Assessment of the iodine deficiency severity in the population by serum thyrotropin levels in newborns

T. V. Sorokman[®]*A-F, M. I. Bachu^{®B,C,D}, O. V. Makarova^{®B,C}, N. O. Popeliuk^{®C,E}

Bukovinian State Medical University, Chernivtsi, Ukraine

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*F-mail: t.sorokman@gmail.com The problem of iodine deficiency (ID) and its adverse effects on the Ukrainian population, especially on children, pregnant and lactating women, does not lose its relevance.

The aim. To assess the state of iodine status of the Northern Bukovina population by the level of thyrotropin (TSH) in newborns during the years 2015-2020.

Methods. Selective screening analysis to determine the serum level of TSH in newborns during 2015–2020 (a total of 47888 results), median ioduria and survey among pregnant women, determination of urinary iodine, ultrasonographic and hormonal profiles of 199 prepubertal children living in Northern Bukovina were performed.

Results. During the analyzed period, there was a positive trend: the median ioduria in pregnant women increased from 89.8 µg/l in 2015 to 140.1 µg/l in 2020, the level of neonatal hyperthyrotropinemia above 5 µIU/l decreased to 5 % in 2020 (P < 0.001), there was an upward trend in the median ioduria among prepubertal children (60.4 ± 9.3 µg/l). The frequency of goiter was different and accounted for 25.3 % among children living in the mountainous area and it was much lower among children living in the plain areas and in Chernivtsi (15.6 % and 13.1 %, respectively, P < 0.05). Thyromegaly among children of the reference group occurred in 15.1 %. 12.3 % of children were characterized by TSH in the range of age standards, which were shifted towards its increase (4.23-5.00 µIU/I).

Conclusions. The increase in the median ioduria and the decrease in the frequency of neonatal hyperthyrotropinemia above 5 µIU/I on the background of iodine supply has been found in the pregnant population. The indicator of neonatal hyperthyrotropinemia above 5 µIU/I can be used to assess iodine deficiency only in the population of pregnant women.

Ключові слова:

вагітні. новонароджені, діти, йод, тиреотропний гормон, зоб.

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Оцінювання тяжкості йодної недостатності в популяції за рівнем тиреотропного гормона у крові новонароджених

Т. В. Сорокман, М. І. Бачу, О. В. Макарова, Н. О. Попелюк

Проблема йодного дефіциту (ЙД) і його несприятливих наслідків для населення України, особливо для дітей, вагітних і жінок, які годують, не втрачає актуальності.

Мета роботи - оцінити стан йодного забезпечення населення Північної Буковини за рівнем тиреотропного гормона у крові новонароджених упродовж 2015-2020 рр.

Матеріали та методи. Здійснили аналіз селективного скринінгу з визначенням рівня тиреотропного гормона (ТТГ) у крові новонароджених протягом 2015–2020 рр. (загалом 47 888 результатів), медіани йодурії у вагітних жінок, а також анкетування, ультрасонографічне та гормонометричне дослідження 199 дітей передпубертатного віку, які проживають на території Північної Буковини.

Результати. Протягом аналізованого періоду спостерігали позитивну динаміку: медіана йодурії у вагітних жінок зросла з 89,8 мкг/л у 2015 р. до 140,1 мкг/л у 2020 р., рівень неонатальної гіпертиреотропінемії понад 5 мкОД/л знизився до 5 % у 2020 р. (р < 0.001); виявили тенденцію до підвищення медіани йодурії в дітей передпубертатного віку (60,4 ± 9,3 мкг/л). Частота зоба різна та становить 25,3 % у дітей, які проживають у гірській зоні; значно нижча частота зоба в дітей, які живуть на рівнинній зоні та в м. Чернівцях, — 15,6 % і 13,1 % відповідно, р < 0,05. Тиреомегалія в дітей референтної групи зафіксована в 15,1 % випадків. У 12,3 % дітей показники ТТГ відповідають віковій нормі, зміщені в бік підвищення (4,23-5,00 мкОД/л).

Висновки. Встановили підвищення показників медіани йодурії у вагітних і зниження частоти неонатальної гіпертиреотропінемії понад 5 мкМО/л на тлі забезпечення йодом популяції вагітних. Індикатор неонатальної гіпертиреотропінемії понад 5 мкМО/л можна використовувати для оцінювання йододефіциту тільки у вагітних жінок.

Оценка тяжести йодной недостаточности в популяции по уровню тиреотропного гормона в крови новорожденных

Т. В. Сорокман, М. И. Бачу, Е. В. Макарова, Н. А. Попелюк

Проблема йодного дефицита (ЙД) и его неблагоприятных последствий для населения Украины, особенно для детей, беременных и кормящих женщин, не теряет актуальности.

Цель работы – оценить состояние йодного обеспечения населения Северной Буковины по уровню тиреотропного гормона в крови новорожденных в течение 2015-2020 гг.

Материалы и методы. Проведен анализ селективного скрининга с определением уровня тиреотропного гормона (ТТГ) в крови новорожденных детей на протяжении 2015–2020 гг. (всего 47 888 результатов), медианы йодурии у беременных женщин, а также анкетирование, ультрасонографическое и гормонометрическое исследование 199 детей препубертатного возраста, проживающих на территории Северной Буковины.

Результаты. В течение анализируемого периода наблюдали положительную динамику: медиана экскреции йода у беременных женщин выросла с 89,8 мкг/л в 2015 г. до 140,1 мкг/л в 2020 г., уровень неонатальной гипертиреотропинемии выше 5 МКОД/л снизился до 5 % в 2020 г. (р < 0,001); отмечена тенденция к повышению медианы йодурии у детей препубертатного возраста (60.4 ± 9.3 мкг/л). Частота зоба разная и составляет 25.3 % у детей, проживающих в горной зоне; значительно ниже частота зоба у детей, проживающих на равнинной зоне и в г. Черновцы, -15,6 % и 13,1 % соответственно, р < 0,05. Тиреомегалия у детей референтной группы диагностирована в 15,1 % случаев. У 12,3 % детей показатели ТТГ отвечают возрастной норме, смещены в сторону его повышения (4,23-5,00 МКОД/л).

Выводы. Установлено повышение показателей медианы йодурии у беременных и снижение частоты неонатальной гипертиреотропинемии выше 5 мкМО/л на фоне обеспечения йодом популяции беременных. Индикатор неонатальной гипертиреотропинемии выше 5 мкМО/л можно использовать для оценки йододефицита только у беременных женщин.

The problem of iodine deficiency (ID) and its adverse effects on the Ukrainian population, especially on children, adolescents, pregnant and lactating women, is still relevant [1]. lodine is an important micronutrient necessary for the normal functioning of the thyroid gland, growth and development. Sub-optimal iodine intake causes inadequate secretion of thyroid hormones, which leads to a spectrum of adverse outcomes, collectively referred to as iodine deficiency disorders (IDD) [2]. The most detrimental effects of IDD are observed in the antenatal period and during the first two years of life [3]. Severe iodine deficiency during this period increases the risk of stillbirth, birth defects, perinatal and infant mortality and impairs physical and cognitive development. Brain damage to the fetus and young children is often irreversible, causing mental retardation and reduced school performance [4]. The term IDD was introduced by the World Health Organization (WHO) in 1983. It has become clear that iodine deficiency causes not only thyroid disease, but also many other disorders caused by lack of thyroid regulation [5]. lodine deficiency in the environment has been reported in large areas of the earth [6,7]. The iodine deficient territories in the world are in all continents [8-11]. In 1985, the International Council for the Control of Iodine Deficiency Diseases (ICCIDD) was established, which works closely with the WHO and the UNICEF. In 1990, IDD was recognized as an important medical and social problem in 118 countries (WHO/UNICEF/ICCIDD), and a historic resolution called for the elimination of iodine deficiency as a public health problem by 2000 [8]. To eliminate the iodine deficiency in Ukraine, the orders of the Ministry of Health of Ukraine No. 58 dated May 24, 2001 "On introduction of priority measures to overcome iodine deficiency in the population of Ukraine" and No. 67 dated October 25 of the same year "On additional measures to overcome iodine deficiency in the population of Ukraine", and the resolution of the Cabinet of Ministers of Ukraine dated September 26, 2002 "About the statement of the State Program for prevention of iodine insufficiency in the population during 2002–2005" were issued [9]. An important area of this program was the need to monitor iodine supply in all regions of Ukraine. A study on urinary iodine excretion showed generally low degree of iodine deficiency (median ioduria – 90.1 µg/l) in Ukraine between 2002-2003 [10]. However, significant differences were found for various clusters (settlements). In particular, the region of Northern Bukovina, which is

Ключевые слова:

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geographically divided into plain and mountainous zones, belongs to the areas with mild (plain zone) and medium (mountainous zone) degree of iodine deficiency. A largescale national study of iodine deficiency in 2001-2003. which covered all regions of Ukraine, found that there have been significant positive changes in improving the iodine supply among the population. However, the problem of the prophylactic measures for IDD remains unresolved in Ukraine generally. To date, Ukraine lacks a legal framework for the organization of mass iodine prophylaxis by general iodization of table salt, which does not allow achieving a significant reduction in iodine deficiency diseases in children and adults. In recent years, high-risk groups of IDD have been identified (pregnant women, breast-feeding mothers, children of the first two years of life), for whom insufficient iodine intake is especially dangerous due to the possibility of irreversible brain disorders development in a child. For these categories of the population, additional iodine medication intake is obligatory [11]. Since the child's brain and cognitive functions develop most intensively in the first years after birth, pediatricians should competently plan the tactics of postnatal iodine prophylaxis for all young children without exception. In order to assess the degree of iodine deficiency in new socio-economic conditions in Ukraine, in particular in Northern Bukovina, the problem of iodine supply must be addressed according to the WHO criteria, especially the level of neonatal hyperthyrotropinemia (above 5 µIU/I) and goiter in children groups.

Aim

To assess the state of iodine status of the Northern Bukovina population by the level of thyrotropin (TSH) in newborns during the years 2015–2020.

Materials and methods

An analysis of selective screening to determine the blood level of TSH in newborns during 2015–2020 (a total of 47888 results) was performed. To determine the correlations, the results of medical and biological monitoring during this period were used (frequency of iodine-deficient goitre and median ioduria in prepubertal children). For this purpose, a survey, ultrasonographic and hormonal study among 199 prepubertal children living in Northern Bukovina (100

Table 1. The number of studies to determine the level of in newborns

Indicator	Years						
	2015	2016	2017	2018	2019	2020	
Number of tests (total = 7888)	8401	8990	8600	8111	7102	6684	
% TSH >5 mIU/L	33.4	31.5	18.6	9.2	7.8	5.0	

Table 2. The content of thyrotropin and thyroid hormones in the peripheral blood of prepubertal children

Indicators	Sex				
	Boys (M ± m), n = 68	Girls (M ± m), n = 131			
TSH (mIU/I)	2.23 ± 0.27	3.04 ± 0.15			
T ₃ (nmol/l)	1.55 ± 0.19	1.71 ± 0.16			
T ₄ (mIU/I)	89.04 ± 8.73	95.44 ± 6.73			
T_3/T_4	0.013 ± 0.003	0.014 ± 0.002			
TSH/T ₄	0.023 ± 0.004	0.022 ± 0.005			

children from the zone of mild iodine deficiency and 99 children from the zone of moderate iodine deficiency) were conducted. Inclusion criteria to enroll prepubertal children in the study: residence in Northern Bukovina from birth, prepubertal age, no diseases of the endocrine system, no use of iodine and thyroid hormones. Exclusion criteria from the study: moving to another place of residence, other thyroid diseases.

Determination of TSH levels in newborns was performed on the 4th day using a test kit for quantitative determination of TSH in samples of dry blood spots on filter paper (Neonatal hTSH EIA, 960 wells, Neonatal Card (903 Body Fluid Collection Paper) manufactured by Ani Labsystems Ltd. Oy (Vantaa, Finland). Assessment of the morphofunctional state of the thyroid gland in children before puberty was performed according to the indicators of visual-manual examination and ultrasound examination (USE) on the Scanner - 100 using a linear sensor with a frequency of 7.5 MHz. According to the parameters obtained via USE, the volume of each thyroid lobe was calculated by the formula: maximum thickness /cm/ × width /cm/ × length /cm/ × 0.478 and compared with the recommended standards of thyroid volumes obtained during the examination of children in iodine-supplied regions of Europe, taking into account age, sex and body area.

The functional state of the pituitary-thyroid system was assessed by clinical symptoms using screening integrated tables, as well as standard kits for RIA T₃-"rio-T₃-PG, T₄-"rio-T₄-PG, (Belarus); the concentration of TSH was determined by standard test kits (Mallinckrodt, Germany). Blood sampling for hormonal examination was implemented using venipuncture of the ulnar vein. Sample counting and result processing were performed using an automatic counter with a microprocessor and computer data processing

Taking into account that the concentration of iodine in a single portion of urine is well correlated with the level of iodine in daily urine, we took children urine into test tubes of 5 ml of urine at a time. The iodine concentration was determined by cerium-arsenite method with wet ashing of the samples. Based on the data obtained, the median ioduria was calculated, which was expressed in µg of iodine per 1 liter of urine.

The results obtained were processed by the method of statistical variation and correlation analysis. Statistical

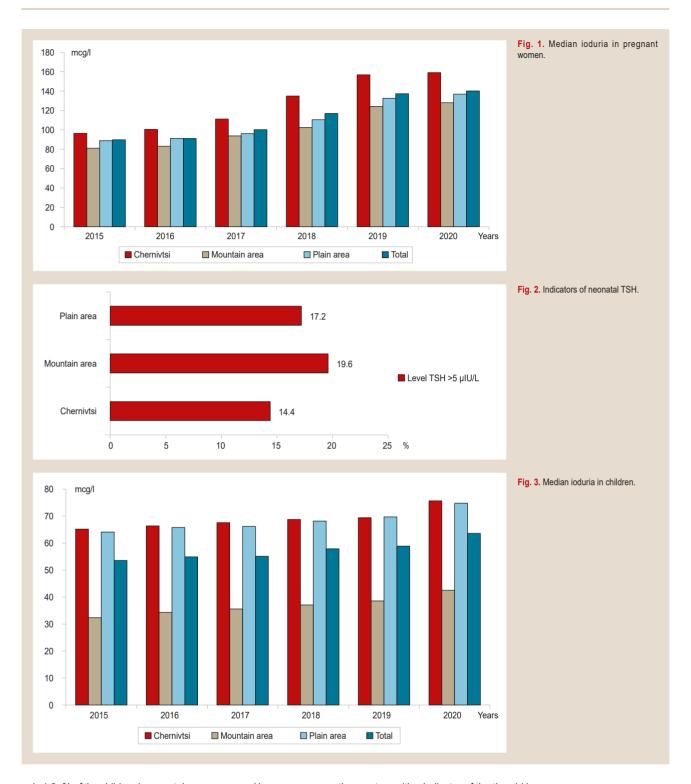
processing included the calculation of the arithmetic mean for each indicator (M), the standard deviation (σ). The statistical significance of the results was evaluated via determining the mean error of the arithmetic mean (m), the significance of differences in the mean values - by t-Studen's test. A computer program "Biostat" was used for statistical processing.

Results

The survey-based results showed that the proportion of families using iodized salt in food was only about 20 % in Ukraine, the prevalence of endemic goiter among schoolchildren remained high and averaged 41 %, reaching 70 % in some regions. In the structure of thyroid pathology in the population of our country, IDD occupied a leading position - 95 % among children. As the main goal of iodine prophylaxis in childhood, the majority (69.4 %) of children chose the prevention of thyroid disease. Only 25 (12.5 %) children correctly indicated the priority task of adequate iodine consumption – prevention of mental deficiency. The study found that the median ioduria in pregnant women did not reach 150 µg/l recommended by the WHO for this population, but during the analyzed period there was a positive trend, as evidenced by the improvement in the median ioduria, which increased from 89.8 µg/l in 2015 to 140.1 μg/l in 2020 (Fig. 1). Determination of TSH levels on the 4th day after birth was performed in 47888 cases (Table 1).

The level of neonatal hyperthyrotropinemia above 5 µIU/I averaged 18.3 %. In the process of screening, there was a statistically significant decrease in the frequency of neonatal TSH above 5 µIU/I to 5 % in 2020 (P < 0.001) characterizing the whole region of Northern Bukovina as the area with mild ID. However, when distributed relative to living in the mountainous or plain area, neonatal TSH levels above 5 µIU/I were distributed as follows (Fig. 2): in the mountainous area, the number of these cases decreased from 38.8 % in 2015 to 19.6 % in 2020, while in the plains - from 32.6 % in 2015 to 17.2 %. Therefore, according to the WHO criteria, these areas belong to the zone with mild iodine deficiency. Since the criteria for the severity of iodine deficiency, defined by the WHO, also include the incidence of goiter and thyromegaly in prepubertal children, we also analyzed these indicators. Determination of the urinary iodine concentration in prepubertal children from different areas of residence showed that in most children, the excretion of iodine in the urine was reduced, but over the past 6 years, there was a tendency to its increase (Fig. 3).

The median ioduria in the examined population as a whole was $60.4 \pm 9.3 \,\mu\text{g/l}$, which according to the WHO criteria indicated the presence of mild iodine deficiency. A more detailed analysis showed that among children living in the plains, 14.2 % had ioduria greater than 100 µg/l, i.e. normal iodine supply, while 4.1 % of children had ioduria less than 20 µg/l corresponding to severe iodine insufficiency. The children living in the plains and the children of Chernivtsi demonstrated a mild iodine deficiency (median ioduria was $68.4 \pm 3.1 \,\mu\text{g/l}$ and $69.1 \pm 1.9 \,\mu\text{g/l}$, respectively), and the children of mountainous areas iodine deficiency of moderate severity (median ioduria was 28.9 ± 1.9 μg/l). loduria greater than 100 μg/l was found in



only 1.9 % of the children in mountainous areas, and lower than 20 μ g/l – in 13.9 %.

The survey findings showed a significant incidence of goiter among children of Bukovina - 17.6 %. In different climatic and geographical zones, the frequency of goiter varied in children living in the mountainous zone (25.3 %) being much lower among children living in the plains and in Chernivtsi (15.6 % and 13.1 %, respectively, P < 0.05). Thyromegaly among children of the reference group occurred in 15.1 %.

As the main characteristic of the thyroid status in the children of prepubertal age, the level of TSH was chosen as the most sensitive indicator of the thyroid hormone deficiency presence (Table 2).

According to this indicator, the examined group of children had no abnormalities in the functional state of the thyroid gland. However, 12.3 % of the children were characterized by TSH in the range of age standards, which was shifted towards its increase (4.23-5.00 µIU/I). When using the indicator TSH/T_4 , we found signs of subclinical hypothyroidism in 2.1 % of children (this indicator was 0.115–0.143). The evaluation of all studied criteria is given in Table 3.

Table 3. Criteria of severe iodine deficiency in Northern Bukovina

Indicators, units	Population Reference	Results	Degree iodine deficiency
Median ioduria, μg/l	Prepubertal children	60.4 ± 9.3	Mild
Goiter (enlargement of the thyroid gland >0 degree), %	Prepubertal children	17.6 ± 2.1	Moderate
Thyromegaly (volume >97th percentile >2 SDS), %	Prepubertal children	14.8 ± 3.2	Moderate
% TSH >5 mIU/L	Pregnant women	18.3 ± 1.3	Mild

Correlation analysis between the neonatal TSH above 5 µMo/l frequency with the frequency of iodine deficiency goiter in prepupertal children showed a statistically significant high positive relationship (r = 0.89, P < 0.01). It is known that the main criterion for the state of iodine saturation in the region is the median ioduria.

Thus, analyzing the nature of iodine deficiency in the surveyed areas based on the WHO criteria, we can conclude a slight degree of iodine deficiency in Northern Bukovina according to the median ioduria in pregnant women and prepupertal children due to the level of neonatal hyperthyrotropinemia above 5 µIU/I/. At the same time, the determination of the goiter frequency by palpation and thyromegaly ultrasonographically indicated the presence of moderate iodine deficiency. Therefore, the incidence of neonatal hyperthyrotropinemia above 5 µIU/I more reflects the presence of iodine deficiency in the cohort of pregnant women than in the general population, which dictates the need to reassess the importance of this indicator as the criterion for iodine deficiency in the general population. However, despite all preventive measures carried out in the region, indicators of neonatal hyperthyrotropinemia above 5 µIU/I occurred with a frequency above the norm of 3 %, recommended by the WHO for iodine-saturated areas. This characterizes the lack of effectiveness of the prevention programs that depends largely on women's awareness.

Discussion

The high frequency of thyroid diseases depends on many reasons, among which the most important are the cessation of centralized iodine prophylaxis, man-made pollution, negative changes in the nutritional structure among the vast majority of the population in the new socio-economic conditions [12]. Prevention of IDD, such as goiter, decreased thyroid function, mental dysfunction in children and adults, congenital anomalies, cretinism, delayed physical and sexual development, miscarriage, infertility, remains an acute problem [13]. According to the WHO, pathological conditions caused by iodine deficiency rank third in the list of the most common non-communicable diseases. In various countries, programs of prevention and elimination of IDD are being implemented at the state level [14,15]. The main coordinators of these programs are the respective national committees, coordinating councils, WHO, UNICEF, ICCIDD which defined criteria of iodine deficiency: goiter frequency according to palpation and thyromegaly according to ultrasound, median urinary iodine excretion, TSH level, serum thyroglobulin level. A separate risk group is pregnant women. The number of pregnant women with this pathology is growing every year, which can be attributed to the lack of timely prevention of existing iodine deficiency in our country.

Although some authors give conflicting values regarding the level of neonatal TSH, this indicator is a common criterion for iodine deficiency. Contradictory data from various authors can be associated with many technical issues that remain unresolved regarding the use of TSH screening in newborns to monitor iodine status, making it questionable as a sensitive and reliable quantitative tool. Additional research is needed to address these issues [16]. The aim of the E. Cortés-Castell et al. study [17] was to analyze possible risk factors for elevated TSH level that may distort its validity as the marker of iodine status. The clinical significance of this issue is that the associated with iodine deficiency factors are known, iodine supplements can be introduced into risk groups both during pregnancy and for newborns [18].

It is probably important to take into account the birth date and birth weight, as well as the nutritional status of a pregnant woman [19]. We support the authors' view that the urinary iodine concentration directly reflects the iodine intake with food and remains the most common indicator used worldwide to assess iodine levels in the population, that are confirmed by studies. Clinical and laboratory studies of thyroid function (including serum concentrations of pituitary hormone thyrotropin) are problematic. Even in regions with severe iodine deficiency, there are a large number of individual changes in the ability of the thyroid gland to adapt. In most institutions and population subgroups, except for newborns, thyroid function tests are not considered as sensitive indicators of the population iodine status.

Obviously, in order to assess the degree of iodine deficiency burden, in addition to the median ioduria, it is necessary to analyze the frequency distribution of urinary iodine concentration in a specific group of subjects. We did not find a significant difference in the urinary iodine concentration in the children depending on age and sex. The inconsistency of certain indicators that serve as criteria for iodine deficiency indicated that the endemic goiter burden in the territory of Northern Bukovina cannot be explained only by iodine deficiency. It is possible that other strumogenic factors are involved in the goiter occurrence. These can be xenobiotics, imbalance of other micro- and macroelements, etc. Northern Bukovina is represented by different climatic and geographical zones (mountainous, foothills, plains), being the largest endemic region of Ukraine in terms of goiter prevalence in children, that can be explained by the weakening of control over iodine prophylaxis among children in the region [20].

Our study had some limitations. We had no data on TSH levels and thyroid volume in pregnant women. Not all factors were taken into account (birth weight, whether thyroid hormones were used during pregnancy, mode of delivery), as well as other possible factors that may affect TSH levels in newborns.

Conclusions

- 1. The territory of Northern Bukovina, according to the median ioduria in prepubertal children and TSH levels in newborns, can be classified as mild iodine deficient, while the incidence of goiter and thyromegaly in children of the reference group - as the zone with moderate iodine deficiency.
- 2. The increase in the median ioduria and the decrease in the frequency of neonatal hyperthyrotropinemia above 5 µIU/I on the background of iodine supply has been found in the pregnant population.
- 3. The indicator of neonatal hyperthyrotropinemia above 5 µIU/I can be used to assess iodine deficiency only in the population of pregnant women.

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Information about authors:

Sorokman T. V., MD, PhD, DSc, Professor of the Department of Pediatrics and Medical Genetics, Bukovinian State Medical University, Chernivtsi, Ukraine.

ORCID ID: 0000-0001-7615-3466

Bachu M. I., MD, PhD student of the Department of Pediatrics and Medical Genetics, Bukovinian State Medical University, Chernivtsi,

ORCID ID: 0000-0002-0606-3243

Makarova O. V., MD, PhD, Associate professor of the Department of Higher Nursing Education, Bukovinian State Medical University, Chernivtsi, Ukraine.

ORCID ID: 0000-0003-3348-2440

Popeliuk N. O., MD, PhD, Associate professor of the Department of Pediatrics, Neonatology and Perinatal Medicine, Bukovinian State Medical University, Chernivtsi, Ukraine. ORCID ID: 0000-0002-9034-774X

Відомості про авторів:

Сорокман Т. В., д-р мед. наук, професор каф. педіатрії та медичної генетики, Буковинський державний медичний університет, м. Чернівці, Україна.

Бачу М. І., аспірант каф. педіатрії та медичної генетики, Буковинський державний медичний університет, м. Чернівці,

Макарова О. В, канд. мед. наук, доцент каф. догляду за хворими та вищої медсестринської освіти, Буковинський державний медичний університет, м. Чернівці, Україна.

Попелюк Н. О., канд. мед. наук, доцент каф. педіатрії, неонатології та перинатальної медицини, Буковинський державний медичний університет, м. Чернівці, Україна.

Сведения об авторах:

Сорокман Т. В., д-р мед. наук, профессор каф. педиатрии и медицинской генетики, Буковинский государственный медицинский университет, г. Черновцы, Украина. Бачу М. И., аспирант каф. педиатрии и медицинской генетики, Буковинский государственный медицинский университет, г. Черновцы, Украина.

Макарова Е. В., канд. мед. наук, доцент каф. ухода за больными и высшего медсестринского образования, Буковинский государственный медицинский университет, г. Черновцы, Украина.

Попелюк Н. А., канд. мед. наук, доцент каф. педиатрии, неонатологии и перинатальной медицины, Буковинский государственный медицинский университет, г. Черновцы, Украина.

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