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STUDYING QUALITATIVE CHARACTERISTICS OF BONE TISSUE OF THE HUMAN MAXILLA ON THE QUANTITATIVE CONTENT OF TRACE ELEMENTS (K, Fe, Co, Sr, Zn) IN THE DYNAMICS OF PRENATAL ONTOGENESIS

Abstract: *Purposes.* The updated and substantiated understanding of the patterns of the upper jaw growth in prenatal ontogenesis contributes both to the diagnosis of congenital malformations and the prevention of prenatal injury to the maxillofacial area. In this regard, determining the density of bone tissue, that is, its mineralization, whose impairment forms the basis for the development of various defects, is as important as studying inter-tissue relations in the process of histo- and organogenesis, including epithelio-mesenchymal ones. This research was conducted to study the quantitative content of trace elements (K, Fe, Co, Sr, Zn) in the dynamics of prenatal ontogenesis as a fundamental material of bone tissue. The research was carried out as part of the implementation of a fragment of the planned comprehensive research work "Features of morphogenesis and structural and functional peculiarities of tissues and organs in human ontogenesis", No. of state registration 0116U002938.

Methods. By means of atomic emission (AES) and atomic absorption (AAS) spectrometry and statistical processing, as well as variational and dynamic analysis programs, the relative values for each

trace element were obtained while studying the bone tissue from abortion and sectional material of the upper jaw in 131 human fetuses (Ukrainians).

Results. These results as the mean value of the studied parameter (M), standard deviation (m), paired student's t-test or reliability value (t), and the probability level, which are shown in Tables 2–4, where the comparison values of the first and fourth groups are: for potassium (K) – 0.188 ± 0.006 in the first and 0.144 ± 0.019 in the fourth group ($t = 2.21$, $p < 0.05$); for iron (Fe) – 0.348 ± 0.027 and 0.435 ± ± 0.057($t = 1.38$, $p > 0.05$); for cobalt (Co) – 0.086 ± 0.006 and 0.059 ± 0.008 ($t = 2.70$, $p < 0.01$); for zinc (Zn) –0.905 ± 0.035 and 0.303 ± 0.032 ($t = 12.81$, $p < 0.001$), which substantiates the high reliability of the findings, the quantitative determination of the content of trace elements simultaneously reflects the quality of the bone tissue of the upper jaw of human fetuses in prenatal ontogenesis.

The investigated growth rate (%) for potassium (K) in the three groups is negative: between the first and second groups (–4.39%), between the second and third (–68.94%). However, a sharp increase in potassium in the fourth group, compared to the third one, is + 318.63%. The overall growth for potassium between the first and fourth groups is + 24.33%.The dynamics of iron trace content (Fe) has a positive growth pattern in almost all age periods of prenatal ontogenesis; accordingly, there is a positive growth rate (%): between the second and third groups it increases by 34.62%; between the third and fourth – by 52.15%; between the first and the fourth – by 102.67%, except for a moderate decline in the second group (17–24 weeks), therefore, the growth rate between the first and second groups has a significant but negative value (–1.05%). The maximum growth rate (%) is set for cobalt (Co) (Figure 5) in the middle (22–27 weeks) of the intrauterine development (IUD) of the fetus, which is more than one hundred and fifty percent (+150.51%), which confirms the intensity of the vascular system development and that of metabolic transformations, is observed in this age period. A slight increase (%) of zinc (Zn) with the sign "+" is observed in the second experimental group (+3.99%), and rapidly decreases in the third (–9.34%) and the fourth (–42.43%) groups, which is a positive reflection of the qualitative parameters of fetal bone tissue.

Conclusion. Our study have found that the age dynamics of all values of the trace elements content in the prenatal ontogenesis of the upper jaw of human fetuses significantly correlates with both the decrease and growth – in the first (11–16 weeks of IUD), the second (17–24 IUD), the third (25–29 weeks of IUD) and the fourth (30–40 weeks of IUD) experimental groups, which is directly proportional to the re-distribution of trace elements for the construction of organs and systems in these age periods. The regularity of the dependence and ratio of the content of cobalt (Co) and iron (Fe) in the first, second and third experimental groups was studied. There was a slight correlation between dependence and direct correlation (Fig. 2) on the reduction of zinc (Zn) and iron (Fe) in all groups. Studying the patterns of dynamics of the density of bone tissue of the upper jaw in human fetuses, depending on the mineral composition and the presence of the revealed synchronism of these processes, suggests that the change in density is indicative of a change in the content of certain mineral elements. In our opinion, this provision may be the basis for the development of new techniques for early diagnosis of congenital anomalies of the maxillofacial area at the preclinical stages of its development and the methods of their prevention, through the correction of the mineral composition.

Keywords: prenatal ontogenesis, maxilla, maxillofacial region, human.

Introduction: Biological behavior of bone in different developmental periods is determined by its main properties: biochemical (content of mineral and organic substances and their correlations), morphological (degree of heterogeneity and features of topographic correlations of major vessels [22], which ensure vascularization and proper construction of the body), biological (content and the ratio of different types of cells per unit of the bone volume [32]). That is, the bone tissue is a dynamic open system that is characterized by a complex multi-level organization with the ability to change its structure and properties in the ontogenetic modeling process in accordance with the state of the regulatory systems and conditions in which it is located. As a result, it has a significant individual and topographic variability of the morphological structure, chemical composition and biological potential [18; 26; 29; 32].

Studying the chemical composition of bone tissue is associated with considerable difficulties, since in order to study the inorganic matrix, it is necessary to isolate the organic saturation and further dissolution of the inorganic one, which may also partially lead to the loss of macro- and micronutrients. In addition, their content is directly proportional to both components, organic and inorganic parts [12; 28].

With the current level of theoretical ideas about the structure and function of the bone tissue, the concept of "bone quality" should be considered as a collective integrated one, which is a certain generalized characteristic of architectonics, density, mineral bone density and its biological potential [23; 30].

A number of authors have described that all these parameters are quite varied in the prenatal ontogenesis, and their impairment leads to a significant pathology of the maxillofacial area [1; 2; 15; 31].

Materials and methods. We have studied the bone rudiments of the upper jaw of the 131-nd human fetuses of Ukrainians, aged 11–40 weeks of the intrauterine development (IUD), obtained from abortion and sectional material of spontaneous miscarriages or stillbirths in preterm labor, who had died of conditions associated with diseases of the maxillofacial area and had developed in the uterus in the absence of the effects of manifestly expressed harmful factors of the human external and internal environment.

The bone tissue sampling was carried out on both sides of the upper jaw of a fetus at different sites, with the most pronounced, macroscopically, density. Methods of macroscopy, morphometry of objects were applied during the study, using the gradation of periods of the intrauterine development on the basis of classical periodization of embryogenesis and post-fetus human ontogenesis according to G. A. Schmidt (1972), which determines: the embryonic period – 45 days, the prefetal period lasting 30 days and the fetal period of 192 days, from 55.0 to 376.0 mm of crown-rump length (CRL). The study involved both gross specimens from the Museum of Chairs of the Medical University and materials received in accordance with the agreement on scientific cooperation with the Chernivtsi Oblast Communal Medical Center "Post-mortem Department" in Chernivtsi (Ukraine).

All studies were conducted in compliance with the main provisions of the GCP (1996), the Council of Europe Convention on Human Rights and Biomedicine (of 04.04.1997), the Helsinki Declaration of the World Medical Association on the Ethical Principles of Scientific Medical Research with Human Participation (1964–2013), orders of MoH of Ukraine No. 690 of September 23, 2009, No. 616 of 03.08.2012, and according to the guidelines [16] and "Procedure for the extraction of biological objects from the dead individuals, whose bodies are subject to forensic examination and pathological anatomical investigation for scientific purposes" [17].

Applying the methods of flame atomic emission and atomic absorption, determination of potassium metal ions (K), strontium (Sr), zinc (Zn) and cobalt (Co) was carried out directly from the initial solutions with the corresponding wavelengths:

– K(potassium) – λ = 766.5 nm, linearity 0.1–0.2 mg/l, C_n = 0.01 mg/l

– Zn(zinc) – λ = 231.9 nm, linearity 0.4–2.0 mg /l, C_n = 0.05 mg/l

– Co (cobalt) – λ = 240.7 nm, linearity 0.1–5.0 mg/l, C_n = 0.05 mg/l

– Sr(strontium) – λ = 460.7 nm, linearity 0.05––0.5 mg/l, C_n = 0.005 mg/l

using atomic absorption spectrophotometer AAS-1N (Carl Zeiss Jena, Germany) by means of the flame of propane-butane-air. We also used a drying chamber 2B-151 (Ukraine) and analytical scales of the second class of accuracy XAS100 / C (RADWAG, Poland).

Determination of Fe (iron) content was carried out using a photometric method, light absorption was measured by means of a photocolorimeter КФК-2-УХЛ 4.2 (Ukraine), as ferrum (III) –yellow three sulfosalicylic complex in an ammonia medium with a wavelength λ = 400.0 nm, linearity 0.1–0.2 mg l, C_n = 0.03 mg/l. Statistical processing of the findings was conducted using the unified program STATISTICA 10, applied in scientific clinical and epidemiological studies in medicine. Standard statistical programs of variation and dynamic analysis by means of computer technology were used as well.

Using the method of statistical groupings in the study of qualitatively homogeneous aggregates, where there are no qualitative transformations yet, but there are quantitative differences, grouping for a large number of observations has been carried out (Table 1).

Table 1. – Grouping the research objects

Ordinal group number	Age, weeks	Number of observations
1	11–16	35
2	17–24	33
3	25–29	32
4	30–40	31
Total number of observations		131

To study the quantitative composition of trace elements of the bone tissue in the human maxilla in the dynamics of the fetal development period, a variational analysis of statistical data with the determination of the average values for each trace element, the error of the average values, was used. An assessment was made of the reliability of the averages and the probability of an error-free prediction.

A comparative analysis of the dynamics of density and content of trace elements in the bone tissue of the maxilla of human fetuses in different age groups of prenatal ontogenesis was carried out with the determination of the reliability of the difference of the indices using the Student's reliability test (t).

As a result of statistical research in the processing of statistical data we received absolute numbers, indicating the size of phenomena. Although absolute numbers have some cognitive value, their use is limited. To determine the level of the phenomenon and to compare the values in dynamics, we took into account the relative values (indices, coefficients), which result from the correlation of statistical quantities among themselves.

All the findings (relative and average values) were evaluated to determine their reliability. The assessment of the reliability of the relative values was carried out by calculating their error ($m_{\%}$) by the formula for a large number of observations.

The result was considered reliable when the fraction from the division of the indicator to its error $\left(P/m\right)$ equaled 2 or more. The criterion of reliability (t) = 2 showed that the result obtained in a sampling population, in 95.5% of cases differed from the result of the general population by 2m. That is, the probability of an error-free prediction (P) was 95.5%. This result is considered acceptable for statistical research in the field of medicine, as shown in (Figure 1).

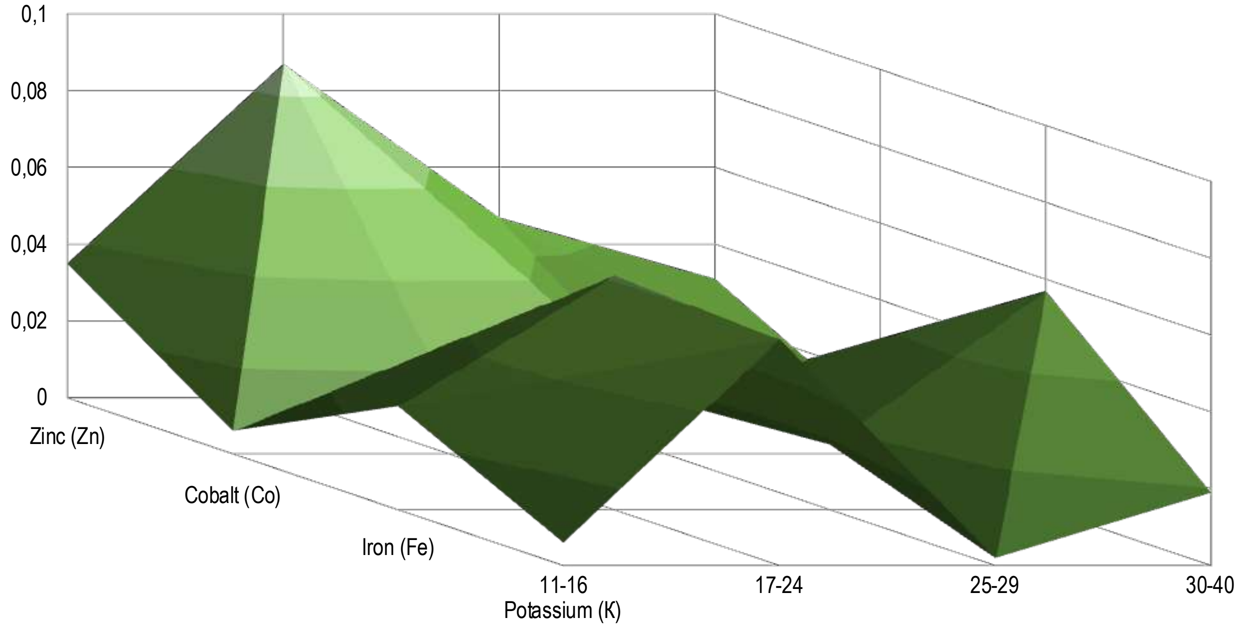

Figure 1. A standard error (11–16, 17–24, 25–29, 30–40) in age groups, weeks

Estimation of reliability of average values (average values of the content of minerals – trace elements of the maxillary tissue of the human fetus) was carried out by calculating their error (m_M) by the formula for a large number of observations.

To determine the significant difference between the values in different groups of prefetal and fetal periods, the reliability of the difference between the values presented in tables 2–4 was done which are given in this section (materials and methods) as the major attention in our study is drawn to analyzing the dynamics – growth rate (%). For relative and average values, Student's test t was calculated using the corresponding formulas. The difference was considered significant at t ≥ 2.

Table 2. – Reliability of the difference between the values of trace element content in the bone tissue of the upper jaw in human fetuses in the age groups of 11–16 weeks (group 1) and 17–24 weeks (group 2)

Groups / Trace elements	Group 1		Group 2		Student's t-test	P
	M_1	m_1	M_2	m_2		
Potassium (K)	0.188	0.006	0.237	0.059	0.83	> 0.05
Iron (Fe)	0.348	0.027	0.455	0.061	1.57	> 0.05
Cobalt (Co)	0.086	0.006	0.081	0.015	0.31	> 0.05
Zinc (Zn)	0.905	0.035	1.244	0.087	3.64	< 0.001

Table 3. – The reliability of the difference between the indexes of trace element content in the bone tissue of the maxilla of human fetuses in the age groups of 11–16 weeks (group 1) and 25–29 weeks (group 3)

Groups / Trace elements	Group 1		Group 3		Student's t-test	P
	M_1	m_1	M_2	m_2		
1	*2*	*3*	*4*	*5*	*6*	*7*
Potassium (K)	0.188	0.006	0.043	0.002	23.02	< 0.001
Iron (Fe)	0.348	0.027	0.359	0.017	0.37	> 0.05

1	2	3	4	5	6	7
Cobalt (Co)	0.086	0.006	0.119	0.014	2.20	< 0.05
Zink (Zn)	0.905	0.035	0.660	0.047	4.22	< 0.001

Table 4.– The reliability of the difference between the indexes of trace element content in the bone tissue of the maxilla of the human fetuses in the age groups of 11–16 weeks (group 1) and 30–40 weeks (group 4)

Groups / Trace elements	Group 1		Group 4		Student's t-test	P
	M_1	m_1	M_2	m_2		
Potassium (K)	0.188	0.006	0.144	0.019	2.21	< 0.05
Iron (Fe)	0.348	0.027	0.435	0.057	1.38	> 0.05
Cobalt (Co)	0.086	0.006	0.059	0.008	2.70	< 0.01
Zink (Zn)	0.905	0.035	0.303	0.032	12.81	< 0.001

To assess the homogeneity of statistical data (average values of the content of trace elements in the human maxillary bone marrow), the determination of the type and reliability of the mean value was determined by the coefficient of variation (CV) presented in Tables 5–8 and assessed according to the scale (low, medium and high variety of the feature). At the same time, it was found that the coefficient of variation (CV) in the second group (17–24 weeks) for potassium (K) was 143.49 and for cobalt (Co) – 104.31, indicating a high diversity of the feature.

Table 5.– Mineral composition of the bone tissue of the upper jaw of a human fetuses aged 11–16 weeks (group 1), trace elements, mg / g, n = 35

Trace elements	mean M	Confidence interval (M-2m)	Confidence interval (M+2m)	Standard deviation (Δ)	Dispersion ($δ^2$)	Coefficient of variation (CV)	Standard error (m)	Probability of error-free forecast (P)
Potassium(K)	0.188	0.175	0.201	0.039	0.002	**20.56**	0.006	< 0.001
Iron (Fe)	0.348	0.294	0.403	0.158	0.025	**45.58**	0.027	< 0.001
Cobalt (Co)	0.086	0.073	0.098	0.035	0.001	**41.55**	0.006	< 0.001
Zink (Zn)	0.905	0.833	0.976	0.208	0.043	**22.99**	0.035	< 0.001

Table 6.– Mineral composition of the bone tissue of the upper jaw of the human fetuses aged 17–24 weeks (group 2), trace elements, mg / g, n = 33

Trace elements	mean M	Confidence interval (M-2m)	Confidence interval (M+2m)	Standard deviation (Δ)	Dispersion (δ2)	Coefficient of variation (CV)	Standard error (m)	Probability of error-free forecast (P)
1	2	3	4	5	6	7	8	9
Potassium (K)	0.237	0.117	0.358	0.340	0.116	**143.49**	0.059	< 0.001
Iron (Fe)	0.455	0.331	0.579	0.350	0.123	**76.97**	0.061	< 0.001

1	2	3	4	5	6	7	8	9
Cobalt (Co)	0.081	0.051	0.111	0.084	0.007	**104.31**	0.015	< 0.001
Zink (Zn)	1.244	1.068	1.421	0.498	0.248	**40.04**	0.087	< 0.001

Table 7.– Mineral composition of bone tissue of the human fetuses upper fetal jaw aged 25–29 weeks (group 3), trace elements, mg / g, n = 32

Trace elements	mean M	Confidence interval (M-2m)	Confidence interval (M+2m)	Standard deviation (Δ)	Dispersion (δ2)	Coefficient of variation (CV)	Standard error (m)	Probability of error-free forecast (P)
Potassium (K)	0.043	0.038	0.047	0.012	0.0001	**29.02**	0.002	< 0.001
Iron (Fe)	0.359	0.323	0.394	0.097	0.009	**27.28**	0.017	< 0.001
Cobalt (Co)	0.119	0.089	0.148	0.081	0.006	**68.38**	0.014	< 0.001
Zink (Zn)	0.660	0.563	0.757	0.268	0.072	**40.60**	0.047	< 0.001

Table 8.– Mineral composition of the bone tissue of the upper jaw of the human fetus aged 30–40 weeks (group 4), trace elements, mg / g, n = 31

Trace elements	mean M	Confidence interval (M-2m)	Confidence interval (M+2m)	Standard deviation (Δ)	Dispersion (δ2)	Coefficient of variation (CV)	Standard error (m)	Probability of error-free forecast (P)
Potassium (K)	0.144	0.104	0.183	0.106	0.011	**74.02**	0.019	< 0.001
Iron (Fe)	0.435	0.318	0.551	0.319	0.101	**73.29**	0.057	< 0.001
Cobalt (Co)	0.059	0.043	0.076	0.045	0.002	**75.49**	0.008	< 0.001
Zink (Zn)	0.303	0.238	0.368	0.177	0.031	**58.43**	0.031	< 0.001

To identify the trends of qualitative characteristics of bone tissue of the maxilla of human fetus in the dynamics of prenatal ontogenesis, a dynamic analysis was used. The patterns of growth or decrease in the content of certain trace elements in the bone tissue of the human upper jaw depending on the age period of prenatal ontogenesis of the fetus have been established.

Using the method of comparative analysis, age dynamics of density values and content of mineral elements of bone tissue of the human upper jaw in prenatal ontogenesis was determined. The processing of the research results was carried out using modern computer technology.

Thus, using the above mentioned methods of photometric research and statistical processing allowed us to obtain qualitatively new and reliable data, which are the basis of the scientific substantiation of the peculiarities of the structure and mineral composition of bone tissue of human fetuses' upper jaw in the early prenatal period of ontogenesis.

Results. Numerical data on the content of trace elements in the structure of human bone tissue at the age of 11–40 weeks of IUD, with dimensions (l = 55.0–376.0 mm of CRL) in grading of periods of fetal development on the basis of classical embryogenesis periodization and after germinal human ontogenesis by G. A. Schmidt are presented in Tables 2–4 (M ± m, mg/g) and in Table 9 (%). In order to make the analysis convenient and to implement it in practice in future, we conducted a dynamic analysis with the determination of the percentage of trace elements in the investigated fragments of the bone tissue of the samples (weighing from 0.15–0.55 g), which, at the same time, provide a complete basis for mineralization and qualitative characteristics of the bone tissue development in prenatal ontogenesis, which presented in (Table 9) and graphically depicted in (Figure 2).

Table 9.– Structure of the bone tissue of the upper jaw of the human fetus based on the content of trace elements,%

Group	Age, weeks	A number of observations	Trace elements,%			
			Potassium(K)	Iron (Fe)	Cobalt(Co)	Zink (Zn)
1	11–16	35	12.29	22.80	5.61	59.30
2	17–24	33	11.75	22.56	4.02	61.67
3	25–29	32	3.65	30.37	10.07	55.91
4	30–40	31	15.58	46.21	6.32	32.19

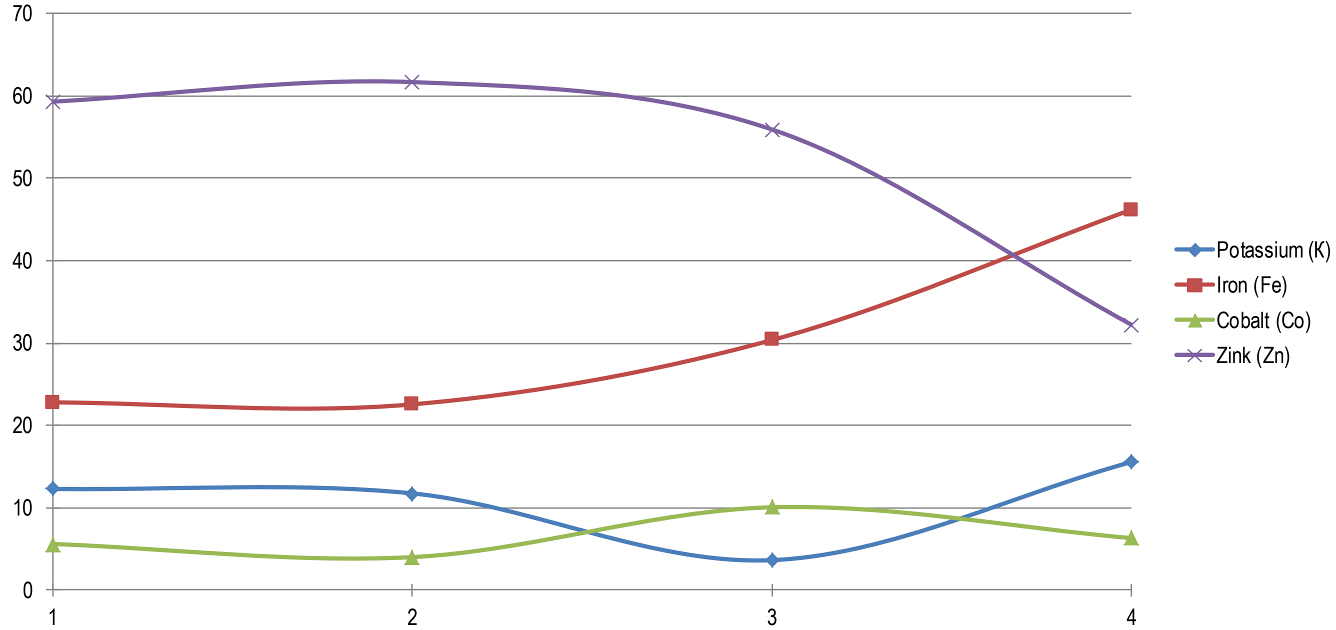

Figure 2. Structure of the bone tissue of the upper jaw of the human fetus based on the content of trace elements,%

It has been established that age dynamics of all indices of trace element content in prenatal ontogenesis significantly correlates both in the direction of decrease and in the direction of growth – in the first (11–16 weeks of IUD), the second (17–24 weeks of IUD), the third (25–29 weeks of IUD) and the fourth (30–40 weeks of IUD) groups, which is directly proportional to the re-distribution of trace elements for the development of fetal organs and systems in these age periods.

The regularity of the dependence and ratio of the content of cobalt (Co) and iron (Fe) in the first, second and third experimental groups has been studied.

There is also a slight correlation between dependence and direct correlation with zinc reduction and iron growth in all experimental groups.

For more detailed analysis, tables (10, 11) provide numerical data on the rate of growth (%) that reveal the essence of the distribution dynamics of these trace elements of the maxillary bone in the prenatal ontogenesis of human fetuses.

The growth rate for potassium (K) in the three groups is negative: between the first and second groups (–4.39%), between the second and third (–68.94%). However, a sharp increase in potassium (K) in the fourth group, compared with the third, is +318.63%. The overall growth rate for potassium (K) between the first and fourth groups is + 24.33%, which is shown in (Figure 3).

Table 10.– Age dynamics of trace element content in the bone tissue of the human fetuses' upper jaw,%

Trace elements	Groups		Growth rate,% (+) – growth (–) – decrease	Groups		Growth rate,% (+) – growth (–) – decrease
	1	2		2	3	
Potassium (K)	12.29	11.75	– 4.39	11.75	3.65	– 68.94
Iron (Fe)	22.80	22.56	– 1.05	22.56	30.37	+ 34.62
Cobalt (Co)	5.61	4.02	– 28.34	4.02	10.07	+150.51
Zink (Zn)	59.30	61.67	+ 3.99	61.67	55.91	– 9.34

Table 11.– Age dynamics of trace element content in the bone tissue of the maxilla in human fetuses,%

Trace elements	Groups		Growth rate,% (+) – growth (–) – decrease	Groups		Growth rate,% (+) – growth (–) – decrease
	1	2		2	3	
Potassium (K)	3.65	15.58	+ 318.63	12.29	15.58	+ 24.33
Iron (Fe)	30.37	46.21	+ 52.15	22.80	46.21	+ 102.67
Cobalt(Co)	10.07	6.32	– 37.24	5.61	6.32	+ 12.65
Zink (Zn)	55.91	32.19	– 42.43	59.30	32.19	– 45.72

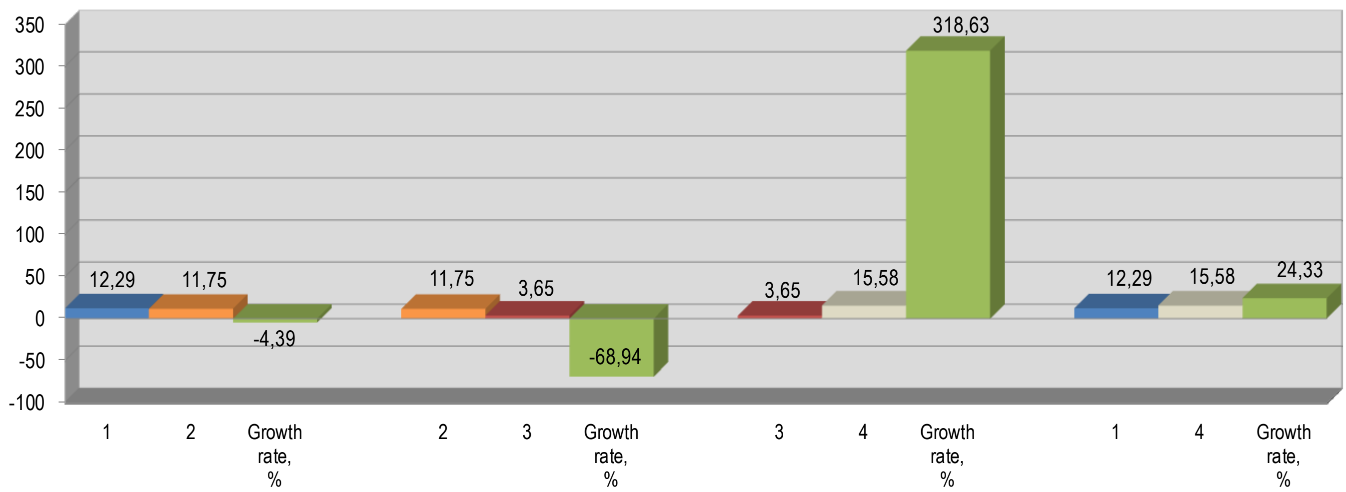

Figure 3. Rate of growth of potassium (K) trace elements,%

The dynamics of the iron (Fe) trace element content (Figure 4) has a positive growth pattern in almost all age periods of prenatal ontogenesis, therefore it increases: between the second and third groups by 34.62%; between the third and fourth by 52.15%; between the first and the fourth by 102.67%, except for a slight decrease in the second group (17–24 weeks), consequently, the growth rate between the first and second groups has an insignificant but negative value (–0.05%).

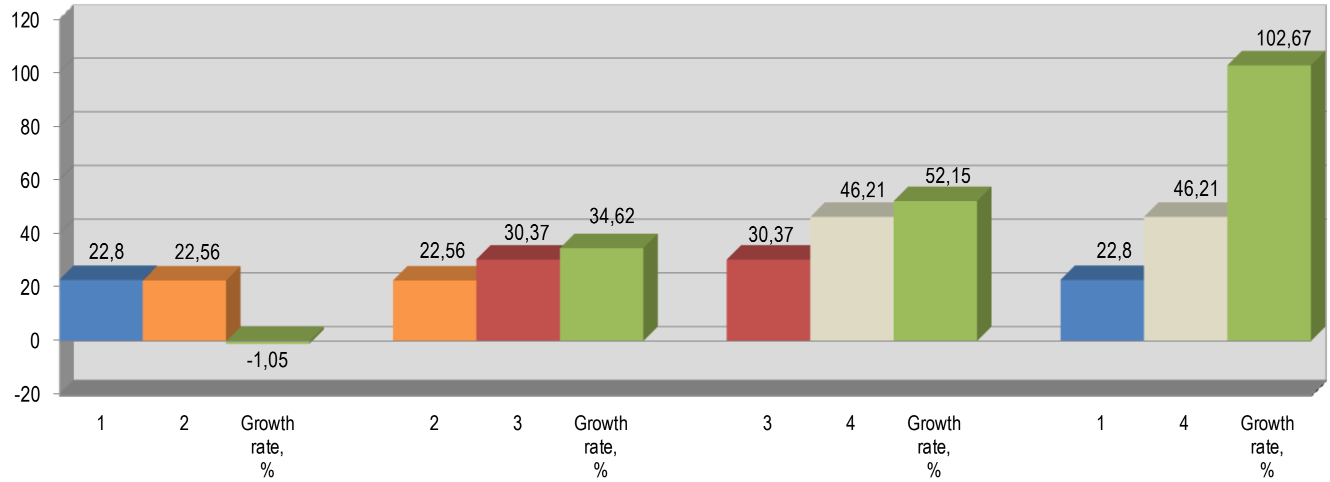

Figure 4. Rate of growth of iron (Fe) trace elements, %

The maximum growth rate was found for cobalt (Co) (Figure 5) in the middle of 22–27 weeks of IUD of human fetuses, which is more than one hundred and fifty percent (+150.51%), which confirms the intensity of development of the vascular system in this age period.

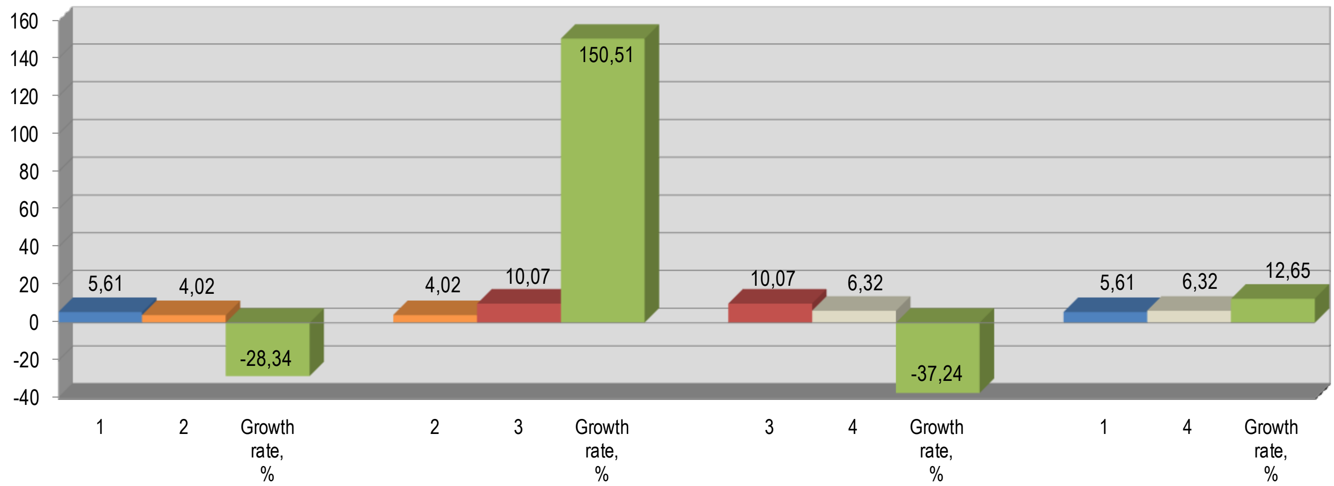

Figure 5. Growth rate of cobalt (Co) trace elements, %

A slight increase in zinc (Zn) (%) (Figure 6) is observed in the second experimental group (+ 3.99%), and rapidly decreases in the third (–9.34%) and fourth (–42.43%) groups, which is a positive reflection of the qualitative indices of the fetal bone tissue.

Analyzing the results of the average value of the studied parameter (M), the standard deviation (m), the paired Student's test, or the reliability indicator (t) and probability level, which are given above (see Table 2–4), stating that the comparisonvalues between the first and fourth groups are: for potassium

(K) – 0.188 ± 0.006 in the first and 0.144 ± 0.019 in the fourth group ($t = 2.21$, $p < 0.05$); for iron (Fe) – 0.348 ± 0.027 and 0.435 ± 0.057 ($t = 1.38$, $p > 0.05$); for cobalt (Co) – 0.086 ± 0.006 and 0.059 ± ± 0.008 ($t = 2.70$, $p < 0.01$); for zinc (Zn) – 0.905 ± ± 0.035 and 0.303 ± 0.032 ($t = 12.81$, $p < 0.001$), which indicates the high reliability of the difference between the indicators in the quantitative determination of the content of trace elements in the bone tissue of the upper jaw of human fetuses in the results obtained.

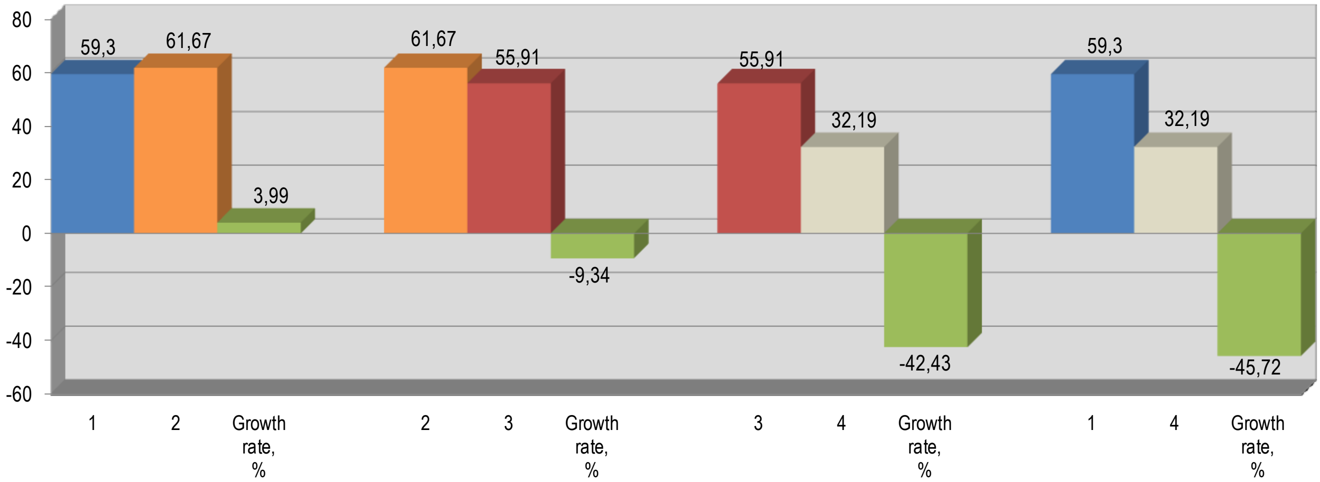

Figure 6. Growth rate of zink (Zn) trace elements,%

Discussion. Nowadays, the advancement of science often requires a determination of the content of trace elements, which cannot be found by means of a certain method of analysis [10; 23; 28].

With scientific progress and the ever-increasing manifestation of birth defects [1; 2; 15; 31], the question arises of the need to choose simple, precise and sensitive techniques that will make it possible to identify a component in complex biological mixtures.

To solve this problem, we have chosen the methods of separation and concentration for this study, which allow us to largely eliminate difficult low predicted situations. In addition, in many cases, concentration has expanded the limits of application of instrumental methods (atomic absorption spectrometry, spectrophotometry) [11; 12].

The amount of scientific research is growing significantly as well as the prospect of using combined and hybrid methods to determine the qualitative and quantitative characteristics of biological objects during relevant and progressive research directions [10–12].

At the same time, the data of scientific literature show that in recent years there has been an increasing interest in the laws of the development of the jaw system components [2; 18; 22; 26; 29; 32]. The processes of the formation and development of jaws and teeth have attracted the attention of many researchers [25].

The results of our literature review and our own histological studies, which are presented in papers [19–22], confirm that epithelio-mesenchymal interactions with the transformation of the latter into the coarse-fiber tissue (7–12 weeks of IUD) and the subsequent gradual formation of jaw bone during the studied periods of prenatal ontogenesis is a precursor to the development of the upper jaw in the human fetus.

The scientific studies [14; 26; 32] say that the bone tissue of the jaws in the 17–24-week old fetuses is represented by areas of a spongy bone of varying degrees of formation with heterogeneous forms and sizes of bone beams and interstitial spaces surrounded by peripheral zones of cartilage tissue.

In 25–32-week old fetuses the bone tissue of the jaw is represented by the formed bony beams, some of which lie separately, and the other – are connected by bridges, forming a spongy bone, surrounded by periphery islets of cartilage tissue. The bone tissue in the jaws of fetuses aged 33–40 weeks of IUD and newborns is represented by heterogeneous shaped and sized bone beams with hemopoiesis islets in the interstitial spaces. The bone beams, among which the large ones predominate, form a spongy bone of a usual structure.

A considerable number of scientific works study the mineral composition of hard tissues of the jaw system [9–12; 23; 24; 28]. Meanwhile, such important aspects of the problem as the study of the mineral composition of human bone tissue in the dynamics of prenatal ontogenesis, patterns of their correlation and distribution of mineral elements in the bone tissue remain beyond the attention of researchers.

That is why the purpose of our work was to study the features of the mineral composition of the bone tissue of the upper jaw of the human fetus during the stages of prenatal ontogenesis and the patterns of distribution of the content of mineral elements in the investigated objects, which ensure the quality and proper ossification of the bone itself.

We know that the collarbone [27] and the mandible are the bones, in which the islets of osteogenesis appear first, but the upper jaw is significantly lagging behind in time with its development and proper mineralization, which ensures the density and quality of bone tissue. Therefore, malformations are most common in the upper jaw [1; 2; 15; 31; 30] due to the influence of conditions of the internal environment in which the fetus stays.

Scientific papers [3–6; 8; 13] cover the responses of the bone tissue on the effects of dehydration, which is associated with the value of bones as depots of mineral substances in the body, which in turn determines their role in the water-salt metabolism.

The bone tissue is characterized by a constant renewal of its components, accompanied by processes of formation and destruction, compensatory-adaptive reactions in response to changing conditions of existence. These facts indicate bone tissue as a dynamic rather than static structure as evidenced by the authors of the works (Prylyska O. I., 2004; Pushyna S. A., 2004; Tekuchenko E. V., 2006; Pashkova I. G., 2016;). The plasticity and dynamism of the bone tissue make it one of the important factors in maintaining the homeostasis of an organism: it is an active participant in the general metabolism, it actively participates in salt metabolism. Nevertheless, a number of aspects in the study of this problem remain unclear, in particular, the change in the bone tissue mineral composition depending on the influence of the environmental conditions of the fetal bone marrow, which is a topical issue of the present [5; 7].

Numerical data on the content of trace elements in the structure of human bone tissue at the age of 11–40 weeks of IUD, with dimensions (l = 55.0– – 376.0 mm of CRL) in grading of periods of fetal development on the basis of classical embryogenesis periodization and after germinal human ontogenesis by G. A. Schmidt are presented in Tables 2–4 (M ± ± m, mg/g) and in Table 9 (%).

In order to make the analysis convenient and to implement it in practice in future, we conducted a dynamic analysis with the determination of the percentage of trace elements in the investigated fragments of the bone tissue of the samples (weighing from 0.15–0.55 g), which, at the same time, provide a complete basis for mineralization and qualitative characteristics of the bone tissue development in prenatal ontogenesis. Due to the fact that we are not aware of similar studies, we were not able to conduct a comparative analysis of the findings, which obviously limits the discussion on this issue.

The quantitative data we obtained can help to monitor the normal development of bone tissue of the human fetal maxilla, as well as to screen early for birth defects and anomalies, as well as significantly improve the study of quantitative morphology with relative ossification and be selected for a theoretical basis in the development of new preventive and therapeutic measures.

Conclusions. In the course of our research, we found that age dynamics of trace element content in prenatal ontogenesis in all values significantly correlated both with the decrease and the growth – in the first (11–16 weeks of IUD), the second (17–24 weeks of IUD), the third (25–29 weeks of IUD) and the fourth (30–40 weeks of IUD) experimental groups, which is directly proportional to the redistribution of trace elements for the construction of organs and systems in these age periods.

The regularity of the dependence and the ratio of content of cobalt (Co) and iron (Fe) in the first, second and third experimental groups have been studied.

There is also a slight correlation between dependence and direct correlation (see Fig. 2) with respect to the reduction of zinc (Zn) and iron (Fe) in all experimental groups.

Studying the patterns of density dynamics depending on the mineral composition of the bone tissue and the presence of the revealed synchrony of these processes, suggests that the change in density is indicative of a change in the content of certain mineral elements. In our opinion, this provision may be the basis for developing new methods of early diagnosis of congenital anomalies of the maxillofacial areas at pre-clinical stages of its development and methods of their prevention, by correcting the mineral composition.

Compliance with ethical standards. All studies were conducted in compliance with the main provisions of the GCI (1996), the Council of Europe Convention on Human Rights and Biomedicine (of 04.04.1997), the Helsinki Declaration of the World Medical Association on the Ethical Principles of Scientific Medical Research with Human Participation (1964–2013), Orders of MoH of Ukraine No. 690 of September 23, 2009, No. 616 of 03.08.2012, and according to the guidelines [16] and "Procedure for the extraction of biological objects from the dead, whose bodies are subject to forensic examination and pathological anatomical investigation, for scientific purposes" [17].

Conflict of interest. The authors declare that they have no conflict of interest.

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