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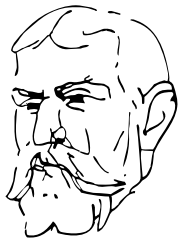

Memory of
dr Władysław
Biegański

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ORIGINAL ARTICLE

PECULIARITIES OF THE HUMAN MAXILLA MORPHOGENESIS

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ABSTRACT

The aim: To find out the sources of formation and the chronological sequence of the morphogenesis of the maxilla at the early stages of human ontogenesis.

Materials and methods: 14 series of consecutive histological specimens of human embryos and prefetuses (4,0-66,0 mm of parietal-coccygeal length) aged from 4 to 11 weeks of intrauterine development with the use of a complex of modern morphological methods of investigation (anthropometry, morphometry, microscopy, and 3D computer reconstruction) were studied.

Results: On the basis of a complex of morphological research methods, data were obtained that made it possible to establish the general patterns of development of the human maxilla: separation of the pharyngeal apparatus (4th week), convergence and fusion of the jaw processes (5-8th weeks), formation of tooth buds (7-8th weeks), which allows considering the specified periods as critical in the formation of possible anomalies in the facial part of the skull. At the same time, a tendency of heterochrony of morphological transformations in the maxilla and maxilla was revealed.

Conclusions: 1. At the beginning of the 4th week of intrauterine development, 3 pairs of pharyngeal arches are formed. Detachment of the mandibular and maxillary processes of the mandibular pharyngeal arch is planned. 2. During the 7th week of intrauterine development, the maximum convergence of the maxillary processes with the lateral and medial nasals occurs, and in embryos of 20.0 mm PCL grow with the frontal process, forming the maxilla and upper lip. During the 8th week of intrauterine development, the bone base of the jaws is modeled as a result of the increase in the size of osteogenic islands and their fusion, alveolar processes are formed. 3. During the 9-10th weeks of intrauterine development, the primary palate is formed as a result of the fusion of the palatine processes. 4. At the 11th week of intrauterine development, the bone base models both jaws. Due to the processes of histogenesis of the soft tissues of the maxillofacial apparatus, the face acquires anthropomorphic definitive human features.

KEY WORDS: morphogenesis, maxilla, human ontogenesis

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INTRODUCTION

Research of sources and age periodization of morphogenesis of the facial bones of the skull at the early stages of prenatal human ontogenesis is an actual issue of modern morphology, age-related and variation anatomy, surgical stomatology and reconstructive surgery. Congenital malformations occupy one of the first places in the structure of causes of child mortality and disability [1-3]. Among them – cleft lip and/or palate – the most common craniofacial congenital defect in the human body, occurring once in 500-2500 live births worldwide. From 420 to 450 children with cleft lip are born annually in Ukraine. More than 300 Mendelian syndromes in humans include cleft lip as part of the phenotype [4, 5].

The maxilla is formed by the fusion of facial processes with the participation of many genetic and environmental factors [5, 6].

In modern scientific literature there is uncertainty regarding the temporal sequence of morphological processes and mechanisms that lead to the formation of the normal structure of the mandible, topographic relationships of the structures of the middle part of the human face in ontogenesis, and the formation of congenital defects of the face.

A clear understanding of the development of the structure and formation of the topography of the facial part of the head will allow to create a theoretical basis for improving the methods of interpretation of diagnostic medical imaging and surgical correction of congenital defects of the maxillofacial region [6].

THE AIM

The aim of the study is to find out the sources of formation and the chronological sequence of the morphogenesis of the maxilla at the early stages of human ontogenesis.

MATERIALS AND METHODS

14 series of consecutive histological specimens of human embryos and prefetuses (4,0-66,0 mm of parietal-coccygeal length (PCL)) aged from 4 to 11 weeks of intrauterine development (IUD) with the use of a complex of modern morphological methods of investigation (anthropometry, morphometry, microscopy, and 3D computer reconstruction) were studied. Dynamics of morphological changes of structural components of the pharyngeal arches were stud-

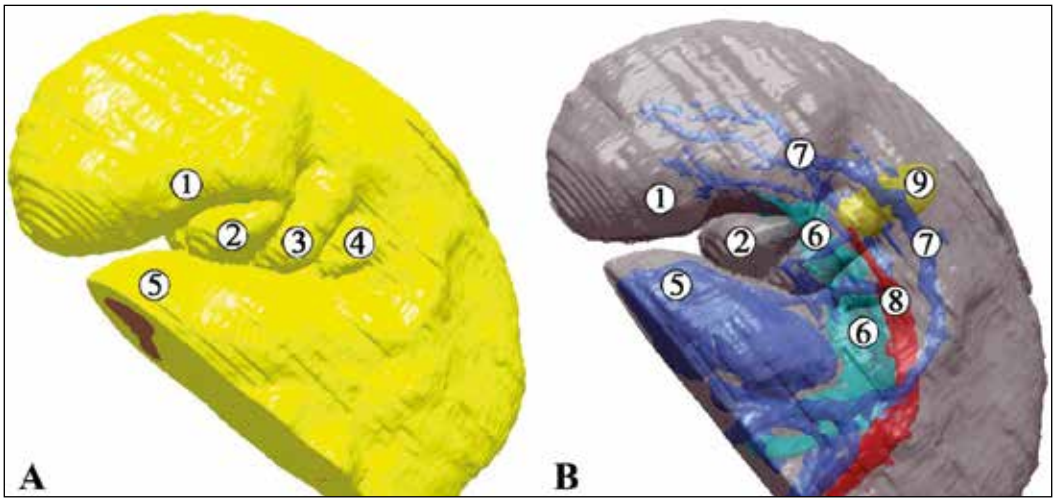

Fig. 1. Three-dimensional computer reconstruction model of the upper half of a human embryo 4.5 mm PCL (4th week of IUD). Left side projection. A – external covers, B – internal structures. x12: 1 – frontal process; 2 – maxillary process of the I (mandibular) branchial arch; 3 – mandibular process of the I branchial arch; 4 – II (hyoid) branchial arch; 5 – cardiac hump; 6 – internal contours of the foregut; 7 – cardinal veins; 8 – left dorsal aorta.

ied on series of archival microspecimens from collection of Department of Histology, Cytology and Embryology of Bukovinian State Medical University.

The study was carried out in compliance with the basic bioethical provisions of the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), the Helsinki Declaration of the World Medical Association on ethical Principles of Scientific Medical Research with the participation of Human beings (1964-2008), as well as the order of the Ministry of Health of Ukraine No. 690 of 23.09.2009.

RESULTS

During the study of a series of histological sections of human embryos 3.5-4.5 mm PCL (the end of the 3rd – the beginning of the 4th week of IUD), the presence of 3 pairs of branchial arches was established. Together with the frontal process, the first pair limits on both sides the entrance to the primary oral cavity – the stomodeum, which is lined with ectodermal simple cuboidal epithelium. Caudally, it adjoins the cranial end of the rudiment of the foregut. Between the stomodem and the foregut is the pharyngeal membrane, which is also lined with a single-layer cuboidal epithelium of endodermal origin from the side of the intestinal tube. Characterizing the morphology of the beginnings of the branchial arches, it should be noted that the largest of them are the mandibular, and the rudiment of the III arch are still weakly expressed. The branchial arches are separated by paired branchial grooves, of which the first are the deepest. In the thickness of the mesenchyme of the mandibular and hyoid branchial arches, the rudiments of branchial arteries are visualized in the form of hollow formations of various sizes.

In a 4-month-old human embryo (4.5 mm PCL), separation of the maxillary and mandibular processes was detected in the paired rudiments of the mandibular branchial arch (Fig. 1).

In human embryos of the 5th week of IUD, the rudiments of all 4 branchial arches from the side of the skin surface are covered with a 1-2-layer cuboidal epithelium, under which mesenchyme is located. In some places, signs of the basement membrane are determined. The primary oral cavity is lined with a sinple single-row epithelium. In embryos of this age group, the depth of branchial grooves and pockets reaches a maximum, as a result of which their ectodermal and endodermal epithelial linings come into direct contact with each other, and the mesenchymal layer between them disappears. At the end of the 5th week of IUD (embryos of 7.5 mm PCL), bilaterally located mandibular primordia converge as much as possible. The rudiments of the maxillary processes, which are directed cranially in relation to the mandibular processes, become clearer. On cross-sections of the head, the paired nasal medial and lateral processes that limit the nasal fossae, between which the frontal ridge is located rostrally, are clearly visible.

Analysis of serial histological sections of 5-week-old embryos showed that mandibular and maxillary processes, formed from the first branchial arch, differentiate asynchronously. We noted that the rate of morphogenesis in the maxillary processes is less pronounced than in the mandibular processes. In particular, this is manifested by the fact that at this stage of the IUD in the maxillary processes, we did not find clear areas of mesenchymal compaction, which would indicate its divergent differentiation.

By the end of the 5th week of IUD, both already formed primary hemocapillaries and their predecessors in the form of peculiar slit-like formations are determined in both mandibular and maxillary rudiments (Fig. 2). In the indicated vascular formations, formed elements of blood are still missing. Along with this, blood islands in the form of clusters of megaloblasts are also found, around which cells transforming into endotheliocytes are located.

In human embryos of the 6th week of IUD, the maxillofacial apparatus only vaguely resembles anthropomorphic facial features, since during this period the nasal processes that converge with each other and with the maxillary processes do not yet fully form the maxilla as such. By the end of the 6th week of IUD (embryos 12.0-13.0 mm PCL), the ventral processes of the mandibular arch are as close as possible to each other, forming the mandible.

Therefore, in the 6th week of IUD in the rudiments of the

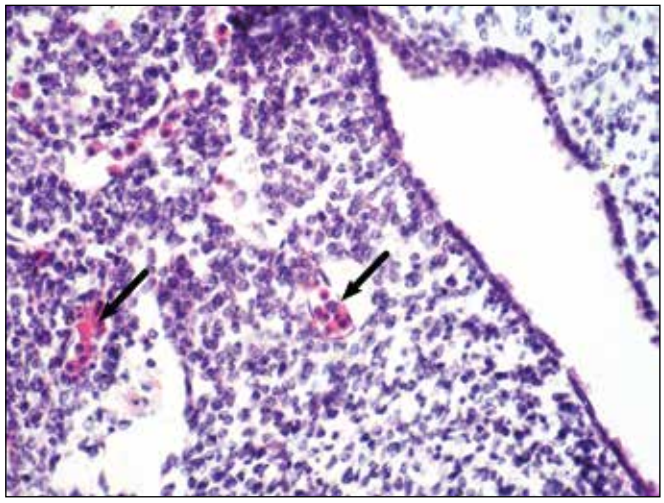

Fig. 2. Section of the maxillary process of I branchial arch of the human embryo 7.0 mm PCL (5th week of IUD). Staining with hematoxylin and eosin. Photomicrograph. x100. Blood islands in the mesenchyme are indicated by arrows.

maxillofacial part of the human head, the rates of cyto- and histogenetic rearrangements are more accelerated compared to the previous stages. This is manifested by increased proliferation of mesenchymocytes in peri-epithelial zones and their divergent differentiation towards both fibroblastic and osteogenic differentiation, which, we believe, is directly related to accelerated vasculogenesis in this area. At the same time, signs of asynchrony of morphogenetic transformations in mandibular and maxillary rudiments persist even in the 6th week of IUD.

On 3D reconstructions of serial sections of 7-week-old embryos, external signs of the formation of the visceral part of the head are more clearly defined, as a result of which human facial features are acquired (Fig. 3). Histological specimens of embryos 16.0-17.0 mm PCL in the epithelium lining the maxilla and mandible from the side of the primary oral cavity reveal small thickenings immersed in the underlying mesenchyme, which are the rudiments of the vestibular plates (Fig. 4).

At the end of the 7th week of IUD (embryos 19.0-20.0 mm PCL) qualitative morphological transformations occur in the maxilla – the maxillary, lateral and medial nasal processes come into contact with each other, as a result of which we can speak of signs of the completion of the formation of the maxilla. But, unlike the mandible, osteogenic islands are less pronounced in the maxillary rudiments, and cartilaginous rudiments are absent.

The rudiments of the maxillofacial apparatus are covered with epithelium, the structure of which is different on the outside and on the side of the oral cavity. Thus, the skin surface of the lips and cheeks is covered with a 1-2-layered epithelium, and when moving to the future border of the lips, the number of cell layers increases. The mucous membrane of the oral cavity is also lined with a stratified epithelium. The epithelium is separated from the mesenchyme by a clearly contoured basement membrane.

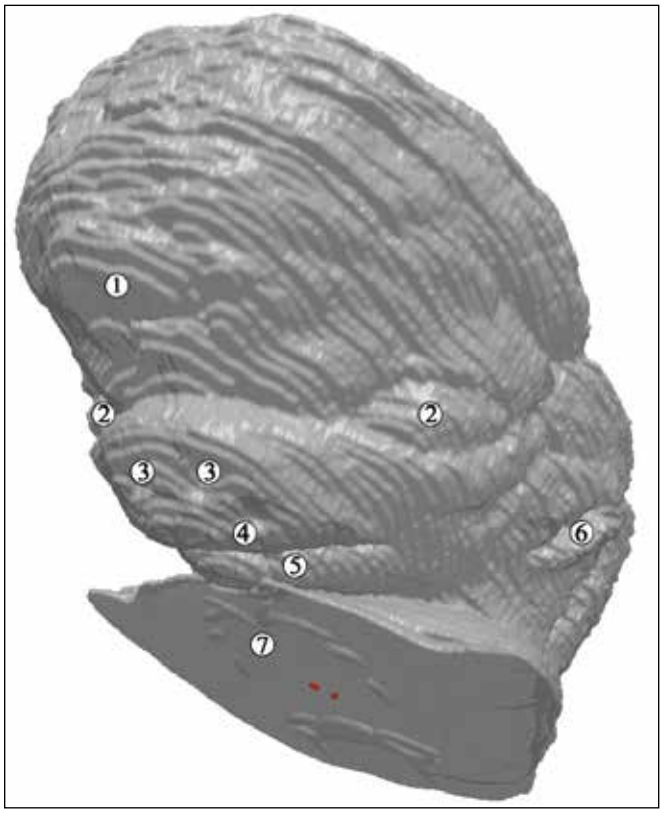

Fig. 3. 3D reconstruction model of the upper part of the human embryo 15.0 mm PCL. Left anterio-lateral projection. x15: 1 – frontal process; 2 – eye placodes; 3 – rudiment of external nose; 4 – rudiment of the maxilla; 5 – rudiment of the mandible; 6 – ear placode; 7 – cardiac hump.

By the end of the 7th week of embryogenesis in the converging mandible and maxillary processes, the formation of dental plates is noted, which on sections have the appearance of continuous epithelial cords consisting of densely packed cells immersed in the gingiva from their distal ends. A new feature that characterizes progressive transformations in the human maxillofacial apparatus during the 7th week of IUD is the beginning of the formation of masticatory muscles and muscles of face expression, which are represented by myoblasts. Morphological transformations in the constituent parts of the rudiments of the maxillofacial apparatus are accompanied by an increased course of vasculogenesis.

So, in the 7th week of IUD, there is an intense pace of differentiation of the structures of the maxillofacial apparatus. Frontal and lateral nasal processes forming the maxilla converge. Osteogenesis occurs more actively in the mandible. In the maxilla, mesenchyme densification cells begin to turn into osteogenic islands. The formation of the oral vestibule and dental plates are noted, and by the end of the 7th week of IUD, the rudiments of tooth buds are noted. Separation of masticatory muscles and muscles of facial expression are determined. At the same time, the rate of histogenetic transformations in the maxillary primordia continues to lag behind in comparison with the mandibular primordia.

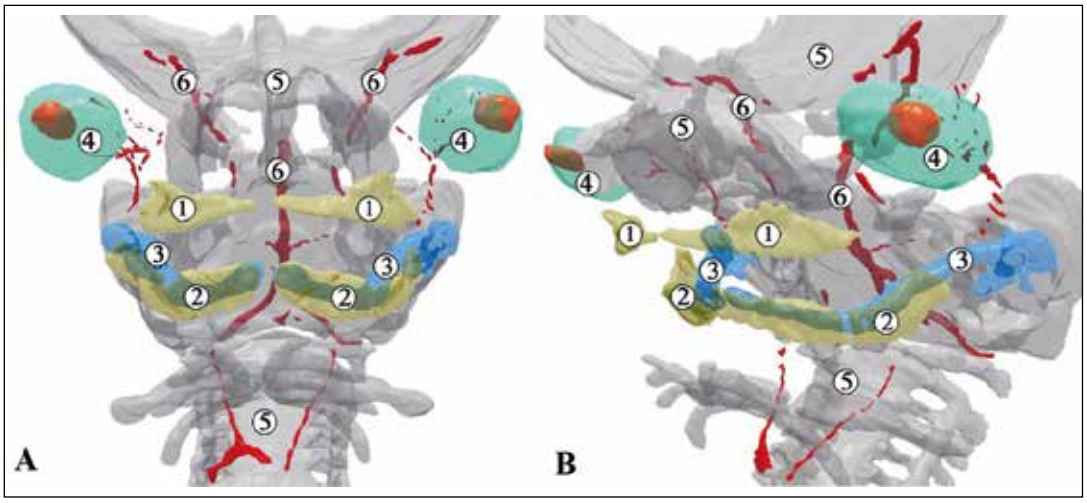

Fig. 4. 3D reconstruction model of the upper part of the human embryo 17.0 mm PCL. A – front projection, B – left anterolateral projection. x12: 1 – maxillary vestibular plates; 2 – mandibular vestibular plates; 3 – Meckel's cartilage; 4 – eyeballs; 5 – cartilaginous rudiments of bones; 6 – blood vessels.

At the end of the embryonic period (the 8th week of VUR), high rates of embryogenesis are observed, accompanied by pronounced step-by-step dynamic qualitative and quantitative transformations in the structures of various organ sources, including those that form the maxillofacial apparatus.

The analysis of the 3D-reconstructional models made from a series of micro-specimens showed that during the 8th week of IUD at the organ level, due to the convergence of the processes forming the maxilla, the formation of the upper lip is completed, and in the mandible, the convergence of the ventral ends of Meckel's cartilage continues. The resulting palatal plates begin to acquire a horizontal position, being located bilaterally from the tongue. They have osteogenic structures. Medially between the converging palatal plates is the nasal septum, in which foci of osteogenesis are also found. At the tissue level, the shaping processes of the oral vestibule become more pronounced. Vestibular plates, formed by stratified epithelium, in the form of parallel strands separate the lips and cheeks from the gingivae. Shallow grooves are found in them, which is evidence of separation of the gingival surface of the lips and, accordingly, the labial surface of the gingivae, which are lined with stratified epithelium.

In both jaws, 3D reconstructions of serial histological sections clearly show dental plates that sink into the gingival mesenchyme in the form of cords, on the outer surface of which there are forming tooth buds (Fig. 5).

In the maxilla, the centers of osteogenesis are visualized in the form of separate osteogenic islands of different sizes, which are stained oxyphilically, along the periphery of which osteoblasts are localized, and in the middle of such islands, single osteocytes, separated from each other by the intercellular matrix, can be seen. Some of the osteogenic islands are at the initial stages of osteogenesis in the form of osteoid masses surrounded by osteogenic cells. There are still no cells in the middle of such formations.

It should be emphasized that oxyphilia in the foci of osteogenesis of the maxillary rudiments is less pronounced than in the osteogenic islands of the mandible. Thus, the morphological features and tinctorial properties of the intercellular matrix of osteogenic rudiments testify to the heterochrony of bone formation in the mandible and maxilla.

The structural components of the rudiments of the lips, cheeks, and gingivae, which are located around the dense rudiments of both jaws, are represented by mesenchymocytes that differentiate in different directions, therefore, in different zones of the mesenchyme, their morphology and distribution density are not the same. Some of the mesenchymocytes are transformed into cellular elements of loose fibrous connective tissue, others continue to participate in vasculogenesis. At the same time, together with exchange channels, primordial hemocapillaries and blood islands, vessels of a more complex structure are already revealed.

At the end of the 8th week of IUD, the rudiments of the buccal muscles, as well as the omohyoid muscle and the muscles of the tongue are more clearly visible, the separation of which occurs earlier than anything else.

Therefore, by the end of the embryonic period of human development, morphogenetic processes in the maxillofacial apparatus are characterized by further transformations, as a result of which a dense base of the jaws is formed, and the soft tissues surrounding them lose the features characteristic of mesenchyme, transforming into structures of loose fibrous connective tissue and muscle tissue. Corresponding progressive changes are also observed in the ectodermal derivatives of the maxillofacial apparatus, which participate in the formation of the oral cavity and in the formation of tooth buds.

During the 9th week of IUD, morphogenetic transformations in the sources of the maxillofacial apparatus of human fetuses continue to be characterized by qualitative and quantitative changes that are manifested both at the organ and tissue levels. Thus, at the organ level, there is a consolidation of the lateral palatine processes that form the hard palate, which in the ventro-dorsal direction merge over a longer distance with each other, as a result of which the oral cavity is separated from the nasal cavity. The nasal septum comes into contact with the lateral palatal plates that depart from the maxillary processes. In the places of

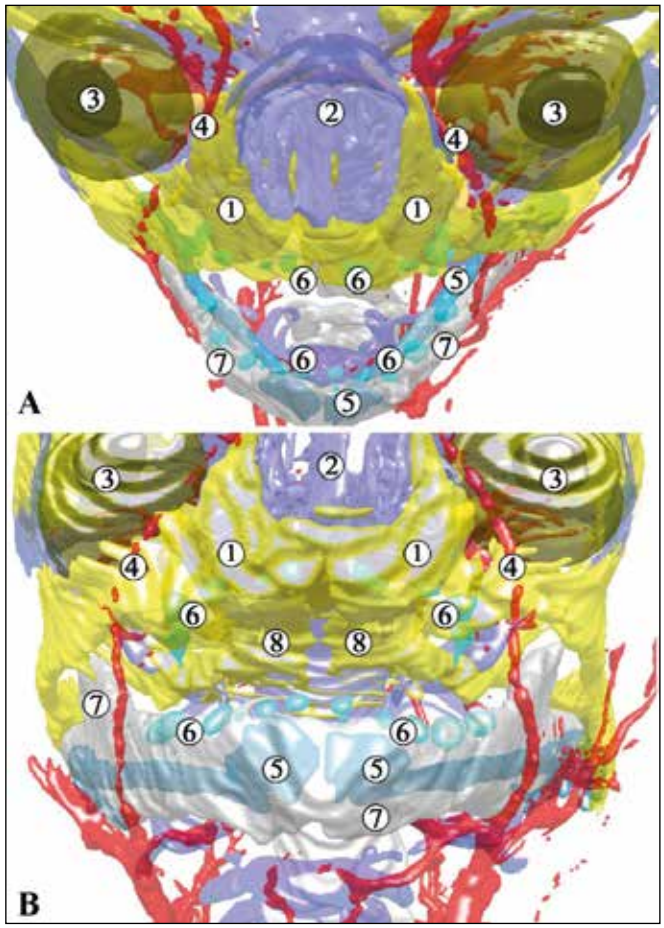

Fig. 5. 3D reconstruction model of the upper part of the human embryo 22.0 mm PCL. A – front projection, B – anterior-inferior projection. x10: 1 – rudiment of the maxilla; 2 – cartilaginous nasal capsule; 3 – eyeballs; 4 – blood vessels (facial artery); 5 – Meckel's cartilage; 6 – tooth buds; 7 – mandible.

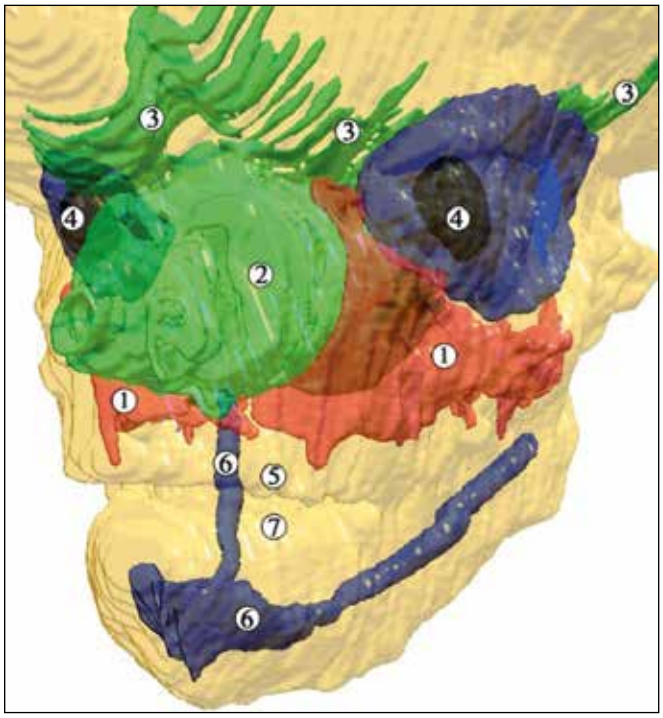

Fig. 6. 3D reconstruction model of the upper part of the human embryo 48.0 mm PCL. Left antero-lateral projection. x10: 1 – maxilla; 2 – cartilaginous tissue of the nasal capsule; 3 – rudiments of the bones of the skull base; 4 – eyeballs; 5 – soft tissues of the upper lip; 6 – soft tissues of the lower lip; 6 – Meckel's cartilage.

contact of the palatal plates with each other and with the nasal septum, clear boundaries are defined. The basis of the septum is hyaline cartilage, which slightly expands downwards. Osteogenic formations surrounded by compacted young connective tissue are located around it in a narrow strip. Osteogenesis is actively taking place in both jaws, as a result of which their bone base is formed. In the maxilla, foci of osteogenesis noticeably increase compared to the previous stage of development and consolidate. In both jaws, alveolar processes are formed in the form of bone plates that connect at the base.

Soft tissue structures that form around the dence base of the jaws are involved in the formation of gingivae, lips and cheeks. The outer lips and cheeks are covered with a stratified epithelium of ectodermal origin, the number of cell layers in which reaches 3-4. The epithelial lining of the lateral palatine processes from the side of the oral cavity is represented by a single layer of cuboidal cells with spherical nuclei, and during its transition to the inner surface of the gums, it becomes two-layered.

Therefore, by the end of the 9th week of the human IUD, the formation of a secondary oral cavity occurs, which is accompanied by further complication of intercellular and intertissue relations in heterogeneous rudiments of the maxillofacial apparatus.

In the 10th week of IUD, the rate of differentiation of hard and soft tissues of the human maxillofacial apparatus continues to increase. As our studies have shown, in fetuses in the middle of the 9th week of IUD (36.0 mm PCL), the separation of the primary oral cavity, which began at the end of the 2nd month of gestational age, into the definitive oral cavity and nasal cavity due to the convergence and fusion of the palatine processes, practically ends, and only the edges of both halves of the soft palate in the very final section are still at some distance from each other.

The nasal septum also grows along the middle line for a longer period with palatal processes, where in places there are islands of compactly located epitheliocytes undergoing apoptotic changes, the signs of which are more intense staining of their cytoplasm, compaction of the matrix and shrinkage of the nuclei. In the distal part, the surface of the nasal septum in contact with the palatine processes is still completely covered by a stratified squamous epithelium.

The maxilla is modeled by islands of bone tissue that merge with each other (Fig. 6), and the hard base of the mandible, together with bone tissue, continues to form Meckel's cartilage. The bone plates of both jaws have a typical structure characteristic of bone tissue. In places along their periphery, signs of periosteum formation are revealed, in which the presence of outer and inner layers can be ascertained. Fuchsinophilic stained collagen fibers

are found in the outer layer, and osteoblasts are localized in the inner layer.

The matrix of bone tissue contrasts heterogeneously. Its peripheral zone exhibits oxyphilic properties, and the central zone is stained with basic dyes. Lacunae with osteocytes with cytoplasmic processes are defined in it. In the mandible, the foci of ossification in the lateral zones are more developed than in the medial direction, where they form the palatine processes and the hard palate.

Therefore, during the 10th week of the human IUD, the formation of connective tissue structures continues in the soft tissues of the maxillofacial apparatus, and facial and masticatory muscles differentiate.

During the 11th-12th weeks of IUD, a complete separation of the oral and nasal cavities occurs due to the completion of the formation of the soft palate, the oral cavity is formed, as a result of which the lips and cheeks are separated from the gingivae by a deep furrow, the bottom of which is lined with several layers of epithelial cells. The maxilla is represented by bone trabeculae that unite with each other.

DISCUSSION

In our study, we used the method of making three-dimensional computer reconstructions of a series of consecutive histological sections, which made it possible to clearly determine the syntopy of the component rudiments of the maxillofacial apparatus, as well as to trace the features of histo- and organogenesis in the dynamics of prenatal human development.

In 4-week-old embryos, the stomodeal depression is clearly visualized, and at the 5th week of IUD, the structural components involved in the formation of the maxillofacial apparatus are well defined [7-9].

Thus, it is stated that on the 33-36th day, when the parieto-coccygeal length of the embryos reaches 7.0-9.0 mm, the rudiments of both jaws are determined [5]. However, according to other data, the presence of mandibular and maxillary processes is visualized earlier, on the 25-26th day, when embryos have from 14 [10] to 20 [11] pairs of somites, and even earlier – in 21-day-old embryos [12].

Our research established that the division of the distal parts of the mandibular arch into paired dorsal (maxillary) and ventral (mandibular) processes is visualized in the embryo of 4.5 mm PCL. At the same time, the formation of the structures of the processes initially occurs asynchronously. This is manifested in the difference in their sizes and, in our opinion, is due to the fact that in the mandibular rudiments the rates of cell proliferative processes and their differentiation are more accelerated than in the maxillary ones, therefore the latter lag behind in their growth and in the further stages of embryogenesis, which is manifested by the delay of their convergence between themselves in comparison with the mandibular processes.

According to our data, during the 5th week of embryogenesis, the mandibular processes of 7.0 mm PCL embryos converge as much as possible, while the maxillary processes are still at a sufficient distance from each other during this period. Their convergence with the nasal processes occurs in embryos of 19.0 mm PCL and only by the end of the 8th week (embryos of 26.0 mm PCL) it is possible to talk about the completion of the formation of the mandible.

As the facial part of the head forms in the sources of the maxillofacial apparatus, progressive morphogenetic transformations take place, when initially seemingly homogeneous, indifferent structures of the mesenchyme under the influence of various inducers and conditions [13] undergo divergent differentiation, as a result of which it is transformed into various types of connective tissue [14]. The transformation of mesenchyme into connective tissue is based on phylo- and ontogenetic determination, i.e. programming of the path of cellular differentiation, the characteristic feature of which is its wide range [15]. At the same time, "the main general feature of cell differentiation of mesenchyme derivatives, unlike cells of other tissue types, is the pronounced ability to form intercellular substance" [16].

In the maxilla, foci of direct (membranous) osteogenesis appear at the end of the 6th week of IUD, that is, a week later than in the mandible, after the fusion of the maxillary processes with the nasal and middle frontal processes. As noted by researchers [17-19], foci of membranous ossification in both jaws are clearly defined in embryos 8-week-old embryos (23.5 mm PCL), totally stained with alizarin and illuminated in xylene. At the same time, there are several centers of ossification in the maxilla, which develop from heterogeneous sources. In particular, its incisal part is formed from the material of the medial nasal processes, and the branches originate from the maxillary ridges of the mandibular pharyngeal arch. In the future, the bone tissue of these branches of the maxilla is the first to undergo calcification, while in its incisor part this process is carried out somewhat later.

According to literature data [18, 19], human embryos of 12.5-13.0 mm PCL already have a primary palate. It is known to be isolated as a result of the fusion of the distal ends of the palatine processes, observed, according to some data [20, 21], somewhat later, on the 7th week, in embryos 15,0-18,0 mm PCL, due to which the central part of the upper lip is also formed [22]. According to other information [23], this process occurs in the 8th week of embryogenesis. In the fetal period, which begins at the 9th week of IUD, the proximal parts of the palatine processes continue to converge, the fusion of which is completed for a longer period at the end of the 9th week of IUD (33.0 mm PCL), as a result of which the secondary palate is formed. These data are confirmed in our research. Other sources also state that this process only begins in the 7-8th week, and ends only in the 10th week [21, 24]. Attention is focused on the fact that precisely in such periods, when certain embryonic rudiments are isolated, there is a danger of development anomalies caused by both hereditary and environmental factors [21, 23].

According to literature data [24], on the 9th week of IUD, the beginnings of the maxillary sinuses separate in the form

of small cavity formations. In the maxilla, the process of formation of the alveolar groove is slightly behind in time compared to the mandible.

On the 10th week of IUD, osteogenic islands continue to consolidate in the maxilla. Merging with each other, they gradually spread into palatal processes, which in the area of the hard palate are already growing along the entire length, and only in the zone of formation of the soft palate there is still a small slit-like lumen between them.

In 6-week-old embryos, the formation of the lower lip is completed, and the formation of the upper lip occurs during the 7-8th week of IUD as a result of the maximum convergence and fusion of the maxillary processes with the medial nasal processes of the frontal ridge. At the same time, if the lower lip is completely derived from the mandibular arch, then the upper lip is formed from heterogeneous rudiments: its lateral parts are formed by maxillary processes, and the middle part is formed by medial nasal processes [25]. Together with these processes, the cheeks and alveolar processes of both jaws are formed, while the own plate of the mucous membrane of the oral cavity is formed from the ectomesenchyme [16].

In the oral region, as a result of complex reciprocal relations between the epithelium and the proper mesenchyme, the formation of maxillary and mandibular vestibular plates occurs, which separate the rudiments of the lips and cheeks from the gingivae, as a result of which the formation of the oral cavity begins. According to our data, the leading role in its formation belongs to the epithelium, which actively proliferates and gradually sinks into the proper mesenchyme. At the same time, the laying of epithelial dental plates takes place, which grow in the form of continuous cords into alveolar processes, on the outer surface of which tooth buds are formed during the 7-8th week of IUD, and by the end of the 8th week of IUD, mesenchyme growth is observed in them in the form small papillae, as a result of which enamel organs are formed. In the 9th week of IUD, they begin to acquire the shape of a "cap", which is also indicated in other works [19, 21, 26-30].

CONCLUSIONS

1. On the basis of a complex of morphological research methods, data were obtained that made it possible to establish the general patterns of development of the human mandible: separation of the pharyngeal apparatus (4th week), convergence and fusion of the jaw processes (5-8th weeks), formation of tooth buds (7-8th weeks), which allows considering the specified periods as critical in the formation of possible anomalies in the facial part of the skull. At the same time, a tendency of heterochrony of morphological transformations in the mandible and maxilla was revealed.
2. At the beginning of the 4th week of intrauterine development, 3 pairs of pharyngeal arches are formed. Detachment of the mandibular and maxillary processes of the mandibular pharyngeal arch is planned. In embryos of the middle of the 5th week of intrauterine development, the nasal medial and lateral processes are structurally formed, between which the rostral overhangs the frontal process. At the 6th week of intrauterine development, the ventral processes of the mandibular arch are connected along the midline, forming the mandible.
3. During the 7th week of intrauterine development, the maximum convergence of the maxillary processes with the lateral and medial nasals occurs, and in embryos of 20.0 mm PCL grow with the frontal process, forming the maxilla and upper lip. Osteogenic islands are defined in the maxillary processes. During the 8th week of intrauterine development, the bone base of the jaws is modeled as a result of the increase in the size of osteogenic islands and their fusion, alveolar processes are formed. The palatal plates, in which osteogenic formations are defined, begin to change their position to a horizontal one.

During the 9-10th weeks of intrauterine development, the primary palate is formed as a result of the fusion of the palatine processes, the separation of the oral and nasal cavities begins, and the nasal septum is formed, which comes into contact with the lateral palatal plates. In both jaws, the mass of bone tissue grows, enamel organs are separated.

At the 11th week of intrauterine development, the bone base models both jaws. Due to the processes of histogenesis of the soft tissues of the maxillofacial apparatus, the face acquires anthropomorphic definitive human features.

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