CONTENT

INNOVATIVE APPROACHES IN THE TREATMENT OF PATIENTS WITH GENERAL PURULENT PERITONITIS

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Improving treatments for complicated forms of peritonitis is one of the key issues of modern surgery. Despite the variety of surgical intervention technologies, as well as the improvement of algorithms and guidelines, lethality in secondary prevalent peritonitis remains at a high level, due to which the search and development of methods of management of patients remains relevant, combining both the technique of surgery and the methods of perioperative management. Peritonitis treatment, implying the use of vacuum therapy at the present stage, is the flagship in the field of abdominal surgery, and therefore the issue of improving this technology is prioritized by both domestic and foreign specialists. One of the innovative ways to modernize the vacuum technology of conducting an open abdomen or laparostomy is the use of the sparging perioperative abdominal sanitation in the perioperative period. In modern literature, references to the management of patients with general purulent peritonitis, implying the use of sparging, are single and fragmentary, which in turn causes the need for more research in this area.

Keywords: *peritonitis, open abdomen, laparotomy, vacuum-assisted dressing, vacuum-instillation laparostomy, sparging.*

The problem of mortality due to advanced diffuse purulent peritonitis (DPP) takes one of the most important positions in the modern clinical medicine comprising from 75 to 80%. In cases of peritonitis complications with sepsis and septic shock mortality rates increase to 95% [1]. The analysis of literature proves that often sepsis is caused by forming of non-drained spaces, interloop fluid collections, and inadequate intraoperative sanitation of the peritoneal cavity [2].

Over the course of more than 150 years, a number of domestic and foreign specialists provide plenty of surgical intervention performing technologies and peritoneal cavity management strategies during the perioperative period, but the majority of the authors agree that the strategy of open abdomen remains as the most promising and right [3, 4, 5]. During the last decade, plenty of recommendations and guidelines of open abdomen management have been elaborated considering the progress of peritonitis and individual features of patients [3, 4]. According to the Russian and foreign specialists, the leading method of diffuse purulent peritonitis treatment is the vacuum therapy which includes performing of sanitation with the use of instillation of the peritoneal cavity followed by vacuuming. However, DPP is still one of the most dangerous complications of urgent surgical pathologies; it requires elaboration of innovative treatment methods and modernization of the methods already existing. One of the treatment methods is performing vacuum-assisted laparostomy with instillation of sparged solution.

The purpose of the work was to estimate quantitative and qualitative parameters of sanitation performed at a three-dimensional polymer model of the peritoneal cavity based on CT scans of a real anonymous patient and in the conditions identical to diffuse purulent peritonitis.

Materials and methods

On the basis of the Department and Clinic for Surgical Pathologies named after Professor A.M. Dykhno with the VE Endoscopy and Endosurgery Course, the experimental study was conducted. This study projects higher effectiveness of intra- and perioperative sanitation of the peritoneal cavity using combined vacuum therapy with instillation of sparged solution performed with the original instillation-sparging unit (ISU) (Figure 1).
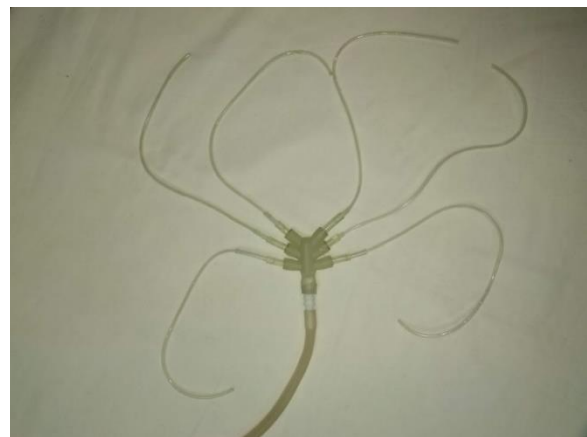
Figure 1. Original intillation-sparging unit.

The second step of the experiment was sanitation of the peritoneal cavity using the vacuum-assisted therapy with the instillation of saline solution through ISU in laminar feed rate. Qualitative and quantitative experiment results of the two sanitation methods of the peritoneal cavity model are compared. The following tasks were performed while conducting the experimental study:

1. Creating the three-dimensional polymer model of the peritoneal cavity based on CT scans of a real patient; the model indicates the native peritoneal cavity (flanks, anatomic spaces, organs positions, tissues integrity).

2. Elaborating of preparation technology of sparging saline solution considering intra-abdominal delivery through ISU and under the control of intra-abdominal pressure, according to the temperature range +36–43° C.

3. Preparing of the solution, which is identical to purulent exudate considering maximum chemical and physical constitution.

4. Calculating of the vacuuming parameters for more qualitative intra-abdominal sanitation.

5. Estimating of qualitative and quantitative results gained during sanitation using vacuum-assisted instillation cleaning with sparging solution.

6. Estimating of qualitative and quantitative results gained during sanitation using vacuum-assisted instillaion cleaning with saline solution in laminar feed rate.

Estimating of qualitative and quantitative indicators of sanitation was based on:

1. Subjective estimation of integrity of the peritoneal cavity interior according to the elaborated Visual Analog Scale (VAS).

2. Indicators of the density of solution in the peritoneal cavity remained after performed sanitation steps.

3. Indicators of the viscosity of solution in the peritoneal cavity remained after performed sanitation steps.

The surgical intervention algorithm for DPP implies the sanitation step of the peritoneal cavity using saline solution (NaCl 0.9%) accepted as standard. However, data of the using effectiveness of this solution have not been mentioned in the academic literature. It is understood that during sanitation such products as necrotic tissular detritus, blood, bile, and purulent matter are discharged, the forming of biofilms is prevented and the quantity of bacterial units is reduced.

J.L. Regner et al. conducted the experimental research in vitro and in vivo and proved that using of saline solution increases the cytotoxic effect on the mesothelial epithelium of the parietal and visceral peritoneums [5]. As no alternative exists, saline solution is used in clinical practice. Using of saline solution is appropriate because mortality rates and the quantity of complications are higher if the peritoneal cavity in the conditions of DPP is not sanitated at all.

Conventional approaches to local foci of pyogenic infection treatment imply using of antiseptic solutions in the "mild" irrigation regime and in the temperature range from +18 to +25°C, where the solution is cold. The pH is less than 7, thus the solution is acid. As a consequence of implying the given parameters, purulent exudate condenses, it complicates appropriate sanitation and supposes probable forming of the hardly drained focus. Thus, non-drained spaces worsen the progress of peritonitis, bed days in hospital, the chance of a consecutive infection overlay and risks of poor yield treatment increase [2, 6].

Previously warmed and alkalized solutions used in sanitation may be supposed to dissolve purulent substances more effectively.

Over the past thirty years, plenty of clinic researches in abdominal surgery have been conducted. They prove the effectiveness of open abdomen method as the management strategy for patients with intra-abdominal infection. The method means the peritoneal cavity opened and circumscribed with the help of temporary tensed plasty to control the condition while performing elective and immediate repalarotomies after basic surgical manipulations were performed. Among the barrier dressings separating the peritoneal cavity organs, the more frequently used are the Bogota bag, the Wittmann patch and the Barker's vacuum but a high risk of complications while using these methods should be mentioned. The more frequent complications are: adhesion of the visceral peritoneum organs, bleeding, forming of non-drained fluid substances and enteric fistulas, laterality of laparotomy wound lips, and generalization of surgical infections [7, 8, 9].

The vacuum method of closing the peritoneal cavity described in the mid- 90s has become the most perspective and promising method completing the strategy of open abdomen. Vacuuming prevented lost of the domain, contributed to the reduction of bacterial contamination and its generalization but at the same time supposed emerging of the above described complications, though less frequently [9].

Due to the frequent use of the elaborated method, the majority of unwanted deviations were reduced and it was recommended as the preferred method of intra-abdominal surgical infection treatment.

Vacuum-assisted therapy with instillation of previously sparged saline solution through the original polydrainage silicone system is one of the options to modernize vacuum therapy.
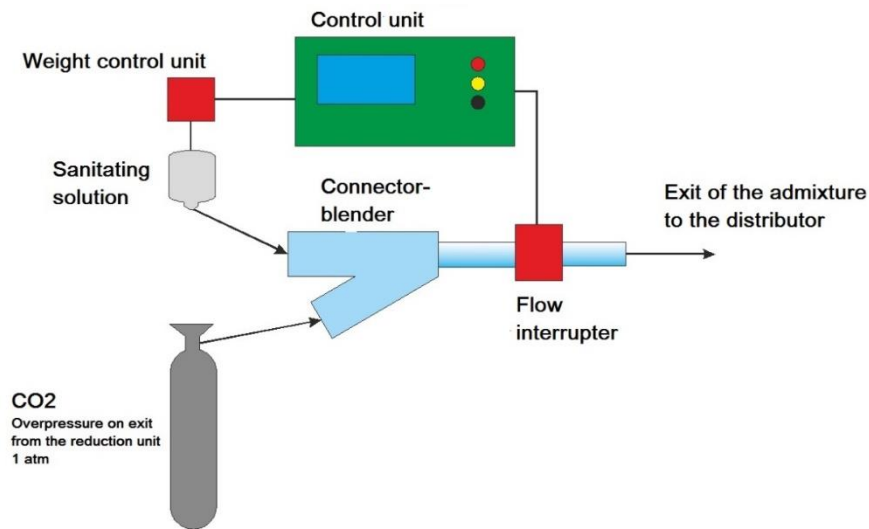
Algorithm of the apparatus work:
1. Control of weight of the water vessel.
2. Opening of CO_2 delivery.
3. Pumping with pressure from the vessel with solution for 30 seconds. The gas flow occurs in the triple junction of the blender. 4. If mass of the solution exceeds 250 grams, the interrupter opens for 20 seconds, otherwise the interrupter closure occurs with 50 grams remained.
5. The overlap of gas delivery.
6. 10-minutes pause.

Repetition of the cycle until the solution vessel is empty.

Figure 2. Flowchart of the instillation-sparging apparatus.

Sparging means appearance of the bubbling effect or cavitation gained with flushing the over-pressurized medical gas CO_2 through sparged saline solution. The process of sparged solution forming occurs in the connector-blender between the exit of the admixture into the distributor (ISU) and the gas bag with CO_2 (Figure 2).

The peritoneal cavity model was made with 3D printing technology, with the 3D printer Wanhao Duplicator 7 v1.5. As the material for the model, polylactide was used. As the scheme of the model, multi-slice CT scans of a real patient were used. Also the organs and the anterior abdominal wall were based on the scans of triple silicone and laid in the anatomical positions. In the abdominal flanks, in the right and left lateral canals, the subhepatic space and the interloop spaces, the solution imitating purulent matter was poured. Then, on the organs, the polydrainage system (ISU) consisting of 6 silicone tubes was laid in the flanks and the interloops. The proximate end of ISU was taken out through the counteropening on the anterior abdominal wall. The components of the vacuum-assisted dressing included in VivanoMed Abdominal Kit were installed along with VivanoTec. Above the intra-abdominal polyurethane sponge laid, the adhesive film was applied. In the projection above the sponge, the cruciate incision to 2 cm was made, the port (VivanoTecPort) connected with Hartmann VivanoTec unit was installed. In case of the components of dressing arranged properly, vacuum-assisted instillation was performed. All the mentioned actions are performed equally for each solution type (Figure 3).

As the components for preparation of the solution imitating purulent matter, food starch of mass 175 g was used at a dilution of 7.5 L saline solution, then boiled with 10 minutes' exposure with constant stirring. The solution was put equally in the peritoneal cavity with the priority of the spaces difficult to reach (Figure 4).

Preparation of the instillation aerated solution (solution 1).

The instillation solution is previously aerated with CO_2 through the obstructive conduction system connected to the gas bag with CO_2 controlled with the aerotonometer. The maximum limit of dissolved gas is 3 L. During the delivery of this solution with overpressure 1 atm and at the flow rate 0.75 L/min, ISU distributes the instillation solution at equal rate and later evolves the dissolved gas as small bubbles, which coat detritus and make with positive buoyancy, i.e. the effect of flotation. Time of instillation is 15 seconds. Consumption of the instillation solution reduced by half in comparison with usual capacity.
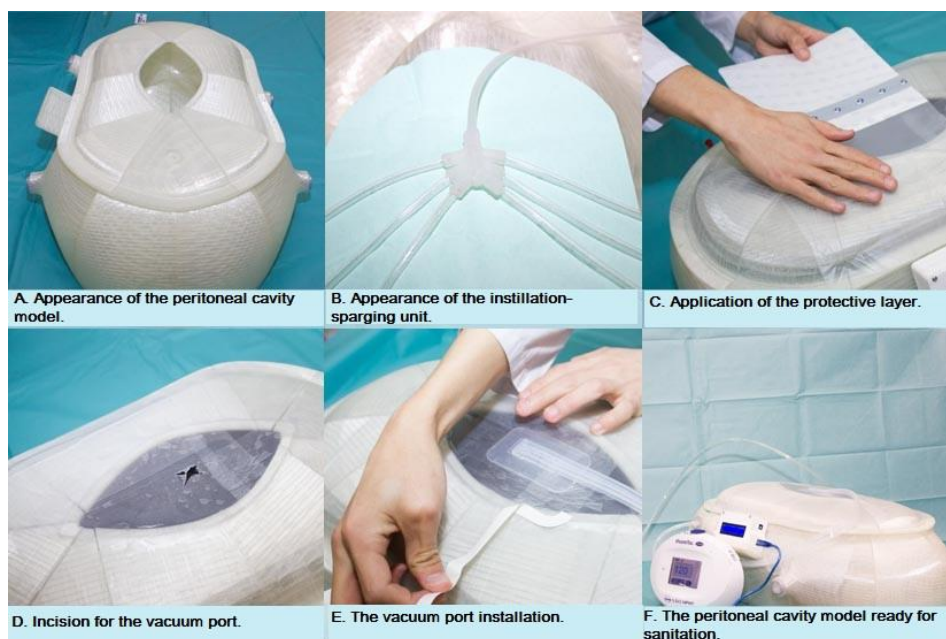
Figure 3. Steps of the vacuum unit and ISU installation.

Figure 4. Appearance of the solution in imitating purulent matter of the peritoneal cavity.

Preparation of the instillation non-aerated solution (solution 2).

Instillation solution is not previously aerated with CO2 and delivered with pressure 1 atm, at the flow rate 0.75 L/min in the pulse sequence regime. This regime means that for 15 seconds the admixture of gas and the solution is delivered through ISU, then for 30 seconds pressure smooths in the vessel with the solution. While the solution goes through ISU, its density and flow rate change compulsively and quickly creating the effect similar to the hydraulic ram work principle. As a result, there is no laminar flow, more detritus is discharged and cleared through vacuum. Consumption of the instillation solution reduced more than three times in comparison with the usual sanitation method.

With the purpose of prevention intra-abdominal compartment, the PVC sparging shut while making local negative pressure (LNP) was previously set.

Table 1

Dynamics of the instillation solution density change after instillation performed

	$T^1_{instill}$		$T^2_{instill}$		$T^3_{instill}$	
	Density of purulent before, g/cm3	Density of purulent after, g/cm 3	Density of purulent before, g/cm3	Density of purulent after, g/cm 3	Density of purulent before, g/cm3	Density of purulent after, g/cm 3
Solution 1	1.8	1.5	1.8	1.5	1.8	1.18
Solution 2	1.8	1.22	1.8	0.9	1.8	0.9

Results and discussion

Density of the solutions was counted with the formula mass divided by volume. The indicators gained are shown in Table 1. According to the results, solution 2 has smaller density than solution 1, it shows low concentration of starch and high potential of sanitation accordingly.

Viscosity of solution was measured with the Brookfield viscometer DV2TLV in the SI (L^2/T, i.e. (kg x sec)/m³). The use of this viscometer is reasoned by its main technical feature: due to the slow rotor float and axis, the studied solution flows in laminar flow, thus the fixed indicators are more accurate. It is stated that viscosity of each solution reduces after instillation (Table 2). Herewith, viscosity indicators of solution 2 reduce by half and draw to get closer to water, it shows the high potential of sanitation.

Table 2

Dynamics of the instillation solution viscosity change after instillation performed

	$T^1_{instill}$ (kg x sec)/m³		$T^2_{instill}$ (kg x sec)/m³		$T^3_{instill}$ (kg x sec)/m³	
	Viscosity of purulent before	Viscosity of purulent after	Viscosity of purulent before	Viscosity of purulent after	Viscosity of purulent before	Viscosity of purulent after
Solution 1	987	712	987	709	987	602
Solution 2	962	613	962	428	962	212

During usual sanitation of the peritoneal cavity regardless the type of surgical intervention, a surgeon estimates integrity of the peritoneal cavity at first. Despite the estimation is very subjective, it is the necessary part of the intra-operative management of a patient. While estimating sanitation of the peritoneal cavity, the quality indicator was used additionally, it was based on the visual estimation of the peritoneal cavity integrity shown in the gradation from one to four pluses (Table 3).

Table 3

Visual estimation of the peritoneal cavity integrity after vacuum-instillation therapy

	$T^1_{instill}$	$T^2_{instill}$	$T^3_{instill}$
	Visual estimation of the peritoneal cavity integrity	Visual estimation of the peritoneal cavity integrity	Visual estimation of the peritoneal cavity integrity
Solution 1	+	++	++
Solution 2	+++	+++	++++

Note: + – stained tissues are noticeable and starch clots remain in the flanks and inter loops; ++ – stained tissues are not so noticeable, small starch limps remain on tissues, they are cleaned easily; +++ – no stained tissues, there are thin layers of starch which are easily cleaned with water; ++++ – no stained tissues, layers of starch are not seen.

While cleaning the peritoneal cavity using the usual method, to gain the visual effect as with solution 1, 5 L of it are needed; as with solution 2, up to 7.2 L are needed.

Conclusion

During the experimental study, vacuum-instillation therapy with ISU was performed on the three-dimensional polymer model. It is proved apparently and by quantity that the solution with CO2 delivered through it by impulses is more effective for the peritoneal cavity sanitation. Purulent matter in the flanks and interloop spaces becomes less dense, viscous and adhesive, it makes it easier to evacuate from the peritoneal cavity through the vacuum apparatus. We may suppose that this sanitation method is probably more effective, it reduces the risk of such complications as abdominal sepsis and septic shock. It is necessary to conduct a clinical trial to prove the

obtained results.

Conflict of interest. The author declares no conflict of interest.

References:

1. Dyabkin E.V., Vinnik Yu.S. Factory-etiological analysis of peritonitis rate. *Scientific Review*. 2015; 22: 75–77.

2. Urakov A.L., Urakova N.A. Original hygiene products for the prevention of postoperative adhesions, effective diluent thinning of thick purulent masses, sulfur plugs and tear stones. *Modern Problems of Science and Education*. 2013; 1. URL: https://www.science-education.ru/pdf/2013/1/11.pdf

3. Ceresoli M. et al. Open abdomen in obese patients: pay attention! New evidences from IROA, the international register of open abdomen. *World journal of surgery*. 2020; 44(1): 53-62.

4. Fernández L.G. Management of the open abdomen: clinical recommendations for the trauma/acute care surgeon and general surgeon. *International Wound Journal.* 2016;13(3):25-34. DOI:10.1111/iwj.12655.

5. Regner J.L., Kobayashi L., Coimbra R. Surgical strategies for management of the open abdomen. *World Journal of Surgery*. 2012; 36(3): 497–510.

6. Bjarnason T. Open abdomen therapy with vacuum-assisted wound closure and mesh-mediated fascial traction. *Lund University, Faculty of Medicine Doctoral Dissertation Series*. 2014; 2014(7).

7. Wittmann D.H. Intraabdominal infections—introduction. *World journal of surgery*. 1990; 14(2): 145-147.

8. Bradley M.J., Dubose J.J., Scalea T.M. et al. Independent predictors of enteric fistula and abdominal sepsis after damage control laparotomy: results from the prospective AAST Open Abdomen registry. *JAMA Surg*. 2013;148:947–954.

9. Jang J.Y., Shim H., Lee Y.J. et al. Application of negative pressure wound therapy in patients with wound dehiscence after abdominal open surgery: a single center experience. *J Korean Surg Soc*. 2013;85:180–184.

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COMBINATION OF URETEROHYDRONEPHROSIS WITH MULTICYSTOSIS: WAYS TO SOLVE THE PROBLEM ON CLINICAL EXPERIENCE

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Every year, about 250 children are examined and treated for obstructive uropathies in the Altai Regional Center for Maternity and Child Welfare. Patients with a combination of malformations of the urinary system demand most attention. Children with the afunction of one of the kidneys, recurrent pyelonephritis, gross organic pathology of the second kidney and, as a result, a high risk of development of chronic renal failure require particularly subtle approach to the treatment tactics. Observing the dynamics of preoperative and postoperative periods, good results of treatment of a combination of obstructive megaureter and multicystic disease in a child, the authors saw it necessary to highlight this clinical case in the scientific world.
Keywords: *pediatric urology, obstructive uropathies, megaureter, ureterocystoneoanastomosis, multicystosis, chronic renal failure.*

Currently, most scientific papers are devoted to modern methods of treatment of congenital malformations of the urinary system [1]. According to statistical data, obstructive uropathies prevail among malformations of the urinary system, which leads to the prevalence of works on this subject [2]. There are sources that report that the multicystic kidney, being a unilateral pathology, is combined with a normal contralateral kidney in most cases [3]. With the increasing number of observations in the scientific literature, there are reports of the presence of various malformations in the opposite kidney in 2/3 of patients. In practice, pediatric surgeons, nephrologists, pediatricians often have to observe combined defects and solve such issues as the priority of surgery and technology execution of the latter [4, 5]. According to the established canons of determining the tactics of the side of surgical treatment, in patients with bilateral lesions of the urinary tract, initial attention is given to correction of the disease on the side where the organ functions better. Most authors recognize the application of ureterocystoneoanastomosis with antireflux protection of the ureter by Cohen or Politano in children aged 12–18 months as the main surgical procedure in obstructive megaureter due to its high efficacy [5]. This article presents the successful experience of treating a child with a diagnosis: "Obstructive megaureter on the left. Multicystic right kidney". Frequent recrudescences of chronic pyelonephritis complicated the patient's management. Due to the timely diagnosis and treatment of combined defects, the authors managed to prevent the development of renal failure in the child [6].

When starting this work, the authors aimed to share the experience of treatment of combined malformation of the urinary system, as well as to demonstrate a possible combination of the classical treatment technique and the surgery with the use of endoscopic technologies.

Materials and methods

The work is based on the retrospective analysis of a child's medical history with the diagnosis: "Obstructive megaureter on the left. Multicystic right kidney", as well as the data of the studies in dynamics for 4 years.

Results and discussion

A child first entered the surgical department for children of RSHI "Altai Regional Clinical Children's Hospital" (now – "Altai Regional Clinical Center for Maternity and Child Welfare") at the age of 1 year after treatment of pyelonephritis attack in the nephrological department. From the history, it is known that the disease of the urinary system was detected prenatally at the 18th week of pregnancy according to ultrasound (CM of US: Multicystic dysplasia of the right kidney, megaureter on the left). After birth, the diagnosis was confirmed. From the maternity hospital, the child was transferred to the department of neonatal pathology. Ultrasound of internal organs from 10.02.2015: CM of the kidneys. Multicystic dysplasia of the right kidney. Ureter extension on the right. Ureterohydronephrosis on the left. Periodically, there were leukocyturia-type changes in urine tests. In May 2016, the child was hospitalized in the nephrology department of "Altai Regional Clinical

Children's Hospital". Ultrasound of internal organs from 11.05.2016: echo signs of multicystic dysplasia of the right kidney. Ureterohydronephrosis on the left. Dimensions of the right kidney were 51*26*37 mm, multiple cystic structures from 5 to 22 mm, on the left – 77*36*42 mm, residual urine volume was 7 ml from the initial 30 ml. Duplex of the vessels of the kidneys from 12.05.2016: no vascularization of the right kidney. Cystography from 12.05.2016: no visible pathological changes (Figure 1). Excretory urography from 18.05.2016: signs of ureterohydronephrosis on the left. Unvisualized right kidney (Figures 2, 3, 4).

Facts of history of life: boy from the II pregnancy, I childbirth. Urgent delivery at the gestation period of 38–39 weeks. Birth weight 3900 g. Height 53 cm. The Apgar score of 7/8 points. The obstetrician-gynecological history of the mother was burdened: arteriovenous malformation of the spinal cord, surgical treatment in 2003. KSD, chronic pyelonephritis. CFI. Carrying thrombogenic mutations. Mixed feeding (Nutrilon-comfort). The child does not lag behind peers in physical and neuropsychic development. The child is under regular medical check-up of the nephrologist for the main disease, is not subject to regular check-ups of other narrow specialists. Of the past diseases, there were: frequent ARVI (pharyngitis, nasopharyngitis – 5-6 times a year).

Figure 1. Cystography of the boy, 1 year (absence of vesicoureteral reflux).

Figure 2. Urogram of the child, 1 year (5th minute of examination before surgery).

Given the active course of the microbial inflammatory process in the urinary system (active growth of microbial bodies, mainly Enterococcus faecalis, in the urine culture, the presence of inflammatory changes in the general blood test: leukocytosis, shift of the leukogram to the left, ESR acceleration, as well as leukocyturia), it was decided to abstain from surgical treatment, stabilize the changed indicators of the blood and urine on outpatient basis in the home area, continue observations in dynamics.

Given the presence of two pathologies of the urinary system, a nephrologist was involved in the consultation of pediatric surgeons to choose the priority surgical treatment. Despite the fact that at the current stage of medicine development there are studies indicating the possibility of conservative management of patients with multicystic kidney dysplasia [7], the authors decided to perform nephrectomy on the right at the first stage, taking into account the inability to exclude the important role of the multicystic kidney in maintaining recurrence of inflammatory processes of the urinary system at the diagnostic stage, as well as taking into account the lack of propensity to the regress of the multicystic kidney in the dynamics and preservation of the function of the contralateral kidney. The advantage of laparoscopic nephrectomy over traditional one is now obvious [8], so there was no doubt in the choice of approach to the tactics of removing the multicystic kidney.

On 04.04.2017, surgery was performed under endotracheal anesthesia: Endoscopic nephrectomy on the right. Histological diagnosis No. 792 of 08.04.2017: congenital fibrocystic kidney. The

Figure 3. Urogram of the child, 1 year (15th minute of examination before surgery).

Figure 4. Urogram of the child, 1 year (60th minute of examination before surgery).

postoperative period proceeded steadily, without complications. Ultrasound of the abdominal cavity and retroperitoneal space from 14.08.2017: right kidney: condition after nephrectomy. Left kidney: normal position, even contour. Dimensions enlarged 92*38*44 mm, renal mass index 0.59%. Cortico-medullary differentiation is clear, blood flow retained to capsule in CDI. The ratio of the central and peripheral echozones is not changed. No concrements. RCS: a mixed type pelvis APD 15 mm, LCG 16 mm, UCG 17 mm. Ureter: the upper third of 8 mm, the middle third of 14 mm, the lower third of 24 mm. After micturition, RCS and ureter without dynamics. Bladder: filled with 80 ml. Normal form. Even, sharp contours. Thin walls. Anechogenic content of the cavity. After micturition, residual urine volume of 3 ml. Conclusion: Megaureter on the left with extension of the collector system of the left kidney. Condition after nephrectomy on the right. Vicarious hypertrophy of the left kidney.

In subsequent hospitalization on 16.08.2017, ureterocystoneoimplantation with antireflux protection of the left ureter by Politano-Leadbetter was performed under e/t anesthesia. The surgery course: transverse incision of the skin above the pubis to the retroperitoneal space. Exploration. The bladder is enlarged, signs of neuromuscular dysplasia are defined visually. Cystotomy. The ureteric orifice with a diameter of 0.3 cm is catheterized, the catheter is sewn, the ureter with a diameter of up to 0.3 mm is isolated, thinned, which goes to the right from the midline to a depth

of 6.0 cm, then blindly ends. The ureter is excised. Apparently, there was the orifice of the right ureter of the previously removed kidney. The orifice of the left ureter is not visualized. The exploration of the retroperitoneal space outside the bladder on the left is performed. A ureter with a width of up to 2.5 cm is found, convoluted, the ureter is mobilized, convolutions are eliminated. In the juxtavesical segment, pronounced stenosis of the ureter with a diameter of up to 0.2 cm is revealed. The distal segment of the ureter is bounded up twice, excised. The internal lumen of the ureter is less than 1 mm. A submucous tunnel in the bladder has been formed. The ureter is moved to the bladder through the previously removed right ureter. Fixation of the ureter is performed outside the bladder and from the inside with PDS 5/0 thread. Foley catheter No. 10 is carried out in the bladder through the urethra. The ureter catheter is excreted through the counterpuncture on the right wall of the bladder. Hemostasis dry. Double-row sutures on the bladder wound. The retroperitoneal drainage on the left. The wound is sewn layered by layer. Histological diagnosis No. 2355 from 18.08.2017: stenosis of the ureter.

The postoperative period proceeded without specific features, blood and urine tests on outpatient basis in the home area showed no signs of inflammation.

Control in a surgical hospital in August 2018, March 2019, September 2019: positive dynamics of the disease. Ultrasound of the abdominal cavity and retroperitoneal space from 06.09.2019. Right

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kidney: not located. Left kidney: normal position, even contour. Dimensions 92*40*41 mm, RMI 0.42%. Cortico-medullary differentiation is preserved, blood flow retained to capsule in CDI and PDI. The ratio of the central and peripheral echozones is not changed. No concrements. RCS: pelvis 3 mm, LCG 8 mm, UCG 7 mm; after micturition, slit-like pelvis, LCG 7.6 mm, MCG and UCG 5 mm. Bladder: volume of 155 ml. Normal form. Even, sharp contours. The walls are not thickened. The content of the cavity has sludge on the back wall. After micturition, volume of 12 ml (8%; the norm is not more than 10%). Left ureter: proximal segment 5 mm, middle third 12 mm,

distal segment 5 mm; after micturition, proximal segment 5 mm, middle third 10 mm, distal segment 5 mm. Conclusion: Condition after nephrectomy for multicystic right kidney. Vicarious hypertrophy of the left kidney. Calycectasis and extension of the ureter on the left. IV urography from 11.09.2019. Conclusion: Signs of moderately pronounced hydrocalycosis on the right (Figures 5, 6, 7). In control tests of blood, urine, there were no significant pathological and inflammatory changes.

For clarity, the dynamics of contraction of RCS and ureter on the left (on the side of obstructive ureterohydronephrosis) is given in Table 1.

Table 1

Dynamics of contraction of RCS and ureter

Parameters	Before surgery (2017)	After surgery (2019)
Dimensions of the left kidney	92*38*44 mm	92*40*41 mm
RMI	0.59%	0.42%
Pelvis APD	15 mm	3 mm
LCG	16 mm	8 mm
UCG	17 mm	7 mm
U/3rd of the ureter	8 mm	5 mm
M/3rd of the ureter	14 mm	12 mm
L/3rd of the ureter	24 mm	5 mm

Figure 5. Urogram of the child on the 5th minute of examination (after surgery).

Figure 6. Urogram of the child on the 15th minute of examination (after surgery).

It should be noted that all postoperative scars were healed with primary tension with the formation of normotrophic scars. Given the performance of the first surgery through laparoscopic access and the second surgery through the anatomical fold of the skin above the

pubis, the cosmetic result of surgical interventions can be regarded as good, which is of no small importance in the modern world. Also, an interesting observation from the history of this patient is the fact that after the surgical interventions, the boy has become extremely rare

Figure 7. Urogram of the child on the 60th minute of examination (after surgery).

to get ill with ARVI.

Conclusion

This observation helps emphasize the need for collective succession management of patients with severe malformations of the urinary system by pediatric surgeons, local pediatricians, nephrologists. Timely identification of the problem and regular medical check-up of patients with urinary malformations allow not to miss time and minimize possible complications. The solution of the issue of priority correction of combined malformations of the urinary system is most optimal to approach individually in each case. Endoscopic surgeries are currently a priority in the treatment of CM of the urinary system in most cases. However, with a combination of US malformations in one patient, a combination of surgical techniques is often the most optimal solution in clinical practice for successful treatment of the patient. In our clinic, the greatest preference for surgical correction of ureterohydronephrosis is given to the method of ureterocystoneoimplantation by Cohen, including pneumovesicoscopic; but in the observed patient, the orifice of the pathological left ureter was not visualized intraoperatively intravesically, so when correcting obstructive ureterohydronephrosis, the patient required a classical technique of ureterocystoneoimplantation by Politano-Leadbetter, which indicates the need for pediatric surgeons' perfect performance of the arsenal of all possible surgical techniques, knowledge, and experience in order to correct the course of surgical intervention if necessary.

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References:

1. Osipov I.B., Lebedev D.A. Minimally invasive treatment of obstructive megaureter in children. *Collection of Proceeding of the 3rd Congress of Pediatric Urologists-Andrologists*. Moscow; 2013: 115–6.

2. Rumyantseva G.N., Kartashev V.N., Medvedev A.A., Avrasin A.L., Semakina N.V. The choice of therapeutic tactics for megaureter in children. *Materials of the 4th Congress of Pediatric Urologists-Andrologists*. Moscow: 2015; 44.

3. Rabadanov G.R. Multicystic kidney in children. *Perm Medical Journal*. 2008; 25 (4): 14–16.

4. Sal'nikov V.Yu., Zorkin S.N., Gubarev V.I., Filinov I.V., Petrov E.I., Akopyan A.I. et al. Modern aspects of low-invasive treatment of primary obstructive megaloureter in children. *Pediatric Surgery*. 2016; 20 (3): 155–159.

5. Hoquétis L., Le Mandat A., Bouali O., Ballouhey Q., Mouttalib S., Moscovici J. et al. Primary obstructive megaureters: long-term follow-up. *Prog. en Urol*. 2013; 23 (7): 470–3.

6. Sal'nikov V.Yu., Zorkin S.N. The first experience with refluxing ureteral reimplantation in the staged treatment of obstructive megaureter in children during the first year of life. *Pediatric Surgery*. 2017; 21 (5): 244–248.

7. Chang A., Sivananthan D., Nataraja R.M., Johnstone L., Webb N., Lopez P-J. Evidence-based treatment of multicystic dysplastic kidney: A systematic review. *J. Pediatr. Urol*. 2018; 14 (6): 510–519.

8. Steven L.S., Li A.G.K., Driver C.P., Mahomed A.A. Laparoscopic nephrectomy for unilateral multicystic dysplastic kidney in children. *Surgical endoscopy and other interventional techniques*. 2005; 19: 1135 – 1138.

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ECOPHYSIOLOGICAL ROLE OF PHOTOPERIOD IN ACTIVITY OF FEMALE REPRODUCTIVE SYSTEM DURING ONTOGENESIS

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This paper systematizes the data of literary sources and presents the results of own research on the role of photoperiod in the female reproductive system.

Objective: to analyze and summarize the data of literary sources and own research to identify the ecophysiological role of photoperiod in the activity of the reproductive system of the female organism at different periods of ontogenesis. It is revealed that the role of photoperiod in the reproductive system in ontogenesis of the female organism consists in the production of photo-dependent hormone epiphysis: melatonin, which has an effect on the menstrual cycle and the ability to conceive. It is shown that the maximum of conception is observed in April and the minimum in February, which is due to the seasonality of photoperiodical phenomena and the production of melatonin, which controls the activity of the reproductive system.

Keywords: *photoperiod, melatonin, chronoperiodic system, ontogenesis, conception, reproductive system.*

The environment in which living organisms are present is subject to profound changes in almost all geophysical parameters: duration and intensity of lighting, temperature, atmospheric absolute pressure and humidity, geomagnetic field, electromagnetic fluctuations in the atmosphere, electrical potential gradient, electrical conductivity and air ionization, air velocity [1]. Such changes are more or less rhythmic during the day, associated with the continuous rotation of the Earth in outer space on its axis (circadian rhythms). The inclination of the Earth's axis to the plane of the Earth's rotation around the Sun results in a seasonal component of the frequency of geophysical changes throughout the year. Among the geophysical parameters, the most clear and astronomical pattern on the Earth's surface is light effect.

The chronoperiodic system, which is located at all levels of the organization of a living organism, generates fluctuations in its own activity with frequencies close to those of the main external geophysical cycles (daily, monthly, annual) and is capable of capturing a rhythm that is called 'Zeitgeber' or 'time-giver', thus synchronizing its activity with external rhythmic changes. The main function of the chronoperiodic system is to synchronize congenital periodic programmes with each other within the body and with external periodic changes [2].

In order to synchronize its own rhythms with external periodic changes, the chronoperiodic system of the body must be oriented towards some of these changes, perceive them and "capture" their rhythm with its own 'circadian clock'. These external periodic changes, which can affect the endogenous rhythms of the body, are called 'time-givers'.

The main time-giver (a time sensor or an external synchronizing factor) is the photoperiod, i.e. daily (or seasonal) day length or the duration of daily illumination. It is the most stable and reliable rate of all environmental parameters, proof to interference, fully coincides with the main external periodical factor: the rotation of the Earth, and is isolated in time from those "essential" factors (daily temperature, the amount of food available) that directly determine the survival of both individuals and species as a whole. That is, photoperiod in this case is a "pre-emptive" (predictive) factor for the body's chronoperiodic system [3].

Among the photoperiod-controlled rhythms, our focus has been on the rhythms of the reproductive system as procreation. In terms of the severity of photoperiodic changes in the reproductive system, animals are divided into 'photoperiodic' with highly accelerated changes in sexual functions depending on the season and 'non-photoperiodic' with no such changes and reproduction throughout the year [4]. People also have a fairly clear seasonal increase in sexual activity, although this data on seasonality remain contradictory. Therefore, the objective of our study has been defined.

Objective of the work: to analyze and summarize data from literature sources and our own research to identify the eco-physiological role of the photoperiod in the activity of the female reproductive system during various periods of ontogenesis.

Materials and methods

The study analyzed data on the number of children born in the hospital of the Barnaul City

Maternity Hospital over a period of one year. The sample included women who, according to medical records, had a normal singleton pregnancy that ended in delivery through birth canal. The size of the practical part of the study sample was 2,150 newborns of both genders. The analysis took into account the daily number of births, on the basis of which the estimated conception dates were calculated using the Negele formula.

The LibreOffice Calc software package was used for statistical processing of the results and charting.

Results and discussion

The plan was to collect and analyze literary sources in the first phase, which identified the following regularities.

The photoperiod affects the functioning of the pineal gland – epiphysis. Information on the intensity of light reaches this organ indirectly, through the eye retina, the retino-hypothalamic tract, the hypothalamic suprachiasmatic nuclei, the lateral intermedious nucleui of the spinal cord, and the sympathetic neurons of the upper cervical ganglion. Thus, the light information perceived by retinal photoreceptors through the melanopsin pigment is transmitted to the pineal gland via the suprachiasmatic neurons. In the dark, signals from suprachiasmatic nucleui amplify the synthesis and release of noradrenaline from sympathetic nerve endings. In turn, this neurotransmitter provoke receptors on the surface of epiphysis cells, thus stimulating the synthesis of the main hormone, melatonin.

Although the woman's reproductive system has its own rhythms, still depends on the rhythms of the neuroendocrine system, which coincide with the rhythms of the environment. Melatonin of both central and peripheral origin ensures the connection and synchronization of these rhythms [5].

For a long time, melatonin was thought to be produced only in epiphysis. Melatonin was first discovered in 1958. It is the main regulator of biological rhythms in the human body [6] and is a 5-methoxy-N-acetylated serotonin derivative (N-acetyl-methoxytryptamine), while the key enzymes for its synthesis are N-acetyl transferase and hydroxyindol-O-methyl transferase.

Melatonin concentration varies in different parts of cells. Moreover, the 24-hour rhythm of melatonin in tissues differs from the epiphysis rhythm. Researchers have proven that melatonin is synthesized by airway epithelium, skin, intestines, liver, kidneys, thyroid gland, thymus, spleen, immune system cells, and endothelium. Enzymes responsible for its synthesis have been found in almost all these tissues [7].

Today, scientists believe that all cells in the body are capable of producing melatonin. It is most likely synthesized in mitochondria, but not as a system regulator, but as a local antioxidant.

Melatonin plays a special role in various tissues of the reproductive system. Melatonin plays a special role in the maturation of the follicle and ovulation. The concentration of melatonin in the follicle is many times higher than the concentration in the blood. The follicle either accumulates melatonin despite the concentration gradient or synthesizes it itself. The peripheral tissues are known to prevent melatonin from entering the systemic circulation, i.e. synthesizing it for its own needs.

Melatonin modulates the synthesis of progesterone after ovulation. A rupture in the follicle wall is a local inflammatory reaction. It requires high levels of prostaglandins and cytokines and active work of proteolytic enzymes. All this is naturally accompanied by increased cell respiration and increased free radical concentration due to the work of macrophages and neutrophils. Due to the combination of these reactions, the oocyte is able to 'break out' from the follicle [8]. But in order to preserve the genetic material of the oocyte and protect it from free radicals under the conditions of an inflammatory reaction, a well-coordinated antioxidant system and the presence of melatonin are necessary [5]. Melatonin has been found to delay the vaginal delivery, reduce the volume of the ovaries, the frequency of the estrous cycle and determine the rhythmicity of gonadotropic effects, including menstrual cycle length [9].

A very important property of melatonin is its effect on cell division processes. In the course of the work of other authors, data have been obtained that melatonin can inhibit cell growth dependent on sex steroid hormones [6].

Studies in recent years have convincingly shown that epiphysis through melatonin plays a key role in regulating sex hormone content, puberty, ovulation synchronisation and steroidogenesis in gonads.

During ontogenesis, the amount of melatonin changes. Changes in the formation of melatonin during life coincide with the developmental stages of the body, are associated with them and have a direct impact on physiological processes. Embryos and newborns do not form melatonin themselves; they use the mother's, which comes through the placenta, and then – with the mother's milk. Hormone secretion begins at the third month of the child's development and its concentration reaches the peak in the first years of life (no later than 5 years). Melatonin synthesis remains at a constant and high level before puberty, then the amount of melatonin decreases sharply and continues to

decrease for another 5 years. There are no changes in melatonin formation after this until the age of 40–45, and then the amount of melatonin starts to decline steadily, which coincides with the onset of menopause and this process continues for the rest of a person's life.

According to a number of researchers, the circadian rhythms of melatonin synthesis are well traced in the younger age group (18–54 years) and are not found in the group of practically healthy people at the age of 55–92. For people at the age of 53–65, the night-time peak of melatonin secretion occurs at earlier hours (3 hours 48 minutes) compared to younger people (20–30 years old, at 4 hours 47 minutes) [9].

Women who have reached puberty up to the perimenopause period, morning melatonin concentrations are significantly lower in the luteal phase of the menstrual cycle. The late yellow body phase usually occurs on day 24–28 of the menstrual cycle and is accompanied by premenstrual syndrome. Especially during this period, women experience sleep disturbances that are actually related to the menstrual cycle. It has been established that in 10% of women of childbearing age, the onset of the menstrual cycle is

accompanied by mood changes, insomnia, appetite disorders, and reduced work capacities. There is abundant evidence that there is a correlation between a decrease in melatonin synthesis and the onset of menopause.

There are seasonal rhythms of melatonin levels fluctuation. Human blood melatonin levels are minimal between May and July, i.e. during the maximum daylight hours and the maximum illumination period. In May, the maximum value also reaches the amplitude between the minimum (day) and maximum (night) levels of melatonin during the day. Night-time melatonin levels rise longer in winter than in summer, which is a signal to reduce the activity of the hypothalamic GnRH secretion generator. These changes lead to a decrease in the capacity to conceive during the winter months.

The activity of the human reproductive system is characterized by the timing of child conception. In this regard, an analysis was made of data on the number of babies born at maternity hospital No. 2 in the city of Barnaul for a period of one calendar year. According to the Negele formula, the expected dates of conception were calculated by adding three months to the date of birth. The results are shown in Figures 1 and 2.
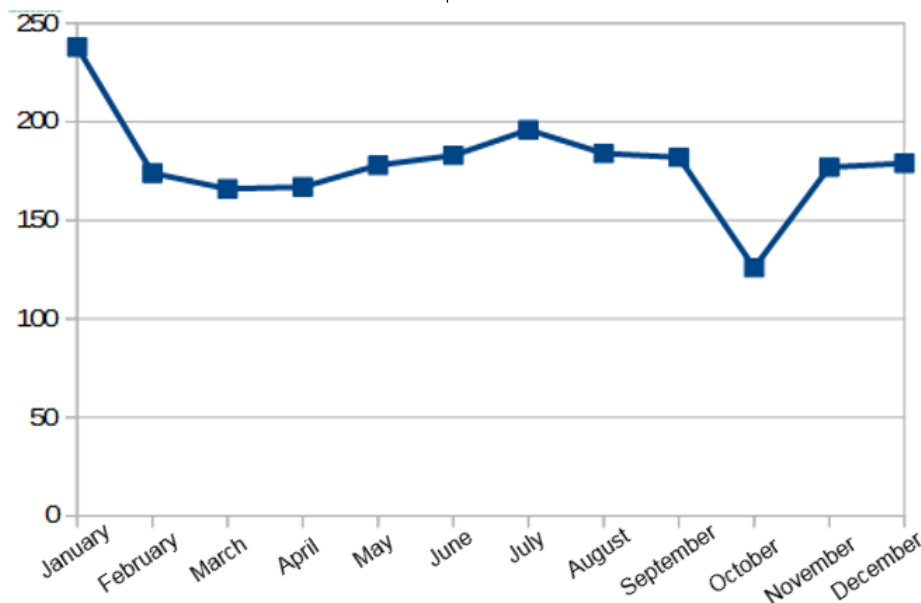
Figure 1. Distribution of births by months of the year.

As can be seen from Figure 1, the distribution of the number of births looks like a curve with maximum births in January and minimum births in October respectively.

The distribution of the number of supposed conception by calendar year (Figure 2) shows the maximum number of conception in April and the minimum number in February. This distribution is explained by the seasonality of photoperiodic

phenomena and the production of melatonin, which controls the activity of the reproductive system. Slight differences with the authors of other studies can be explained by the climatic characteristics of the region in which the study was conducted (April is the month of positive temperatures that are established during the day in Siberia, etc., which provokes hormonal changes in the female body, affecting melatonin production).
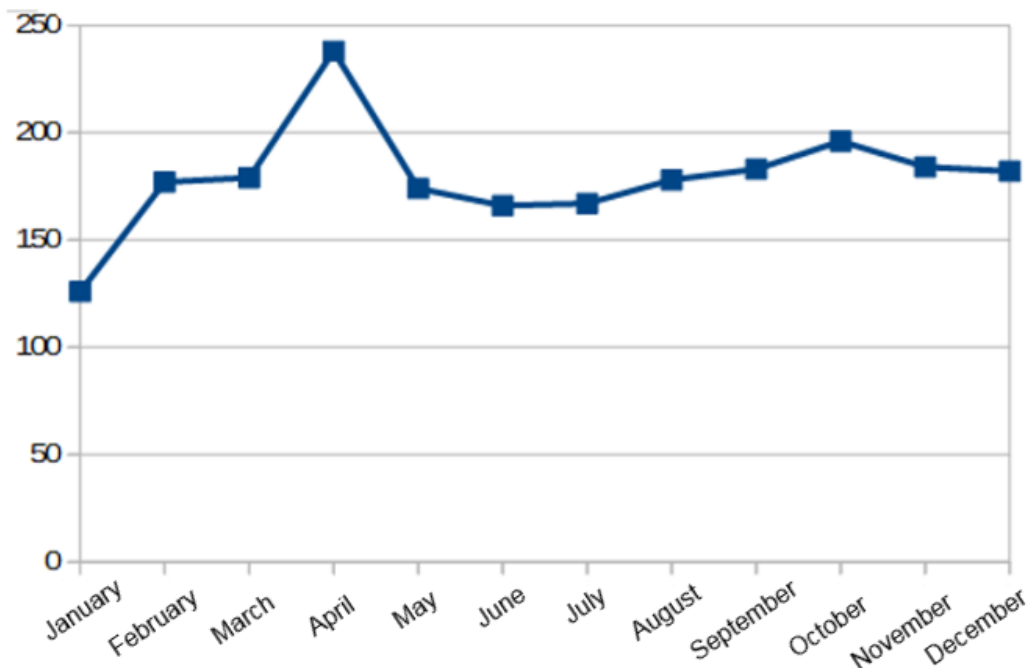
Figure 2. Distribution of the number of supposed conception by months.

Conclusion

The eco-physiological role of photoperiod in the ontogenesis of the female body in the reproductive system is to produce the epiphysis photo-dependent hormone – melatonin, which affects the menstrual cycle and the capacity to conceive. An increase in the concentration of melatonin is observed in the blood at night, it decreases with increasing light period and is seasonal. In a study of the activity of the human reproductive system, which is characterized by the timing of conception, it was found that the maximum number of conception occurs in April and the minimum in February, which is explained by the seasonality of photoperiodic phenomena and the production of melatonin, which monitors the activity of the reproductive system.

Conflict of interest. The authors declare no conflict of interest.

References

1. Pishak V.P. Photoperiodism and functioning of the reproductive system in mammals and humans. *International Journal of Endocrinology*. 2013; 2 (50): 77-80.

2. Zamorsky I.I. Photoperiod as the main time integrator of physiological systems. *Modern issues of biomedicine*. 2018; 2(3).

3. Ferrazzi E., Romualdi C., Ocello M., Frighetto G., Turco M., Vigolo S., Fabris F., Angeli P., Vettore G., Costa R., Montagnese S. Changes in accident & emergency visits and return visits in relation to the enforcement of daylight saving time and photoperiod. *J. Biol. Rhythms*. 2018: 748730418791097. DOI: 10.1177/0748730418791097.

4. Korf H.W. Signaling pathways to and from the hypophysial pars tuberalis, an important center for the control of seasonal rhythms. *Gen. Comp. Endocrinol*. 2018; 258: 236–243.

5. Burchakov D.I. Melatonin – an adaptogen for female reproductive system. *Effective Pharmacotherapy*. 2015; 5: 14-18.

6. Kachurina M.S., Zaynetdinova L.F., Kurenkov E.L. Melatonin influence on the processes of cell renewal in genital endometriosis. *Modern Problems of Science and Education*. 2018;2.

7. Acuña-Castroviejo D., Escames G., Venegas C. et al. Extrapineal melatonin: sources, regulation, and potential functions. *Cell. Mol. Life Sci*. 2014; 71(16): 2997– 3025.

8. Cruz M.H., Leal C.L., Cruz J.F. et al. Essential actions of melatonin in protecting the ovary from oxidative damage. *Theriogenology*. 2014; 82(7): 925–932.

9. Anisimov V.N., Vinogradova I.A. *Aging of the female reproductive system and melatonin*. Saint Petersburg: Systema; 2008: 44.

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EFFICACY OF PREGRAVID PREPARATION OF WOMEN WITH SPORADIC CASE OF NON-DEVELOPING PREGNANCY

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The analysis of the course and outcome of pregnancy in 92 women with sporadic reproductive loss according to the type of non-developing pregnancy in history was performed, including 42 patients after pregravid preparation in accordance with the identified nutrient-deficient conditions and the presence of antibodies to xenobiotic benzo[a]pyrene compared to a group of 50 women who did not receive preparation before the onset of pregnancy. Repeated non-developing pregnancy in the group without pregravid preparation was recorded 3 times more often. In children born to women after pregravid preparation in the early neonatal period, posthypoxic CNS lesions were significantly less likely to be recorded (21.9% and 65.2%, p=0.0001) and there were less diseases that required the second stage of treatment (17.1% and 63.0%, p<0.0001).
Conclusion: pathogenetically substantiated pregravid preparation of women with the sporadic case of non-developing pregnancy allows to improve the prognosis of gestation and reduce the frequency of perinatal complications.
Keywords: *non-developing pregnancy, sporadic miscarriage, pregravid preparation.*

Sporadic pregnancy loss is defined as a loss of pregnancy that occurs randomly throughout the reproductive period of a woman's life. The lack of rehabilitation and pregravid preparation leads to repeated pregnancy loss in each second case; and in 27.4% of observations, there are three or more episodes of miscarriage [1].

Pregravid preparation is a set of preventive measures aimed at minimizing risks in the realization of the reproductive function of a particular married couple [2]. The main task of this type of preparation is to correct existing parental health disorders in order to ensure that the couple enter the gestational period in the best state of health and full psychological readiness.

Objective of the study: to assess the peculiarities of the course and outcome of gestation in women with the sporadic case of non-developing pregnancy after pathogenetically substantiated pregravid preparation.

Materials and methods

We analyzed the course and outcome of pregnancy in 92 women aged 19 to 44 years with the sporadic case of non-developing pregnancy in history. At the stage of pregravid examination, these patients revealed violations of the nutrient status, namely, deficiency of ions of magnesium (0.74±0.36 mmol/L) and copper (4.57±5.77 μmol/l) in comparison with the control group of women without reproductive loss (concentration of magnesium ions – 0,89±0.22 mmol/L, p=0.047; concentration of copper ions – 6.57±7.28 μmol/L, p=0.172) [3]. In addition, during the examination at the pregravid stage, significant differences in the level of IgG antibodies to benzo[a]pyrene were revealed in patients with the sporadic case of non-developing pregnancy (11.76±6.09 CU) compared to the indicators of women without reproductive loss (8.77±4.65 CU,p=0.047).

Women with non-developing pregnancy were divided into two groups depending on the pregravid measures carried out, taking into account the revealed violations. Group I included 42 patients who received pregravid preparation in accordance with the revealed violations in full. Group II included 50 women whose pregnancy occurred without pathogenetically based preparation due to the lack of pregravid examination or refusal to complete preparation in full for various reasons.

The planned pregravid preparation was individual and included correction of detected violations: sanitation of foci of infection, treatment of somatic diseases. According to the clinical recommendations "Non-developing pregnancy" (2015), therapy with progesterone drugs was performed in the second phase of the menstrual cycle and in the first trimester of pregnancy [4]. In accordance with the identified deviations of the nutrient status, the patients received the supplement of multivitamin drugs containing active forms of folates. Taking into account the results of the study of the level of antibodies to xenobiotic benzo[a]pyrene, women were recommended rational nutrition from the pregravid stage and during pregnancy with the exception of fats and smoked products, smoking cessation (passive and active), stay in areas with "clean" air. When deviations were detected in laboratory tests of the hemostasis system, the patients were consulted by a hematologist and

received treatment in accordance with established violations. The onset of pregnancy was planned no earlier than 3 months after the beginning of pregravid preparation.

The average age of pregnant women in group I was 32.1±4.2 years, group II – 30.7±5.8 years (p=0.344). 10 women of group I (24.4%) and 9 women of group II (19.6%, p=0.779) were primiparous. 10 patients of group I (24.4%) and 16 women of group II (34.8%, p=0.41) had a history of artificial abortions. The uterine scar after caesarean section was found in 11 women of group I (26.8%) and 21 patients of group II (45.7%, p=0.109).

The analysis of somatic load showed almost the same incidence of chronic infectious and inflammatory diseases of the urinary tract (21.9% and 26.1%, p=0.837), pregravid obesity (17.1% and 32.6%, p=0.158) and chronic arterial hypertension (7.3% and 6.5%, p=0.781) in women of the compared groups.

All pregnant women were examined in accordance with the regulatory standards of preventive medical examination (Order of the Ministry of Health of the Russian Federation No. 572-n dated 01.11.2012). After the completion of pregnancy, the analysis of medical documentation was performed: medical card of a pregnant woman and new mother, form No. 111(u); prenatal record, form No. 113(u); labor record, form No. 096(u); hospital neonatal record, form 097(u).

Statistical processing of the results was carried out using the computer program MedCalc 9.1.0.1. The results are presented in the form of M values (arithmetic mean value) ±σ (mean square deviation). The critical level of significance when checking statistical hypotheses was taken as ≤0.05.

Results and discussion

In group I patients, there was a repeated non-developing pregnancy of the anembryonic gestation type in the early period in one case (2.4%), whereas in group II, this complication was registered 3 times more often (in 4 women, which is 8.0%, p=0.473). In the comparative analysis of the course of the gestational process in comparison groups, the comparable specific weight of threatened abortions (24.4% and 26.1%, p=0.948) and threatening premature birth (31.7% and 45.7%, p=0.265) was established. Anemia complicated the course of pregnancy in 36.6% of group I patients and 41.3% of group II patients (p=0.819). Gestational diabetes mellitus was registered in 9.8% of pregnant women of group I and 15.2% of patients of group II (p=0.665), there were no significant differences in the specific weight of gestational arterial hypertension (in 12.2% and 15.2%, p=0.925). Pregnancy ended with premature birth in 3 women of group I (7.3%) and 9 patients of group II (19.6%, p=0.177). In 14 women of group I (34.1%) and 20 women of group II (43.5%, p=0.499), delivery by caesarean section took place.

When assessing the fetoplacental system state, a number of features were revealed depending on the pregravid preparation of patients. According to the results of Doppler velocimetry during antenatal examination, hemodynamic violations in the mother–placenta–fetus system were much more likely to occur in group II (24 women, which is 52.2%) in comparison with group I (11 pregnant women, which is 26.8%, p=0.028). Intrauterine growth restriction during antenatal ultrasound was recorded only in the group of patients with non-developing pregnancy in history, who did not receive pregravid preparation in full (6 pregnant women, which is 13.0%, p=0.049).

All the children of mothers of both groups were born alive, there were no perinatal deaths. At the same time, perinatal outcomes were substantially better in mothers who received pregravid preparation. Anthropometric indicators of full-term children of group I significantly differed from the parameters of children of the comparison group: the average body weight was higher and amounted to 3641.2±488.9 g (in group II – 3283,8±574.9 g, p=0.005), the average body length was 52.9±2.8 cm and 51.5±2.3 cm (p=0.014). First-second degree intrauterine growth retardation of the hypotrophic type was recorded only in newborns whose mothers did not receive pathogenetically substantiated pregravid preparation (10.9%, p=0.086).

6 children of group I (14.6%) and 18 children of group II (39.1%, p=0.021) had the Apgar score of 6 points and less. The average Apgar score was 6.9±0.5 points in group I, 6.4±0.9 points (p=0.004) in group II. In the early neonatal period in children born to mothers who did not receive pathogenetically substantiated pregravid preparation, posthypoxic central nervous system lesions were more often recorded: in group I – 9 children, which is 21.9%, in group II – 30 children, i.e. 65.2% (p=0.0001). It should be noted that moderate disorders prevailed in group II (52.2%, in group I – 12.2%, p=0.0002). Respiratory disorders with respiratory failure were observed in 7 children (17.1%) from mothers with pregravid preparation and in 17 children (36.9%) of the comparison group (p=0.068). Children born to women after pregravid preparation were significantly less likely to have diseases requiring transfer to the second stage of treatment (17.1% and 63.0%, p<0.0001).

The study suggests that the high incidence of gestational and perinatal complications in patients of group II was a natural consequence of the lack of correction of pregravid violations.

Conclusion

Carrying out pathogenetically substantiated pregravid preparation in women with the sporadic case of non-developing pregnancy allows to improve the prognosis of gestation, reduce the frequency of gestational and perinatal complications and optimize pregnancy outcomes for newborns.

Conflict of interest. The authors declare no conflict of interest.

References:

1. Selikhova M.S., Dmitrienko G.V., Kuznetsova O.A., Vdovin S.V. Non-developing pregnancy: how to avoid losses in the future? *Journal of New Medical Technologies*. 2012. 2: 303.

2. Radzinsky V.E. et al. *Pregravid preparation: clinical protocol*. Moscow: Editorial Board of StatusPraesens; 2016: 80.

3. Igitova M.B., Korenovskiy Yu.V., Safarova G.A., Zharikova G.V., Filippova O.V., Pyankova I.V. Nutritional status of women with a blighted ovum. *Gynecology, Obstetrics and Perinatology*. 2019; 18(6): 46-50.

4. Radzinsky V.E. et al. *Non-developing pregnancy*. Methodological recommendations of MARS (Interdisciplinary Association of Reproductive Medicine Specialists). Moscow: Editorial Board of StatusPraesens; 2015:48.

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HISTORICAL EVOLUTION OF ECLAMPSIA/PREECLAMPSIA PARADIGM

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Eclampsia/preeclampsia continues to be not completely recognized, pathological condition of gestation determining perinatal/maternal morbidity/mortality, occupying the 3rd place in their structure up to the present time. This review examines the major historical steps of evolution in understanding eclampsia/preeclampsia: the "strange" disease of humanity associated with reproduction. The stages of description, definition, and understanding of the "disease of theories" are presented. The focus is on freely available information on the role of biological markers and the balance of modulators of hemostatic reactions specific to this pathology. Determination of the role of biologically active factors in the pathogenesis of the development of preeclampsia can contribute not only to the deepening of knowledge about the pathogenesis of this pathology, but also involves the search for drugs that have the ability to target specific PE markers.

Keywords*: eclampsia, preeclampsia, biological markers, tissue factor.*

Eclampsia (along with epilepsy) was the first disease described since the appearance of writing in humanity more than 5,000 years ago [1]. The term preeclampsia (PE) appeared in the 20th century, when in 1916 P. Zweifel described PE as a "disease of theories", the symptoms of which are associated with pregnancy [2]. Until now, the only method of treating PE is the extraction of the fetus and, definitely, the placenta [3]. In this review, we offer to consider the main stages of evolution in understanding the pathogenesis of eclampsia/PE and, possibly, its prediction.

Eclampsia – "historical" disease (more than 5,000 years ago)

Eclampsia is such a memorable condition that the elements of its description have survived from the time of the existence of writing (3,000 BC) from all parts of the world: India (Veda/Sushruta), China (Wang Dui Me), Africa (Egyptian papyrus), Europe (Hyppocrates/Galen). Eclampsia scared our ancestors: pronounced muscle contractions and seizures, severe anxiety, unusual movements of the head and eyes, changes in the shape of the mouth, loss of consciousness, and complete amnesia after the case were regarded in all civilizations as attempts of invasion of the evil spirit/devil.

Eclampsia was more likely to target first-pregnant, very young women (by modern standards, adolescents), with the risk of mother's death in about a third of cases. At the end of the 17th century, Mauriceau (1694) noticed that first-pregnant women were more prone to the development of eclampsia, unlike pluripara. "The oldest human mother" ever found by paleoanthropologists was a buried pregnant 20-year-old woman who died, perhaps, of eclampsia in gestation time of 32 weeks, dated 28,000 BC [4]. In the mid-18th century, Bossier de Sauvage (1739) proposed the term "eclampsia", diverting it from epilepsy [5].

The emergence of the concepts of "toxemia" and "preeclampsia". Discovery of proteinuria (1840–1843)

The era of fatalistic conception of eclampsia as a sudden and unpredicted pregnancy complication ended in the mid-19th century by the discovery of proteinuria. In 1840, French Pierre Rayer described the presence of proteinuria in women with eclampsia [6]. Later, in 1843, J.C.W. Lever, a British physician, published a paper where he suggested the possibility of predicting convulsive syndrome by the presence of proteinuria in a pregnant woman and its relief after delivery, thereby separating the concept "eclampsia" from the kidney disease [7]. Given that 2/3 of women with proteinuria required additional clinical factors to develop seizures, the term "toxemia" and the concept of "preeclampsia" emerged. In 1843, R. Johns, an Irish physician, described a number of symptoms in women with proteinuria that led to the development of eclampsia [8]. It is interesting to note that these symptoms are found in all modern textbooks for obstetrician-gynecologists: headache, temporary visual impairment, intense pain in the epigastrium [9].

The discovery of hypertension (1897–1903)

After Riva Rossi, a young Italian physician, discovered the possibility of measuring blood pressure with an inflatable arm cuff in 1896, the method has firmly entered clinical practice. Hypertension in eclampsia was first documented in 1897 by N. Vaquez in France [10], which in 1903 was confirmed by researchers Cook and Briggs in the United States [11]. The understanding has come that eclampsia is just the tip of the iceberg: about 10% of all pregnancies are complicated by reversible hypertensive disorders, of which 3% develop under the scenario of preeclampsia (proteinuria), and eventually without medical intervention, 1% of such pregnancies end in eclampsia.

The 20th century was marked by numerous comprehensive studies of the epidemiology and pathogenesis of hypertensive disorders during pregnancy and the writing of a large number of fundamental scientific papers on preeclampsia/eclampsia under the general motto: PE is the disease of first-pregnant women [12].

The concept of "double wave" of invasion of cytotrophoblast and its inferiority in PE (1970)

In the early 70s of the 20th century I.A. Brosens described that cytotrophoblast invasion in humans, unlike other mammals, occurs in significantly deeper layers and affects the myometrial segment of spiral arteries [13]. The multistage cytotrophoblast invasion process continues until week 14–16 of gestation, unlike other mammals in which the invasion process ends within two weeks of implantation. In 2008, I.A. Brosens and R. Pijnenborg proposed the concept of "double wave" [14], while pointing out that in women with PE the process of the second wave of thophoblast invasion is disturbed, and as a result,

there is insufficient depth of implementation in myometrium layers. This discovery allowed to understand 2 facts: first, why eclampsia/PE is strictly a human disease, and second, there was a logical explanation for the presence of hypertension. As known, adequate maternal blood flow to the placenta depends on two factors: the number of spiral arteries communicating with the intervillous space and the depth of cytotrophoblast invasion. Pathological placentation is characterized by a large number of spiral arteries, but the absence or insufficiency of their gestational transformation. It is shown that in patients with PE, an increase in the number of spiral arteries with violation or absence of their gestational remodeling and pathological deposition of fibrin are determined. Predominantly, the pathological process is localized in myometrial segments of spiral arteries [15]. Therefore, increased blood pressure in the mother may be a compensatory mechanism to ensure the delivery of the necessary amount of nutrients to the embryo/fetus through a defectively embedded placenta.

"Paternal contribution" to the PE development, or immunological theory (1970s–1990s)

In 1970, D. Ikedife from Nigeria conducted an epidemiological study of eclampsia and concluded that PE/eclampsia were often characteristic of re-pregnant women and, more importantly, 2/3 of these patients changed partners. The same proportion (2/3) of partner change among women with eclampsia was described some time later by P.Y. Robillard in Guadalupe [16]. The observations presented challenged dogma: PE is a disease of only first-pregnant women, and led researchers to study the connection of PE and immunology. Some of the main achievements of immunology in reproductology are summarized in Table 1.

Table 1

The most important achievements in immunology in the study of PE [17]

The year of discovery	The essence of discovery
1990s	The lack of HLA-G in PE
1990s	The role of cytokines (paradigm Th1/Th2)
1998	The immunological role of seminal fluid (TGF β)
2000-2004	The main role of NK cells (implantation and angiogenesis)
2006	Violation of regulation of angiogenic factors by activation of the compliment system
2007	The effect of hyperglycosylated HCG on trophoblast invasion depth
2008	Immunological animalistic model of PE
2010s	The main role of T Reg cells

Endothelial dysfunction – the main link of pathogenesis of preeclampsia/eclampsia (1980s)

During this decade, it was shown that hypertension and polysystemacity of organ damage in PE are united by one factor: endothelial dysfunction. Specialized endothelial cells in the kidneys (glomeruloendotheliocytes), Kupffer cells in the liver (in HELLP-syndrome) and endotheliocytes of the hematoencephalic barrier (eclamptic convulsions) become target points in the PE development, determining clinical variants of its course. Findings on systemic dysfunction of endothelial cells perpetuated the names of James Roberts, Robert Taylor, Christopher Redman and others in the history of understanding the pathogenesis of PE [18]. The identified problem of endothelial dysfunction led researchers to understand PE (at least PE with early onset and intrauterine growth restriction) as a two-stage disease [19]. It was concluded that violation of thophoblast invasion during the first pregnancies has nothing to do with PE with later onset in endothelial cell dysfunction [20].

Distinction of placental (early) and maternal (late) PE (late 1990s)

The concept of various PE phenotypes, which arose at the end of the 20th century [21], was further developed in 2013 in the work of J.M Roberts [22]. Early placental PE (<34 weeks) and late maternal PE (≥34 weeks) have very different outcomes for neonatal morbidity and mortality levels, as well as the rate of intrauterine growth restriction (IGR) development [23]. Early onset PE, as opposed to late, is usually accompanied by ischemic impairment in the placenta due to impaired cytotrophoblast invasion and IGR formation. Late is associated with low-gradient chronic inflammation, a higher body mass index of a pregnant woman, and insulin resistance. These differences between PE phenotypes made it possible to draw an important epidemiological finding of prevalence (up to 90%) of late PE phenotype in developed countries, as opposed to developing countries where the proportion of early PE reaches 30% [24]. In other words, the relatively high level of placental PE in developing countries presents a huge epidemiological problem regarding maternal and neonatal morbidity and mortality.

Highly specific markers of early and late PE (late 20th – early 21st century)

Taking into account the fact of various pathogenetic mechanisms of placental and maternal PE development, as well as understanding and adoption of the "double wave concept" of cytotrophoblast invasion, modern research is aimed at studying biological markers and their interaction at the stage of placenta formation, including the study of steroid hormones, growth factors (VEGF, PLGF), cytokines (IL6, IL10, IL11, TNF-$\acute{\alpha}$), adhesion molecules (L-selectin and E-cadherin), matrix metalloproteinases (MMPs), and modulators of the hemostasis system (thrombin, TF, PAI-1 and T-PA). Schematically, 3 ambiguous solution search vectors can be distinguished:

1. There is no specific marker of PE development.

In his review, J. Roberts (2013) concluded that there is no specific marker in the blood plasma of a pregnant woman both at the preclinical stage and in the implementation of PE/eclampsia, and gave valid arguments [25].

2. There are many biological markers of PE development.

A huge step forward in understanding the pathogenesis of PE was made by a team of researchers who in 2004 published a paper on the role of imbalance of angiogenic factors, such as placental growth factor (PlGF), vascular endothelial growth factor (VEGF), and factors preventing angiogenesis, such as soluble fins-like tyrozine kinase 1 (SFLT-1) [26]. Increased synthesis of soluble sFlt-1 is known to lead to pathological binding of VEGF and PlGF. As a result, proteins are unable to perform the angiogenic function and maintain endothelial hemostasis, determining the condition of severe preeclampsia. In pregnancies complicated by PE, the level of PlGF in serum is significantly reduced, and deviations of MOM (multiple of median) indicators from normal are more significant at the early rather than late gestation, so that the efficacy of determining serum PlGF levels is higher for early PE than for late [27].

A group of authors from Italy (2017) in vitro investigated the expression of gene and cytokine mediator of inflammation (HMGB1) and RAGE protein by placentas in women with PE compared to placentas in the physiological course of pregnancy. It has been shown that in patients with PE, the HMGB1/RAGE axis in the human placenta is shifted towards the inflammatory response and is accompanied by the increased expression of IL-6 and TNF-α [28].

A while later (2019), another PE sensitive marker was found, the inositol phosphoglycan P-type molecule (IPG-P), which is found in patients' urine 2–4 weeks before the clinical onset of PE and may be used as a screening test for PE [29].

3. Modulators of the hemostasis system – additional markers of PE development.

The gestation period is associated with a significant procoagulant shift in the balance of the hemostasis system. Physiological changes in the coagulation properties of blood during pregnancy are adaptive mechanisms aimed at preventing

bleeding during cytotrophoblast implantation, ensuring laminar blood flow in the intervillous space, as well as preventing massive bleeding during childbirth. The pathological shift of the hemostatic balance determines not only the risk of thrombotic events during pregnancy, but can also can cause the violation of perfusion at the placenta level [30]. Changes in the hemostasis system of maternal circulation primarily concern the activation of platelets and coagulation factors. A key role in their initiation belongs to increased formation of thrombin. An increase in thrombin formation may be associated with hemorrhage into the decidual membrane followed by the formation of a retroplacental hematoma; with intra-amniotic infection that can lead to decidual bleeding and enhancement of the systemic inflammatory response of the mother. The latter, in turn, can stimulate the synthesis and release of tissue factor by monocytes. Tissue factor (TF), also called factor III, is a transmembrane glycoprotein, is an integral part of cell walls in various tissues and is produced when the integrity of the cell wall is violated. TF can be detected on the surface of activated endothelial cells, leukocytes, and platelets [31]. Certain organs express different amounts of TF. The greatest expression occurs in the brain (astrocytes), placenta (thophoblast cells), and lungs (alveoli) [32].

Tissue factor is a key product of blood clotting in all tissues; the high level of TF expression in the placenta provides additional hemostatic protection during gestation and childbirth [33]. It is determined that hyperexpression of TF followed by a shift of hemostatic equilibrium towards hypercoagulation is observed in pregnant women in PE implementation [34]. In addition, in the binding of TF to factor VII, a range of biological effects are realized on the cell surface, such as the synthesis of cytokines, adhesion molecules, and growth factors. These products play a key role in the pathogenetic mechanism of PE development, namely the processes of inflammation, angiogenesis, and apoptosis [35]. TF activation is carried out by two pathogenetic mechanisms that enhance each other: platelet activation and inflammation [31]. TF activation products, factors IIa, VIIa and Xa, cause further hyperexpression of tissue factor, which closes the vicious cycle: thrombosis – inflammation – thrombosis [36].

TF is suppressed by a specific inhibitor, tissue factor pathway inhibitor (TFPI), which is up to 80% synthesized and expressed by endothelial cells and platelets [37]. TFPI prevents excessive formation of thrombin by binding activated factor X [38]. Despite the apparent role of the TF/TFPI relationship in PE pathogenesis, the results of many studies are ambiguous and often contradictory. Some studies described increased

plasma TF levels in PE compared to normal pregnancy [39], and others described the unchanged ones [40]. According to the same studies, the level of TFPI in plasma was unchanged [41], increased [42] or even decreased [43]. Indeed, patients with vascular pregnancy complications (PE/eclampsia, placenta detachment, IGR, and fetal death) have a lower concentration of total TFPI in placenta rather than women with uncomplicated pregnancy [44], which may be associated with reduced placental formation of TFPI [45]. Contradicting literature data may indicate that it is worth estimating not so much the concentration of TF and TFPI separately as the overall balance between blood clotting factors and their inhibitors. So, for example, in the work of S.A. Mastrolia et al. (2014), a lower ratio of TF/TFPI is shown in pregnant women with PE, despite an increase in the median plasma concentration of TFPI in these patients [46]. These observations show that attention should be focused not only on coagulation factors but also on their inhibitors, as the imbalance between them contributes to the supergeneration of thrombin, which may be leading in the pathophysiology of PE.

Possibilities of secondary prevention of PE (beginning of the 21st century)

The use of low doses of aspirin for the prevention of PE in high-risk groups has been more studied. The most large-scale international multicenter study of ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) was conducted in 2017. Stratification of patients into the PE development high-risk group was based on routine screening of premature PE at the gestation period of 11–13 weeks in accordance with the FMF algorithm (Fetal Medicine Foundation): constitutional maternal characteristics and biomarkers in 27,000 women with singlet pregnancy were analyzed and taken into account. In the high-risk group, a part of patients from 11–14 to 36 weeks of pregnancy received aspirin (150 mg per day), others received placebo. According to the results of the study, the application of aspirin was associated with a reliable decrease in the frequency of occurrence of maternal PE by 62% and a decrease in the frequency of placental PE at the term of <34 weeks at 82%. The ineffectiveness of PE prevention by aspirin in patients with concomitant chronic hypertension was also determined [47].

Conclusion

Despite significant advances in understanding and deciphering of certain pathogenetic mechanisms for the development of preeclampsia, the "disease of theories" continues to be a

pathological state of gestation determining perinatal/maternal morbidity/mortality rates. At the present stage, understanding of the role of biologically active factors in the pathogenesis of PE development involves the search for drugs that have the possibility of targeted effects on specific PE markers, which would allow delaying the time of early delivery for the maximum possible period for the benefit of the fetus, especially in early PE.

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Participation of authors

Shchekleina K.V. – search of primary sources, material processing, writing of the text.

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References:

1. Ghulmiyyah L., Sibai B. Maternal mortality from preeclampsia/eclampsia. *Semin Perinatol*. 2012;36(1):56-59.

2. Zweifel P. Eklampsie. In: Dederlein A. (Ed.) *Handbuch Der Geburtshilfe*. Bergman; 1916: 672–723. https://doi.org/10.1159 / 000354200

3. Roberts J.M., Bell M.J. If we know so much about preeclampsia, why haven't we cured the disease? *J. Reprod. Immunol*. 2013; 99:1-9 https://doi.org/10.1016/j.jri.2013.05.003

4. Robillard P.Y., Scioscia M., Coppola D. La Donna di Ostuni, a case of eclampsia 28,000 years ago. *J. Matern. Fetal Neonatal Med*. 2017; 24: 1–4. https://doi.org/10.1080/14767058.2017.1312333

5. Bell M.J. A historical overview of preeclampsia-eclampsia. *J. Obstet. Gynecol. Neonatal. Nurs*. 2010; 39 (5): 510–518. https://doi.org/10.1111/j.1552-6909.2010.01172.x

6. Rayer P.E. (Ed.) *Traité Des Maladies Des Reins Et Des Altérations De La sécrétion Urinaire*. Baillières, Paris; 1840: 1837-1841

7. Lever J. *Cases of Puerperal Convulsions with Remarks 2*. Guy's Hospital Report. London; 1843: 495–517

8. Johns R. Observations of puerperal convulsions. *Dublin J. Med. Sci*. 1843. 24 (1):101–115.

9. Bell M.J. A historical overview of preeclampsia-eclampsia. *J. Obstet. Gynecol. Neonatal. Nurs*. 2010. 39 (5):510–518. https://doi.org/10.1111/j.1552-6909.2010.01172.x

10. Vaquez N. De la pression artérielle dans l'éclampsie puerpérale. *Bull. Soc. Med. Hop. Paris* 1897; 119: 14

11. Lindheimer M.D., Roberts J.M., Cunnigham F.G., Chesley L. Introduction, history, controversies and definitions. In: Lindheimer J.M., Roberts F.G., Cunningham F.G. (Eds.). *Chesley's Hypertensive Disorders in Pregnancy*. Appelton and Lange, Stamford, Connecticut; 1999: 3-41. https://doi.org/10.1016/j.jri.2017.09.006

12. Robillard P.Y., Dekker G.A., Chaouat G. et al. Preeclampsia and the 20th century: le siècle des Lumières. *Pregnancy Hypertens*. 2018;13:107-109.

13. Brosens I.A., Robertson W.B., Dixon H.G. The role of the spiral arteries in the pathogenesis of preeclampsia. *Obstet. Gynecol. Annu*. 1972; 1: 177-191.

14. Pijnenborg R., Dixon G., Robertson W.B., Brosens I. Trophoblastic invasion of human deciduas from 8 to 18 weeks of pregnancy. *Placenta*. 1980; 1 (1): 3-19. https://doi.org/10.1016/S0143-4004(80)80012-9

15. Espitia O., Fouassier M. Thrombin generation test. *Rev Med Interne*. 2015; 36(10): 690-693. https://doi.org/10.1016/j.revmed. 2015.04.013

16. Robillard P.Y., Hulsey T.C., Périanin J. Association of pregnancy-induced hypertension with duration of sexual cohabitation before conception. *Lancet*. 1994; 344: 973–975. https://doi.org/10.1016/S0140-6736(94)91638-1

17. Redman C.W., Sargent I.L. Immunology of pre-eclampsia. *Am. J. Reprod. Immunol*. 2010; 63 (6): 534–543. https://doi.org/10.1111/j.1600-0897.2010.00831.x

18. Roberts J.M., Taylor R.N., Musci T.J. et al. Preeclampsia: an endothelial cell disorder. *Am. J. Obstet. Gynecol*. 1989; 161: 1200-1204. https://doi.org/10.1016/0002-9378(89)90665-0

19. Redman C.W., Sargent I.L. The pathogenesis of pre-eclampsia. *Gynecol. Obstet Fertil*. 2001. 29 (7-8): 518–522. https://doi.org/10.1016/S1297-9589(01)00180-1

20. Redman C.W., Sacks G.P., Sargent I.L. Preeclampsia: an excessive maternal inflammatory response to pregnancy. *Am. J. Obstet. Gynecol*. 1999; 180 (2): 499-506. https://doi.org/10.1016/S0002-9378(99)70239-5

21. Redman C.W., Sargent I.L. The pathogenesis of pre-eclampsia. *Gynecol. Obstet Fertil*. 2001; 29 (7-8): 518–522. https://doi.org/10.1016/S1297-9589(01)00180-1

22. Roberts J.M., Bell M.J. If we know so much about preeclampsia, why haven't we cured the disease? *J. Reprod. Immunol*. 2013; 99: 1-99. https://doi.org/10.1016/j.jri.2013.05.003

23. Kho E.M., McCowan L.M., North R.A.; SCOPE Consortium. Duration of sexual relationship and its effect on preeclampsia and small For gestational age perinatal outcomes. *J.*

Reprod. Immunol. 2009; 82 (1): 66-73. https://doi.org/10.1016/j.jri.2009.04.011

24. Robillard P.Y., Dekker G., Iacobelli S., Chaouat G. An essay of reflection: why does preeclampsia exist in humans, and why are there such huge geographical differences in epidemiology? *J. Reprod. Immunol.* 2016; 114: 44–47. https://doi.org/10.1016/j.jri.2015.07.001

25. Roberts J.M., Bell M.J. If we know so much about preeclampsia, why haven't we cured the disease? *J. Reprod. Immunol.* 2013; 99: 1-99. https://doi.org/10.1016/j.jri.2013.05.003

26. Levine R.J., Maynard S.E., Qian C. et al. Circulating angiogenic factors and the risk of preeclampsia. *N. Engl. J. Med.* 2004; 350 (7): 672-683.

27. Schmidt M., Dogan C., Birdir C. et al. Placental growth factor: a predictive marker for preeclampsia? *Gynakol Geburtshilfliche Rundsch.* 2009;49(2):94-9. doi: 10.1159/000197908

28. Zenerino C., Nuzzo A.M., Giuffrida D., Biolcati M. The HMGB1/RAGE Pro-Inflammatory Axis in the Human Placenta: Modulating Effect of Low Molecular Weight Heparin. *Molecules.* 2017; 22(11). https://doi.org/10.3390/molecules22111997

29. Scioscia M., Noventa M., Cavallin F. Exploring strengths and limits of urinary D-chiro inositol phosphoglycans (IPG-P) as a screening test for preeclampsia: A systematic review and meta-analysis. *J Reprod Immunol.* 2019 Sep;134-135:21-27. doi: 10.1016/j.jri.2019.07.005

30. Momot A.P., Nikolaeva M.G., Serdyuk G.V., Elykomov V.A., Mamaev A.N., Romanov V.V., Fadeeva N.I., Kudinova I.Yu., Belozerov D.E., Trukhina D.A., Maksimova N.V., Vakhlova Zh.I. Assessment of the state of the hemostasis system in physiologically occurring pregnancy. Methodological recommendations. *Russian Bulletin of Obstetrician-Gynecologist.* 2018; 3.

31. Chu A.J. Tissue Factor, Blood Coagulation, and Beyond: An Overview. *International Journal of Inflammation.* 2011; Article ID 367284. https://doi.org/10.4061/2011/367284

32. Osterud B., Bjorklid E. Sources of tissue factor. *Seminars in Thrombosis and Hemostasis.* 2006;32(1):11-23. DOI: 10.1055 / s-2006-933336

33. Mackman N. Role of Tissue Factor in Haemostasis, Thrombosis, and Vascular Development. *Arterioscler Thromb Vasc Biol.* 2004; 24:1015-1022. DOI: 10.1161 / 01.ATV.0000130465.23430.74

34. Marmur J.D., Thiruvikraman S.V., Fyfe B.S., Guha A., Sharma S.K., Ambrose J.A., Fallon J.T., Nemerson Y., Taubman M.B. Identification of active tissue factor in human coronary atheroma. *Circulation.* 1996;94:1226-1232.

35. Belting M., Ahamed J., Ruf W. Signaling of the tissue factor coagulation pathway in angiogenesis and cancer. *Arteiroscler Thromb Vasc Biol.* 2005;25:1545-1550.

https://doi.org/10.1161/01.ATV.0000171155.05809.bf

36. Chen D., Riesbeck K., McVey J.H., Kemball-Cook G., Tuddenham E.G., Lechler R.I., Dorling A. Human thrombin and FXa mediate porcine endothelial cell activation; modulation by expression of TFPI-CD4 and hirudin-CD4 fusion proteins. *Xenotransplantation.* 2001;8(4):258-265.

37. Sandset P.M. Tissue factor pathway inhibitor (TFPI) – an update. *Haemostasis.* 1996; 26:154-165. DOI: 10.1159 / 000217293

38. Broze Jr G.J. Tissue factor pathway inhibitor. *Thromb Haemost.* 1995;74:90-93.

39. Di Paolo S., Volpe P., Grandaliano G. Increased placental expression of tissue factor is associated with abnormal uterine and umbilical Doppler waveforms in severe preeclampsia with fetal growth restriction. *J Nephrol.* 2003;16:650-657. doi:10.1016/j.ajog.2005.10.813

40. Dusse L.M., Carvalho M.G., Getliffe K., Voegeli D., Cooper A.J., Lwaleed B.A. Total plasma tissue factor pathway inhibitor levels in pre-eclampsia. *Clin Chim Acta.* 2008;388:230-232. https://doi.org/10.1016/j.cca.2007.10.029

41. Rousseau A., Favier R., Van Dreden P. Elevated circulating soluble thrombomodulin activity, tissue factor activity and circulating procoagulant phospholipids: new and useful markers for pre-eclampsia? *Eur J Obstet Gynecol Reprod Biol.* 2009;146:46-49. https://doi.org/10.1016/j.ejogrb.2009.06.001

42. Erez O., Romero R., Hoppensteadt D., Than N.G. Tissue factor and its natural inhibitor in pre-eclampsia and SGA. *J Matern Fetal Neonatal Med.* 2008;21:855-869. DOI : 10.1080 / 14767050802361872

43. Teng Y., Jiang R., Lin Q., Ding C., Ye Z. The relationship between plasma and placental tissue factor, and tissue factor pathway inhibitors in severe pre-eclampsia patients. *Thromb Res.* 2010;.126:.e41-5. https://doi.org/10.1016/j.thromres.2010.02.012

44. Xiong Y., Zhou Q., Jiang F., Zhou S., Lou Y., Guo Q., Liang W., Kong D., Ma D., Li X. Changes of plasma and placental tissue factor pathway inhibitor-2 in women with preeclampsia and normal pregnancy. *Thrombosis Research.* 2010. 125:e317–e322. https://doi.org/10.1016/j.thromres.2010.02.017.

45. Abdel Gader A.M., Al-Mishari A.A., Awadalla S.A., Buyuomi N.M., Khashoggi T., Al-Hakeem M. Total and free tissue factor pathway inhibitor in pregnancy hypertension. *International Journal of Gynaecology and Obstetrics.* 2006. 95:248–253. https://doi.org/10.1016/j.ijgo.2006.07.014.

46. Mastrolia S.A., Mazor M., Loverro G., Klaitman V., Erez O. Placental vascular pathology and increased thrombin generation as mechanisms of disease in obstetrical syndromes. *Peer J.*

2014;2:e653. doi: 10.7717 / peerj.653

47. Rolnik D.L., Wright D., Poon L.C., O'Gorman N. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med*. 2017. DOI: 10.1056 / NEJMoa1704559

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ASSESSMENT OF THE IMPACT OF CLINICAL FACTORS ON PREMATURE RUPTURE OF FETAL MEMBRANES AT 24-33 WEEKS OF GESTATION

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Research objective: to study and assess the impact of major clinical factors on premature rupture of fetal membranes at 24–33 weeks of pregnancy.

Materials and methods. The study included 119 pregnant women in the period of 24–33 weeks of gestation: 27 women with a whole fetal bladder, who subsequently had an urgent birth with the timely discharge of amniotic fluid and birth of healthy full-term babies; 92 women with premature rupture of fetal membranes at 24–33 weeks of gestation, giving birth to premature babies. The statistical analysis was carried out using logistic regression.

Results and discussion. There were no significant differences in the structure of somatic diseases of the major group of pregnant women and the control group, which indicates the absence of adverse effects of chronic diseases on the PRFM. It was found that in the PRFM group, there was a statistically significantly higher proportion of women with STD in history (65% vs. 19%, p<0.001), in particular, with Candida albicans (18% vs. 0%, p=0.01) and Chlamydia trachomatis (14% vs. 0%, p=0.01). The analysis of fertility demonstrated the following: the control group and the PRFM group differ statistically significantly in pregnancy parity (p=0.001), in particular, in the PRFM group, there is a higher proportion of women with third pregnancy or more (57% vs. 26%, p=0.005) due to a lower proportion of women with the first pregnancy (12% vs. 41%, p=0.001). The proportion of women with history of pregnancy loss (32% vs. 0%, p=0.001) and abortion (57% vs. 19%, p=0.001) is also statistically significantly higher in the PRFM group than in control. In the analysis of complications of pregnancies in the control group and the PRFM group, there were no statistically significant differences, but in most women with PRFM pregnancy occurred against the background of the threat of premature birth (49%). In the PRFM group compared to the control on the first day after the fluid discharge, the level of hemoglobin 121 (111;129.5) g/L vs. 129(121–132) (p = 0.03) and an increased concentration of leukocytes – 13.7(8.2;17.2)×10[9] IU/L vs. 6.7(6.6–7.6)×10[9] IU/L (p<0.001) were noted.

Conclusion. PRFM at 24–33 weeks of gestation is associated with an increased level of leukocytes (above 13×10^{9} IU/L) in the blood serum, the parity in a woman (first, third and more), the presence of pregnancy losses and abortion in history, carrying the pathogens of sexually transmitted diseases (STD).

Keywords: *premature rupture of fetal membranes, premature birth, parity, STD.*

The relevance of the problem is significant not only in obstetrics, but also in neonatology: amniotic fluid is a biologically active environment surrounding the fetus [1], and premature rupture of fetal membranes (PRFM) reaches 35–60% in the structure of causes of premature birth [2] and is the cause of neonatal morbidity and mortality [3, 17]. According to statistics, about one million premature children annually die from complications (mortality up to 28%); 8–10% of surviving children develop cerebral palsy, 5–8% – intellectual disability, 3–5% – decompensated hydrocephalus, 2-3% – epilepsy, 3% – vision loss, 1% – hearing loss; on average, disability is about 44% [4]. Relationship of PRFM with high parity, as well as premature birth, habitual miscarriage and PRFM in history [5] was revealed; most women (88.6%) had an infectious pathology of vagina and uterine cervix, of which half was diagnosed with cervicitis [6, 16]. Fusion of differentiated cytotrophoblast forms syncytiotrophoblast, fully enveloping the developing placenta and forming an effective barrier, selectively regulating gas exchange as well as transfer of nutrients and exogenous agents (drugs, toxins, viruses, etc.) [7, 8, 9]. Connective tissue dysplasia plays a significant role in the PRFM development during preterm pregnancy, which offers clinical manifestations to assess the risk of PRFM at prematurity [10, 11, 12, 13, 14].

However, much remains unclear in the pathogenesis of this pregnancy pathology. Currently, not only the mechanisms for the PRFM development are being actively studied, but also its predictors are being sought.

The research objective was to study and assess the impact of major clinical factors on premature rupture of fetal membranes at 24–33 weeks of pregnancy.

Materials and methods

The study was conducted on the basis of the Clinical Maternity Hospital of the State Autonomous Healthcare Institution of Kemerovo

Oblast "Novokuznetsk Perinatal Center" and female health department No. 1 of the State Budgetary Healthcare Institution of Kemerovo Oblast "City Clinical Hospital No. 2". The study included 119 pregnant women, divided into 2 groups:

1) The control group: 27 women with a whole fetal bladder, who subsequently had an urgent birth with the timely outpouring of amniotic fluid and the birth of healthy full-term babies;

2) The major group: 92 women with premature rupture of fetal membranes at 24–33 weeks of gestation, who gave birth to premature babies.

In all cases, births occurred through natural birth canals. The study met the ethical standards developed under the WMA Declaration of Helsinki, all women who participated in the study gave the informed consent.

The study excluded women who had oncological, autoimmune and chronic inflammatory diseases of the lesser pelvis, as well as oncological diseases in history, acute inflammatory diseases at the time of examination, decompensated cardiovascular, respiratory, hepatic or renal failure, pregnancy with ABO- and Rh-isosensibilization or HIV infection.

The prenatal records of pregnant women and the labor records of women of the control group and the study group were analyzed.

After checking the normality of the distribution, non-parametric methods of statistical processing of the study results were used. The median and interquartile range were used as descriptive statistics – Me (Q1;Q3). The study groups were compared through the Kruskal–Wallis test with the Conover-Inman tests. For the construction of the classification model, the discriminant analysis was used with the step-by-step selection of variables based on the value of criterion F (inclusion at F more than 3.84). In order to comply with the condition of application of discriminant analysis, the initial data went through the Box-Cox transformation with the subsequent reverse transformation of the results obtained. The 95% confidence interval calculated by the Clopper-Pearson method is given for model quality indicators. The statistical significance of differences between frequencies was verified using the criterion χ^2. The differences were considered statistically significant at p≤0.05. All calculations were carried out in the opensource free software environment of statistical calculations R v.3.5.2.

Results and discussion

All pregnant women in the study were aged 18–40 (Table 1). Of the total number of those surveyed (n=119), the largest number of women n=67 (55.8%) were between the ages of 21 and 29. At the age of 30 and more, there were 48 women (40%) and under 20 years – (4.2%) 5 women.

There were no age differences in the comparison group of pregnant women with PRFM and the control group (Table 1).

Table 1

Comparison of pregnant women by age

Indicators	Study groups		Statistical indicators
	Control group	Major group	
Age, years – Me(Q1;Q3)	28(26;32)	28(25;31.5)	U=0.47, p=0.641

Note: [1] – the Mann-Whitney test was applied.

In the study of blood types and Rh factors, no statistically significant differences between groups were found, but the main number of women with PRFM had blood type II (40%), the lowest percentage of women had blood group IV (7%) (Table 2).

Table 2

The study of blood types and Rh factor

Indicators		Study groups		Comparisons between groups
		Control (n=27)	PRFM (n=92)	
Blood type, n (%)	O (I)	11 (40%)	30 (33%)	χ^2=0.7, p=0.88[2]
	A (II)	9 (33%)	37 (40%)	
	B (III)	6 (22%)	19 (21%)	
	AB(IV)	1 (4%)	6 (7%)	
Rh negative, n (%)		4 (15%)	19 (26%)	χ^2=0.4, p=0.55

Note: [1] – the Mann-Whitney test was applied; [2] – the chi-squared test was applied here and elsewhere.

As can be seen from the table (Table 3), there were no significant differences in the structure of somatic diseases of the major group of pregnant women and the control group, which indicates the absence of adverse effects of chronic diseases on the PRFM.

Table 3

The frequency of occurrence of certain extragenital diseases in the PRFM group and control

Indicators, n (%)	Study groups		Comparisons between groups[1]
	Control (n=27)	PRFM (n=92)	
Endocrine system diseases	3 (11%)	14 (15%)	p=0.76
Anemia	1 (4%)	12 (13%)	p=0.29
Vegetative-vascular dystonia	5 (19%)	15 (16%)	p=0.76
Gastritis	2 (7%)	8 (9%)	p=1.00
Bronchitis	1 (4%)	5 (5%)	p=1.00
Myopia	2 (7%)	10 (11%)	p=0.73
Kidney diseases	2 (7%)	5 (5%)	p=0.66

Note: [1] – the Fisher's exact test was applied.

The analysis of history of gynecological diseases found no statistically significant differences between the control group and the group of pregnant women with PRFM (Table 4).

Table 4

The frequency of occurrence of certain gynecological diseases in the PRFM group and control

Indicators, n (%)	Study groups		Comparisons between groups[1]
	Control (n=27)	PRFM (n=92)	
Uterine cervix ectopia	6 (22%)	32 (35%)	χ^2=1.5, p=0.22
Endometriosis	0 (0%)	4 (4%)	p=0.57[2]
Chronic adnexitis	2 (7%)	6 (7%)	p=1.00
Bacterial vaginosis	4 (15%)	6 (7%)	p=0.23
Ovarian cyst	1 (4%)	3 (3%)	p=1.00
Uterine fibroid	2 (7%)	6 (7%)	p=1.00
Chronic endometritis	0 (0%)	6 (7%)	p=0.34

Note: [1] – the chi-squared test was applied; [2] – the Fisher's exact test was applied here and elsewhere.

The prevalence of STD in the PRFM group and control is presented in Table 5.

It was found that in the PRFM group, there was a statistically significantly higher proportion of women with STD in history (65% vs. 19%, p<0.001), in particular, with Candida albicans (18% vs. 0%, p=0.01) and Chlamydia trachomatis (14% vs. 0%, p=0.01).

Table 5

The prevalence of STD in history in the PRFM group and control

Indicators, n (%)		Study groups		Comparisons between groups[1]
		Control (n=27)	PRFM (n=92)	
STD in history		5 (19%)	60 (65%)	χ^2=18.0, p<0.001
This includes:	Staphylococcus aureus	0 (0%)	3 (3%)	p=1.00[2]
	Candida albicans	0 (0%)	17 (18%)	p=0.01
	Herpes simplex 1, 2	0 (0%)	6 (7%)	p=0.34
	Chlamydia trachomatis	0 (0%)	13 (14%)	p=0.04

Note: [1] – the chi-squared test was applied; [2] – the Fisher's exact test was applied here and elsewhere.

The analysis of fertility demonstrated the following: the control group and the combined PRFM group differ statistically significantly in pregnancy parity (p=0.001), in particular, in the PRFM group, there is a higher proportion of women with third pregnancy or more (57% vs. 26%, p=0.005) due to a lower proportion of women with the first pregnancy (12% vs. 41%, p=0.001). The proportion of women with history of pregnancy loss (32% vs. 0%, p=0.001) and abortion (57% vs. 19%, p=0.001) is also statistically significantly higher in the PRFM group than in control (Table 6).

Table 6

Indicators of obstetric history in the PRFM group and control

Indicators, n (%)		Study groups		Comparison between groups[1]	
		Control (n=27)	PRFM (n=92)	Omnibus test	Paired comparisons
Parity of pregnancy	First	11 (41%)	11 (12%)	$\chi^2=13.3$, p=0.001	p=0.001
	Second	9 (33%)	29 (32%)		p=0.89
	Third and more	7 (26%)	52 (57%)		p=0.005
Pregnancy loss in history		0 (0%)	29 (32%)	$\chi^2=11.3$, p=0.001	
Abortions in history		5 (19%)	52 (57%)	$\chi^2=12.1$, p=0.001	

Note: [1] – the chi-squared test was applied as an omnibus test, posterior paired comparisons were carried out using the Haberman residue test.

When analyzing complications of pregnancies in the control group and the PRFM group, there were no statistically significant differences (Table 7). However, in most women with PRFM, pregnancy occurred against the background of the threat of premature birth (49%), which suggests that the thinning of the membrane and its rupture are due to pathological contractions of the uterus [15, 16].

Table 7

The frequency of occurrence of certain pregnancy complications in the PRFM group and control

Indicators, n (%)	Study groups		Comparisons between groups[1]
	Control (n=27)	PRFM (n=92)	
Threatened miscarriage	14 (52%)	45 (49%)	$\chi^2=0.1$, p=0.79
Low placentation	4 (15%)	14 (15%)	p=1.002
ARD	4 (15%)	5 (5%)	p=0.12
Early toxicosis	2 (7%)	7 (8%)	p=1.00
Marginal placenta previa	0 (0%)	4 (4%)	p=0.57
Cervical insufficiency	0 (0%)	4 (4%)	p=0.57

Note: [1] – the chi-squared test was applied; [2] – the Fisher's exact test was applied here and elsewhere.

There were no complications of the postpartum period in the study groups. For determining the course of pregnancy, its complications, the indicators are important such as the level of hemoglobin, hematocrit, leukocytes, LII, total protein, transaminases, which were measured in the blood of pregnant women on the first day of the outpouring of amniotic fluid. In the PRFM group compared to the control on the first day after the fluid outpour, the level of hemoglobin 121(111;129.5) g/L vs. 129(121–132) (p=0.03) and an increased concentration of leukocytes – 13.7(8.2;17.2)×10^9 IU/L vs. 6.7(6.6–7.6)×10^9 IU/L (p<0.001) were noted.

Conclusion

Thus, premature rupture of fetal membranes at 24–33 weeks of pregnancy is associated with an increased level of leukocytes (above 13×10^9 IU/L) in the blood serum, the parity in a woman (first, third and more), the presence of pregnancy losses and abortion in history, carrying the pathogens of sexually transmitted diseases (STD).

Conflict of interest. The authors declare no conflict of interest.

Table 8

Biochemical indicators of venous blood serum in the PRFM group and control

Indicators, Me(Q1;Q3)	Study groups		Comparisons between groups[1]
	Control (n=27)	PRFM (n=92)	
HB, g/L	129(121;132)	121(111;129.5)	2.20, p=0.03
HT	0.36(0.34;0.4)	0.36(0.36;0.38)	0.22, p=0.82
Leukocytes, ×10^9 IU/L	6.7(6.6;7.6)	13.7(8.2;17.2)	χ^2=5.76, p<0.001
LII	1.2(1,1;1.4)	1.2(1,1;1.4)	0.48, p=0.63
Total protein, g/L	67(64;71)	67(63;71.6)	0.12, p=0.91
ALT, IU/L	15(13;17)	16(12;21)	1.41, p=0.16
AST, IU/L	24.5(21;30)	22(21;28)	0.72, p=0.47

Note: [1] – the Mann-Whitney test was applied.

References:

1. Knyazeva T.P. Causes and risk factors of premature rupture membranes. *Far East Medical Journal*. 2016; 2: 128-135.

2. Kuzmin V.N. Perinatal outcomes with premature rupture of fetal membranes. *Lechaschii Vrach Journal*. 2018; 3: 34-38.

3. Di Renzo G.C. Cabero L.R., Facchinetti F. European Association of Perinatal Medicine-Study group on "Preterm Birth": Guidelines for the management of spontaneous preterm labor: Identification of spontaneous preterm labor, diagnosis of preterm premature rupture of membranes, and preventive tools for preterm birth. *J. Matern. Fetal Neonatal Med*. 2011;24:5:659-667.

4. Lucaroni F., Morciano L., Rizzo G.D., Antonio F., Buonuomo E., Palombi L., Arduini D. Biomarkers for predicting spontaneous preterm birth: an umbrella systematic review. *J Matern Fetal Neonatal Med*. 2018; 31(6): 726-734. doi:10.10801/14767058

5. Artymuk N.V., Elizarova N.N. Risk factors of premature rupture of membranes in women with preterm birth in the Kemerovo region. *Fundamental and Clinical Medicine*. 2016; 2: 6-11.

6. Artymuk N.V., Elizarova N.N., Chernyaeva V.I. et al. Outcomes of pregnancy and delivery preterm in women with premature rupture of membranes. *Mother and Baby in Kuzbass*. 2015; 2: 98-102.

7. Hui P. Molecular diagnosis of gestational trophoblastic disease. *Expert Rev Mol Diagn*. 2010; 10(8): 1023–1034. doi: 10.1586/erm.10.93.

8. Hui P. *Gestational Trophoblastic Disease: Diagnostic and Molecular Genetic Pathology*. New York: Humana Press; 2011.

9. Delorme-Axford E., Sadovsky Y., Coyne C.B. The Placenta as a barrier to viral infections. *Annu. Rev. Virol*. 2014; 1: 133–146. doi: 10.1146/annurev-virology-031413-085524.

10. Ushakova G.A., Novikova O.N., Renge L.V. et al. *Infected gestational sac: from conception to birth*. M.; 2018: 271.

11. Dyatlova L.I., Mikhailov A.V., Chesnokova N.P. et al. On the role of cytokine balance disorders in the pathogenesis of premature departure of amniotic fluid, their diagnostic and prognostic value. *Fundamental Research*. 2013; 5: 271-275.

12. Artymuk N.V., Elizarova N.N., Chernyaeva V.I. et al. Outcomes of pregnancy and delivery preterm in women with premature rupture of membranes. *Mother and Baby in Kuzbass*. 2015; 2: 98-102.

13. Belotserkovtseva L.D., Pankratova V.V., Ivannikov S.E., Kilicheva I.I., Purnov O.Yu., Gilmanova A.E. Preterm prelabour rupture of membranes before 34 weeks. Choosing a safe latency period. *Gynecology, Obstetrics and Perinatology*. 2020; 19; 1:83-89.

14. Kan N.E., Sannikova M.V., Amiraslanov E.Yu., Tyutyunnik V.L. Clinical predictors in prognosis of premature rupture of membranes. *Gynecology, Obstetrics and Perinatology*. 2013; 12; 3: 12-18.

15. Astrakhantseva M.M. *Threat of termination of pregnancy in the second trimester. Diagnosis. Prediction. Therapy*. Author's abstract of the Candidate of Medical Sciences: 14.01.01. Moscow; 2018.

16. Kurnosenko I.V., Dolgushina V.F., Alikhanova E.S., Nadvikova T.V., Shumkova P.V., Nedzvetskaya I.S. Preterm prelabor rupture of membranes in terms of less than 34 weeks of gestation, results of prolongation of pregnancy. *Modern Problems of Science and Education*. 2018; 6.

17. Shadeeva Yu.A., Guryeva V.A., Nikolaeva M.G., Evtushenko N.V. Predicting intrauterine fetal infection risk in extremely preterm and early preterm births induced by rupture of the amniotic membranes. *Obstetrics, Gynecology and Reproduction*. 2020; 14(4): 490-501.

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OPTICAL COHERENCE TOMOGRAPHY OPPORTUNITIES IN GLAUCOMA DIAGNOSTICS

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The increasing incidence of glaucoma worldwide shows objective difficulties in both diagnosis and treatment. The introduction of optical coherent tomography into the algorithm of diagnostic examination of patients with glaucoma allows to objectively assess patterns of structural and hemodynamic changes. The article discusses the opportunities of OCT and OCT-angio for the purpose of early detection of the disease and dynamic observation of patients.
Keywords: *glaucoma, OCT.*

Primary open-angle glaucoma (POAG) is an urgent modern ophthalmology problem since it is one of the causes of irreversible loss of visual functions in the elderly and senile people [1, 2]. According to WHO, the number of patients with glaucoma worldwide will increase to 111.8 million by 2040 (in 2013, the number of patients (aged 40–80 years) with glaucoma was estimated at 64.3 million, in 2020 – 76.0 million worldwide) [3].

Primary open-angle glaucoma is a multifactorial disease with the insufficiently studied pathogenesis. The search for the most informative and accurate method of studying the optic disk (OD) and its blood flow has been carried out for many decades [4, 5]. The appearance of a new noninvasive technology – high-resolution optical coherence tomography (OCT) – has opened up new prospects in the study of both the structure of the OD and the ocular blood flow in glaucoma.

The principle of the OCT method is that the light wave is directed into the tissue, where it spreads and is reflected or scattered from the inner layers which have different properties. The resulting tomographic images are, in fact, the dependence of the intensity of the signal scattered or reflected from the structures inside the tissues on the distance to them. The process of building images can be considered as follows: a signal from the source is sent to the tissue, and the intensity of the returning signal is measured sequentially at certain time intervals. Since the speed of signal propagation is known, the distance is determined by this indicator and the time of its passing. Thus, a one-dimensional tomogram (A-scan) is obtained. If one consistently moves along one of the axes (vertical, horizontal, oblique) and repeats the previous measurements, one can get a two-dimensional tomogram. If one moves along one more axis sequentially, one can get a set of such sections, or a volumetric tomogram [6].

OCT is a reliable, informative, sensitive method in the diagnosis of many diseases of the fundus. It allows viewing the structure of the retinal tissue and its pathology in real time with a resolution of 1 to 15 microns, which is much higher than in other studies (ultrasound examination, MRI or CT). The obtained images can be analyzed, quantified, stored in the patient's database and compared with subsequent results, which allows obtaining objective information for the diagnosis and monitoring of the disease [7].

OCT visualizes not only the structures of the retina (macular zone, fovea, optic disc) but also its various layers (photoreceptors, ganglion cell layer, etc.) [8]. Studies have established a significant role of OCT in the diagnosis and monitoring of a number of macular diseases, including macular edema, macular cysts, age-related macular dystrophy, central serous chorioretinopathy, and epiretinal membranes [9, 10, 11, 12, 13].

Changes in the optic disc are a marker of glaucoma. SD-OCT is able to provide topographic measurements of the OD, including its area, neuroretinal rim volume and area, as well as the area and volume of the excavation (Figure 1). A number of studies have shown that the OCT measurement data are comparable with other methods of studying the optic disk [14, 15].

The optic disk consists of axons of retinal ganglion cells, blood vessels, and nerve and connective tissue. Accurate clinical identification of the OD boundaries is the main point in quantifying the ratio of the excavation diameter and its size. The reference point for determining the edge of the disk is the interruption of layers of photoreceptors, pigment epithelium, and choriocapillaries. In this case, the retinal pigment epithelium and choriocapillaries are visualized as an optically dense layer, the ellipsoid zone of photoreceptors is defined as a thin, hyperreflective structure in front of the pigment epithelium and choroid. The outer and inner plexiform layers are defined as moderately reflective, while the outer and inner nuclear layers are hyporeflective.
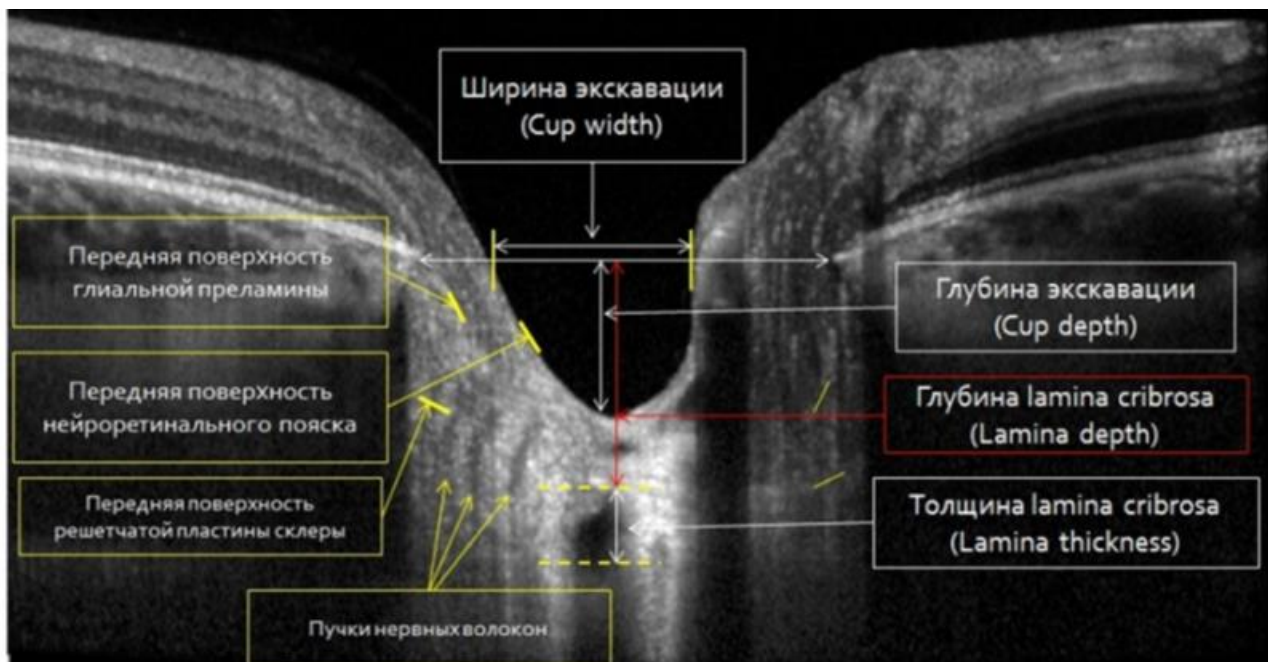
Figure 1. Parameters of the optic nerve disk. From the left top to bottom: The front surface of the glial prelamina, The front surface of the disc rim, The front surface of the cribriform plate of the sclera, Bundles of nerve fibers.

Determination of the thickness of the retinal nerve fiber layer in the peripapillary zone plays an important role in the diagnosis and monitoring of glaucoma (Figure 2). When assessing the thickness of the retinal nerve fiber layer, its average value around the OD is taken into account, as well as the thickness measured by quadrants (in the upper, lower, temporal and nasal) or by narrow sectors [16, 17, 18].

According to the literature, the average thickness of the peripapillary retinal nerve fiber layer and the thickness in the lower and upper quadrants were the parameters with the highest diagnostic confidence [18, 19]. This is consistent with other studies showing that the upper and lower parts of the optic nerve are most often affected in glaucoma [20, 21]. Therefore, when examining patients in clinical practice, this OCT parameter is most often taken into account. Numerous studies have shown that the thickness of the retinal nerve fiber layer correlates with perimetry parameters [22, 23]. Depending on the specific parameter and characteristics of the population under study, the sensitivity of glaucoma detection by the retinal nerve fiber layer research is approximately in the range of 60–98%, and in some cases – 80–95% [24, 25].

Modern tomographs can detect not only structural changes in the retinal nerve fiber layer but also determine the progression of the neurodegenerative process. Thus, the study of the retinal nerve fiber layer in dynamics revealed the progression of the glaucoma process in 22% of the eyes [26]. Wollstein G. et al. were monitoring
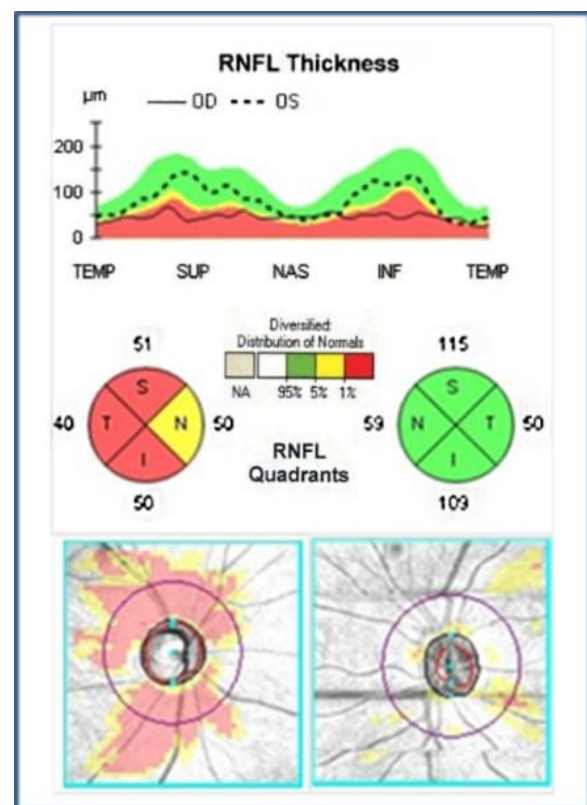
Figure 2. Estimation of the thickness of the retinal nerve fiber layer.

patients with glaucoma for 4 years, performing OCT every 6 months. The authors chose a decrease in the average thickness of the retinal nerve fiber layer by at least 20 microns as a criterion for progression, and this change had to be confirmed during two consecutive visits. The applied trend method allows not only to determine the fact of

glaucoma progression but also to calculate its rate. Thus, the analysis of the retinal nerve fiber layer thickness is relevant for visualizing the development of the retinal nerve fiber layer defects in the progression of glaucoma.

The thickness of the ganglion retinal complex is another marker of the development and progression of glaucoma. Spectral OCT (SD-OST)

allows us to quantify both the entire thickness of the macula and the thickness of individual layers that play an important role in glaucoma (Figure 3) (the so-called retinal ganglion cell complex) [27]. Cho J. et al. reported a correlation between the average light sensitivity of the visual field, the retinal ganglion layer, and the thickness of the retinal nerve fiber layer in glaucoma eyes [28].
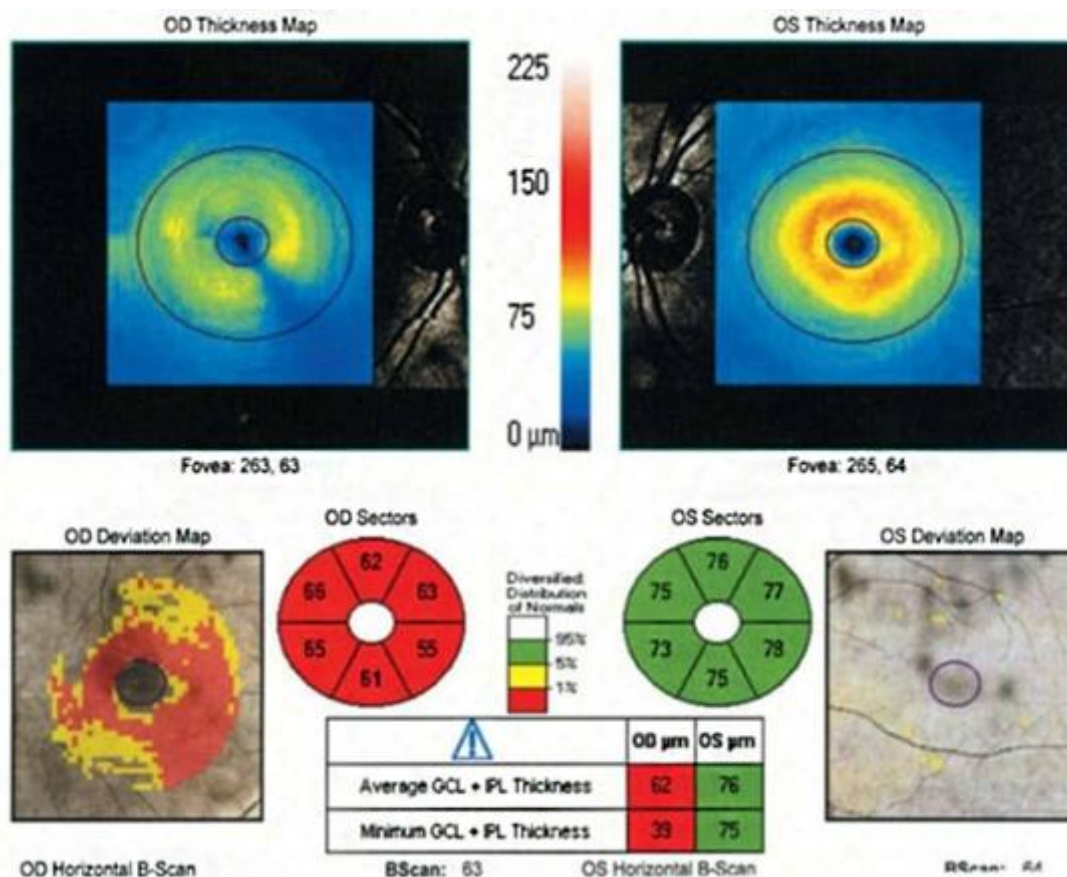
Figure 3. Estimation of the retinal ganglion layer.

OCT in angiography mode (OCT-A) allows visualizing the smallest vessels, up to capillaries in different areas of the retina and at different depths. In contrast to fluorescent angiography, the OCT-A method allows studying not only the superficial plexus of the retina but also the deep plexus without using contrast media (Figures 4, 5) [29, 30, 31].

After performing OCT angiography on patients with early, advanced, and severe stages of glaucoma and comparing them with healthy individuals, Wang X. et al. showed a decrease in the blood flow index and vascular density of the microcirculatory bed in the OD in patients with POAG [32]. The authors found a high correlation of the parameters measured by the OCT-A method with the perimeter indices and the thickness of the retinal ganglion complex. At the same time, it was shown that the latter is an independent predictor of a decrease in the density of the microcirculatory

bed in the OD.

Rao H. et al. revealed an important role of OCT-A in the diagnosis of glaucoma [33]. Comparing patients with glaucoma, these authors found that the significance of vascular density in the lower temporal parts of the peripapillary retina is comparable to the thickness of the retinal nerve fiber layer in the diagnosis of the disease, and the sensitivity of this parameter of OCT-A rose with increasing severity of glaucoma.

An important role in reducing the density of the capillary network in the lower-temporal sector of the peripapillary retina was emphasized by many authors [34, 35], explaining this by the fact that it is in these parts that local defects in the sclera lattice membrane are most often found. According to the authors, such defects create conditions for atrophy of the nervous tissue and the formation of a defect in the microcirculatory bed.
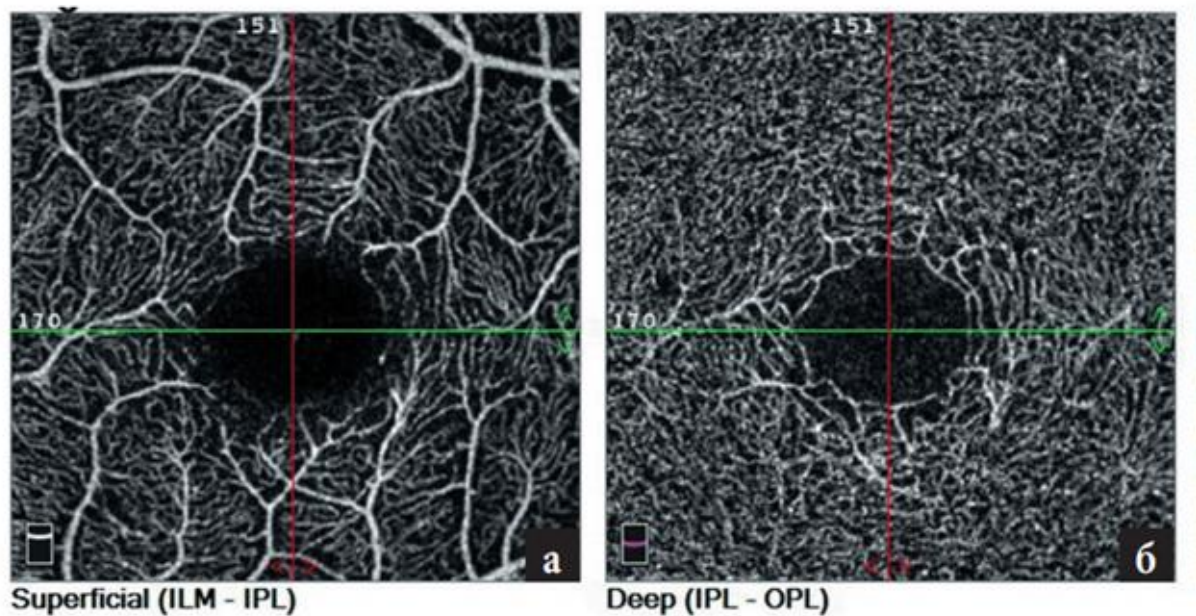
Figure 4. OCT angiography of the macular area (a – superficial, b – deep vascular plexus).
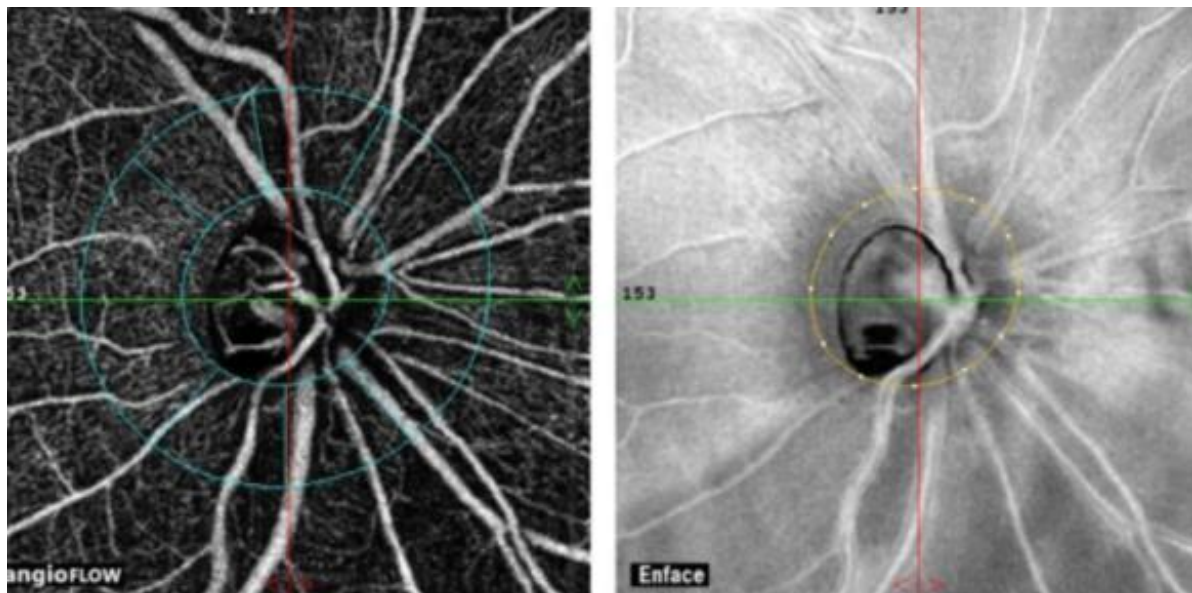
Figure 5. OCT angiography of the OD.

Conclusion

Thus, the appearance of spectral optical tomography, including the angio mode, opens up new prospects in understanding the pathogenesis of the disease, early detection of glaucoma and dynamic observation from the standpoint of morphofunctional relationships, allows not only to detect the disease before the first defects appear in the field of vision but also to determine the rate of its progression.

Conflict of interest. The authors declare no conflict of interest.

References:

1. Libman E.S., Kaleeva E.V., Ryazanov D.P. Complex characteristics of disability due to ophthalmology in the Russian Federation. *Russian Ophthalmology*. 2012; 5: 24-26.

2. Egorov E.A., Astakhov Yu.S., Yerichev V.P. *National guide on glaucoma for practitioners*. Moscow: GEOTAR-Media; 2015:456.

3. Tham Y.C., Li X., Wong T.Y. et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014; 121: 2081–90.

4. Drexler W., Fujimoto J.G. State-of-the-art retinal optical coherence tomography. *Prog Retin Eye Res*. 2008; 45-88.

5. Flock S.T., Wilson B.C., Patterson M.S. Monte Carlo modeling of light propagation in highly scattering tissues. II. Comparison with measurements in phantoms. *IEEE Trans Biomed Eng.* 1989; 36:1169-1173.

6. Hee M.R., Puliafito C.A., Wong C., Duker J.S., Reichel E., Rutledge B., Schuman J.S., Swanson E.A., Fujimoto J.G. Quantitative assessment of macular edema with optical coherence tomography. *Arch Ophthalmol*. 1995; 8: 1019–1029.

7. Lumbroso B., Rispoli M. *Retina OCT. Method of analysis and interpretation*. Moscow: Aprel'; 2012: 83.

8. Hee M.R., Izatt J.A., Swanson E.A. et al. Optical coherence tomography of the human retina. *Arch Ophthalmol*. 1995; 325-332.

9. Puliafito C.A., Hee M.R., Lin C.P. et al. Imaging of macular diseases with optical coherence tomography. *Ophthalmology*. 1995; 217-229.

10. Wilkins J.R., Puliafito C.A., Hee M.R. et al. Characterization of epiretinal membranes using optical coherence tomography. *Ophthalmology*. 1996; 2142-2151.

11. Hee M.R., Baumal C.R., Puliafito C.A. et al. Optical coherence tomography of age-related macular degeneration and choroidal neovascularization. *Ophthalmology*. 1996; 1260-1270.

12. Hee M.R., Puliafito C.A., Wong C. et al. Optical coherencetomography of macular holes. *Ophthalmology*. 1995; 748-756.

13. Hee M.R., Puliafito C.A., Wong C. et al. Optical coherence tomography of central serous chorioretinopathy. *Am J Ophthalmol*. 1995; 65-74.

14. Bowd C., Zangwill L.M., Berry C.C. et al. Detecting early glaucoma by assessment of retinal nerve fiber layer thickness and visual function. *Invest Ophthalmol Vis Sci*. 2001; 42(9):1993-2003.

15. Schuman J.S., Wollstein G., Farra T. et al. Comparison of opticnerve head measurements obtained by optical coherence tomography and confocal scanning laser ophthalmoscopy. *Am J. Ophthalmol*. 2003;135(4):504-512.

16. Kim J.S., Ishikawa H., Gabriele M.L. et al. Retinal nerve fiber layer thickness measurement comparability between time domain optical coherence tomography (OCT) and spectral domain OCT. *Invest Ophthalmol Vis Sci*. 2010; 5: 896-902.

17. Park S.B., Sung K.R., Kang S.Y., Kim K.R., Kook M.S. Comparison of glaucoma diagnostic capabilities of cirrus HD and stratus optical coherence tomography. *Arch Ophthalmol*. 2009; 127:1603-1609.

18. Rao H.L., Zangwill L.M., Weinreb R.N., Sample P.A., Alencar L.M., Medeiros F.A. Comparison of different spectral domain optical coherence tomography scanning areas for glaucoma diagnosis. *Ophthalmology*. 2010; 117:1692-1699.

19. Wang X., Li S., Fu J. et al. Comparative study of retinal nerve fibre layer measurement by RTVue OCT and GDx VCC. *Br J Ophthalmol*. 2011; 95: 509-513.

20. Pechauer A., Liu L., Gao S., Jian C., Huang D. Optical coherence tomography angiography of peripapillary retinal blood flow response to hyperoxia. *Invest Ophthalmol Vis Sci*. 2015; 56: 3287-3291.

21. Jonas J.B., Fernandez M.C., Sturmer J. Pattern of glaucomatous neuroretinal rim loss. *Ophthalmology*. 1993; 100:63-68.

22. Nilforushan N., Nassiri N., Moghimi S. et al. Structure-function relationships between spectral-domain OCT and standard achromatic perimetry. *Invest Ophthalmol Vis Sci*. 2012; 53(6):2740-2748.

23. Rao H.L., Zangwill L.M., Weinreb R.N., Leite M.T., Sample P.A.,Medeiros F.A. Structure-function relationship in glaucoma using spectral-domain optical coherence tomography. *Arch Ophthalmol*. 2011; 129(7): 864-871.

24. Leite M.T., Rao H.L., Zangwill L.M., Weinreb R.N., Medeiros F.A. Comparison of the diagnostic accuracies of the Spectralis, Cirrus, and RTVue optical coherence tomography devices in glaucoma. *Ophthalmology*. 2011; 118:1334-1339.

25. Leung C.K., Lam S., Weinreb R.N. et al. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: analysis of the retinal nerve fiber layer map for glaucoma detection. *Ophthalmology*. 2010; 117: 1684-1691.

26. Wollstein G., Schuman J.S., Price L.L. et al. Optical coherence tomography longitudinal evaluation of retinal nerve fiber layer thickness in glaucoma. *Arch Ophthalmol*. 2005; 123:464-470.

27. Huang J.Y., Pekmezci M., Mesiwala N., Kao A., Lin S. Diagnostic power of optic disc morphology, peripapillary retinal nerve fiber layer thickness, and macular inner retinal layer thickness in glaucoma diagnosis with fourier-domain optical coherence tomography. *J Glaucoma*. 2011; 20: 87-95.

28. Cho J.W., Sung K.R., Lee S. et al. Relationship between visual field sensitivity and macular ganglion cell complex thickness as measured by spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2010; 51:6401-6407.

29. Kurysheva N.I., Apostolova A.S., Ardzhevnishvili T.D., Kiseleva T.N., Fomin A.V. The study of morphological changes and regional hemodynamics in pseudoexfoliative glaucoma. *Ophthalmology in Russia*. 2014; 1: 38-44.

30. Savastano M., Lumbroso B., Rispoli M. In vivo characterization of retinal vascularization morphology using optical coherence tomography angiography. *Retina*. 2015; 35(11): 2196–2203.

31. Spaide R.F., Klancnik Jr. J.M., Cooney M.J. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. *JAMA Ophthalmol*. 2015; 133: 45-50.

32. Wang X. et al. Correlation between optic disc perfusion and glaucomatous severity in

patients with open-angle glaucoma: an optical coherence tomography angiography study. *Graefes Arch Clin Exp Ophthalmol*. 2015; 253:1557–1564.

33. Rao H.L. Diagnostic ability of peripapillary vessel density measurements of optical coherence tomography angiography in primary open-angle and angle-closure glaucoma. *Br J Ophthalmol.* 2016; 29: pii: bjophthalmol-2016-309377.

34. Kurysheva N.I. OCT angiography and its role in the study of retinal microcirculation in glaucoma (part two). *Russian Ophthalmological Journal*. 2018; 11 (3): 95-100.

35. Suh M.H. et al. Optical Coherence Tomography Angiography Vessel Density in Glaucomatous Eyes with Focal Lamina Cribrosa Defects. *Ophthalmology.* 2016; 123(11): 302309-2317.

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AQUAPORINS AND THEIR ROLE IN THE REGULATION OF AQUEOUS FETAL HOMEOSTASIS

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The study of aquaporins, molecular water channels, is of interest in understanding the transport of water and dissolved substances both in the body and between the mother and fetus. The review considers modern data on the aquaporin family, their expression in organs in postembryonic ontogenesis, in fetal membranes, kidneys, lungs, fetal skin, their role in the regulation of amniotic fluid volume.
Keywords: *aquaporins, fetus.*

A successful course of pregnancy requires the accumulation of significant amounts of water to maintain fetal growth. In particular, amniotic fluid (AF) serves as a reservoir of water for the fetus and is necessary for its development. AF protects the fetus from traumatic damage, provides the development of the gastrointestinal tract, muscular system and lungs [11, 12].

Circulation of water between the mother and the fetus, as well as within fetal compartments, is a complex process, and the regulation of water movement mechanisms remains unclear.

However, it is known that in many tissues water travels through the cytoplasmic membrane of cells via AQPs [1, 23], which is 5–50 times more effective than the water transport through a lipid bilayer [28]. The expression of AQPs in the placenta and fetal membranes may play an important role in regulating fluid balance between the mother and fetus. In addition, AQPs are involved in both physiological and pathological processes [23].

Aquaporins

Aquaporins are a family of small (~30 kDa) integral proteins that facilitate the water transport through the plasma membrane of the cell in response to osmotic gradients [132]**.** The HUGO Gene Nomenclature Committee has assigned aquaporin the designation AQP [5]**.** In mammals, 13 AQPs are described, which are present in various organs and tissues [39]. AQPs have been found not only in higher mammals, but also in other vertebrates, invertebrates, plants, eu- and archaebacteria, indicating that these proteins are involved in important biological processes [2]. There is diffuse and channel-mediated movement of water. Diffusion is carried out through all biological membranes at a low rate. In most tissues, diffusion goes in two directions (from the cell and into the cell), whereas aquaporin-mediated water flow in vivo goes along the osmotic and hydraulic gradients [2].

Aquaporins have some selectivity in relation to transferable low-molecular substances. Thus, AQP1, 2, 4, 5, 6, 8, 11 and 12 are permeable only for water, AQP6 for water and anions, AQP8 for urea [55, 140], AQP3, 7 and 10 transport water, urea, and glycerin, and AQP9 carries water, monosaccharides, purines, pyrimidines [54, 126]. According to some data, AQPs can carry CO_2 [15, 51, 99], ammonia [49, 99], NO [47, 137], H_2O_2 [15, 43, 95], and some ions [142].

In most cases, aquaporins are present in the cell membrane (AQP1, 3 in the erythrocyte membrane, AQP1 in the kidney tubules), but they can also be found in intracellular vesicles and embed in the cytoplasmic membrane after stimulation [76]. In particular, in the collector tubules, AQP2 is transferred from the cytoplasmic vesicles to the apical membrane of the cell in response to vasopressin [67].

On membranes, AQPs are organized into tetramers. Thus, AQP1 exists as a tetramer, in which each subunit contains its own pore [2]. The tetrameric organization of the protein is established using 3D electron microscopy [48, 112, 133].

The use of antibodies specific to C- and N-terminal peptides AQP1 allowed the detection of AQP1 in the brush border of the apical membrane of the proximal tubules and a thin segment of the descending knee of the loop of Henle in kidneys of rats [101] and humans [94]. AQP1 is also found in the descending straight tubule [106], it determines the transport pathways of large volumes of water from the lumen of the tubules to the interstitium and into the vascular bed. Protein AQP1 has been shown to be present in the plasma membranes of these sites of nephron rather than inside cells. Water is transported through AQP1 of the epithelium of proximal tubules and a thin segment of the descending department of the loop located in the apical and basolateral plasma membranes, with a driving force provided by small osmotic

gradients created by the directional movement of dissolved substances through specific transport proteins of these membranes [100]. AQP1 is absent in the collector tubules [105], it is expressed in the areas of the nephron where water transport is not regulated by vasopressin.

In mice with AQP1 deficiency, polyuria is observed [88], as well as the lack of the ability to concentrate urine more than 700 mOsm/kg H_2O, leading to rapid dehydration; plasma osmolality dramatically increases to 400–500 mOsm/kg H_2O. Thus, AQP1 is necessary for the formation of concentrated urine. It is suggested that the absence of AQP1 disrupts a back-absorption process dependent on the water movement rate along the concentration gradient through the descending thin tubule of the loop of Henle. Osmotically moving water in proximal tubules in knockout mice without AQP1 has been shown to account for one-fifth of the moving water in proximal kidney tubules in normal mice [116]. The 90% reduction of the moving water along the concentration gradient in the descending thin tubule isolated from the kidneys of AQP1-deficient animals was found [26]. Studies on AQP1-deficient mice and in AQP1-deficient people have shown a great value of AQP1 in water reabsorption in proximal nephron sections and proved that water reabsorption occurs through AQP1 in proximal tubules and a descending thin tubule rather than paracellularly.

The AQP1 protein has also been found in other tissues with important secretory function, including the choroid plexus (cerebrospinal fluid), pigment-free epithelium in the anterior compartment of the eye (aqueous humor), cholangiocytes (bile), and endothelium of capillaries of many organs [104]. The expression of AQP1 in the luminal membranes of the capillary endothelium suggests that the protein may play an important role in the movement of water between the vascular bed and the interstitium [101, 104]. Moreover, the expression of AQP1 in the capillary endothelium appears to be actively modulated by various stimuli in vivo. For example, the expression of AQP1 in the capillary endothelium of rat lungs increases 10 times when exposed to corticosteroids, and the expression of these proteins in rat lungs also occurs at the time of birth [64, 65]. AQP1 in the fibroblast culture is rapidly destroyed by the ubiquitin-proteasomal pathway [72].

AQP2 is hyperexpressed in the epithelial cells of the collector tubules [37, 91]. These water channels are regulated by vasopressin, hence they participate in the regulation of water balance [68, 101, 103] and control the water permeability of the collector tubules. This conclusion is obtained on the basis of: 1) studies at cellular and subcellular levels [37, 101]; 2) the available direct correlation between the AQP2 expression and water permeability in collector tubules in rats [33]; 3) the available direct relationship between the water permeability on the osmotic gradient and the amount of AQP2 on the apical plasma membrane of the main cells of isolated collector tubules [101] as confirmed in animal experiments (only in the first phase of urine formation) [90, 115, 139]; 4) the reduction of the AQP2 expression in 95% of severe diabetes insipidus in humans and rats with AQP2 gene mutation [90].

AQP3,4 have different expression in different segments of the collector tubules and cell sites. Thus, AQP3 is hyperexpressed in the cortical, external and inner medullary area of the collector tubules [35, 124]. AQP4 is abundant in the inner medullary area, it is also expressed in proximal segments [124]. AQP3 is hyperexpressed in the basal and basolateral plasma membranes of the main cells of the collector tubules. AQP4 is mainly present in the basolateral membrane of the S3 segment of the proximal tubules [129].

For information on the role of AQP3 and AQP4, studies have been conducted using knockout mice [27, 86, 87, 130] despite possible inclusion of compensatory mechanisms during embryonic and post-embryonic development. In transgenic knockout mice with AQP4 deficiency, moderate violation of urine concentration was observed [87], a study on isolated collector tubules of the inner medullary area in AQP4-deficient mice showed a quadruple decrease in osmotic water permeability after exposure to vasopressin [27]. This indicates the role of AQP4 in the movement of water through the basolateral membranes of isolated collector tubules of the inner medullary area after maximum vasopressin stimulation. A high content of AQP3,4 was observed in the cortical and external medullary area of collector tubules. AQP3-deficient mice showed defects in urine concentration with severe polyuria [86].

AQP3 is expressed in the basal layer of proliferating epidermis keratinocytes [132]. AQP3-deficient mice reduced epidermis permeability for glycerin, resulting in a decrease in glycerin concentration in the corneal layer, where AQP3 normally acts as a natural moisturizer. Normalization of glycerin content in skin in AQP3-deficient mice during skin transplantation corrects skin hydration and concomitant defects [44]. Some cosmetic companies sell natural AQP3 expression stimulants [34]. However, the hyperexpression of AQP3 can lead to the formation of skin neoplasms [131]. Moreover, AQP3 deficiency is associated with impaired corneal and skin damage healing in mice, as well as impaired epithelium proliferation in the colitis model in mice [73, 42, 125]. AQP3 is also expressed in immune cells, and its absence disrupts macrophage and T-cell functions in

mice [143, 144].

AQP4 is the main water channel in central nervous system astrocytes. AQP4 is most common in astrocytes of the zone adjacent to the subarachnoidal space and capillaries, as well as in ependymocytes that line the ventricles [102, 111].

There is evidence that AQP4 is involved in the transport of water to the spinal and brain cord and vice versa, in the processes of neuroexcitation and astrocyte migration after damage. AQP4 modulators have therapeutic potential in the treatment of brain edema (different etiologies), epilepsy, and neuron regeneration, as well as in spinal and brain injury [109]. Since AQP4 facilitates water transport through the hematoencephalic barrier, AQP4-deficient mice survive better, they have less pronounced water accumulation in the model of cytotoxic brain edema (in aqueous intoxication, focal or global ischemia and bacterial meningitis) in comparison with wild mice [41, 62, 83, 108, 140].

AQP4 also facilitates the release of water from the brain in vasogenic edema. In this process, water moves to the brain when the hematoencephalic barrier is damaged, and exits through AQP4-rich glia in the ventricles of the brain and its surface [107]. AQP4-deficient mice accumulate more water in vasogenic brain edema in models with intraparenchymal fluid infusion, cortex damage in freezing, brain tumors, brain abscesses, and subarachnoidal haemorrhagy [19, 52, 107, 123], as well as in obstructive dropsy of the brain [18]. AQP4 appears to play a similar role in the spinal cord as deletion of the AQP4 gene in mice reduces cytotoxic swelling of the spinal cord when it is damaged [113], but increases vasogenic swelling of the spinal cord in the model of contusion damage [63].

AQP4-deficient mice have elongation and spread of cortical depression in brain damage, the rate of potassium recapture by astrocytes after neuroexcitation was reduced [6, 16], the latter may be due to the slowdown in water recapture by astrocytes and the reduction of extracellular space [60]. AQP4-deficient mice slow the rate of scar formation in brain tissue, which may be due to violated astrocyte migration [7, 114], so inhibition of AQP4 may improve regeneration at damage to the brain, spinal cord, or stroke.

In mammals, AQP5 is expressed in corneal epithelium, sweat and salivary glands, airway submucous glands, type I alveocytes, epidermis. In AQP5-deficient mice, secretion of saliva and mucus of the airway is violated [84, 120]. Decreased secretion of saliva, submucous glands, thinning of the cornea, tear-formation disorder are observed in AQP5-zero mice [84, 119, 120]. In humans, AQP5 mutations are associated with the development of palmoplantar keratoderma [17, 22].

AQP6 is expressed in α-insertion cells of collector tubules of the cortical layer, in collector tubules of the inner and external medullary area [141]. Obtaining antibodies to AQP6 allowed the establishment of cellular and subcellular localization of AQP6 in rat kidneys.

AQP6 has been shown to be located in intracellular vesicles, but not in plasma membranes [89, 141]. AQP6 has been shown to be located together with H^+-ATPase in intracellular vesicles, but not in plasma membranes, which indicates a role in acid secretion [100]. Chronic acidosis in rats did not change the AQP6 expression, and chronic alkalosis and fluid load significantly increased the AQP6 expression [110]. It is now thought that AQP6 may be associated with some forms of acid alkaline balance disorders.

Aquaglyceroporines-AQP7 is hyperexpressed in spermatocytes [53, 55, 57, 122], it can also be expressed in other tissues, mainly in adipocytes [132]. AQP7-zero mice have the age-progressive accumulation of fat mass and hypertrophy of adipocytes, with the accumulation of glycerin and triglycerides in them [45, 48]. AQP7 deficiency reduces the permeability of the plasma membrane to glycerin, which calls for the accumulation of glycerin and triglycerides in adipocytes and hyperexpression of glycerol kinase. In humans, a decrease in AQP7 expression in adipocytes is observed in obesity [92]. These results indicate that the activation and/or hyperexpression of AQP7 may be a novel approach in the treatment of obesity [82]. Studies using mouse and rat antibodies to AQP7 have shown the expression of AQP7 in the brush border of the proximal tubules of the 3rd segment.

AQP8 is present in intracellular domains of proximal tubules, in cells of collector tubules, and in many other organs [36, 38].

AQP9 [57, 69, 70, 126, 127] is not expressed in the kidneys, but is present in many other organs. The real time PCR method established the presence of these aquaporins in the kidneys, but this requires refinement using immunological methods.

AQP9 is expressed in hepatocytes, red blood cells, some neurons [9, 54, 59, 78, 82]. AQP9 participates in the capture of glycerin by hepatocytes and urea secretion [58, 59]. The presence of AQP9 in hepatocytes is due to the fact that it may function as a glycerin channel (to participate in gluconeogenesis) and/or promote urea diffusion [24]. Indeed, the hyperexpression of AQP9 was observed after 4-day fasting, and a decrease in AQP9 was observed after the resumption of food intake [24]. AQP9 may be involved in brain energy metabolism as a

metabolic channel because it may promote the diffusion of glycerin and monosaccharides, i.e., energy substrates for neurons [9]. In addition, the permeability for lactate increases in acidic environment [126]. Consequently, in cerebral ischemia, lactic acidosis can increase the permeability of AQP9 to lactate and thereby promote absorption of excess lactate concentration by astrocytes. Thus, AQP9 can contribute to the clearance of lactate and glycerin from the extracellular space during ischemia. After reperfusion, AQP9 may contribute to the movement of lactate between astrocytes and neurons to use it as an energy substrate after ischemia [8, 9].

Aquaporins in placenta and fetal membranes

From the middle of pregnancy, the main producers of AF are kidneys (in late stages up to 800 ml/day) and lungs (up to 150 ml/day) of the fetus. Despite the fact that the lungs secrete up to 300 ml of liquid per day, about half of this fluid is reabsorbed by the airway or swallowed by the fetus and does not enter the amniotic fluid [20]. AF contains 500–1200 ml of water [40]. Normally, the current of water increases during pregnancy, up to 400 ml per day is transported from the amniotic cavity through the fetal membranes into the fetal blood flow [30], circulates through the fetal body, placenta and forms amniotic fluid [5]. The main ways of removing AF are swallowing it by the fetus and the intramembrane way of resorption (through amnion into the fetus blood flow), which apparently regulates its normal volume [13, 20]. The volume of amniotic fluid is determined by the balance between its production and absorption [13].

Indirect evidence of the participation of aquaporins in the placental fluid current has been obtained [28]. In the placenta and membranes of the human fetus, AQP1, 3, 4, 8 and 9 are expressed. AQP1 is localized in chorion, amnion, and placenta vessels [81, 147]. According to other data, in rats, mice, sheep, and humans, AQP1 is expressed exclusively in placenta vessels [61, 128]. AQP1 mRNA is found in the placenta of mice and sheep, and AQP1 protein is found in fetal membranes throughout whole human pregnancy [12, 61, 75].

In human placenta, AQP1 is found in the endothelium of placenta vessels [147]. The expression of AQP1 in placenta vessels indicates its role in angiogenesis [10]. AQP1 appears to play a key role in the movement of water from the amnion cavity through the amnion and chorion directly into the fetal vessels [81]. The expression of AQP1 increases 33 times in amnion during pregnancy complicated by idiopathic polyhydramnios, which can be a compensatory reaction to an increase in the AF volume [81]. In trophoblast-like cells, the expression of the AQP1 gene is increased by vasopressin and cAMP agonists [14].

AQP3, 8 and 9 are expressed in chorion, amnion, and thophoblast [29, 134, 135, 136, 147]. AQP3 and 9 are hyperexpressed in the apical membrane of syncytiotrophoblast [28]. AQP3 protein is not detected in the capillary endothelium or the vascular network of the chorion or placenta [50]. AQP1 appears to regulate the movement of water in fetal membranes and AQP3 – in placenta [143].

The relationship between the AQP expression in fetal membranes and amniotic fluid volume abnormalities [79, 80, 118] was studied. It was found that the AQP1 expression in human amnion in the group with isolated oligohydramnios was reduced compared to the group with normal amniotic fluid volume, but there was no significant difference in the expression in the chorion and placenta between two groups [147]. The expression of AQP3 in amnion and chorion in the group with isolated oligohydramnios was significantly reduced, whereas the expression in placenta was increased [146]. The expression of AQP8 in amnion and AQP9 in amnion and chorion was increased in patients with idiopathic polyhydramnios, but their expression in placenta was significantly reduced [145]. The expression of AQP8 in fetal membranes significantly decreased in oligohydramnios [50].

The expression of AQP1, 3, 8 and 9 in placenta and fetal membranes may be an adaptive response to changes in amniotic fluid volume as water and dissolved substances can be removed through aquaporins from the amnion cavity into fetal vessels through amnion and chorion [80].

Aquaporins in fetal kidneys

An important regulator of amniotic fluid volume is urine excretion [20]. In humans, nephrogenesis is completed at week 36. The volume of urine of the human fetus increases from ~7.4 ml/h at 24-25 weeks of pregnancy to 71–125 ml/h before delivery [96, 71].

AQP1 is expressed at mid-pregnancy in the proximal tubules and descending part of the loop of Henle and before delivery reaches ~50% of the level in adults [32, 138].

AQP2 is expressed in the cells of collector tubules and transported to apical membranes when the vasopressin level rises; it is the main AQP responsible for urine concentration and is present until the end of pregnancy at less than 40% of the levels seen in adults [21, 32]. The low level of AQP2 in the kidneys of sheep fetuses in the last trimester of pregnancy correlates with fetal kidney immunity to vasopressin [76]. Relatively large intake of diluted urine in amniotic compartment in sheep and human fetuses is the only significant factor in maintaining the amniotic fluid volume

and its composition [31].

Aquaporins in fetal lungs

In the embryonic period, the respiratory tract is filled with fluid, which plays a key role in the growth and development of the lungs, supporting them in an extended state [76]. The fluid produced by the lungs in a volume of about 300 ml/day exits through the trachea into the pharynx, where half of the produced volume of fluid is swallowed and half enters the amniotic cavity [46], where it participates in the formation of amniotic fluid [20].

Excreting fluid from the lungs at birth is vital to ensure air enters the lungs with the onset of external respiration. This process depends largely on the ability of the epithelium to absorb large amounts of water [76]. Factors controlling fluid movement through the pulmonary epithelium remain unclear. Some understanding of the role of aquaporins has been obtained in the study of mice with aquaporin gene deletion, but there may be significant differences from small animals during long pregnancy seen in humans [74]. AQP1 has been found to be present in the apical and basolateral membrane of the mascrovascular endothelium, while deletion of the AQP1 gene in humans reduces lung vessel permeability [66]. AQP1, 3, 4 and 5 are expressed in human bronchi and alveoli, AQP1 and 3 in bronchioles [76]. It was found that the AQP1 expression in the lungs was significantly increased in animals subjected to hypoxia, indicating a possible role of AQP1 in oxygen transport through cell membranes [143].

Aquaporins in fetal skin

In a human fetus from week 4, a double layer of epidermis cells is formed. The corneal layer begins to develop from week 24 and is well expressed by week 34 [25]. Basal and intermediate keratinocytes are below, which express AQP3 [93, 85, 121] permeable to water, urea and glycerin. Initially, the fluid surrounding the embryo and fetus is similar in composition to extracellular fluid and is formed as a fetal skin transudate before keratinization [77]. Deletion of the AQP3 gene in mice reduces skin moisture and significantly changes skin morphology [35].

Conclusion

Aquaporins are widely expressed in the body, especially in cells involved in fluid transport (epithelium of some organs), as well as in certain cells not involved in fluid transport (adipocytes).

The lungs, kidneys and skin in the embryonic period of ontogenesis are important regulators of amniotic fluid volume. At the same time, aquaporins of fetal membranes can regulate the intramembrane current of the amniotic fluid, and violations in the expression of these proteins can be associated with polyhydramnios and oligohydramnios [28]. Therefore, the study of the expression and biological role of aquaporins is necessary to understand the molecular mechanisms of aqueous homeostasis and fluid balance abnormalities, having the most important physiological and pathological significance.

Conflict of interest. The authors declare no conflict of interest.

References:

1. Agre P., Bonhivers M., Bornia M.J. The aquaporins, bruprints for cellular plumbing systems. *J. Biol. Chem.* 1998; 273: 14659-14662.

2. Agre P., King L. S., Yasui M. et al. Aquaporin water channels – from atomic structure to clinical medicine. *J. Physiol*. 2002; 542: 3-16.

3. Agre P. Molecular physiology of water transport: aquaporin nomenclature workshop. Mammalian aquaporins. *Biol. Cell*. 1997; 89: 2552-2557.

4. Agre P. The aquaporin water channels. *Proc. Am. Thorac. Soc*. 2006; 3: 5-13.

5. Agre P., Sasaki S., Chrispeels M.J. Aquaporins: a family of water channel proteins. *Am. J. Physiol. Renal Fluid Electrolyte Physiol*. 1993; 265: 461-466.

6. Amiry-Moghaddam M., Williamson A., Palomba M. et al. Delayed K + clearance associated with aquaporin-4 mislocalization: phenotypic defects in brains of alpha-syntrophin-null mice. *Proc. Natl Acad. Sci. USA*. 2003; 100: 13615-13620.

7. Auguste K.I., Songwan J., Kazunori U. et al. Greatly impaired migration of implanted aquaporin-4-deficient astroglial cells in mouse brain toward a site of injury. *FASEB J*. 2007; 21: 108-116.

8. Badaut J. Aquaglyceroporin 9 in brain pathologies. *Neuroscience*. 2010; 168:1047-1057.

9. Badaut J., Regli L. Distribution and possible roles of aquaporin 9 in the brain. *Neuroscience*. 2004; 129(4): 971-981.

10. Baird R., Wintour E.M. Placentae with haemophagous zones and water channel proteins: a cautionary tale. *Placenta*. 2000; 21: 587-588.

11. Bajoria R., Ward S., Sooranna S.R. Influence of vasopressin in the pathogenesis of oligohydramnios-polyhydramnios in monochorionic twins. *Eur. J. Obstet. Gynecol. Reprod. Biol*. 2004; 113: 49-55.

12. Beall M.H., van den Wijngaard J.P.H.M., van Gemert M.J.C. et al. Amniotic fluid water dynamics. *Placenta*. 2007; 28: 816-823.

13. Beall M.H., van den Wijngaard J.P.H.M., van Gemert M.J.C. et al. Regulation of amniotic fluid volume. *Placenta*. 2007; 28: 824-832.

14. Belkacemi L., Beall M.H., Magee T.R. et al. AQP1 gene expression is upregulated by arginine vasopressin and cyclic AMP agonists in

trophoblast cells. *Life Sci*. 2008; 82: 1272-1280.

15. Bienert G.P., Moller A.L., Kristiansen K.A. et al. Specific aquaporins facilitate the diffusion of hydrogen peroxide across membranes. *J. Biol. Chem*. 2007; 282: 1183-1192.

16. Binder D.K., Yao X., Zador Z. et al. Increased seizure duration and slowed potassium kinetics in mice lacking aquaporin-4 water channels. *Glia*. 2006; 53: 631-636.

17. Blaydon D.C., Lind L.K., Plagnol V. et al. Mutations in AQP5, encoding a water-channel protein, cause autosomal-dominant diffuse nonepidermolytic palmoplantar keratoderma. *Am. J. Hum. Genet*. 2013; 93: 330- 335.

18. Bloch O., Auguste K.I., Manley G.T. et al. Accelerated progression of kaolin- induced hydrocephalus in aquaporin-4-deficient mice. *J. Cereb. Blood Flow Metab*. 2006; 26: 1527-1537.

19. Bloch O., Papadopoulos M.C., Manley G.T. et al. Aquaporin-4 gene deletion in mice increases focal edema associated with staphylococcal brain abscess. *J. Neurochem*. 2005; 95: 254-262.

20. Brace R.A., Cheung C.Y. Regulation of amniotic fluid volume: evolving concepts. *Adv. Exp. Med. Biol*. 2014; 814: 49-68.

21. Butkus A., Earnest L., Jeyaseelan K. et al. Ovine aquaporin-2: cDNA cloning, ontogeny and control of renal gene expression. *Pediatr. Nephrol*. 1999; 13: 379-390.

22. Cao X., Yin J., Wang H. et al. Mutation in AQP5, encoding aquaporin 5, causes palmoplantar keratoderma Bothnia type. *J. Invest. Dermatol*. 2014; 134: 284-287.

23. Carbrey J.M, Agre P. Discovery of the aquaporins and development of the field. *Handb. Exp. Pharmacol*. 2009; 190: 3-28.

24. Carbrey J.M., Gorelick-Feldman D.A., Kozono D. et al. Aquaglyceroporin AQP9: solute permeation and metabolic control of expression in liver. *Proc. Natl. Acad. Sci. USA*. 2003; 100(5): 2945-2950.

25. Cartlidge P. The epidermal barrier. *Neonatol*. 2000; 5: 273-280.

26. Chou C.L., Knepper M.A., Hoek A.N. et al. Reduced water permeability and altered ultrastruc-ture in thin descending limb of Henle in aquaporin-1 null mice. *J. Clin. Invest*. 1999; 3: 491-496.

27. Chou C.L., Ma T., Yang B. et al. Fourfold reduction of water permeability in inner medullary collecting duct of aquaporin-4 knockout mice. *Am. J. Physiol. Cell Physiol*. 1998; 274: 549-554.

28. Damiano A.E. Review: water channel proteins in the human placenta and fetal membranes. *Placenta 32, Supplement B, Trophoblast Research*. 2011; 25: 207-211.

29. Damiano A.E, Zotta E., Goldstein J. et al. Water channel proteins AQP3 and AQP9 are present in syncytiotrophoblast of human term placenta. *Placenta*. 2001; 22: 776-781.

30. Damiano A.E., Zotta E., Ibarra C. Functional and molecular expression Of AQP9 channel and UT-A transporter in normal and preeclamptic human placentas. *Placenta*. 2006; 27: 1073-1081.

31. Dane B., Yayla M., Dane C. et al. Prenatal diagnosis of Bartter syndrome with biochemical examination of amniotic fluid: case report. *Fetal. Diagn. Ther*. 2007; 22: 206-208.

32. Devuyst O., Burrow C.R., Smith B.L. et al. Expression of aquaporins-1 and -2 during nephrogenesis and in autosomal dominant polycystic kidney disease. *Am. J. Physiol*. 1996; 271: 169-183.

33. DiGiovanni S.R., Nielsen S., Christensen E.I. et al. Regulation of collecting duct water channel expression by vasopressin in Brattleboro rat. *Proc. Natl. Acad. Sci. USA*. 1994; 91: 8984-8988.

34. Dumas M. et al. Hydrating skin by stimulating biosynthesis of aquaporins. *J. Drugs Dermatol*. 2007; 6: 20-24.

35. Ecelbarger C.A., Terris J., Frindt G. et al. Aquaporin-3 water channel localization and regulation in rat kidney. *Am. J. Physiol. Renal Fluid Electrolyte Physiol*. 1995; 269: 663-672.

36. Elkjaer M.L., Nejsum L.N., Gresz V. et al. Immunolocalization of aquaporin-8 in rat kidney, liver, testis, epididymis, jejunum, colon, principal bronchi and salivary glands. *Am. J. Physiol. Renal Physiol*. 2001; 281: 1047-1057.

37. Fushimi K., Uchida S., Hara Y. et al. Cloning and expression of apical membrane water channel of rat kidney collecting tubule. *Nature*. 1993; 361: 549-552.

38. Garcia F., Kierbel A., Larocca M.C. et al. The water channel aquaporin-8 is mainly intracellular in rat hepatocytes, and its plasma membrane insertion is stimulated by cyclic AMP. *J. Biol. Chem*. 2001; 276: 12147-12152.

39. Gonen T., Walz T. The structure of aquaporins. *Q. Rev. Biophys*. 2006;39(4): 361-396.

40. Goodwin J.W., Godden J.O., Chance G.W. *Perinatal medicine: the basic science underlying clinical practice*. Baltimore: The Williams and Wilkins Co; 1976:617.

41. Haj-Yasein N.N., Vindedal G.F., Eilert-Olsen F. et al. Glial-conditional deletion of aquaporin-4 (AQP4) reduces blood–brain water uptake and confers barrier function on perivascular astrocyte end feet. *Proc. Natl. Acad. Sci. USA*. 2011; 108: 17815-17820.

42. Hara-Chikuma M., Verkman A.S. Aquaporin-3 facilitates epidermal cell migration and proliferation during wound healing. *J. Mol. Med*. 2008; 86: 221-231.

43. Hara-Chikuma M., Chikuma S., Sugiyama Y. et al. Chemokine-dependent T cell migration requires aquaporin-3-mediated hydrogen peroxide uptake. *J. Exp. Med*. 2012; 209: 1743-1752.

44. Hara M., Verkman A.S. Glycerol replacement corrects defective skin hydration, elasticity, and barrier function in aquaporin-3-deficient mice. *Proc. Natl Acad. Sci. USA*. 2003; 100: 7360-7365.

45. Hara-Chikuma M., Funahashi T., Shimomura I. Progressive adipocyte hypertrophy in aquaporin-7-deficient mice: adipocyte glycerol permeability as a novel regulator of fat accumulation. *J. Biol. Chem*. 2005; 280: 15493-15496.

46. Harding R., Hooper S.B. *Lung development and maturation. In Fetal medicine: Basic science and clinical practice*. Edited by: Rodeck C.H. and Whittle M.J. Churchill Livingstone. London; 1999: 181-196.

47. Herrera M., Hong N.J., Garvin J.L. Aquaporin-1 transports NO across cell membranes. *Hypertension*. 2006; 48: 157-164.

48. Hibuse T. et al. Aquaporin 7 deficiency is associated with development of obesity through activation of adipose glycerol kinase. *Proc. Natl. Acad. Sci*. USA. 2005; 102: 10993-10998.

49. Holm L.M., Jahn T.P., Moller A. L. et al. NH3 and NH4 + permeability in aquaporin-expressing Xenopus oocytes. *Pflugers Arch*. 2005; 450: 415-428.

50. Hua Y., Jiang W., Zhang W. et al. Expression and significance of aquaporins during pregnancy. *Front. Biosci. (Landmark Ed)*. 2013; 18: 1373-1383.

51. Hub J.S., Grubmuller H., de Groot B.L. Dynamics and energetics of permeation through aquaporins. What do we learn from molecular dynamics simulations? *Handb. Exp. Pharmacol*. 2009; 57-76.

52. Iliff J.J. et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid-β. *Sci. Transl. Med*. 2012; 4: 147-148.

53. Ishibashi K., Kuwahara M., Gu Y. et al. Cloning and functional expression of a new water channel abundantly expressed in the testis permeable to water, glycerol, and urea. *J. Biol. Chem*. 1997; 272: 20782-20786.

54. Ishibashi K., Kuwahara M., Gu Y. et al. Cloning and functional expression of a new aquaporin (AQP9) abundantly expressed in the peripheral leukocytes permeable to water and urea, but not to glycerol. *Biochem. Biophys. Res. Commun*. 1998; 244: 268-274.

55. Ishibashi K., Kuwahara M., Kageyama Y. et al. Cloning and functional expression of a second new aquaporin abundantly expressed in testis. *Biochem. Biophys. Res. Commun*. 1997; 237(3): 714-718.

56. Ishibashi K. New members of mammalian aquaporins: AQP10—AQP12. *Handb. Exp. Pharmacol*. 2009; 190: 251-262.

57. Ishibashi K., Yamauchi K., Kageyama Y. et al. Molecular characterization of human aquaporin-7 gene and its chromosomal mapping. *Biochim. Biophys. Acta*. 1998; 1399: 62-66.

58. Jelen S., Gena P., Lebek J. et al. Aquaporin-9 and urea transporter A gene deletions affect urea transmembrane passage in murine hepatocytes. *Am. J. Physiol. Gastrointest. Liver Physiol*. 2012; 303: 1279-1287.

59. Jelen S., Gena P., Lebek J. et al. Aquaporin-9 protein is the primary route of hepatocyte glycerol uptake for glycerol gluconeogenesis in mice. *J. Biol. Chem*. 2011; 286: 44319-44325.

60. Jin B.J., Zhang H., Binder D.K. et al. Aquaporin-4-dependent K + and water transport modeled in brain extracellular space following neuroexcitation. *J. Gen. Physiol*. 2013;141: 119-132.

61. Johnston H., Koukoulas I., Jeyaseelan K. et al. Ontogeny of aquaporins 1 and 3 in ovine placenta and fetal membranes. *Placenta*. 2000; 21: 88-99.

62. Katada R., Akdemir G., Asavapanumas N. et al. Greatly improved survival and neuroprotection in aquaporin-4-knockout mice following global cerebral ischemia. *FASEB J*. 2013; 28: 705-714.

63. Kimura A., Hsu M., Seldin M. et al. Protective role of aquaporin-4 water channels after contusion spinal cord injury. *Ann. Neurol*. 2010; 67: 794-801.

64. King L.S., Nielsen S., Agre P. Aquaporins in complex tissues. I. Developmental patterns in respiratory and glandular tissues of rat. *Am. J. Physiol*. 1997; 273: 1541-1548.

65. King L.S., Nielsen S., Agre P. Aquaporin-1 water channel protein in lung: ontogeny, steroid-induced expression, and distribution in rat. *Journal of Clinical Investigation*. 1996; 97: 2183-2191.

66. King L.S., Yasui M. Aquaporins and disease: lessons from mice to humans. *Trends Endocrinol. Metab*. 2002; 13: 355-360.

67. Klussmann E., Maric K., Rosenthal W. The mechanisms of aquaporin control in the renal collecting duct. *Rev. Physiol. Biochem. Pharmacol*. 2000; 141: 33-95.

68. Knepper M.A., Nielsen S., Chou C.L. et al. Mechanism of vasopressin action in the renal collecting duct. *Semin. Nephrol*. 1994; 14: 302-321.

69. Kobayashi M., Ishibashi O., Tanaka Y. et al. Prolonged disappearance rate of a structurally abnormal mutant insulin from the circulation in humans. *J. Clin. Endocrinol. Metab*. 1985; 61: 1142-1145.

70. Ko S.B., Uchida S., Naruse S. et al. Cloning and functional expression of rAOP9L a new member of aquaporin family from rat liver. *Biochem. Mol. Biol. Int*. 1999; 47: 309-318.

71. Lee S.M., Park S.K., Shim S.S. et al. Measurement of fetal urine production by three-dimensional ultrasonography in normal pregnancy. *Ultrasound. Obstet. Gynecol*. 2007; 30: 281-286.

72. Leitch V., Agre E.P., King L.S. Altered ubiquitination and stability of aquaporin-1 in

hypertonic stress. *Proceedings of the National Academy of Sciences of the USA*. 2001; 98: 2894-2898.

73. Levin M.H., Verkman A.S. Aquaporin-3-dependent cell migration and proliferation during corneal reepithelialization. *Invest. Ophthalmol. Vis. Sci.* 2006; 47: 4365-4372.

74. Liu H., Hooper S.B., Armugam A. et al. Aquaporin gene expression and regulation in the ovine fetal lung. *J. Physiol*. 2003; 551: 503-514.

75. Liu H., Koukoulas I., Ross M.C. et al. Quantitative comparison of placental expression of three aquaporin genes. *Placenta*. 2004; 25: 475-478.

76. Liu H., Wintour E.M. Aquaporins in development — a review. *Reprod. Biol. Endocrinol*. 2005; 3: 18-19.

77. Liu H., Zheng Z., Wintour E.M. Aquaporins and fetal fluid balance. *Placenta*. 2008; 29: 840-847.

78. Liu Y., Promeneur D., Rojek A. et al. Aquaporin 9 is the major pathway for glycerol uptake by mouse erythrocytes, with implications for malarial virulence. *Proc. Natl. Acad. Sci. USA*. 2007;104: 12560-12564.

79. Mann S.E., Dvorak N., Gilbert H. et al. Steady-state levels of aquaporin 1 mRNA expression are increased in idiopathic polyhydramnios. *Am. J. Obstet. Gynecol*. 2006; 194: 884-887.

80. Mann S.E., Ricke E.A., Torres E.A. et al. A novel model of polyhydramnios: amniotic fluid volume is increased in aquaporin 1 knockout mice. *Am. J. Obstet. Gynecol*. 2005; 192: 2041-2044.

81. Mann S.E., Ricke E.A., Yang B.A. et al. Expression and localization of aquaporin 1 and 3 in human fetal membranes. *Am. J. Obstet. Gynecol*. 2002; 187:4: 902-907.

82. Maeda N., Hibuse T., Funahashi T. Role of aquaporin-7 and aquaporin-9 in glycerol metabolism: involvement in obesity. *Handb. Exp. Pharmacol*. 2009: 233-249.

83. Manley G.T., Fujimura M., Noshita N. et al. Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke. *Nature Med*. 2000: 6: 159-163.

84. Ma T., Hara M., Sougrat R. et al. Defective secretion of saliva in transgenic mice lacking aquaporin-5 water channels. *J. Biol. Chem*. 1999; 274: 20071-20074.

85. Ma T., Hara M., Sougrat R. et al. Impaired stratum corneum hydration in mice lacking epidermal water channel aquaporin-3. *J. Biol. Chem*. 2002; 277: 17147-17153.

86. Ma T., Song Y., Yang B. et al. Nephrogenic diabetes insipidus in mice lacking aqua-porin-3 water channels. *Proc. Natl. Acad. Sci. USA*. 2000; 97: 4386-4391.

87. Ma T., Yang B., Gillespie A. et al. Generation and phenotype of a transgenic knockout mouse lacking the mercurial-insensitive water channel aquaporin-4. *J. Clin. Invest*. 1997; 100: 957-962.

88. Ma T., Yang B., Gillesppie A. et al. Severely impaired urinary concentrating ability in transgenic mice lacking aquaporin-1 water channels. *J. Biol. Chem*. 1998; 273: 4296-4299.

89. Ma T., Yang B., Kuo W.L. et al. cDNA cloning and gene structure of a novel water channel expresed exclusively in human kidney. *Genomics*. 1996; 35: 543-550.

90. Marples D., Christensen S., Christensen E.I. et al. Lithium-induced downregulation of aquaporin-2 water channel expression in rat kidney medulla. *J. Clin. Invest*. 1995; 95:1838-1845.

91. Marples D., Knepper M.A., Christensen E.I. et al. Redistribution of aqu-aporin-2 water channels induced by vasopressin in rat kidney inner medullary collecting duct. *Am. J. Physiol. Cell Physiol*. 1995; 269: 655-664.

92. Marrades M.P., Milagro F.I., Martinez J.A. et al. Differential expression of aquaporin 7 in adipose tissue of lean and obese high fat consumers. *Biochem. Biophys. Res. Commun*. 2006; 339: 785-789.

93. Matsuzaki T., Suzuki T., Koyama H. et al. Water channel protein AQP3 is present in epithelia exposed to the environment of possible water loss. *J. Histochem. Cytochem.* 1999; 47: 1275-1286.

94. Maunsbach A.B., Mapples D., Chin E. et al. Aquaporin-1 water channel expression in human kidney. *Journal of the American Society of Nephrology*. 1997; 8: 1–14.

95. Miller E.W., Dickinson B.C., Chang C.J. Aquaporin-3 mediates hydrogen peroxide uptake to regulate downstream intracellular signaling. *Proc. Natl. Acad. Sci. USA*. 2010; 107: 15681-15686.

96. Moritz K.M., Dodic M., Wintour E.M. Kidney development and the fetal programming of adult disease. *Bioessays*. 2003; 25: 212-220.

97. Seeds A.E. Current concepts of amniotic fluid dynamics. *Am. J. Obstet. Gynecol*. 1980; 138: 575-586.

98. Murata K., Mitsuoka K., Hirai T. et al. Structural determinants of water permeation through aquaporin-1. *Nature.* 2002; 407: 599-605.

99. Musa-Aziz R., Chen L.M., Pelletier M.F. et al. Relative CO_2/NH_3 selectivity's of AQP1, AQP4, AQP5, AmtB, and RhAG. *Proc. Natl. Acad. Sci. USA*. 2009; 106: 5406–5411.

100. Nielsen S., Agre P. The aquaporin family of water channels in kidney. *Kidney International*. 1995; 48: 1057-1068.

101. Nielsen S., DiGiovanni S.R., Christensen E.I. et al. Cellular and subcellular immunolocalization of vasopressin-regulated water channel in rat kidney. *Proc. Natl. Acad. Sci. USA*. 1993; 90: 11663-11667.

102. Nielsen S., Nagelhus E.A., Amiry-Moghaddam M. et al. Specialized membrane domains for water transport in glial cells: high-

resolution immunogold cytochemistry of aquaporin-4 in rat brain. *J. Neurosci*. 1997; 17: 171-180.

103. Nielsen S., Kwon T.H., Christensen B.M. et al. Physiology and pathophysiology of renal aquaporins. *J. Am. Soc. Nephrol*. 1999; 10: 647-663.

104. Nielsen S., Smith B.L., Christensen E.I. et al. Distribution of the aquaporin CHIP in secretory and resorptive epithelia and capillary endothelia. *Proceedings of the National Academy of Sciences of the USA*. 1993; 90: 7275-7279.

105. Nielsen S., Smith B. L., Christensen E.I. et al. CHIP28 water channels are localized in constitutively water-permeable segments of the nephron. *Journal of Cell Biology*. 1993; 120: 371-383.

106. Pallone T.L., Kishore B. K., Nielsen S. et al. Evidence that aquaporin-1 mediates NaCl-induced water flux across descending vasa recta. *American Journal of Physiology*. 1997; 272: 587-596.

107. Papadopoulos M.C., Manley G.T., Krishna S. et al. Aquaporin-4 facilitates reabsorption of excess fluid in vasogenic brain edema. *FASEB J*. 2004; 18: 1291-1293.

108. Papadopoulos M.C., Verkman A.S. Aquaporin-4 gene disruption in mice reduces brain swelling and mortality in pneumococcal meningitis. *J. Biol. Chem*. 2005; 280: 13906-13912.

109. Papadopoulos M.C., Verkman A.S. Potential utility of aquaporin modulators for therapy of brain disorders. *Prog. Brain Res*. 2008; 170: 589-601.

110. Promeneur D., Kwon T.H., Yasui M. et al. Regulation of AQP6 mRNA and protein expression in rats in response to altered acidbase or water balance. *American Journal of Physiology. Renal Physiology*. 2000; 279: 1014-1026.

111. Rash J.E., Yasumura T., Hudson C.S. et al. Direct immunogold labeling of aquaporin-4 in square arrays of astrocyte and ependymocyte plasma membranes in rat brain and spinal cord. *Proc. Natl. Acad. Sci. USA*. 1998; 95: 11981-11986.

112. Ren G., Reddy V. S., Cheng A. et al. Visualization of a water-selective pore by electron crystallography in vitreous ice. *Proceedings of the National Academy of Sciences of the USA*. 2001; 98: 1398-1403.

113. Saadoun S., Bell B.A., Verkman A.S. et al. Greatly improved neurological outcome after spinal cord compression injury in AQP4-deficient mice. *Brain*. 2008;131: 1087-1098.

114. Saadoun S. et al. Involvement of aquaporin-4 in astroglial cell migration and glial scar formation. *J. Cell Sci*. 2005; 118: 5691-5698.

115. Sabolic I., Katsura T., Verbavatz J.M. et al. The AQP2 water channel: effect of vasopressin treatment, microtubule disruption, and distribution in neonatal rats. *J. Membr. Biol*. 1995; 143: 165-175.

116. Schnermann J., Chou C.L., Ma T. et al. Defective proximal tubular fluid reabsorption in transgenic aquaporin-1 null mice. *Proc. Natl. Acad. Sci. USA*. 1998; 95: 9660-9664.

117. Sha X.Y., Xiong Z.F., Liu H.S. et al. Maternal-fetal fluid balance and aquaporins: from molecule to physiology. *Act. Pharmacologica Sinica*. 2011; 32: 716-720.

118. Shioji M., Fukuda H., Kanzaki T. et al. Reduction of aquaporin-8 on fetal membranes under oligohydramnios in mice lacking prostaglandin F2 alpha receptor. *J. Obstet. Gynaecol. Res*. 2006; 32: 373-378.

119. Song Y., Sonawane N., Verkman A. S. Localization of aquaporin-5 in sweat glands and functional analysis using knockout mice. *J. Physiol*. 2002; 541: 561-568.

120. Song Y., Verkman A.S. Aquaporin-5 dependent fluid secretion in airway submucosal glands. *J. Biol. Chem*. 2001; 276: 41288-41292.

121. Sougrat R., Morand M., Gondran C. et al. Functional expression of AQP3 in human skin epidermis and reconstructed epidermis. *J. Invest. Dermatol*. 2002; 118: 678-685.

122. Suzuki-Toyota F., Ishibashi K., Yuasa S. Immunohistochemical localization of a water channel, aquaporin 7 (AQP7), in the rat testis. *Cell Tissue Res*. 1999; 295: 279-285.

123. Tait M.J., Saadoun S., Bell B.A. et al. Increased brain edema in aqp4-null mice in an experimental model of subarachnoid hemorrhage. *Neuroscience*. 2010; 167: 60-67.

124. Terris J., Ecelbarger C.A., Marples D. et al. Distribution of aquaporin-4 water channel expression within rat kidney. *Am. J. Physiol. Renal Fluid Electrolyte Physiol*. 1995; 269: 775-785.

125. Thiagarajah J.R., Zhao D., Verkman A.S. Impaired enterocyte proliferation in aquaporin-3 deficiency in mouse models of colitis. *Gut*. 2007; 56: 1529–1535.

126. Tsukaguchi H., Shayakul C., Berger U.V. et al. Molecular characterization of a broad selectivity neutral solute channel. *J. Biol. Chem*. 1998; 273(38): 24737-24743.

127. Tsukaguchi H., Weremowicz S., Morton C.C. et al. Functional and molecular characterization of the human neutral solute channel aquaporin-9. *Am. J. Physiol. Renal Physiol*. 1999; 277: 685-696.

128. Umenishi F., Verkman A.S., Gropper M.A. Quantitative analysis of aquaporin mRNA expression in rat tissues by RNase protection assay. *DNA Cell Biol*. 1996; 15: 475-480.

129. Van Hoek A.N., Ma T., Yang B. et al. Aquaporin-4 is expressed in basolateral membranes of proximal tubule S3 segments in mouse kidney. *Am. J. Physiol. Renal Physiol*. 2000; 278: 310-316.

130. Verbavatz J.M., Ma T., Gobin R. et al. Absence of orthogonal arrays in kidney, brain and

muscle from transgenic knockout mice lacking water channel aquaporin-4. *J. Cell Sci.* 1997; 110: 2855-2860.

131. Verkman, A.S. A cautionary note on cosmetics containing ingredients that increase aquaporin 3 expression. *Exp. Dermatol.* 2008; 17: 871-872.

132. Verkman A.S., Anderson M.O., Papadopoulos M.C. Aquaporins: important but elusive drug targets. *Nat. Rev. Drug Discov.* 2014; 13(4): 259-277.

133. Walz T., Smith B. L., Agre P. et al. The threedimensional structure of human erythrocyte aquaporin CHIP. *EMBO Journal.* 1994; 13: 2985-2993.

134. Wang S., Amidi F., Beall M. et al. Aquaporin 3 expression in human fetal membranes and its up-regulation by cyclic adenosine monophosphate in amnion epithelial cell culture. *J. Soc. Gynecol. Investig.* 2006; 13: 181-185.

135. Wang S., Chen J., Beall M. et al. Expression of aquaporin 9 in human chorioamniotic membranes and placenta. *Am. J. Obstet. Gynecol.* 2004;191: 2160-2167.

136. Wang S., Kallichanda N., Song W. et al. Expression of aquaporin-8 in human placenta and chorioamniotic membranes: evidence of molecular mechanism for intramembranous amniotic fluid resorption. *Am. J. Obstet. Gynecol.* 2001; 185: 1226-1231.

137. Wang Y., Tajkhorshid E. Nitric oxide conduction by the brain aquaporin AQP4. *Proteins.* 2010; 78: 661-670.

138. Wintour E.M., Earnest L., Alcorn D. et al. Ovine AQP1: cDNA cloning, ontogeny, and control of renal gene expression. *Pediatr. Nephrol.* 1998; 12: 545-553.

139. Yamamoto T., Sasaki S., Fushimi K. et al. Vasopressin increases AQP-CD water channel in apical membrane of collecting duct cells in Brattleboro rats. *Am. J. Physiol. Cell Physiol.* 1995; 268: 1546-1551.

140. Yasui M., Hazama A., Kwon T.H. et al. Rapid gating and anion permeability of an intracellular aquaporin. *Nature.* 1999;402: 184-187.

141. Yasui M., Kwon T.H., Knepper M.A. et al. Aquaporin-6: an intracellular vesicle water channel protein in renal epithelia. *Proc. Natl. Acad. Sci. USA.* 1999; 96: 5808-5813.

142. Yool A.J., Weinstein A.M. New roles for old holes: ion channel function in aquaporin-1. *News Physiol. Sci.* 2002; 17: 68-72.

143. Zhang Y., Ding S., Shen Q. et al. The expression and regulation of aquaporins in placenta and fetal membranes. *Front Biosci. (Landmark Ed).* 2012; 17: 2371-2382.

144. Zhu N., Jiang S.S., Hu Y.C. et al. Defective macrophage function in aquaporin-3-deficiency. *FASEB J.* 2011; 25: 4233-4239.

145. Zhu X.Q., Jiang S.S., Hu Y.C. et al. The expression of aquaporin 8 and aquaporin 9 in fetal membranes and placenta in term pregnancies complicated by idiopathic polyhydramnios. *Early Hum. Dev.* 2010; 86: 657-663.

146. Zhu X.Q., Jiang S.S, Zhu X.J. et al. Expression and localization of aquaporins 8 and 9 in term placenta with oligohydramnios. *Reprod. Sci.* 2012; 19: 1276-1284.

147. Zhu X.Q., Jiang S.S., Zhu X.J. et al. Expression of aquaporin 1 and aquaporin 3 in fetal membranes and placenta in human term pregnancies with oligohydramnios. *Placenta.* 2009; 30: 670-676.

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HISTORY OF CRANIOPLASTY DEVELOPMENT

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The article gives the historical background of the development of cranioplasty: since the Mesolithic or early Neolitic, when cranial trepanation was ritualistic. Since then, reconstructive neurosurgery has undergone several periods of development. Indications for cranioplasty are currently divided into three groups: therapeutic, cosmetic, and preventive. The article lists the main stages contributing to the development of reconstructive neurosurgery. Modern materials used to close skull defects, their properties, features, pre- and intraoperative modeling are described. Previously, "freely" or "manually" simulated biopolymers were used in cranioplasty. Recently, they have seldom been used for the plastic of extensive defects due to a poor aesthetic result. Currently, 3D printing allows to improve the aesthetic effect of reconstructive neurosurgery. Conducting experiments on stem cells and developing morphogenetic proteins solve the problem of transplant rejection.
Keywords: *cranioplasty, additive technologies, 3D printing, skull defects, reconstructive neurosurgery.*

Cranioplasty is a neurosurgical intervention aimed at restoring the integrity of the calvaria bones [1, 2, 3]. Archaeologists describe the consequences of operations on the calvaria dated the epoch of the Mesolithic or early Neolithic period (10-12 thousand years ago) [4]. During the Mesolithic era, much of the interventions were of the character of rituals. There were distinct signs of healing of the edges of the hole, indicating patient survival [5]. The defect of bone structures of the skull is formed after surgical support for traumatic injuries, vascular diseases of the brain, purulent-inflammatory diseases, or treatment of oncological process [6, 7, 8]. The increase in the number of decompressive trepanations performed in the last decade is due to their efficacy as a method of adequate control of brain edema in the conditions listed above [9, 10, 11]. In neurosurgery, the problem of closure of calvaria defects and fixation of grafts continues to be urgent [6, 12, 13]. In the arsenal of the neurosurgeon, there are a lot of methods and materials for cranioplasty [14, 15, 16]. A wide choice indicates constant scientific and technological search and improvement of reconstructive neurosurgery [17, 18, 19].

Indications for cranioplasty [20, 21, 22, 23, 24, 25, 26]:

1) therapeutic (the need to seal the skull, protection from external influences, normalization of intracranial pressure, cerebrospinal fluid circulation and hemodynamics of the brain);

2) cosmetic (defects disfiguring the surface of the head, frontal-orbital region, even relatively small defects);

3) preventive (prevention of cases of additional injuries in persons suffering from epileptic seizures).

The main periods of cranioplasty development

The first period was characterized by the beginning of the systematic study of methods and techniques of cranioplasty. In this period, the fate of the transplanted graft, the role of periosteum, hard cerebral membrane, vascular system (in particular, diploic veins), salt metabolism and various other factors in the process of closing the calvaria defects were studied [6, 27].

The second period of cranioplasty development (from the 00s to the 60s of the 20th century) was characterized by the wide introduction of various materials into neurosurgical practice: auto-, xeno-, allo-, heterografts. This was due to the fact that during the First and Second World Wars a large number of wounded people with extensive cranial bone defects appeared. The presence of such a contingent of patients required the search for new materials to reliably close extensive defects in the skull. Various metals were offered during this period: tantalum, vitallium, silver, lead, stainless steel, polymethyl methacrylate (PMMA). Also during this period, the syndrome of "trepanated" was well studied and described.

The third period of the history of cranioplasty development began (from the 60s to the 80s of the 20th century). Advances in the preservation of organs and tissues for that period made it possible to look for transplant materials which would be

close to recipient tissues in their biological, physiological and biochemical properties and would not cause adverse reactions. Also during this period, various ways of storing the autobone and allobone were developed: formalinization (0.5 and 0.25% formalin solution), lyophilization (freezing followed by drying in vacuum), and rapid freezing with liquid nitrogen (t from –40 to –70°C) followed by storage at t –25°C (Figure 1) [28, 29].
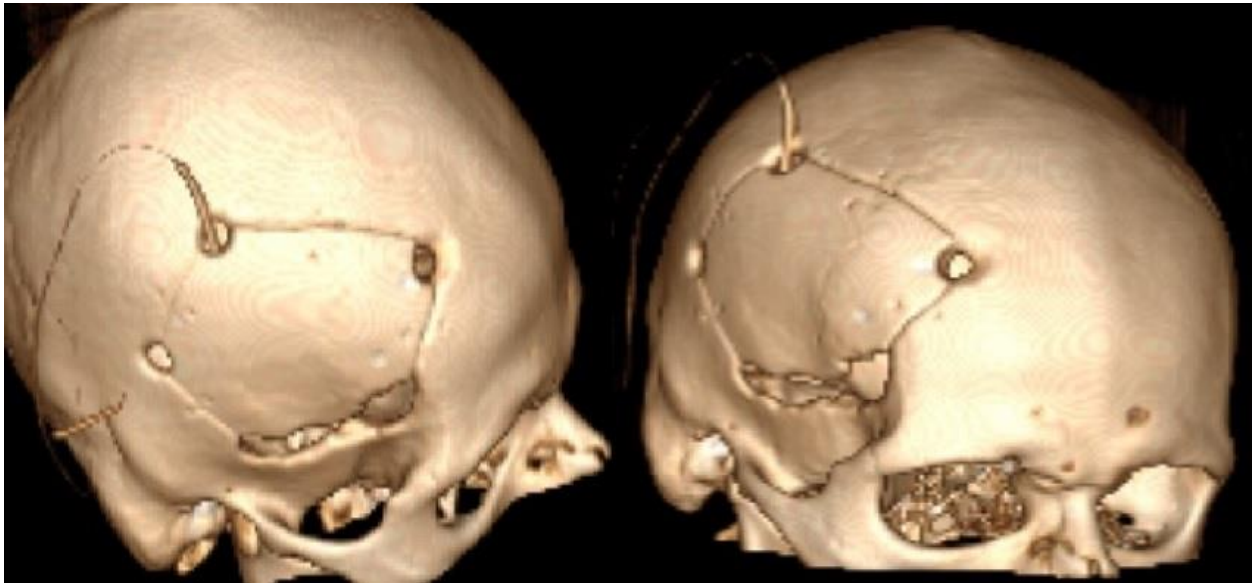

Figure 1. Cranioplasty with autobone (computed tomography). Autobone storage was carried out in the formalin solution.

The fourth period (from the 80s to the 90s of the 20th century) was characterized by the appearance of more user-friendly synthetic materials causing less reactions in the surrounding tissues: ceramics, polyetherketone (REEK), etc. [30].

The fifth period (from the 90s Of the 20th century to the 10s of the 21 century) was characterized by the emergence of additive technologies that allow manufacturing of individual implants [31, 32, 33]. Previously, "freely" or "manually" simulated biopolymers were used (Figure 2, 3) [34, 35].

The most difficult in terms of the exclusivity of geometry, as well as high functional and cosmetic load are defects of frontal-ocular localization [36]. For plastics of extensive and complex defects, these techniques are rarely used due to a poor cosmetic result [23, 37]. Currently, there is a wide range of 3D printing used in cranioplasty: layer-by-layer fusion modeling (FDM), stereolithography (SLA), selective laser sintering (SLS), and direct metal laser sintering (DMLS) (Figure 4, 5) [15, 38, 39].

Additive technologies (prototyping) make it possible to accurately recreate the shape and volume of the implant [40, 41]. The number of scientific publications on this subject has increased by more than 10 times since 2013, which is due to the popularization of 3D printing technology and the decrease in its cost [2, 42, 43]. The use of 3D printing allows closure of skull bone defects of any size and configuration, shortening surgery time, achieving the best cosmetic and functional results [41, 44, 45, 46, 47, 48].

Materials for cranioplasty
1. Using biological materials [27, 49, 50, 51]:
(a) autogenic tissue (of the patient themselves);
(b) allogenic tissue (cadaver material);
(c) heterogeneous tissues (animal origin);
(d) xenoimplants.
Modern materials have a range of requirements [5, 38, 52, 53]:
- biocompatibility;
- lack of carcinogenic effect;
- plasticity;
- convenience in use;
- possibility of sterilization;
- ability to combine with additive technologies;
- ability to fuse with the adjacent bone tissue (osteointegration);
- compatibility with neuroimaging;
- resistance to mechanical loads;
- low levels of thermal and electrical conductivity;
- acceptable cost;
- minimal risk of infectious complications.
Experiments with allografts of skull bones during World War I proved unsuccessful due to the high incidence of complications [1, 54]. It is proved that the bone tissue can be a source of bacterial and viral infections [10, 55]. The preservation of cells and cell membranes leads to the development of a graft rejection reaction.

Figure 2. Cranioplasty with titanium mesh (intraoperative photography). Modeling of titanium mesh geometry was carried out "manually".

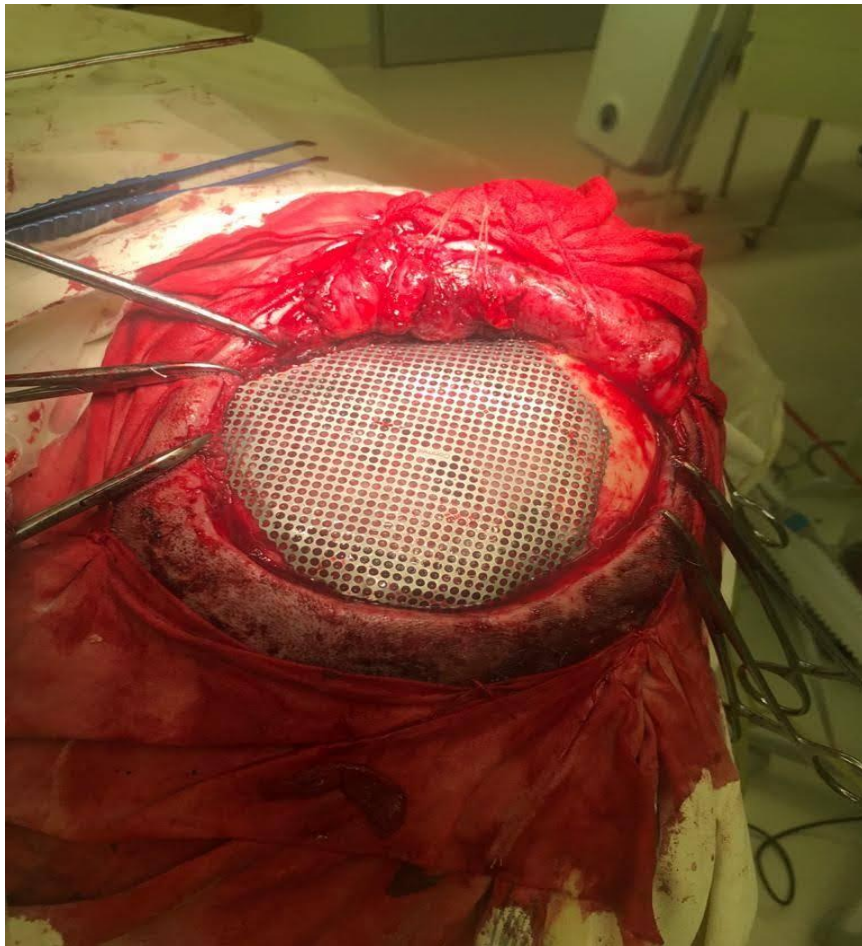Figure 3. Cranioplasty with titanium mesh (computed tomography). Modeling of titanium mesh geometry was carried out "manually".
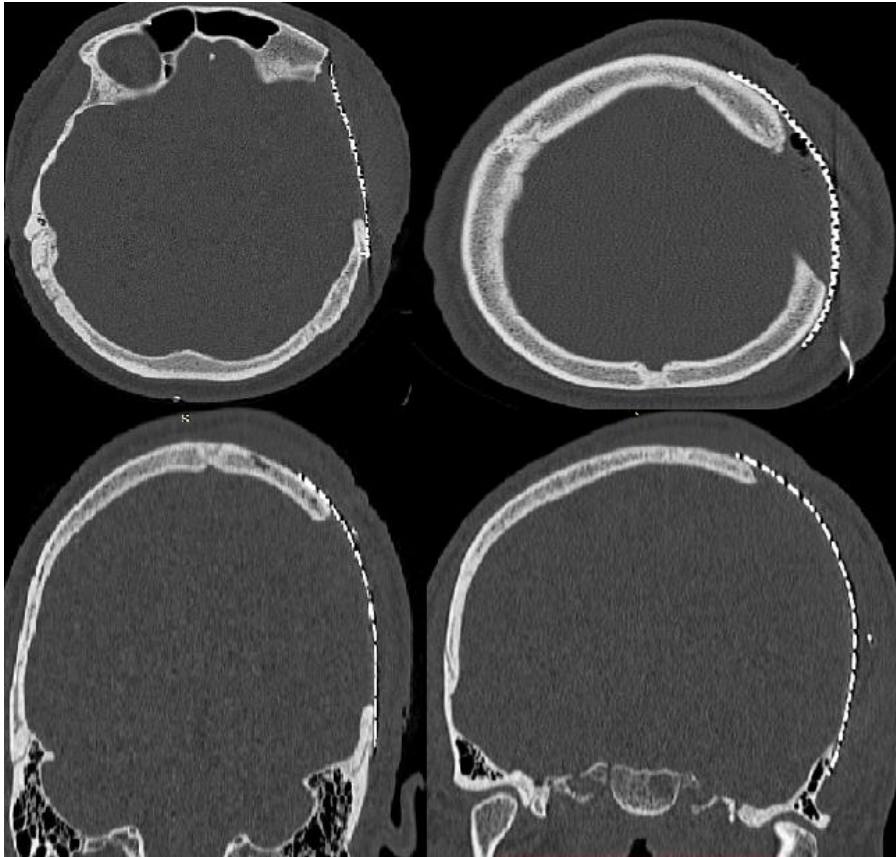
Figure 4. Cranioplasty with titanium mesh (computed tomography). Titanium mesh is made by 3D printing with a DLMS printer.
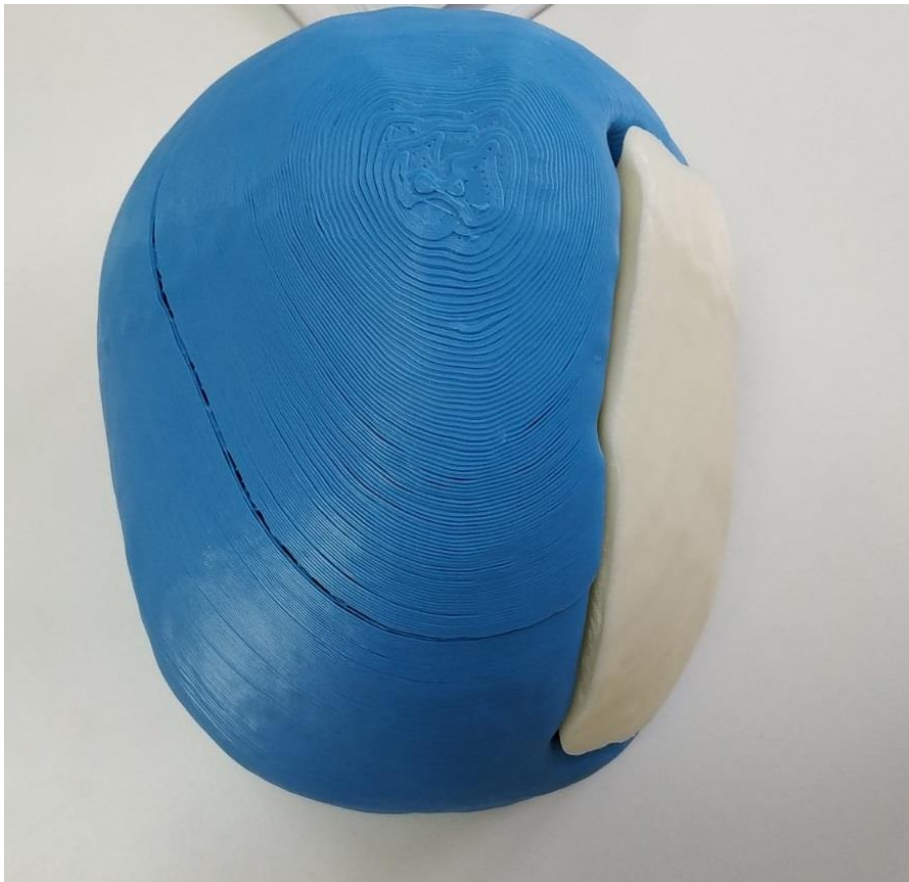

Figure 5. The skull model is made on a 3D printer FDM. The white part is the area of the skull defect, made according to the scheme of symmetrical reflection.

Because of this, modern methods of allograft processing involve the destruction of cellular elements of the allobone to reduce its antigenic properties, but the high risk of resorption limits the application of these implants in reconstructive neurosurgery. There are also large legal problems when using them.

Heterografts are the bone material of animal origin. Despite the fact that experiments on their use as bone-plastic material have been carried out for a long time in various fields of medicine, the results have never been favorable to cope with high rejection rate, low biocompatibility and high risk of infectious complications [8]. Legal problems remain in the use of heteroimplants.

Currently, the method of cryopreservation of autologous bone tissue prepared earlier in craniotomy is used more often. Bone tissue cryopreservation requires the presence of a local bank of bone tissue in the hospital with the implementation of strict aseptic rules and a storage temperature from –80°C to –196°C.

Metals such as gold, silver, aluminum have relatively low strength and have toxic effects [1]. It is possible to use combined implants, and with large sizes of bone defect, it is necessary to reinforce an implant based on hydroxyapatite with titanium mesh.

In the study, D.Y. Chan et al. (2017) proved in the storage of 18 autografts for 4–55 months that in 5 cases (27.8%) the growth of bacterial cultures was registered: Pasteurella multocida in 3 and methicillin-resistant S. aureus in 2 [56]. In addition, they proved that none of the bone flaps retained viable osteoblasts after cryopreservation.

S. Jin et al. (2018) when studying the analysis of 57 autotransplants revealed that the frequency of formation of infectious complications (about 12%) depends on the duration of autobone storage, as well as the possibility of its significant resorption [57]. A.C. Alves Junior et al. (2018) showed that the incidence of infectious complications and resorption of the autograft decrease in early cranioplasty [58].

In the work of S. Honeybul et al. (2018), of 64 patients, 31 were implanted titanium plates and 33 an autobone. In group 1, there were no signs of implant insolvency for 12 months, and in group 2, 7 patients required urgent reoperation due to significant resorption of the autoimplant [59].

In the meta-analysis of J.G. Malcolm et al. (2018), which included 1,586 cranioplasty data from 11 studies, autografts brought a significantly higher risk of resorption formation than the synthetic ones (odds ratio 1.91, 95% confidence interval 1.4–2.61). In 41% of cases, autobone resorptions were accompanied by the development of infectious complications. Among patients whose implants have not undergone resorption, the incidence of infection and other post-operative complications did not differ statistically between the groups [60].

In the study of B. Lethaus et al. (2014), the average cost of autobone cranioplasty was 10,850 €, in the manufacture of an individual synthetic implant – 15,532 €, which is 1.43 times more expensive [61].

M.S. Gilardino et al. (2014) compared the productivity and cost of autografts and individual synthetic grafts. The outcomes of treatment did not differ in the groups. The average cost of treatment was $25,797 for autotransplantation and $28,560 for synthetic implants, that is, 10% more expensive [62].

Reducing the cost of individual grafts for reconstructive neurosurgery can be achieved by 3D modeling of the desired product by medical professionals themselves directly in the clinic. However, it should be noted that this requires special knowledge in the field of CAD/CAM modeling. Currently, many programs for CAD/CAM are freely available for surgeons: 3D Slicer, Cura Slicer, Blender 3D, Autodesk, Mimics Research, etc. (Figure 6, 7) [63, 64, 65].

In Russia, the use of individual implants is regulated by the program of state guarantee of high-tech medical care at the expense of the federal budget in the specialty "neurosurgery", group No. 13, type code 8.010.17 – microsurgical reconstruction in congenital and acquired complex and giant defects and deformities of the calvaria, facial skeleton and base of the skull with computer and stereolithography modeling, additive technologies (3D printing) using biocompatible plastic materials and resource-intensive implants [12, 42].

Main dates in the development of reconstructive neurosurgery [28, 31, 66, 67]

1505 – Ibrahim bin Abdullah substituted skull defects in soldiers using heterografts derived from goats or dogs.

1550 or 1560 – G. Fallopius applied a gold plate when replacing a skull defect.

1668 – J.J. van Meekeren, a Dutch surgeon, performed cranioplasty with the bone of a dog's skull to a Russian nobleman after him being wounded by a sword in Moscow.

19th century – Fiji islanders used the coconut shell for cranioplasty, which was carefully cleaned and placed under the scalp.

1820 – P. von Walther, a German surgeon, used the autobone stored after trepanation for cranioplasty.

1885 – Macewen proposed to maintain the autobone after trepanation. The bone flap was placed under the skin of the anterior abdominal wall or the anteroexternal surface of the thigh.
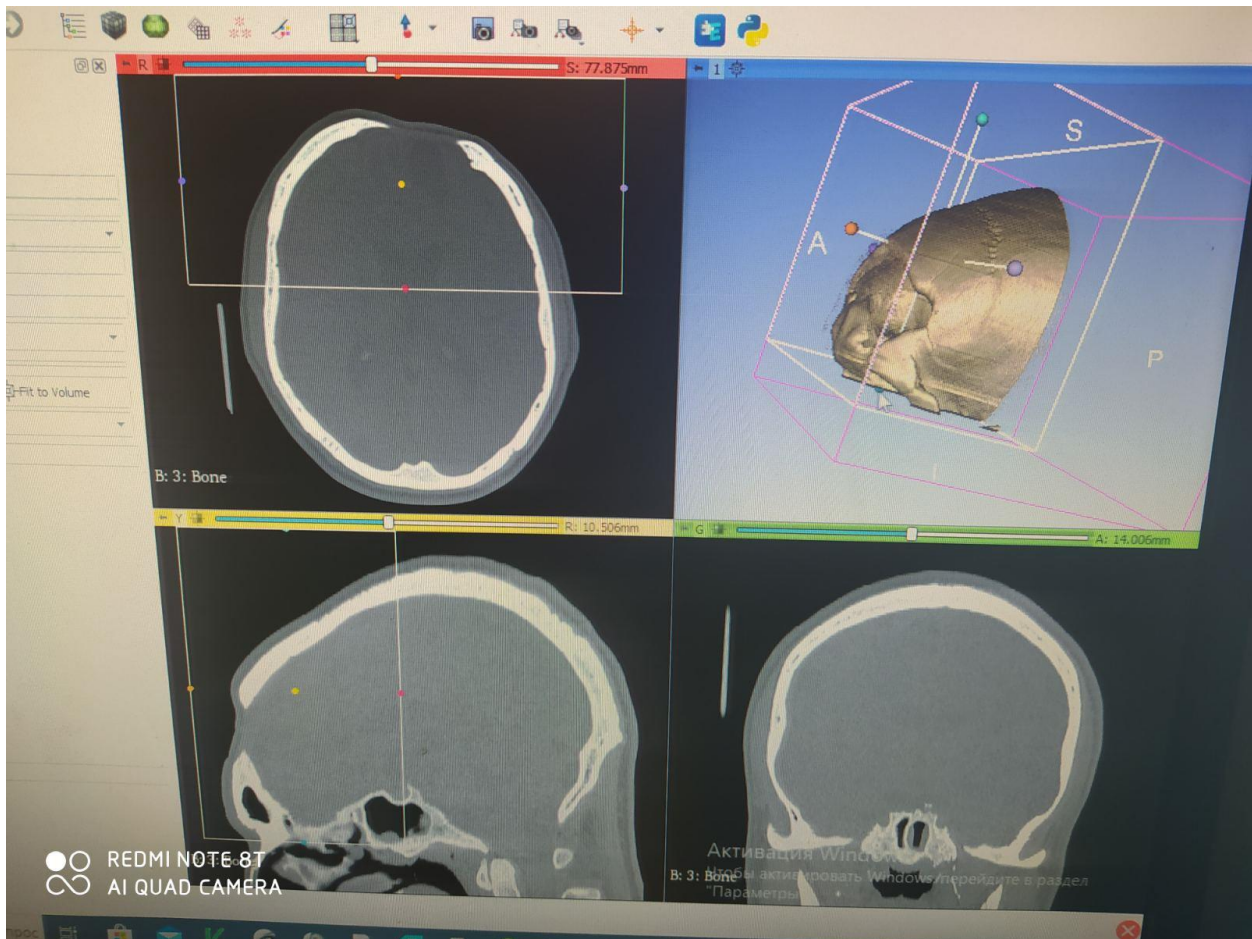
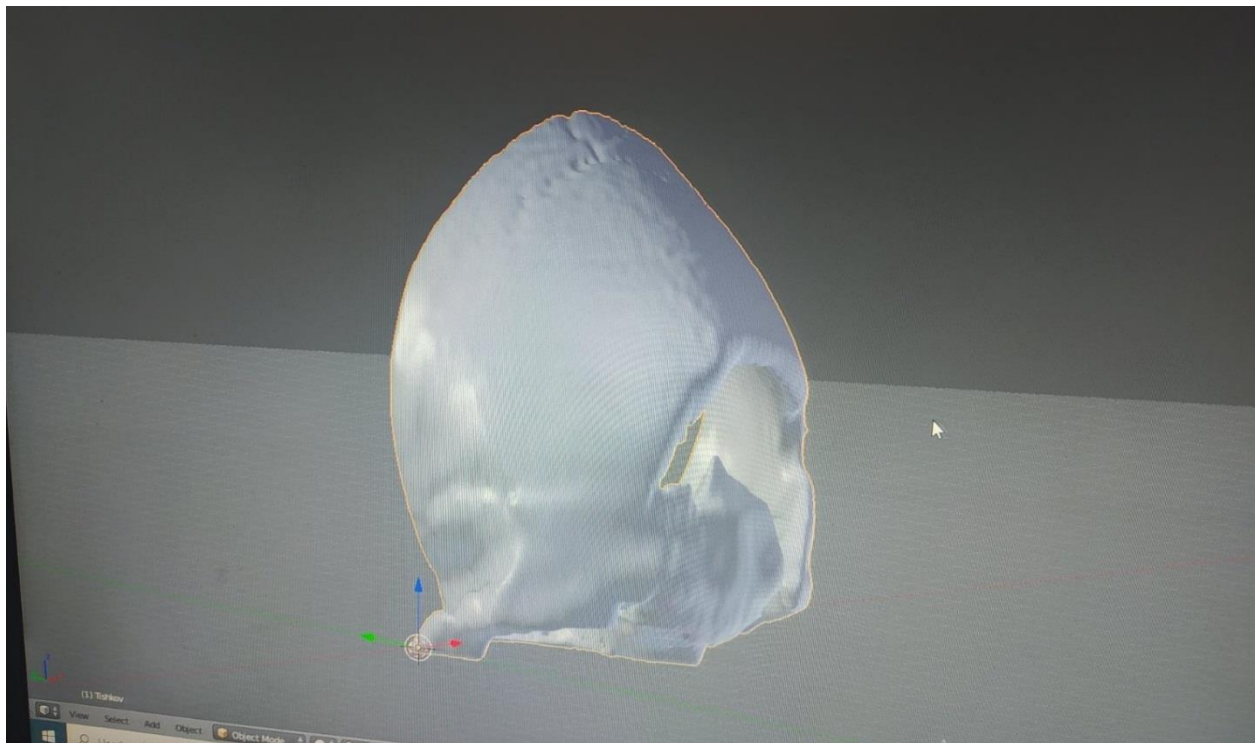Figure 6. Designing a skull model in the 3D Sliser program.

Figure 7. Designing a skull model in the Blender program.

1890 – A. Fraenkel used celluloid to close the skull defect. In the future, it was abandoned due to low biocompatibility.

1890 – P. Muller began to use a cleaved bone flap at small bone window sizes (up to 4 cm).

1893 – J. Booth and B. Curtis, aluminum was

used as a material for cranioplasty. Aluminum showed infectious complications in many cases. Also, many patients suffered epilepsy after cranioplasty using aluminum.

1895 – J. Barth used a calcined corpse bone plate to replace the calvaria defects.

1899 – A.D. Zvorykin used plates made of a mixture of calcareous salts, close in composition to the bone.

1903 – S. Sebileau used silver as a material for cranioplasty. This caused a change in skin color due to oxidation.

1908 – R. Mauclaire and M. Rouvillois used lead. It was characterized by a high level of toxicity leading to the development of plumbism in operated patients.

1912 – E. Kane used sheet mica as a material.

1913 – E. Rehn applied the bull horn.

1914 – R. Mauclaire applied the patient's iliac bone.

1915 – H. Morestin used an allograft made from cadaver cartilage.

1915 – M. Reynier applied the rabbit bone.

1915 – R. Muller applied the patient's sternum for cranioplasty.

1916 — R. Mauclaire used the elephant bone.

1916 – K. Henschen applied the buffalo bone.

1917 – cow shoulders obtained from hospital food were used in cranioplasty, dubbed "soup bone".

1917 – D. Kuttner applied the bone of an anthropoid ape.

1929 – platinum was used for cranioplasty. It showed good biocompatibility without a tissue reaction, but its use was not widespread due to its high cost.

1938 – execution of cranioplasty with PMMA in apes.

1939 – F. C. Grantand and N. C. Norcross described a clinic of "trepanated syndrome."

1940 – PMMA began to be used for the plastics of skull defects.

1943 – O. H. Fulcher first described the use of tantalum. However, due to its high thermal conductivity, patients suffered from headaches when exposed to sunlight or cold.

1943 – vitallium (an alloy of cobalt, molybdenum and chromium) was used for cranioplasty. It had already been used as a dental implant and showed minimal corrosion. Experiments on animals showed that combined metals yield less tissue reaction than pure metals.

1945 – E. Boldrey used stainless steel. Stainless steel mesh, being 290 times cheaper than tantalum, was suitable for closing only small defects due to its significant deformation at the slightest injury.

1949 – E. Busch applied polyethylene. However, it was too soft for the reconstruction of large defects.

1958 – B. Oppenheimer proved that the celluloid plate has high carcinogenic properties.

1965 – D. Simpson applied titanium in cranioplasty.

1968 – A. Courtemanche and G. Thompson used silicone rubber, but its softness limited its use.

1968 – silicon was proposed as a material for cranioplasty, but its soft assembly limited its use.

1987 – the SLA technology was presented at the auto show in Detroit.

1990s – calcium hydroxyapatite, or bioceramics, was presented as a potential substitute for bone, as it is morphologically similar to human bone.

1998 – beginning of REEK application.

1999 – introduction of SLA in clinical practice of the Burdenko Research Institute.

2006 – reperen plates began to be used.

2013 – in Denmark, a titanium jaw fragment was made using 3D printing and successfully implanted.

2014 – the bone substituting material "Recost" began to be used, as well as its cured version "Recost-M".

Conclusion

Interest in cranioplasty is supported not only by the evolution of views on the clinical effects provided, but also by the search for the "perfect material" to close the defect. Over the entire history, a huge variety of materials have been analyzed: from improvised materials of ancient civilizations and gold plates cast by Incas, various types of metal to modern high-tech polymers used in the aerospace industry. Today, research is ongoing to find the optimal plastic material of both biological and non-biological origin. Obviously, a universal method and material for cranioplasty, which could be used to solve all the problems associated with the closure of skull defects, has not been found by now. Experiments on stem cell and development of morphogenic proteins are expected in the near future.

It is also worth noting that currently the popularization of 3D printing and 3D modeling, the manufacture of individual implants for reconstructive neurosurgery can be seen. This is due to a decrease in the cost of these technologies and an increase in their availability.

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References:

1. Ofitserov A.A., Borovkova N.V., Talypov A.E., Ponomarev I.N. Modern materials for the reconstruction of the cranial vault bones. *Transplantologiya. The Russian Journal of Transplantation*. 2019; 11(3):234-243.

2. Mishinov S.V., Stupak V.V., Koporushko N.A., Panchenko A.A., Krasovsky I.B., Desyatykh

I.V. Three-dimensional modeling and printing in neurosurgery. In the book: *VIII All-Russian Congress of Neurosurgeons:* Materials of the Congress. 2018: 169.

3. Mishinov S.V., Koporushko N.A., Larionov P.M., Mukhamadiyarov R.A., Zaydman A.M., Bazlov V.A., Stupak V.V. Morphological evaluation of tissue reaction response to the titanium implants for cranioplasty. Experimental study. *Modern Problems of Science and Education.* 2020; 4: 109.

4. Yarikov A.V., Fraerman A.P., Leonov V.A., Stolyarov I.I., Gunkin I.V., Tsygankov A.M. Scull defect surgery: a review of current techniques, materials and additive technologies. *Amur Medical Journal*. 2019;4 (28): 65-77.

5. Levchenko O.V. Modern methods of cranioplasty. *The Russian Journal of Neurosurgery.* 2010; 2: 5-13.

6. Tikhomirov S.E. Cranioplasty with plates "Reperen"® (experimental and clinical results). *Perm Medical Journal*. 2009; 26(6): 54-59.

7. Tikhomirov S.E. Plasty of defects of calvarium with "Reperen"® material. *Russian Neurosurgical Journal Named After Professor A.L. Polenov*. 2010; 2(3):52-58.

8. Radkevich A.A., Gyunter V.E., Kasparov E.V., Mamedov R.Kh., Siniyuk I.V. Reconstruction of bone defects of the skull vault using titanium nickelide-based implants. In the collection: *Topical Issues of Modern Surgery*: Collection of Scientific and Practical Works Dedicated to the 70th Anniversary of the Head of the Department of General Surgery named after Prof. M.I. Gulman of the KrasSMU named after Prof. V. F. Voino-Yasenetsky, Honoured Scientist of the Russian Federation, Honored Doctor of Russia, Academician of RANS, Professor, Doctor of Medical Sciences, Yuri Semenovich Vinnik. 2018: 225-229.

9. Koporushko N.A., Stupak V.V., Mishinov S.V., Orlov K.Yu., Astrakov S.V., Vardosanidze V.K., Golobokov A.V., Bobylev A.G. Etiology and epidemiology of acquired defects of the skull bones, obtained with different pathologies of the central nervous system and the number of patients needing to their closed case for large industrial city. *Modern Problems of Science and Education.* 2019;2: 120.

10. Koporushko N.A., Mishinov S.V., Kangel'diev A.E., Stupak V.V. Cosmetic results of reconstructive neurosurgical interventions on the skull. *Polytrauma*. 2020;1: 47-55.

11. Kubrakov K.M., Karpuk I.Yu., Fedukovich A.Yu. Reconstructive alloplasty of skull bone defects with titanium implants. *News of Surgery*. 2011; 19(1): 72-76.

12. Koporushko N.A., Stupak V.V., Mishinov S.V., Orlov K.Yu., Astrakov S.V., Vardosanidze V.K., Golobokov A.V., Bobylev A.G. Epidemiology and pidemiology and etiology of acquired skull bone defects on the example of a large industrial city. *Russian Neurosurgical Journal Named After Professor A.L. Polenov*. 2019; 11(S): 209-210.

13. Gevorkov A.V., Davydov E.A., Safarov B.I., Ilyin A.A., Kollerov M.Yu., Cheremkin S.N., Ulitin A.Yu. Application of damper craniofixators from nitinol in plasty of skull defects. *Grekov's Bulletin of Surgery*. 2010; 169(2): 69-73.

14. Mishinov S.V., Stupak V.V., Mamonova N.V., Panchenko A.A., Krasovsky I.B., Lazurenko D.V. Methods of three-dimensional prototyping and printing in reconstructive neurosurgery. *Biomedical Engineering*. 2017; 2 (302): 22-26.

15. Mishinov S.V., Stupak V.V., Panchenko A.A., Krasovsky I.B. Reconstruction of fronto-zygoma-orbital area using a patient specific titanium implant printed by direct metal laser sintering technology. Clinical case. *Russian Neurosurgical Journal Named After Professor A.L. Polenov*. 2017; 9(1): 80-82.

16. Andreeva M.S., Klimtseva E.E., Kiselev A.V., Chertkov A.K. Possibilities of modern cranioplasty. 3D modeling of skull defects. In the collection: *Topical Issues of Modern Medical Science and Healthcare*: Materials of the III International Scientific and Practical Conference of Young Scientists and Students, III Forum of Medical and Pharmaceutical Universities of Russia "For Qualitative Education". 2018: 803-807.

17. Mishinov S.V., Stupak V.V., Koporushko N.A., Panchenko A.A., Krasovsky I.B., Desyatykh I.V. Application of individual titanium implants obtained by three-dimensional printing. In the book: *Second Siberian Neurosurgical Congress:* Collection of Proceedings. 2018: 82.

18. Mishinov S.V., Stupak V.V., Koporushko N.A., Samokhin A.G., Panchenko A.A., Krasovsky I.B., Desyatykh I.V., Kiselev A.S. Reconstructive neurosurgical interventions using individual titanium implants. *Biomedical Engineering*. 2018; 3 (309): 5-7.

19. Ginzburg E.R., Starykh V.S., Ulunov Yu.D., Dubovoy A.V. Fracture of the skull prosthesis. *Medicine in Kuzbass*. 2006; 5(2): 44-45.

20. Ivanov O.V., Semichev E.V., Sobakar' E.G., Dryannykh A.A., Shnyakin P.G., Milekhina I.E. Experience of plastic of skull defects with titanium mesh implants in the Siberian Scientific and Clinical Center of FMBA of Russia. In the collection: *Topical Issues of Modern Surgery*: Collection of Scientific and Practical Works Dedicated to the 70th Anniversary of the Head of the Department of General Surgery named after Prof. M.I. Gulman of the KrasSMU named after Prof. V. F. Voino-Yasenetsky, Honoured Scientist of the Russian Federation, Honored Doctor of Russia, Academician of RANS, Professor, Doctor of

Medical Sciences, Yuri Semenovich Vinnik. 2018: 285-289.

21. Ivanov O.V., Semichev E.V., Sobakar' E.E., Dryannykh A.A., Shnyakin P.E., Milekhina I.E. Experience of plastic of extensive skull defects with titanium implants. In the collection: *Modern Technologies of Treatment of Patients with Trauma of the Musculoskeletal System and the Central Nervous System*: Collection of Articles of Scientific and Practical Conference. Pub. ed. T.G. Ruksha. 2019: 97-102.

22. Kravchuk A.D., Maryakhin A.D., Potapov A.A., Panchenko V.Ya., Komlev V.S., Novikov M.M., Okhlopkov V.A., Duvidzon V.G., Latyshev Ya.A., Chelushkin D.M., Chobulov S.A., Aleksandrov A.P., Shkarubo A.N. Additive technologies in neurosurgery. In the collection: *Additive Technologies: Present and Future*: Materials of the V International Conference. 2019: 253-274.

23. Konovalov An.N., Pilipenko Yu.V., Eliava Sh.Sh. Technical features and complications of cranioplasty in patients after decompressive craniectomy in the acute period of subarachnoid hemorrhage. *Burdenko's Journal of Neurosurgery.* 2018;82(5):88-95.

24. Arushanyan M.Yu. Correction of skull defects. *Eurasian Scientific Association*. 2020;7-3 (65): 149-154.

25. Tsekh D.V., Sakovich V.P., Bukher M.M. Definition of the timing of interventions for the closure of defects of the skull vault. *Genij Ortopedii*. 2011; 1: 44-47.

26. Tsekh D.V. Early reconstructive interventions after decompressive cranioectomies. In the collection: *Postgraduate Readings - 2010. Materials of the reports of the All-Russian Conference "Young Scientists - to Medicine"*. 2010: 48-50.

27. Tikhomirov S.E., Tsybusov S.N., Kravets L.Ya. Use of the material "Reperen"® for plastic of defects of the skull vault (experimental and clinical results). *Siberian Medical Journal (Irkutsk)*. 2010; 93(2): 121-124.

28 Ivanov O.V., Semichev E.V., Shnyakin P.G., Sobakar' E.G. Plastic of skull defects: from autobone to modern biomaterials (literature review). *Medical Science and Education in the Urals*. 2018; 19(3(95)): 143-149.

29. Pak O.I., Antonenko F.F., Sidorov G.A., Don O.A., Yelitsky A.S., Nazarov D.V. Autocranioplasty with ribs of postoperative bone defects of the skull in children. *Pediatric Neurology and Neurosurgery*. 2009;2 (20):32-41.

30. Eolchiyan S.A., Potapov A.A., Serova N.K., Kataev M.G., Sergeeva L.A., Zakharova N.E., Van Damme F. Reconstructive surgery of cranioorbital injuries. *Burdenko's Journal of Neurosurgery*. 2011; 75(2): 25-40.

31. Eolchiyan S.A. Complex skull defects reconstruction with cad/cam titanium and polyetheretherketone (PEEK) implants. *Burdenko's Journal of Neurosurgery*. 2014; 78(4): 3-13.

32. Gavrilova L.O., Mishinov S.V., Aronov A.M., Mamonova E.V., Mamonova N.V., Grif A.M. Development of the automated information system for designing and simulation of individual implants obtained by additive methods on the example of draft drawers substitution. *International Journal of Applied and Fundamental Research*. 2017;11-2: 209-213.

33. Levchenko O.V., Shalumov A.Z., Krylov V.V. Plastic of defects of frontal-eye localization using frameless navigation. *The Russian Journal of Neurosurgery*. 2010; 3: 30.

34. Gaibov S.S.Kh., Vorobyev D.P., Zakharchuk I.A., Zakharchuk E.V. Plastic of complex giant skull defect (clinical case). *University Medicine of the Urals*. 2018; 4(3 (14): 7-9.

35. Ivanov A.L., Satanin L.A., Agapov P.I., Roginsky V.V., Sakharov A.V. Computer planning and biomodeling in the treatment of a patient with complex post-traumatic defect and craniofacial deformity (clinical observation). *Pediatric Neurology and Neurosurgery*. 2012;2-3 (32-33): 144-151.

36. Levchenko O.V., Shalumov A.Z., Krylov V.V. The use of frameless navigation for plastic elimination of bone defects of frontal ocular localization. *Annals of Plastic, Reconstructive and Aesthetic Surgery*. 2011;3: 30-36.

37. Krylov V.V., Petrikov S.S., Talypov A.E., Puras Yu.V., Solodov A.A., Levchenko O.V., Grigoryeva E.V., Kordonsky A.Yu. Modern principles of surgery of severe craniocerebral trauma. Russian Sklifosovsky Journal "Emergency Medical Care". 2013; 4: 39-47.

38. Potapov A.A., Kornienko V.N., Kravchuk A.D., Likhterman L.B., Okhlopkov V.A., Eolchiyan S.A., Gavrilov A.G., Zakharova N.E., Yakovlev S.B., Shurkhai V.A. Modern technologies in the surgical treatment of head injury sequelae. *Annals of the Russian Academy of Medical Sciences*. 2012; 67(9): 31-38.

39. Byval'tsev V.A., Kalinin A.A., Malkov F.S., Ochkal S.V., Pol'kin R.A. Prospects of application of 3D printing technologies in the Baikal region. In the book: *Prospects of Development of Biomedical Technologies in the Baikal Region. Collection of Proceedings of the International Scientific Conference*. 2019: 11-12.

40. Levchenko O.V., Mikhaylyukov V.M., Davydov D.V. Frameless navigation in surgery of post-traumatic defects and deformities of the cranioorbital region. *The Russian Journal of Neurosurgery*. 2013; 3:9-14.

41. Medvedev M.P., Fomina M.A. 3D-printing as a new era in medicine. *New Science: from Idea to Result*. 2016; 11-4: 16-19.

42. Stupak V.V., Koporushko N.A., Mishinov

S.V., Guzev A.K., Astrakov S.V., Vardosanidze V.K., Golobokov A.V., Bobylev A.G. Epidemiological data of acquired skull defects in patients after traumatic brain injury through the example of a big industrial city (Novosibirsk). *Polytrauma*. 2019; 1: 6-10.

43. Ivanov V.P., Kim A.V., Khachatryan V.A. 3D printing in craniofacial surgery and neurosurgery. Experience of the Almazov National Medical Research Centre. *Pediatric Neurology and Neurosurgery*. 2018; 3 (57): 28-39.

44. Dyusembekov E.K., Isataev B.S., Sadykova Zh.B., Aglakov B.M., Li K.Yu. Cranioplasty: using 3D implants for repair skull defect. *Vestnik KazNMU*. 2016; 4: 82-

45. Safonov M.G., Strogy V.V. Application of 3D printing in medicine. *European Student Scientific Journal*. 2015;3-3: 394-395.

46. Kholodilov A.A., Yakovleva A.V. Innovative application of additive technologies in medicine. *Young Scientist*. 2019;5 (243): 35-38.

47. Cherebylo S.A., Evseev A.V., Ippolitov E.V., Novikova L.V., Panchenko V.Ya., Kravchuk A.D., Potapov A.A. Plastic of skull defects using three-dimensional modeling and laser stereolithography. *Perspektivnye Materialy*. 2011;S13: 917-922.

48. Dyusembekov E.K., Mirzabaev M.Zh., Aglakov B.M., Sadykova Zh.B. Computer simulation of 3D implants for plastic of the defect of the base and vault of the skull. *Neurosurgery and Neurology of Kazakhstan*. 2017;2 (47): 4-13.

49. Tikhomirov S.E., Tsybusov S.N., Kravets L.Ya., Fraerman A.P., Balmasov A.A. Plastic of defects of skull vault and hard cerebral membrane with new polymer material Reperen. *Modern Technologies in Medicine*. 2010;2: 6-11.

50. Mishinov S.V., Stupak V.V., Koporushko N.A. Cranioplasty: review of techniques and new technologies in the creation of implants. Current state of the problem. *Polytrauma*. 2018;4: 82-89.

51. Yarikov A.V., Fraerman A.P., Leonov V.A., Perl'mutter O.A., Tikhomirov S.E., Yaksargin A.V., Smirnov P.V. Cranioplasty: review of materials and methods. *Creative surgery and oncology*. 2019; 9(4): 278-284.

52. Mishinov S.V., Stupak V.V., Koporushko N.A., Samokhin A.G., Panchenko A.A., Krasovsky I.B., Desyatykh I.V., Kiselev A.S. Reconstructive neurosurgical interventions using individual titanium implants. *Biomedical Engineering*. 2018;3 (309): 5-7.

53. Levchenko O.V., Krylov V.V. Modern methods of cranioplasty. *Consilium Medicum. Neurology and Rheumatology*. 2009;1: 9-15.

54. Stupak V.V., Mishinov S.V., Sadovoy M.A., Koporushko N.A., Mamonova E.V., Panchenko A.A., Krasovsky I.B. Modern materials used to close skull bone defects. *Modern Problems of Science*

and Education. 2017;4: 38.

55. Levchenko O.V., Krylov V.V. Modern methods of cranioplasty. *Handbook of a Polyclinical Doctor*. 2009: 2: 63-66.

56. Chan D.Y.C., Mok Y.T., Lam P.K., Tong C.S.W., Ng S.C.P., Sun T.F.D. et al. Cryostored autologous skull bone for cranioplasty? A study on cranial bone flaps' viability and microbial contamination after deep-frozen storage at -80°C. *J Clin Neurosci*. 2017;42:81-83. DOI: 10.1016/j.jocn.2017.04.016

57. Jin S., Kim S.D., Ha S.K., Lim D.J., Lee H., You H.J. Analysis of the factors affecting surgical site infection and bone flap resorption after cranioplasty with autologous cryopreserved bone: the importance of temporalis muscle preservation. *Turk Neurosurg*. 2018;28(6):882-888. DOI: 10.5137/1019-5149.JTN.21333-17.2

58. Alves Junior A.C., Hamamoto Filho P.T., Gonçalves M.P., Palhares Neto A.A., Zanini M.A. Cranioplasty: An Institutional Experience. *J Craniofac Surg*. 2018;29(6):1402-1405. DOI: 10.1097/SCS.0000000000004512

59. Honeybul S., Morrison D.A., Ho K.M., Lind C.R.P., Geelhoed E. A randomised controlled trial comparing autologous cranioplasty with custom-made titanium cranioplasty: long-term follow-up. *Acta Neurochir (Wien)*. 2018;160(5):885-891. DOI: 10.1007/s00701-018-3514

60. Malcolm J.G., Mahmooth Z., Rindler R.S., Allen J.W., Grossberg J.A., Pradilla G. et al. Autologous Cranioplasty is Associated with Increased Reoperation Rate: A Systematic Review and Meta-Analysis. *World Neurosurg*. 2018;116:60-68. DOI: 10.1016/j.wneu.2018.05.009

61. Lethaus B., Bloebaum M., Koper D., Poort-Ter Laak M., Kessler P. Interval cranioplasty with patient-specific implants and autogenous bone grafts - Success and cost analysis. *J Cranio-Maxillofacial Surg*. 2014;42(8):1948-1951. DOI: 10.1016/j.jcms.2014.08.006

62. Gilardino M.S., Karunanayake M., Al-Humsi T., Izadpanah A., Al-Ajmi H., Marcoux J. et al. A Comparison and Cost Analysis of Cranioplasty Techniques. *J Craniofac Surg*. 2015;26(1):113–117. https://doi.org/10.1097/SCS.0000000000001305

63. Semenov V.V., Verkhozina Yu.A. 3D printers as the basis of our future. *Youth Bulletin of INRTU*. 2017; 4: 1.

64. Kashin V.A., Kovalenko R.A., Cherebillo V.Yu. Technical possibilities of individual 3D biomodeling in neurosurgery. In the book: *3D Technologies in Medicine. Materials of the IV All-Russian Scientific and Practical Conference*. 2019: 14-15.

65. Kovalenko R.A., Ptashnikov D.A., Cherebillo V.Yu., Rudenko V.V., Kashin V.A. Application of individual 3D models in spine

surgery - literature review and first experience of use. *Russian Neurosurgical Journal Named After Professor A.L. Polenov*. 2018; 10(3-4): 43-48.

66. Mishinov S.V., Stupak V.V., Mamuladze T.Z., Koporushko N.A., Mamonova N.V., Panchenko A.A., Krasovsky I.B., Rabinovich S.S., Lar'kin V.I., Dolzhenko D.A., Novokshonov A.V. The use of three-dimensional modeling and three-dimensional printing in the training of neurosurgeons. *International Journal of Applied and Fundamental Research*. 2016; 11-6: 1063-1067.

67. Kolmogorov Yu.N., Uspensky I.V., Maslov A.N., Novikov A.E., Tarasov D.A., Myachin N.L., Goncharov A.Yu., Korzun A.S., Latypov T.F., Yadykov D.A., Balyazin-Parfenov I.V. Rekost-M bone replacement implants based on 3D modeling for closing post-craniotomy skull defects: pre-clinical and clinical studies. *Modern Technologies in Medicine*. 2018; 10(3): 95-103.

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