

## Alcoholic fetal syndrome - a problem of the 21 st century?

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### Summary

Fetal Alcohol Syndrome (FAS) is a disease entity that occurs in children who have been exposed to teratogenic alcohol during fetal life. It includes neurobehavioral abnormalities and changes in the body structure and internal organs. The only reason for the occurrence of this type of disorder is the consumption of alcohol by a pregnant woman (even in small amounts). It is estimated that in Poland about 30% of women consume alcohol in this period (also in small amounts), while in the US every year is born about 40,000 children who are diagnosed with FAS or related disorders.

**Keywords:** pregnancy, alcohol, growth of child, teratogenic factors

## **Admission**

Fetal Alcohol Syndrome (FAS) or Fetal Alcohol Syndrome Disorder (FASD) is a description of a set of characteristic symptoms resulting from the effects of alcohol on the developing fetus (the body of the child), mainly the brain [1,2,3,4,5]. The effects of alcohol consumption by pregnant women lead to the development of physical, mental changes, behavior, learning (and thus the spectrum of congenital structural, neurocognitive and behavioral abnormalities [3]), which may additionally last a lifetime of offspring [6]. In addition, there are changes in the face - dysmorphs [2,4,7,8,9]. The term FAS was first used in 1973 by Jones and Smith [6, 10, 11]. The development and use of FAS definitions gave the possibility to classify a new and clinically diagnosed disease syndrome related to congenital malformations in mothers who consume alcohol during pregnancy [10]. It should be realized that alcoholism is a 21st century problem, and children who suffer from the teratogenic effects of alcohol consumed by their mothers are born more often than children with Down Syndrome - it is assumed that 1-3 children with FAS are born in Poland per 1,000 births [12], while the incidence rate of Down's syndrome is 1 in 660/800 births [9,13]. PARPA research shows that about 30% of Polish women drink alcohol while pregnant [14]. In Poland there are no verified, uniform guidelines or standards for the diagnosis, treatment and rehabilitation of children with FAS [3].

## **Teratogenic factors**

Teratogenic factors are those that interfere with the development of the child in fetal life as a result of intoxication and lead to congenital impairments [1,15]. Their teratogenicity depends on genetic predisposition (mother, embryo), pregnancy period, as well as the path and time of action of the harmful agent, as well as sensitivity and susceptibility to their action [1,16]. There are often exposure to several teratogens at the same time (often people consuming alcohol, also smoking cigarettes). The fetus, under the influence of teratogen on it, is exposed to a higher risk of death, developmental anomalies, delayed growth or occurrence of functional disorders [15,16,17]. Acetaldehyde - a metabolite of ethyl alcohol, is considered to be the main factor resulting in damage to the fetus. It has been classified as so-called neurobehavioral teratogen.

## **Effect of teratogenic alcohol on the developing fetus**

Two models are considered to characterize the effect of toxins on the developing fetus:

- linear dependence: direct correlation between effects and magnitude of operation,
- threshold relationship: the appearance of effects of toxins only after exceeding a certain level (minimum) [18].

The first model, indicating a linear relationship between mother's alcohol consumption and the development of offspring, emphasizes that there is no "safe" amount of alcohol consumed during pregnancy, because even a minimal amount can lead to undesirable effects. In turn, the threshold model proves the existence of a "safe" amount of alcohol consumed, the failure of which will prevent the occurrence of any undesirable symptoms. In practice, both models are confirmed in clinical trials depending on which of the effects of consuming ethanol is considered.

For this reason, in order to prevent any effects of alcohol prenatal treatment, total abstinence maintained by pregnant women is necessary [18]. The highest sensitivity to the harmful effects of teratogens occurs between the second and tenth week of pregnancy. The first two weeks after fertilization, due to the small number of embryo-producing cells, are relatively safe (self-healing of damage or death of the embryo). By the tenth week, all embryo structures are shaped, hence the subsequent exposure carries a lower risk. The effects of alcohol consumption depending on the period of pregnancy are presented in the table below.

Table 1. Hazards resulting from drinking alcohol depending on the period of pregnancy

TRIMESTER	EFFECTS OF ALCOHOL CONSUMPTION
I	brain damage, abnormal cell development, damage to important organs (liver, kidneys, heart), face deformities, miscarriage;
II	brain damage, miscarriage (dangerous for mother's life and health), damage to muscle cells, skin, teeth, glands or bones of the child;
III	disorders of brain and lung development, slower fetal weight gain, premature labor;

Source: own study based on: Klecka M. : Pregnancy and alcohol. Caring for a child with FAS, ed. Educational PARPAMEDIA, Warsaw, 2013.

Nevertheless, the development of the Fetal Alcohol Syndrome is conditioned by many factors, i.e.:

- the amount of alcohol that mother will consume during pregnancy,
- frequency of alcohol consumption,
- the stage of fetal development in which it was exposed to alcohol,
- pregnancy phase, during which the woman drank the most alcohol,
- the state of nutrition of the pregnant woman during pregnancy, but also the state of nutrition before conception,
- receiving other psychoactive substances (belonging to teratogens),
- genetic predisposition in relation to the fetus and to a pregnant woman,
- the general health of a woman during pregnancy [6].

The consequences of intrauterine exposure to alcohol are called the alcoholic spectrum of developmental disorders (Fetal Alcohol Spectrum Disorders - FASD). It includes:

- full-blown fetal alcohol syndrome (FAS),
- partial Fetal Alcohol Syndrome (pFAS),
- alcohol-related neurodevelopmental disorder (Alcohol - Related Neurodevelopmental Disorders - ARND),
- alcohol-related birth defects (Alcohol - Related Birth Defects - ARBD) [8,13],
- alcoholic brain damage that occurs without physical, visible external deformities (Fetal Alcohol Effects - FAE) [13, 14, 15].

Fetal Alcohol Syndrome is a disease entity in which neurobehavioral abnormalities occur as well as changes in the body structure and internal organs affecting children of mothers who consumed alcohol while pregnant [16]. It should be emphasized that children with FAS, although they are most often found in dysfunctional families, may be born in every family [16].

### Primary and secondary disorders

Primary disorders are disorders with which a newborn baby is born. They mainly include brain damage [16] including major changes in structure, incomplete development, lack of

corpus callosum, or lack of structure connecting two cerebral hemispheres with each other [6, 11]. However, some of the changes may remain very subtle and not noticeable at birth. Drinking alcohol by a pregnant woman leads to disorders of cell proliferation and migration. The changes may also concern electrophysiology and neurochemical balance of the brain which results in ineffective transmission of impulses [6], and also include synaptic connections, which leads to improper receptor work [11]. On the other hand, secondary disorders include those that have developed over the course of life, and are primarily conditioned by environmental factors: mental health problems, unfinished education, legal problems, early and / or irresponsible motherhood, institutionalization, inappropriate sexual behavior or problems with alcohol and drugs [6,8,11,16]. In addition, the following symptoms are distinguished: anxiety, anger, avoidance/ withdrawal, entering into the role of victim or persecutor, closure, impulsiveness or violent and shocking behavior [7].

### **Characteristics of the appearance of children affected by FAS**

FAS includes structural abnormalities related primarily to the face, limitation of the range of motion in the joints and other (encountered sporadically). Nevertheless, it is the facial appearance that is the easiest part of diagnostics. The most specific and characteristic changes are associated with the eyelids. Visible wide eye spacing is visible. This is the result of shortening the facial swelling (reducing the distance between the inner and outer corners of the eyes). As a result, the eyes appear to be smaller and more remote [5,8,17]. Obligatory measurement of the length of the occlusal gap should be performed to exclude other reasons for this condition. In addition, one or both eyelid dips are observed [14,16, 17]. Other changes concern the slow development of the middle part of the face. The area under the upper lip and the eyes is underdeveloped. Hypoplasia includes flattening or collapse of this area, lowering the back of the nose. Delaying the growth of the nose over the face plane may result in the formation of a rounded skin fold covering the inner corner of the eye, while the delay of nasal growth to length contributes to directing the nostrils' opening towards the front and down [5].

Another, also a characteristic change, concerns philtrum located between the nose and the upper lip. Correctly there is a vertical, middle-lying furrow bounded by two vertical ridges made of leather. At the point of contact with the lip of the labium, there are small notches that cause the lip to form a Cupid arc. In turn, in people affected by the Fetal Alcohol Syndrome, the philtrum is elongated and at the same time smooth. It does not have skin combs, and the upper lip of the lips forms a gentle arch [5,14,17]. Another important feature that makes up the child's FAS face phenotype is the thin upper lip [2,8,14,17].

It should be noted that the differences in the facial structure including the smoothing of the philtrum, thin upper lip and shortened eyelid gaps, indicate the strongest recognition of FAS, regardless of ethnicity and gender. They are so-called screening criteria, which are characterized by 100% sensitivity and specificity of 89.4% [8]. For the quantitative assessment of the upper lip thickness and the smoothing degree of the Astley and Clarren sump gutters, they have developed corresponding reference images covering a scale of 1 to 5 points. Result 4 or 5, indicates the occurrence of pathology [8]. The small periphery of the face - microcephaly, is not a feature that defines the characteristics of the phenotype, but is a feature of the central nervous system [18].

### **Brain injuries occurring in children with FAS / FASD**

The characteristic facial phenotype does not occur among all children who were exposed to harmful effects of alcohol in their intrauterine life. In turn, alcohol in each of them has a destructive effect on the brain tissue, resulting in the presence of changes in its structures. This is particularly reflected in the presence of abnormalities in the frontal lobes, corpus callosum, subcortical nuclei or cerebellum, as they show considerable sensitivity to

alcohol. The result is irreversible disturbances in the child's functioning [17,21]. For this reason, neuroimaging methods gain more and more importance for the accurate and accurate diagnosis of FAS [21]. The changes taking place in the brain in children affected by FASD are referred to as static encephalopathy: they are persistent - they do not undergo treatment and static - they do not deepen or retract [5].

The most commonly reported brain damage in the literature are:

- the cerebellum region: the area in which neurons are created at the latest during fetal life. Exposure of the fetus to alcohol in the third trimester of pregnancy results in a permanent reduction in the number of nerve cells and glial cells in this region (decreased volume and surface of the cerebellum [5, 18],
- reduce the volume of the frontal lobes compared to healthy children.
- reduce the total size of the brain. Children with FAS have an average of 13% smaller brain than healthy children of the same age. This is the result of reducing the gray matter of the brain and white matter [5],
- reduction of the corpus callosum (the element connecting the two hemispheres, responsible for the smooth flow of information between them) [5, 18],
- reducing the size of the hippocampus conditioning the creation of memories and enabling memorization and the almond body responsible for the creation and regulation of emotions [5],
- reduction of subcortical nuclei [5,17,18],
- additionally, as a result of brain damage, problems with sensation of pain, hypersensitivity to touch, hypotonia and / or hypertonia appear [5].

Properly targeted and individualized therapy enables the greatest possible use of the possibilities inherent in the child and prevents the appearance of secondary symptoms [5].

### **Changes in the skeletal system**

The most important changes in the skeletal system, occurring as a result of exposure to alcohol in intrauterine life, in addition to the most frequently mentioned growth inhibition, include:

- syndactyl (the arcuate of the fifth finger) and shortening of the fifth finger in hands and feet),
- hypoplastic nails
- scoliosis,
- Klipp - Feil syndrome - flattening or anastomosis of two (or more) cervical vertebrae in the form of a block,
- dust or funnel-shaped chest,
- changed construction of joints,
- radial-elbow adhesions limiting the range of movement in the elbows [5].

### **FAS diagnosis**

The complete medical and psychological documentation is an indispensable tool for making accurate diagnosis. Another very important stage enabling recognition are evaluations assessing the level of functioning of the senses [7]. Full and comprehensive neurodevelopmental examination consists of:

- an interview covering the period of pregnancy and childbirth, full history of the disease,
- general medical examination,
- child developmental interview,
- assessment of the characteristic face phenotype,
- psychological examination, which consists of texts defining opportunities and developmental losses,
- examination of motor functions and adaptive abilities,
- study of speech advancement, assessment of reasoning and communication [7].

Over the past three decades, several diagnostic criteria have been formulated, among others, by Clarren and Smith, as well as the Group of Researchers on the Fetal Alcohol Syndrome at the Alcoholism Society, a team working at the Institute of Medicine (Institute of Medicine, IOM) [12]. The 4-Digit Diagnostic Code was presented by researchers from the Washington State FAS Diagnostic and Prevention Network in 1997. It is a diagnostic method used to comprehensively diagnose the spectrum of developmental disorders associated with prenatal alcohol exposure. It is more accurate and more reproducible than the previous scales [12]. It contains 4 levels related to four key characteristics of FAS:

1. delay of growth,
2. presence of characteristic dysmorphic features,
3. damage to the central nervous system,
4. prenatal alcohol exposure [12].

At each level, the intensity of expression of features is assessed using a four-level Likert scale (1 point means the total absence of FAS features, and 4 points "classic"). In 2004, the scale was updated. It is widely used in the Washington State FAS Diagnostic & Prevention Network [12].

### **Psychological tests**

In order to diagnose FAS (FASD), and thus to determine the neuropsychological and social problems of ill children, many psychological tests are used.

The WISC-R test (Wechsler Intelligence Scale) is the most commonly used and until recently the only test. It is used to examine the general IQ (IQ) and to determine the current cognitive functioning. It also allows the diagnosis of individual talents and intellectual abilities as well as negligence or spheres of cognitive functioning at a low level. In total, it gives the opportunity to determine the areas in which the child's development should be stimulated. It consists of the scale of verbal abilities and the scale of performance abilities. Each of them is built of subscales. For example, the verbal scales build elements: messages, repeating numbers, dictionary, arithmetic, understanding and similarities [22].

### **Summary**

In Poland, alcohol consumption increased from 3 liters of pure alcohol per capita in 1950, to 9.3 liters of alcohol per capita in 2007 [23]. The age of alcohol initiation is also steadily decreasing (currently it is between 12 and 15 years of age), and the number of unplanned pregnancies among teenagers is increasing [23].

At the same time, there is a noticeable increase in the interest in various fields and scientific disciplines of the physical, mental and social condition of children from families with an alcohol-related problem. The interest of the society in the influence of alcohol on the occurrence of various pathologies in offspring is also growing. Alcohol and drugs, X-rays, is a

teratogenic factor playing an important role in the pathogenesis of fetal developmental disorders, and then - a newborn and a child in the future [23].

Excessive regular drinking of alcohol disrupts the functioning of the kidneys and weakens their filtering qualities, maintaining an optimal balance of fluids and proteins in the body, dehydrating and de-salting the body, exacerbates kidney diseases. Very frequent Proteinuria. The filtration ability of the glomeruli of the kidneys, the glomerular filtration rate is disturbed, the tender renal cells are destroyed, and renal dystrophy, glomerulonephritis and renal hydronephrosis gradually develop [24-52].

Responsibility for the occurrence of FAS lies entirely with the mother of a sick child, because it can be completely prevented from occurring by stopping drinking alcohol (total abandonment even of the smallest glass of wine) while pregnant [16]. According to the public, there is still a belief that a "glass" of wine will not hurt, and on the Internet, you can still find recommendations and information to promote the consumption of small amounts of alcohol by pregnant women.

Another very important fact is the frequency of birth of children with FAS. They are born relatively often; in Poland, 1-3 children are born with FAS per 1,000 births [12], while the incidence rate of Down Syndrome is 1 in 660/800 births [3]. The indicator applies only to children who have been diagnosed, however, the nomenclature emphasizes the problem of incorrectly diagnosed ADHD or Asperger syndromes or the diagnosis of Fetal Alcohol Syndrome among adolescents, which is very late.

## Literature

1. Banach M.: *Alkoholowy Zespół Płodowy. Teoria. Diagnoza. Praktyka*, wyd. WAM, Kraków, 2011.
2. Czech E., Hartleb M.: Poalkoholowe uszkodzenia płodu jako niedoceniana przyczyna wad rozwojowych i zaburzeń neurobehawioralnych u dzieci, [w:] *Alkoholizm i Narkomania*, Tom 17, nr ½.
3. Klecka M.: Raczone alkoholem w łonie matki, [w:] *Magazyn pielęgniarstwa i położnej*, nr 7-8, 2008.
4. Liszcz K.: *Dziecko z FAS w szkole i w domu*, wyd. Rubikon, Kraków, 2011.
5. Ślósarska M.: *Alkohol a zdrowie. Uszkodzenia płodu wywołane alkoholem*, wyd. Państwowa Agencja Rozwiązywania Problemów Alkoholowych, Warszawa, 1998.
6. Klecka M., Janas-Kozik M.: *Dziecko z FASD. Rozpoznanie różnicowe i podstawy terapii*, wyd. Państwowa Agencja Rozwiązywania Problemów Alkoholowych, Warszawa, 2009.
7. Klecka M.: *Ciąża a alkohol. W trosce o dziecko z FAS*, wyd. Edukacyjne PARPAMEDIA, Warszawa, 2013.
8. Landgraf M. N., Nothacker M., Kopp I., Heinen F.: Rozpoznawanie płodowego zespołu alkoholowego, [w:] *Medycyna Praktyczna. Pediatria*, nr 2 (92), 2014.
9. Sawaściuk E.: Z FAS-trygowane dzieci, [w:] *Charaktery. Magazyn Psychologiczny*, nr 8 (127), 2007.
10. Jacobson S. W.: Ocena skutków działania alkoholu wypijanego przez matkę w czasie ciąży i po urodzeniu dziecka, [w:] *Alkohol a zdrowie. Badania nad dziećmi alkoholików*, Zbucka L., wyd. Państwowa Agencja Rozwiązywania Problemów Alkoholowych, Warszawa, 2000.
11. Klecka M.: *Objawy i wczesne rozpoznanie FAS*, [w:] *Niebieska Linia*, nr 3 (44), 2006.
12. Klecka M., Janas-Kozik M., Krupka-Matuszczyk I.: Rozwój diagnostyki poalkoholowego spektrum zaburzeń rozwojowych, [w:] *Psychiatria i Psychologia Kliniczna*, nr 4 (10), vol. 10, 2010.
13. Komorowska M.: Diagnoza FAS w praktyce, [w:] *Remedium*, nr 11 (177), 2007.

14. Cierpiałkowska L.: Modele i programy terapii jednostki i rodziny z zaburzeniami spowodowanymi używaniem alkoholu, [w:] *Psychologia uzależnień – alkoholizm*, Cierpiałkowska L., Ziarko M., wyd. Wydawnictwa Akademickie i Profesjonalne, Warszawa, 2010.
15. Klecka M.: *FAScynujące dzieci*, wyd. Św. Stanisława BM Archidiecezji Krakowskiej, Kraków, 2007.
16. Sochocka L., Wojtal M., Wróblewska I., Wojtyłko A.: FAS – problem zdrowotny, z którego się nie wyrasta, [w:] *Pielęgnacyjne i kliniczne aspekty opieki nad chorym*, Steciwko A., Wojtal M., Żurawicka D., wyd. Continuo, Wrocław, 2011, Tom 4.
17. Łuczak I.: Żurawicka D., Zimnowoda M.: Alkohol, nikotyna i narkotyki w ciąży – analiza skutków, [w:] *Pielęgnacyjne i kliniczne aspekty opieki nad chorym*, Steciwko A., Wojtal M., Żurawicka D., wyd. Continuo, Wrocław, 2009, Tom 2.
18. Larkby C., Day N.: Skutki działania alkoholu na płód, [w:] *Alkohol a zdrowie. Badania nad dziećmi alkoholików*, Zbucka L., wyd. Państwowa Agencja Rozwiązywania Problemów Alkoholowych, Warszawa, 2000.
19. Lex B. W.: Nadużywanie alkoholu i innych substancji uzależniających przez kobiety, [w:] *Alkohol a zdrowie. Kobiety i alkohol*, Ślósarska M., wyd. Państwowa Agencja Rozwiązywania Problemów Alkoholowych, Warszawa, 1997.
20. Lis M.: Zdążyć przed FAS, [w:] *Wychowawca*, nr 10 (225), 2011.
21. Komorowska M.: Uszkodzenia mózgu u dzieci z FASD, [w:] *Remedium*, nr 12 (178), 2007.
22. Jadczyk-Szumilo T.: *Neuropsychologiczny profil dziecka z FASD. Studium przypadku*, wyd. Edukacyjne PARPAMEDIA, Warszawa, 2008.
23. Kowalczykiewicz-Kuta A.: Wpływ alkoholu na rozwój dzieci, [w:] *Pielęgnacyjne i kliniczne aspekty opieki nad chorym*, Steciwko A., Wojtal M., Żurawicka D., wyd. Continuo, Wrocław, 2012, Tom 5.
24. Долوماتов СИ, Гоженко АИ, Москаленко ТЯ, Реутов ВП, Долomatova ЕА. Влияние аскорбиновой кислоты на почечный транспорт эндогенных нитратов и нитритов у человека. Экспериментальная и клиническая фармакология. 2005; 68 (1): 50-52. = Dolomatov SI, Gozhenko AI, Moskalenko TJa, Reutov VP, Dolomatova EA. Vlijanie askorbinovoj kisloty na pochechnyj transport jendogennyh nitratov i nitritov u cheloveka. Jeksperimental'naja i klinicheskaja farmakologija. 2005; 68 (1): 50-52. = Dolomatov SI, Gozhenko AI, Moskalenko TY, Reutov VP, Dolomatova EA. [Effect of ascorbic acid on renal transport of endogenous nitrates and nitrites in humans]. Jeksperimental'naja i klinicheskaja farmakologija. 2005; 68 (1): 50-52. [in Russian].
25. Гоженко АИ, Доренский ВС, Рудина ЕИ, Распутняк Г, Котюжинская Г, Котюжинский АЛ, Славина НГ. Причины и механизмы интоксикации нитратами и нитритами. Медицина труда и промышленная экология. 1996; 4: 15-20. = Gozhenko AI, Dorenskij VS, Rudina EI, Rasputnjak G, Kotjuzhinskaja G, Kotjuzhinskij AL, Slavina NG. Prichiny i mehanizmy intoksikacii nitratami i nitritami. Medicina truda i promyshlennaja jekologija. 1996; 4: 15-20. = Gozhenko AI, Dorenskiy VS, Rudina YeI, Rasputnyak G, Kotyuzhinskaya G, Kotyuzhinsky AL, Slavina NG. [Causes and mechanisms of intoxication with nitrates and nitrites]. Medicina truda i promyshlennaja jekologija. 1996; 4: 15-20. [in Russian].
26. Попович ІЛ. Факторний і канонікальний аналізи параметрів нейро-ендокринно-імунного комплексу, метаболізму та ерозивно-виразкових пошкоджень слизової шлунку у щурів за умов гострого водно-імерсійного стресу. Медична гідрологія та реабілітація. 2007. = Popovych IL. Faktornyj i kanonikal"nyj analizu parametriv nejro-endokrynno-imunnoho kompleksu, metabolizmu ta erozyvno-vyrazkovyx poshkodzhen" slyzovoyi shlunku u shhuriv za umov hostroho vodno-imersijnoho stresu. Medychna hidrolohiya ta rehabilitaciya. 2007. = Popovych IL. [Factor and canonical analysis

- parameters of neuro-endocrine-immune complex, metabolism and erosive and ulcerative injuries of stomach mucosa in rats under acute water-immersion stress]. Popovych IL. Medychna hidrolohiya ta reabilitaciya. 2007. [in Ukrainian].
27. Чебаненко ОІ, Чебаненко ЛО, Попович ІЛ. Поліваріантність бальнеоефектив чинників курорту Трускавець та їх прогнозування. К. ЮНЕСКО-СОЦІО. 2012. = Chebanenko OI, Chebanenko LO, Popovych IL. Polivariantnist" bal"neofektiv chynnykiv kurortu Truskavec" ta yix prohnozuvannya. K. YuNESKO-SOCIO. 2012. = Chebanenko OI, Chebanenko LO, Popovych IL. [Multivariate Balneoeffects of Factors of Spa Truskavets' and Forecasting]. Kyiv. UNESCO-SOCIO. 2012. [in Ukrainian].
  28. Kostyuk PG, Popovych IL, Ivassivka SV, Chebanenko LO, Kyenko VM (editors). Chornobyl', Adaptive and Defensive systems, Rehabilitation. Rehabilitation. Kyiv. Computerpress. 2006. 348 p. = Kostyuk PG, Popovych IL, Ivassivka SV, Chebanenko LO, Kyenko VM (editors). [Chornobyl', Adaptive and Defensive systems, Rehabilitation. Rehabilitation]. Kyiv. Computerpress. 2006. 348 p.
  29. Гоженко АІ. Роль оксиду азоту в молекулярно клітинних механізмах функції нирок. Український біохімічний журнал. 2002; 74 (4a): 96. = Hozhenko AI. Rol' oksydu azotu v molekulyarno klitynnux mexanizmax funkciyi nyrok. Ukrayins"kyj bioximichnyj zhurnal. 2002; 74 (4a): 96. = Gozhenko AI. [Role of nitric oxide in molecular cellular mechanisms of renal function]. Ukrayins"kyj bioximichnyj zhurnal. 2002; 74 (4a): 96. [in Ukrainian].
  30. Гоженко АИ, Долوماتов СИ, Шумилова ПА, Топор ЕА, Пятенко ВА, Бад'ин ИЮ. Влияние осмотических нагрузок на функциональное состояние почек здоровых людей. Нефрология. 2004;8(2): 44-48 = Gozhenko AI, Dolomatov SI, Shumilova PA, Topor EA, Pjatenko VA, Bad'in IJu. Vlijanie osmoticheskikh nagruzok na funkcional'noe sostojanie pochek zdorovyh ljudej. Nefrologija. 2004;8(2): 44-48 = Gozenko AI, Dolomatov SI, Shumilova PA, Topor EA, Pyatenko VA, Badin IY. [The effect of osmotic stresses on the functional state of healthy kidneys]. Nefrologija. 2004;8(2): 44-48. [in Russian].
  31. Реутов, В. П.; Гоженко, Е. А.; Охотин, В. Е.; Котюжинская, С. Г.; Шуклин, А. В.; Сорокина, Е. Г. Роль оксида азота в регуляции работы миокарда цикл оксида азота и NO-синтазные системы в миокарде. Актуальные проблемы транспортной медицины. 2007; 4(10): 89-112 = Reutov, V. P.; Gozhenko, E. A.; Ohotin, V. E.; Kotjuzhinskaja, S. G.; Shuklin, A. V.; Sorokina, E. G. Rol' oksida azota v reguljaciji raboty miokarda cikl oksida azota i NO-sintaznye sistemy v miokarde. Aktual"nye problemy transportnoj medicyny. 2007; 4(10): 89-112 = Reutov, V. P.; Gozhenko, A. I.; Okhotin, V. E.; Kotuzhinskaya, S. G.; Shuklin, A. V.; Sorokina, E. G. [Role of nitrogen oxide in myocardium work adjusting. Cycle of nitrogen oxide and NO-synthetase systems in myocardium]. Aktual"nye problemy transportnoj medicyny. 2007; 4(10): 89-112. [in Russian].
  32. Гоженко АИ, Долوماتов СИ, Романив ЛВ, Долomatова ЕА. Возрастные особенности осморегулирующей функции почек белых крыс. Нефрология. 2003; 7(2): 82-85 = Gozhenko AI, Dolomatov SI, Romaniv LV, Dolomatova EA. Vozrastnye osobennosti osmoregulirujushhej funkcii pochek belyh krys. Nefrologija. 2003; 7(2): 82-85 = Gozhenko, A. I., Dolomatov, S. I., Romaniv, L. V. [Age peculiarities of the liver osmoregulating function in white rats]. Nefrologija. 2003; 7(2): 82-85. [in Russian].
  33. Гоженко АИ, Федорук АС, Котюжинская СГ. Изменение функции почек при острой интоксикации нитритом натрия в эксперименте. Патологическая физиология и экспериментальная терапия. 2003; 1: 28-30. = Gozhenko AI, Fedoruk AS, Kotjuzhinskaja SG. Izmenenie funkcii pochek pri ostroj intoksikacii nitritom natrija v jeksperimente. Patologicheskaja fiziologija i jeksperimental'naja terapija. 2003; 1: 28-30. = Gozhenko AI, Fedoruk AS, Kotyuzhinskaya SG. [Changes in renal function during

- acute intoxication with sodium nitrite in the experiment]. *Patologicheskaja fiziologija i jeksperimental'naja terapija*. 2003; 1: 28-30. [in Russian].
34. Гоженко АИ, Бабий ВП, Котюжинская СГ, Николаевская ИВ. Роль оксида азота в механизмах воспаления. *Экспериментальная и клиническая медицина*. 2001; (3): 13-17. = Gozhenko AI, Babij VP, Kotjuzhinskaja SG, Nikolaevskaja IV. Rol' oksida azota v mehanizmah vospaleniya. *Jeksperimental'naja i klinicheskaja medicina*. 2001; (3): 13-17. = Gozhenko AI, Babij VP, Kotyuzhinskaya SG, Nikolaev IV. [The role of nitric oxide in the mechanisms of inflammation]. *Jeksperimental'naja i klinicheskaja medicina*. 2001; (3): 13-17. [in Russian].
  35. Федорчук АС, Гоженко АИ, Роговый ЮЕ. Защитное воздействие  $\alpha$ -токоферола на функцию почек и перекисное окисление липидов при острой гемической гипоксии. *Патол. физиол. и эксперим. терапия*. 1998; (4): 35-38. = Fedorchuk AS, Gozhenko AI, Rogovyj JuE. Zashhitnoe vozdejstvie  $\alpha$ -tokoferola na funkciju pochek i perekisnoe okislenie lipidov pri ostroj gemicheskoy gipoksii. *Patol. fiziol. i jeksperim. terapija*. 1998; (4): 35-38. = Fedorchuk AS, Gozhenko AI, Rohovyi YU. [Protective effect of  $\alpha$ -tocopherol on kidney function and lipid peroxidation in acute hemic hypoxia]. *Patol. fiziol. i jeksperim. Terapija*. 1998; (4): 35-8. [in Russian].
  36. Филипец НД, Гоженко АИ. Сравнительная оценка нефропротекторных свойств модуляторов калиевых и кальциевых каналов при экспериментальном поражении почек. *Экспериментальная и клиническая фармакология*. 2014; 77(1): 10-12. = Filipec ND, Gozhenko AI. Sravnitel'naja ocenka nefroprotektornyh svojstv moduljatorov kalievyh i kal'cievyh kanalov pri jeksperimental'nom porazhenii pochek. *Jeksperimental'naja i klinicheskaja farmakologija*. 2014; 77(1): 10-12. = Filipets ND, Gozhenko AI. [Comparative evaluation of the nephroprotective properties of potassium and calcium channel modulators with experimental kidney damage]. *Jeksperimental'naja i klinicheskaja farmakologija*. 2014; 77(1): 10-12. [in Russian].
  37. Гоженко АИ. Функціональний нирковий резерв: Монографія. Одеса. Фенікс. 2015. = Hozhenko AI. Funkcional'nyj nyrkovyj rezerv: Monohrafiya. Odesa. Feniks. 2015. = Gozhenko AI. [Functional renal reserve]. Monograph. Odesa. Feniks. 2015. [in Ukrainian].
  38. Гоженко АИ, Карчаускас ВЮ, Доломатов СИ. Влияние водной и гиперосмотической нагрузок на клиренс креатинина при экспериментальной нефропатии, вызванной хлоридом ртути. *Нефрология*. 2002; 6(3): 72-74. = Gozhenko AI, Karchauskas VJu, Dolomatov SI. Vlijanie vodnoj i giperosmoticheskoy nagruzok na klirens kreatinina pri jeksperimental'noj nefropatii, vyzvannoj hloridom rtuti. *Nefrologija*. 2002; 6(3): 72-74. = Gozhenko AI, Karchauskas Vu, Dolomatov SI. [Effect of water and hyperosmotic loads on creatinine clearance in experimental nephropathy caused by mercury chloride]. *Nefrologija*. 2002; 6(3): 72-74. [in Russian].
  39. Гоженко АИ, Филипец НД. Нефротропные эффекты при активации аденозинтрифосфатчувствительных калиевых каналов в зависимости от функционального состояния почек крыс. *Нефрология*. 2013; 17(2): 87-90. = Gozhenko AI, Filipec ND. Nefrotropnye jeffekty pri aktivacii adenzintri-fosfatchuvstvitel'nyh kalievyh kanalov v zavisimosti ot funkcional'nogo sostojanija pochek krysv. *Nefrologija*. 2013; 17(2): 87-90. = Gozhenko AI, Filipets ND. [Nephrotropic effects upon activation of adenosine triphosphate-sensitive potassium channels, depending on the functional state of the kidneys of rats]. *Nefrologija*. 2013; 17(2): 87-90. [in Russian].
  40. Гоженко АИ. Функціональний стан нирок при хронічній блокаді синтезу оксиду азоту в щурів. *Медична хімія*. 2002; 4(4): 65-68. = Hozhenko AI. Funkcional'nyj stan nyrok pry khronichnij blokadi syntezy oksydu azotu v shhuriv. *Medychna ximiya*. 2002; 4(4): 65-68. = Gozhenko AI. [Functional state of the kidneys in chronic blockade of nitric oxide synthesis in rats]. *Medychna ximiya*. 2002; 4(4): 65-68. [in Ukrainian].

41. Гоженко АИ, Лебедева ТЛ, Бадюк НС. Физиологические основы гигиенического нормирования солевого состава питьевых режимов человека (сообщение первое). Вода: гигиена и экология. 2013 ; 3-4(1): 6-11. = Gozhenko AI, Lebedeva TL, Badjuk NS. Fiziologicheskie osnovy gigienicheskogo normirovaniya solevogo sostava pit'evykh rezhimov cheloveka (soobshhenie pervoe). Voda: gigiena i jekologija. 2013 ; 3-4(1): 6-11. = Gozhenko AI, Lebedev TL, Badyuk NS. [The physiological basis of the hygienic regulation of the salt composition of drinking regimes of a person (the first message)]. Voda: gigiena i jekologija. 2013 ; 3-4(1): 6-11. [in Russian].
42. Шафран ЛМ, Мокиенко АВ, Петренко НФ, Гоженко АИ, Насибуллин БА. К обоснованию гормезиса как фундаментальной биомедицинской парадигмы (обзор литературы и результатов собственных исследований). Современные проблемы токсикологии. 2010; 2(3): 13-23. = Shafran LM, Mokienko AV, Petrenko NF, Gozhenko AI, Nasibullin BA. K obosnovaniju gormezisa kak fundamental'noj biomedicinskoj paradigmy (obzor literatury i rezul'tatov sobstvennyh issledovanij). Sovremennye problemy toksikologii. 2010; 2(3): 13-23. = Safran LM, Mokienko AV, Petrenko NF, Gozhenko AI, Nasibullin BA. [To the substantiation of hormesis as a fundamental biomedical paradigm (review of literature and the results of our own research)]. Sovremennye problemy toksikologii. 2010; 2(3): 13-23. [in Russian].
43. Хамініч АВ, Гоженко АІ, Романів ЛВ, Лебедева ТЛ, Жуков ВА. Функціональний стан нирок в умовах спонтанного та індукованого діурезу у нефрологічно здорових осіб. Вісник морської медицини. 2008; (3-4): 70-75. = Xaminich AV, Hozhenko AI, Romaniv LV, Lyebyedyeva TL, Zhukov VA. Funkcional"nyj stan nyrok v umovax spontannoho ta indukovanoho diurezu u nefrolohichno zdorovyx osib. Visnyk mors"koji medycyny. 2008; (3-4): 70-75. = Khaminich AV, Gozhenko AI, Romanov LV, Lebedev TL, Zhukov VA. [Functional state of the kidneys under conditions of spontaneous and induced diuresis in nephrologically healthy persons]. Visnyk mors"koji medycyny. 2008; (3-4): 70-75. [in Ukrainian].
44. Гоженко АИ, Зубкова ЛП, Доломатов СИ. Возрастные особенности регуляции минерального обмена у человека. Нефрология. 2002; 6(3). 60-63. = Gozhenko AI, Zubkova LP, Dolomatov SI. Vozrastnye osobennosti reguljaccii mineral'nogo obmena u cheloveka. Nefrologija. 2002; 6(3). 60-63. = Gozhenko AI, Zubkov LP, Dolomatov SI. [Age-related regulation of mineral metabolism in humans]. Nefrolohyya. 2002; 6(3). 60-63. [in Russian].
45. Гоженко АИ, Федорук ОС, Погоріла ІВ. Вплив аргініну на функціональний стан нирок щурів при сулемовій нефропатії. Фізіологічний журнал. 2002; 48(6): 26-30. = Hozhenko AI, Fedoruk OS, Pohorila IV. Vplyv arhininu na funkcional"nyj stan nyrok shhuriv pry sulemovij nefropatiji. Fiziolohichnyj zhurnal. 2002; 48(6): 26-30. = Gozhenko AI, Fedoruk OS, Pogorila IV. [Influence of arginine on the functional state of kidney of rats during sulfate nephropathy]. Fiziolohichnyj zhurnal. 2002; 48(6): 26-30. [in Ukrainian].
46. Гоженко АИ, Славина ИГ, Катюжинская СГ. Методика определения нитрит-нитратной экологической нагрузки на организм человека. Медицина труда и промышленная экология. 2001; (3): 38-39. = Gozhenko AI, Slavina IG, Katjuzhinskaja SG. Metodika opredelenija nitrit-nitratnoj jekologicheskoj nagruzki na organizm cheloveka. Medicina truda i promyshlennaja jekologija. 2001; (3): 38-39. = Gozhenko AI, Slavina IG, Katyuzhinskaya SG. [The method of determining the nitrite-nitrate environmental load on the human body]. Medicina truda i promyshlennaja jekologija. 2001; (3): 38-39. [in Russian].
47. Gozhenko AI, Sydoruk NO, Babelyuk VY, Dubkova GI, Flyunt VR, Hubyts'kyi VY, Zukow W, Barylyak LG, Popovych IL. Modulating effects of bioactive water Naftussya from layers Truskavets' and Pomyarky on some metabolic and biophysic parameters at humans with dysfunction of neuro-endocrine-immune complex. Journal of Education, Health and Sport. 2016; 6(12): 826-842.

48. Kul'chyns'kyi AB, Kovbasnyuk MM, Korolyshyn TA, Kyjenko VM, Zukow W, Popovych IL. Neuro-immune relationships at patients with chronic pyelonephrite and cholecystite. Communication 2. Correlations between parameters EEG, HRV and Phagocytosis. Journal of Education, Health and Sport. 2016; 6(10): 377-401.
49. Билецкий, С.В., Гоженко, А.И. Гипоксически-гиперкапнические тренировки в кардиологии. Черновцы. 2007. = Bileckij, S.V., Gozhenko, A.I. Gipoksicheski-giperkapnicheskie trenirovki v kardiologii. Chernovcy. 2007. = Bileckij, S.V., Gozhenko, A.I. [Hypoxic-hypercapnic exercises in cardiology]. Chernovcy. 2007. [in Russian].
50. Гоженко АИ. Патопфизиология почек: от эксперимента к клинике. Актовая речь на торжественном заседании ученого совета Украинского НИИ медицины транспорта 16.02. 2013. Одесса. 2013. 32 с. = Gozhenko AI. Patofiziologija pochek: ot jeksperimenta k klinike. Aktovaja rech' na torzhestvennom zasedanii uchenogo soveta Ukrainskogo NII mediciny transporta 16.02. 2013. Odessa. 2013. 32 s. = Gozhenko AI. [Pathophysiology of the kidneys: from experiment to clinic]. Acting speech at the ceremonial meeting of the Scientific Council of the Ukrainian Research Institute of Medicine of Transport 16.02. 2013. Odessa. 2013. 32 p. [in Russian].
51. Dolgova E, Kurushin D, Fayzrahmanov R, Gozhenko A, Prokhorov V, Zukow W. About use of neural network models to evaluate the trainee's actions on training complexes complex systems. Journal of Health Sciences. 2012; 2(6): 55-63.
52. Гоженко АИ. Патогенез токсических нефропатий. Актуальные проблемы транспортной медицины. 2006; 2(4): 9-15. = Gozhenko AI. Patogenez toksicheskikh nefropatij. Aktual'nye problemy transportnoj mediciny. 2006; 2(4): 9-15. = Gozhenko AI. [Pathogenesis of toxic nephropathy]. Aktual'nye problemy transportnoj mediciny. 2006; 2(4): 9-15. [in Russian].