methods of microscopy, macro- and microscopic preparation, morphometry. Objects age defined using tables by B.M. Patten (1959), B.P. Hvatova, J.N. Shapovalov (1969). All data was processed by the methods of variation statistics with calculation t-test using the software package Primer of Biostatistics, 4th Edition, S.A. Glantz, McGraw-Hill. To reject the null hypothesis the significance level was used equal to  $p < 0,05$ . Research has been conducted according to "Following the Ethical and Legal Standards and requirements during carrying out scientific morphological research" and the main theses of Helsinki Declaration of the World Medical Association on ethical principles of scientific and medical research involving human subjects (1964-2000) as part of the National Project "New Life - a new quality of maternity and childhood" and the State Program of transition of Ukraine from 01.01.2007 to the International System of Accounting and Statistics (Order of Ministry of Health of Ukraine №179 on 29.03.2006 "On approval the instruction on definition the criteria of perinatal period and live births and stillbirths, order registration of live births and stillbirths").

**Results and its discussion.** It was established that at the beginning of 7th week of IUHD in prefetuses 14,0-16,0 mm PCL the terminal part of CBD with the duct of ventral pancreas are into the thickness of dorsocaudal semicircumference of the upper part of duodenum. In this area the walls of such ducts are surrounded by an adjacent layer of mesenchymal cells that acquire a circular orientation and are separated from the muscular layer of intestinal wall. It can be considered as the morphologic preconditions for formation of anlage of CBD sphincter. In prefetuses 19,0 mm PCL in the middle semicircumference of the lower part of duodenum, a hepatopancreatic ampulla (HPA) with a diameter of up to 100  $\mu$ m has been detected in area of the connection CBD and ventral pancreatic duct. Epithelial walls of HPA are surrounded by mesenchymal cells, which oriented in a circular direction with the formation of clearly demarcated layer. The thickness of last one is up to 60  $\mu$ m and that is considered as the anlage of HPA sphincter. In prefetuses 24,0-29,0 mm PCL both the hepatopancreatic ampulla and intramural parts of CBD and ventral pancreatic duct are surrounded by a common mesenchymal ring 75  $\mu$ m in thickness.

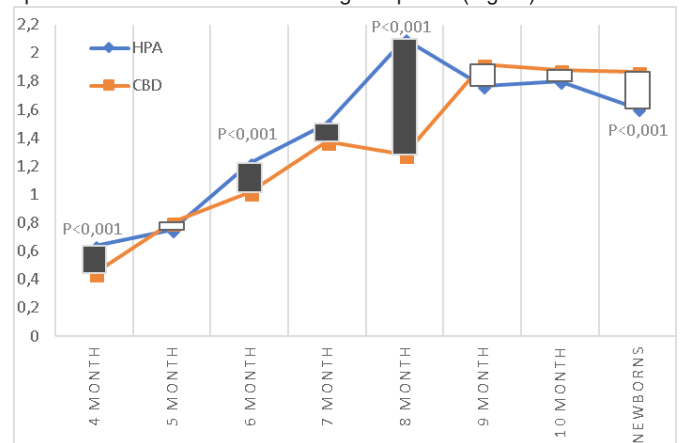
Starting from prefetuses 52,0 mm PCL, the intramural parts both the CBD and the pancreatic duct are surrounded by separate circular bundles of myocytes, which form the basis of their own sphincters. The thickness of CBD sphincter is up to 100  $\mu$ m and thickness of sphincter

of pancreatic duct less than 80  $\mu$ m. Around the hepatopancreatic ampulla a solid circular muscular layer of 150  $\mu$ m in thickness has been revealed, which is a sphincter of the ampulla. Just outside of last one the longitudinal muscle bundles are situated in the downward direction from the pancreatic part of CBD.

At the beginning of the fetal period (fetuses 82,0-135,0 mm PCL) caudal parts both the CBD and pancreatic duct are joined together with the formation of HPA into the thickness of the medial wall of the duodenum. Externally the walls of HPA are surrounded by circular bundles of smooth muscle fibers, which form the HPA sphincter of 0,642 $\pm$ 0,021 mm in length and 0,157 $\pm$ 0,008 mm in thickness. Intramural parts both the CBD and pancreatic duct are surrounded by circular muscular bundles which form own CBD sphincter and sphincter of pancreatic duct appropriately. During this period, the sizes of CBD sphincter are 0,447 $\pm$ 0,028 mm in length and 0,113 $\pm$ 0,005 mm in thickness. Around the last one single longitudinal bundles of myocytes spread from the walls of the pancreatic part of CBD in the downward direction, and individual bundles of fibers of the longitudinal muscular layer of the duodenum adjoin them externally in the ascending direction.

Since the 5<sup>th</sup> month of IUHD (fetuses 145,0-182,0 mm PCL), HPA sphincter becomes a solid circular layer of smooth muscle fibers 0,167 $\pm$ 0,031 mm in thickness. CBD sphincter is formed by circular bundles of myocytes 0,125 $\pm$ 0,019 mm in thickness. The lengths of these sphincters did not reliable differ during this period (fig.1.).

During the 6<sup>th</sup> month of IUHD (fetuses 188,0-230,0 mm PCL) change of the size of muscular sphincters is due to the increase of the length of HPA sphincter, which is up to 1,219 $\pm$ 0,251 mm, and is reliably different from the length of CBD sphincter which is 1,019 $\pm$ 0,244 mm ( $P < 0,001$ ). The reliable differences of the thickness of the investigated sphincters were not detected during this period (Fig. 2.).



**Fig. 1. Comparative dynamics of changes the length (mm) of the hepatopancreatic ampulla (HPA) sphincter and the common bile duct (CBD) sphincter in fetuses and newborns.**

In 7-8th-month fetuses (235,0-306,0 mm PCL) the CBD sphincter acquires the form of a continuous smooth muscle ring, and an increase in its size occurs due to an increase in its thickness, which is up to 0,174 $\pm$ 0,034 mm (Fig. 2). In the next periods the change of the sizes of HPA sphincter and CBD sphincter occurs asynchronously. In particular, the maximum increase of the length of HPA sphincter was detected during the 8th month of IUHD, which reaches 2,096 $\pm$ 0,293 mm ( $P < 0,001$ ), while the maximum increase of the length of CBD sphincter occurs during the 9th month of IUHD (fetuses 312,0-342,0 mm PCL), which is up to 1,916 $\pm$ 0,202 mm (Fig. 1). In the last period we proved the maximum increase in the thickness of HPA sphincter, which reaches 0,296 $\pm$ 0,046 mm and is reliably to exceed the thickness of CBD sphincter ( $P < 0,001$ ) (Fig. 2).

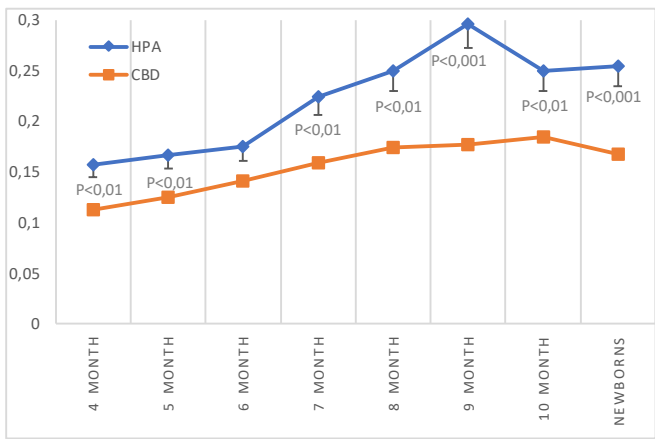
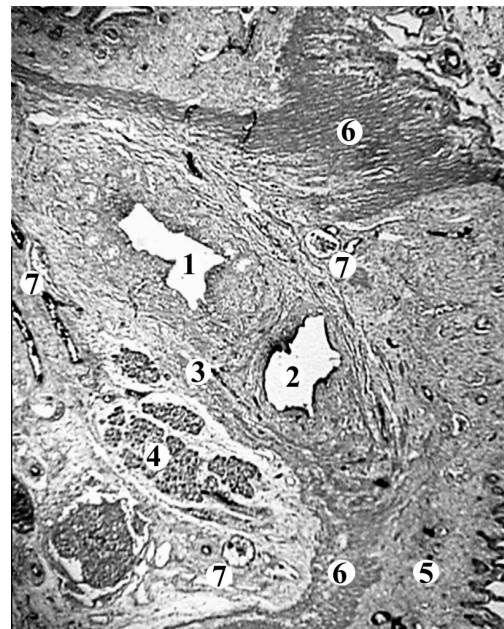


Fig. 2. Comparative dynamics of changes the thickness (mm) of the hepatopancreatic ampulla (HPA) sphincter and the common bile duct (CBD) sphincter in fetuses and newborns.

At the end of fetal period (fetuses 315,0-375,0 mm PCL) the structure of CBD sphincters acquires the definitive features (fig. 3).

CBD sphincter represents as a solid muscular ring of  $1,881 \pm 0,127$  mm in length and  $0,185 \pm 0,023$  mm in thickness. HPA sphincter is formed by circular muscular bundles covering the intramural parts both the CBD and pancreatic duct with a common muscle ring  $0,250 \pm 0,039$  mm in thickness. Externally HPA sphincter is surrounded by the longitudinal muscle bundles that extend from the wall of CBD in the downward direction. In the HPA lumen the numerous epithelial folds are found, which localized spirally around the circumference of the ampulla, and a frontal fold that separates the lumens of CBD and pancreatic duct. In newborns the reliable changes of the sizes of CBD sphincter were not detected. At the same time, the length of HPA sphincter tends to decrease, compared with the late fetal period, and is reliable less than the length of CBD sphincter. Such a morphological reorganization of CBD sphincter in newborns may be associated with an increase of intraductal pressure of the end portion of CBD due to increased secretory function of the liver and the transition to the lactotrophic nutrition. [4].



Sagittal sections of the duodenum of fetus 363,0 mm in PCL. Hematoxylin-eosin. Microfoto. Magnification  $\times 35$ :

1 - common bile duct; 2 - pancreatic duct; 3 - sphincter of the common bile duct; 4 - pancreas; 5 - submucosal basis of the duodenum; 6 - muscle of the duodenum; 7 - blood vessels.

**Conclusions.** 1. The formation of a definitive structure of the muscular sphincters of the common bile duct occurs during the fetal period of ontogenesis. 2. Changes the sizes of the common bile duct sphincter and the hepatopancreatic ampulla sphincter in fetuses and newborns occurs asynchronously. 3. The maximum increase of the length of the hepatopancreatic ampulla sphincter occurs has been detected at the 8th month, and the length of the common bile duct sphincter becomes maximal during the 9th month of intrauterine period of human development.

Prospects of scientific research. We consider it expedient to continue research the vasculogenetic peculiarities of the common bile duct sphincters in the human fetuses and newborns.

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