



## Microscopical Indices Of Thymus in Newborn Fetuses

<b>Khusanov Erkin Uktamovich</b>	<b>Samarkand State Medical University</b>
<b>Korzhavov Sherali Oblakulovich</b>	<b>Samarkand State Medical University</b>
<b>Miniyarova Alyona Rustamovna</b>	<b>Samarkand State Medical University</b>

### ABSTRACT

The formation of the immune system in ontogenesis, in particular its central organ, the thymus, is determined by a set of relationships between mother and fetus and the course of the offspring's early adaptation to the conditions outside utero. As a rule, in early postnatal ontogenesis the immune system is in a transient state and continues to form under the influence of a variety of external factors. An uncomplicated pregnancy largely determines the normal course of maternal-fetal immunological relations and determines the development of a complete immune system and its central and peripheral organs in the offspring in postnatal ontogenesis.

### Keywords:

newborn, thymus, thymus gland, thymus anatomy, thymus histology, gestational thymus maturity.

### Introduction

From an embryonic perspective, the thymus gland is one of the first endocrine organs and the first lymphoid organ. In the early embryonic development bone marrow lymphoblasts passing through the thymus become thymocytes which enter the blood and other lymphoid organs not only during the embryonic period but during the whole life of the organism. Thus, the thymus is an organ regulator of the immune system and at the same time a producer of lymphoid cells, which represent the basis of the body's defense system against pathogenic microorganisms and foreign molecules [5,7,9,11,14,16]. Structurally, the thymus is a complex organ consisting of stroma and regenerative lymphoid tissue. The stroma constitutes about 10% of the organ mass and consists of reticular and epithelial cells [1,4,14,16]. The thymus parenchyma is composed of thymocytes and lymphocytes migrating from the bone marrow. Exposure to

pathogenic climatic and environmental factors cause maternal and fetal immune system dysfunction in almost all major body systems [2,3,9,11]. It is known that the thymus, as a central organ of immunogenesis, can undergo transformations under the influence of various pathogenic factors occurring in the maternal organism during pregnancy. New data on the morphofunctional organization of the thymus have been obtained by modern submicroscopic, radiographic, immunohistochemical and biochemical methods of study. Histologically thymus represents, as if a three-layered organ, consisting of connective tissue stroma, epithelial base and lymphoid contents, the latter in a developed thymus accounts for the bulk of the organ. The connective-tissue stroma is represented by septa and the organ capsule. The perivascular space is formed by intercellular matrix, fibroblasts, fibers, reticular cells and labrocytes and macrophages [10,13,19].

Material and methods of investigation. The thymus of newborns born at term and who died mainly from asphyxia or craniocerebral trauma at the time of delivery was studied. General morphological examination by hematoxylin and eosin staining; histometry: measurement of thickness of capsule, cortex and medullary layer of lobules; volume ratio of structural and cellular elements of thymus; statistical processing of the received digital data.

Autopsy materials for the review histological, histochemical, immunohistochemical, electron-microscopic techniques were taken not later than 30 minutes after death with the following fixation in solutions of Carnua, Buena, Becker and 10% neutral buffered formalin. Paraffin sections 4-5  $\mu\text{m}$  thick were stained with Ehrlich's haematoxylin with eosin prepaint, Weigert's iron haematoxylin with van Gieson and Mallory prepaint. Glycosaminoglycans (GAGs) were differentiated by 0.1% toluidine blue solution on citrate-phosphate buffer at different pH values (3.5-6.5) and slice control with bacterial and testicular haluronidase.

Results of the study. Depending on the significance of the fetal factor in the organ complex and its development as well as in the formation of the elements of the "mother-placenta-fetus" functional system, we compared the measured organ parameters and morphological features of the thymus gland with 15 somatometric parameters of fetuses at 21-26 weeks of gestation in the induced termination of pregnancy for medical reasons. Analysis of somatometric parameters in fetuses and neonates with induced and spontaneous termination at 21-26 weeks' gestation showed that uncomplicated pregnancy is characterized by harmonious and proportional somatic development. In this type of somatic development, body weight and length, head circumference, chest, shoulder length, hip length, weight and height in coefficient increase evenly and in direct proportion to the gestational period. The positive dynamics of the above somatometric parameters were revealed both in the whole group and in subgroups with two-week intervals: 21-22; 23-24 and 25-26 weeks. Thus, the fetal weight gain at 23-24 weeks is 171 g, at 30 weeks - 193 g. Body length

(calf-length) increases by 3-4 cm every fortnight. The positive dynamics of the calvarial measurement is directly related to the increase in the linear parameters of the lower extremity, particularly of the femur, which is 1.5 times longer at 25-26 weeks than at 23-24 weeks. The increase in linear parameters of the tibia within the considered subgroups is statistically insignificant. The length of the upper extremity varies in the range from 1.1 to 1.5 cm, with the shoulder growing most intensively (0.7 - 0.9 cm). The intensity of growth of the upper limbs as well as the lower limbs stabilises from 26-27 weeks of gestation. The circumferences of the upper arm, forearm, thigh and lower leg, which characterise the growth of muscle mass and subcutaneous fatty tissue, change according to the increase of gestational age, reaching maximum values at weeks of gestation. It is not valid to consider the analysis of anthropometric parameters as complete without taking into account certain coefficients. The weight-for-height coefficient at 21-26 weeks of gestation tends to increase progressively, especially at weeks of intrauterine development, which confirms the positive dynamics of weight and linear body parameters at this stage of ontogenesis. The thoracic growth coefficient is  $0.58 \pm 0.06$  and remains stable within this gestational age, indicating proportional somatic development of the fetuses in the mid-gestational period. In addition, the proportionality of fetal development was assessed using coefficients such as the ratio of upper and lower limb length to body length. The coefficient (arm-length to calf-length ratio), as well as the thoracolumbar coefficient, did not change statistically significantly and was  $0.39 \pm 0.015$ . Somewhat different dynamics were found in the ratio of lower limb length to calf-length. Against the background of stability of this parameter in fetuses of 21-22 and 23-24 weeks of gestation, an increase in this coefficient by weeks of development is noted, which confirms the enhanced growth of the lower limb at this stage of ontogenesis. The harmony and proportionality of fetal somatic development is confirmed by the presence of a strong direct ( $r=0.7$ ) correlation between fetal weight and the circumference of the chest, head,

tibia length, as well as linear parameters of the arm and shoulder. There was a moderate positive association ( $r=0.5$ ) between fetal weight and leg and thigh lengths, as well as the circumferences of both the limbs as a whole and their component parts. The observed dynamics of somatometric parameters in fetuses at 21-26 weeks of gestation are consistent with the physiological type of intrauterine development, which is characterized by a relatively uniform increase in body weight and length, head circumference, chest, shoulder and hip length and mass-to-stature coefficient. The correlation between somatic development and formation of central organ of immune system in 21-26 weeks' gestation is proved by presence of moderate direct ( $r=0.6$ ) relation between fetal weight and thymus linear weight parameters. At 21.4%, the direct positive correlation ( $r=0.6$ ) was found between fetal weight, fetal length, chest circumference and organometric parameters of thymus, i.e. its mass, length and width. In enlarged subgroups (21-24 and 25-26 weeks), as well as in general at 21-26 weeks of development, thymus organometric parameters increased significantly ( $p<0,001$ ) in proportion to gestational age. Maximal increase of the mentioned values and two-fold increase of correlations at 25-26 weeks of gestation testify to the intensive development of both soma and the central organ of immune system at this stage of foetogenesis. The rate of thymus weight gain in fetuses at 25-26 weeks of gestation was 3-fold higher than the corresponding parameter in fetuses at 21-22 weeks of development and averaged 2.7 - 3.2 g. A significant increase in the linear size of the organ confirms its growth, both in length and width. The expression of cytokeratin by outer layer reticuloepithelial cells reflects the degree of their differentiation and indicates their ectodermal origin [2,3,7,8,14,20]. The second type of reticuloepithelial cells acquires a stellate shape due to cytoplasmic outgrowths. Epithelial cells of this type contain a circular nucleus, 12  $\mu\text{m}$  in diameter, with 1-2 nuclei and finely condensed chromatin. Among ultrastructure, few tonofilaments, multivesicular bodies, vacuoles, short profiles of rough endoplasmic network and well developed lamina complex

are visualized in cytoplasm. In subcapsular zone epithelial cells are found, whose cytoplasm contains single thymocytes along with vacuoles and small electron-dense inclusions. The cytoplasmic outgrowths of reticuloepithelial cells are located between lymphocytes, are in contact with them and are "nurse" cells [12,14,15,16]. [12,14,15,16,18]. In the early stages of the mid-petal period, i.e. in 21-22 weeks gestation fetuses, epithelial cells of a number of lobules migrate to the surrounding mesenchyme, forming various cell strands in length. The latter in the thymuses of 23-24 weeks gestation fetuses, having a high growth potency, perform a cambial function and contribute to the formation of growth zones at the periphery of the lobules. Lymphoblasts, corresponding to pre-T lymphocytes by antigen composition and expressing CD2 antigens on the membrane (expression ratio 2.79 units), prevail among lymphocytes in the subcapsular zone. The lymphoblast nucleus has a reticulated chromatin structure with 1 to 2 nuclei located amongst it. The cytoplasm occupies minimal area, contains free ribosomes, single cisternae of granular endoplasmic reticulum and mitochondria. An additional indication of thymocyte proliferation activity was an increase in the mean histochemical coefficient (MHC) of deoxyribonucleic substances in lymphocytes of the subcapsular zone up to 0.42 wt%. The SCC value within all structural and functional zones increases in parallel with gestational age and averages 0.27 units.

Apart from lymphoid and epithelial cells, single macrophages with PAS-positive inclusions are found in the subcapsular zone, and they are more frequently detected in the thymus of 26-27 weeks gestation fetuses. The density of cellular elements in the subcapsular zone is  $17.76 \pm 02$  cells and increases in direct proportion to gestational age. At 26-27 weeks of gestation, the number of cells per unit area increases to 22. The inner cortical zone of the lobules is dominated by medium-diameter lymphocytes expressing CD2, CD1 antigens, indicating continued antigen-independent lymphocyte differentiation. However, this zone is also characterized by the formation of receptors to the antigen, as evidenced by a

significant increase in the expression of CD3 T-lymphocytes. Of the cellular microenvironment of lymphocytes, dark-type epithelial cells predominate, characterized by an abundance of ultrastructure, which indicates their functional activity [6,9,10,11,13,19]. T-lymphocytes of the medullary zone, unlike cortical lymphocytes, mostly have a mature phenotype, with CD 2, CD3 antigens, which confirms the completion of their differentiation stage.

### Conclusion

Thus, the intrauterine period from 21 to 26 weeks of gestation is characterized by intensive somatic development, which, according to the theory of intrauterine cell growth, is based on high proliferative activity of cells in combination with progressive increase in their size. A comparative analysis of somatometric parameters in the enlarged groups (weeks 21-22 and 25-26) confirmed the intensity of somatic development of fetuses at weeks 25-26. Considering the dynamics of somatometric parameters and their specifying coefficients, this stage of ontogenesis should be classified as critical. Exposure to pathogenic factors, including intrauterine infections, can cause a failure of compensation at this stage of gestation and lead to preterm birth and the birth of children with intrauterine developmental delay syndrome. The thymus gland in fetuses 21-26 weeks of gestation is shaped like a thymian leaf and is represented by two lobes connected at the base by an isthmus and covered by a thin connective tissue capsule. In 85 fetuses (74.7%), asymmetry of the lobes was detected as early as 21-22 weeks of gestation and the left lobe exceeded the right lobe in linear parameters. In addition to the two lobes, 91 fetuses (80%) showed additional lobules (up to 4 in number) rounded in diameter from 0.4 to 0.8 cm at the base of the thymus. Thus, the main criteria of gestational thymus maturity in fetuses at 23-24 weeks are incomplete cortico-medullary differentiation in 18-20% slices, more than twofold prevalence of cortical ( $58,29 \pm 2,11\%$ ) over medullary ( $23,87 \pm 0,75\%$ ) specific volume with cortico-medullary coefficient equal to 2,5 units. and specific vessel volume in interstitial tissue  $0.46 \pm 0.07\%$ , with maximum density of

cellular elements ( $29.94 \pm 0.06$  cells) in the inner cortical zone, with an average histochemical ratio of deoxyribonucleic substances in lymphocyte nuclei of 0.27 count units and glycoproteins (0.36 count units).

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