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# Dynamics of lymph nodes weight characteristics in cattle during the prenatal period of their ontogenesis

**M. A. Lieshchova, A. V. Oliyar, D. D. Bilyi, P. M. Skliarov, D. M. Masiuk, V. V. Logvinova, A. A. Bohomaz**
*Dnipro State Agrarian and Economic University, Dnipro, Ukraine*

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Dnipro State Agrarian and Economic University, S. Efremov St. 25, 49600, Dnipro, Ukraine

Tel.: +38-067-256-24-86
**E-mail**: lieshchova.m.o@dsau.dp.ua

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**Abstract.** In lymph nodes, as peripheral organs of the immune system, the patterns of their growth and development are unique in many ways, especially during the prenatal period of ontogenesis. The changes in the absolute and relative mass of lymph nodes in 66 bovine fetuses of different gestational ages (2–9 months) were studied. The weight of the fetuses and organs was determined with an accuracy of 0.001 g. According to the indicators of weight, body length, and the degree of development of the fetal skin derivatives, their age was established. It was found that in the first third of the fetal period of ontogenesis, the dynamics of the lymph nodes' absolute mass was characterized by a moderate increase, which occurred simultaneously with an increase in the weight of the fetus itself. The relative weight at the beginning of the fetal period changed unevenly: it decreased in the superficial cervical and mandibular and increased in the popliteal and caudal mediastinal lymph nodes. In the second third of the fetal period, both the absolute and the relative weight of the examined organs increased dramatically (with the maximum at 7 months-old age). During the last third of the fetal period, a gradual increase in the absolute mass of all lymph nodes was found, and their relative mass, on the contrary, decreased moderately. In the second and last third of prenatal development, there was no direct relationship between the growth of the lymph nodes mass and the fetal total mass.

**Keywords:** ontogenesis; bovine fetuses; hemopoietic and lymphopoietic organs; lymphoid tissue; the absolute and relative organ's mass

# Динаміки вагових характеристик лімфатичних вузлів великої рогатої худоби в пренатальному періоді онтогенезу

**М. О. Лєщова, А. В. Оліяр, Д. Д. Білий, П. М. Скляров, Д. М. Масюк, В. В. Логвінова, А. А. Богомаз**
*Дніпровський державний аграрно-економічний університет, Дніпро, Україна*

**Анотація.** У лімфатичних вузлів, як периферичних органів імунної системи, закономірності росту і розвитку являються багато в чому унікальними, особливо в пренатальному періоді онтогенезу. Досліджено зміну абсолютної і відносної маси лімфатичних вузлів 66 плодів великої рогатої худоби різних строків гестації (2–9 місяців). Масу плодів і органів визначали з точністю 0,001 г. За показниками маси, довжини тіла та ступенем развитку похідних шкіри плодів визначали їх вік. Встановлено, що в першій третині плодового періоду онтогенезу динаміка абсолютної маси лімфатичних вузлів характеризувалася помірним збільшенням, що відбувалося синхронно зі збільшенням маси самого плоду. Відносна маса на початку плодового періоду змінювалася неоднаково: зменшувалася у поверхневому шийному і нижньощелепному та збільшувалася у підколінному і каудальному середостінному. У другій третині плодового періоду різко зростала як абсолютна, так і відносна маса досліджуваних органів (максимально у 7-місячному віці). Протягом останньої третини плодового періоду виявили поступове збільшення абсолютної маси усіх лімфовузлів, а їх відносна маса навпаки – помірно знижувалася. У другій і останній третині пренатального розвитку не встановлено прямої залежності росту маси лімфатичних вузлів від загальної маси плоду.

**Ключові слова:** онтогенез; плоди великої рогатої худоби; органи гемо- і лімфопоезу; лімфоїдна тканина; абсолютна і відносна маса органів

## Introduction

It is well known that during the prenatal period of ontogenesis there is a significant increase in the fetal total weight. The total prenatal growth of the body, which is the sum of the growth of various organs and tissues making up the body, has been analyzed by many researchers for both humans and different animal species using various methods (Clatworthy & Anderson, 1944; Shmal'gauzen, 1984; Snow, 1986; Luecke et al., 1995; Randall et al., 2008)

It is a fact that the growth of animals proceeds unevenly: periods of acceleration are replaced by periods of decline, when growth slows down, and sometimes even almost stops. The highest growth rate (mass increase rate of a growing animal) is characteristic of the early stages of life, and by the end of prenatal development, it decreases. It has been established that the mass of a calf embryo during the first month of uterine development increases 600 times, during the second month by 43.3 times, during the sixth month by 2.3 times, and during the ninth month only by 1.4 times. Uneven growth is characteristic not only of the organism as a whole but also of individual organs and tissues. The whole organism growth periods do not coincide with the growth periods of individual organs, since they do not stop growing at the same time (Jackson, 1909; Ferrell, 1991; Chaudhuri, 2016). The task of each organ is to perform a specific function in the body, for the performing of which there is a certain pattern of its growth (Luecke et al., 1995; Arora, 2011). It is also known that the growth rate of the fetus and its organs depends on the influence of various factors both on the maternal organism and on the fetus itself (Heggestad & Wells, 1965; Ferrell, 1991).

The immune system is one of the most important homeostatic systems of the body, which determines the state of health and its adaptive capacity. For the organs of the immune defense, which include the lymph nodes, their growth and development patterns are in many respects unique. All these organs are characterized by their early initiation during embryogenesis, almost complete morphofunctional maturity, sufficient to perform definitive functions (proliferation of various lymphocytes clones and immunobiological function) by the time of birth, and early age-related involution (Mebius, 2003; Nishikawa et al., 2003; Sapin, 2006; Benezech et al., 2010; Islam et al., 2018). Also, one of the main regularities in the development of those organs is an intensive increase in their morphometric characteristics, accompanied by accelerated differentiation of lymphoid tissue during the early postnatal ontogenesis due to the entry of an organism from relatively sterile intrauterine conditions into the external environment with numerous antigens (Sapin, 2006; Gavrilin et al., 2017). It is known that the fetal immune system is able to carry out protective reactions, but at the same time it functions in an extremely difficult situation: on one hand, it ensures the maintenance of the internal fetal homeostasis, on the other hand, being immature, but constantly subjected to antigenic pressure from the mother, it must quickly adapt and respond to these impact. Under these conditions, the functioning and morphology of the fetal immune system is different from those of adult animals (Galeeva, 2012; Petrenko, 2016; Galeeva & Ul'yanov, 2019).

Lymph nodes perform both general functions specific to nodes of any localization and particular ones associated with their regional features. Among the most important and universal functions of the lymph nodes, regardless of their topography, distinguish hematopoietic, immunopoietic, protective-filtration, exchange, and reservoir functions (Beyer & Meyer-Hermann, 2007).

At the same time, literature analysis shows that along with the general, there are specific features specific to each lymph node. They are associated, first of all, with the transformation of their tissue and cellular ratios and reflect the diversity of the development and functional state of animal's body areas and organs. This how the differences in the lymph nodes' mass of various regional groups in rabbits were determined, and it was noted that the individual weight features of the same group of lymph nodes were very significant. The mass of the same lymph node type in rabbits can normally differ by 8–15 times (Jeklova et al., 2007).

Ontogenesis and age-related structural features and cellular composition of lymph nodes in cattle have been studied in detail by many authors at different levels of their structural organization (Casteleyn et al., 2008). It was noted that the formation of the pre-scapular and posterior mediastinal nodes began in 2-month-old fetuses. At 3-4 months-old, the submaxillary, bronchial and mesenteric lymph nodes were formed. In 8-month-old fetuses and 1.5–2-year-old calves, there was a decrease in the lymph nodes mass (Ohtani & Ohtani, 2008; Grigor'ev & Moljanova, 2009).

The state of the lymph nodes, including their morphometric parameters both at the time of birth and during various stages of the pre- and postnatal period of ontogenesis, is one of the criteria for their morphofunctional maturity. This is necessary to take into account for various experimental studies, preventive and therapeutic measures (Martinez-H et al., 2012). In addition, the study of the morphological patterns of animals prenatal ontogenesis, the development of its tissues, organs and systems is necessary to understand the essence of the processes occurring during intrauterine development, to study the critical periods of the embryonal and fetal development.

The aim of the study was to determine the dynamics of the weight characteristics of the lymph nodes in cattle during their prenatal development.

## Material and Methods

The material for the study included 66 bovine fetuses of red steppe cattle, both sexes ranging from 60 g to 27 000 g. The fetuses were obtained from the slaughterhouse of Dnipro city (Ukraine) without visible damage and deformations from clinically healthy cows after slaughter (for reasons not associated with either infectious or invasive diseases). The fetuses were examined fresh, without fixation, immediately after slaughter. The body weight of fetuses up to 10 kg was determined with an accuracy of 10 g, larger fetuses with an accuracy of 100 g. Fetal lymph nodes of various localization were selected: superficial cervical *(Limphonodi cervicales superficiales)*, mandibular *(L. mandibularis)*, popliteal *(L. poplitei),* caudal mediastinal *(L. mediastinales caudales)*, portal *(L. portele)*, jejunum *(L. jejunales)*, medial iliac *(L. iliaci mediales)* (Zelenevsky, 2013). Their mass was determined with an accuracy of 0.001 g using a VLIT-500-M weighing scale. According to the indicators of weight, body length and the degree of development of fetal skin derivatives, their age was determined (Studentsov et al., 1999). The absolute and relative mass of an individual organ was defined. Statistical analysis of the results was carried out in Statistica 10.0 (StatSoft Inc., USA), including a regression analysis to determine the relationship between changes in the mass of individual lymph nodes and the total fetal body weight during prenatal ontogenesis. The differences between samples were determined using ANOVA and were considered significant at $P < 0.05$.

## Results

Lymph nodes in 2-month-old fetuses were characterized by a low visualization degree among the connective tissue that surrounded them through the absence of lymphoid tissue in their composition. Therefore, due to the methodological difficulties in determining the anatomical boundaries of the lymph nodes, organs with a large amount of connective tissue were selected for research from 2-month-old fetuses. At the same time, the indicators of the fragment mass, to determine the age dynamics patterns of the lymph nodes mass indicators, we considered incorrect and did not enter them into statistical tables. Weight measurements were started at the age of 3-month-old.

**Table 1.** Dynamics of the absolute weight of some lymph node of bovine fetuses, g

| Lymph node | Age, month | | | | | | |
|---|---|---|---|---|---|---|---|
| | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Superficial cervical | 0.13 ± 0.02[a] | 0.13 ± 0.02[a] | 0.78 ± 0.02[b] | 1.39 ± 0.23[c] | 3.52 ± 0.19[d] | 4.78 ± 0.32[e] | 5.68 ± 0.37[e] |
| Popliteal | 0.12 ± 0.06[a] | 0.25 ± 0.08[a] | 0.47 ± 0.04[b] | 0.51 ± 0.12[b] | 1.34 ± 0.21[c] | 2.91 ± 0.30[d] | 3.20 ± 0.44[d] |
| Mandibular | 0.20 ± 0.07[a] | 0.22 ± 0.07[a] | 0.26 ± 0.03[a] | 0.30 ± 0.06[a] | 0.67 ± 0.22[a] | 0.98 ± 0.25[a] | 1.09 ± 0.18[a] |
| Caudal mediastinal | 0.05 ± 0.001[a] | 0.25 ± 0.04[b] | 0.35 ± 0.09[b] | 0.54 ± 0.08[b] | 1.32 ± 0.49[b] | 2.33 ± 0.62[b] | 3.25 ± 0.63[b] |
| Weight of fetuses, kg | 0.68 ± 0.09[a] | 0.96 ± 0.13[a] | 3.48 ± 0.23[a] | 5.19 ± 0.43[a] | 10.69 ± 0.95[a] | 21.50 ± 3.37[a] | 25.17 ± 1.24[a] |

*Note:* different Latin letters designate samples that significantly differ from one another ($P < 0.05$) according to the Tukey's test results.

**Table 2.** Dynamics of the relative mass (to the fetus's weight) of the cattle lymph nodes, %

| Lymph node | Age, month | | | | | | |
|---|---|---|---|---|---|---|---|
| | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Superficial cervical | 0.0191 | 0.0135 | 0.0224 | 0.0268 | 0.0329 | 0.0222 | 0.0226 |
| Popliteal | 0.0176 | 0.0260 | 0.0135 | 0.0098 | 0.0125 | 0.0135 | 0.0127 |
| Mandibular | 0.0294 | 0.0229 | 0.0075 | 0.0058 | 0.0063 | 0.0046 | 0.0043 |
| Caudal mediastinal | 0.0010 | 0.0260 | 0.0101 | 0.0104 | 0.0123 | 0.0108 | 0.0129 |

In 3-month-old fetuses, the mandibular lymph nodes had the maximum absolute mass, the superficial cervical and popliteal lymph nodes were slightly smaller, and the caudal mediastinal lymph nodes had the minimum absolute mass. The relative weight (to fetal weight) ranged from 0.0294% in the mandibular lymph node and to 0.0010% in the caudal mediastinal one. It is at this age that morphological signs of structural and functional differentiation and specialization of the lymph node parenchyma were first identified (Gavrilin, 2018).

By the age of 4-month-old, the absolute weight was increased significantly in the caudal mediastinal (by 80%) and popliteal (by 52%), insignificantly in the mandibular (by 9.1%) and did not change in the superficial cervical lymph node. The relative lymph node mass of this age fetuses was increased in the popliteal and caudal mediastinal and decreased in the superficial cervical and mandibular ones.

By the age of 5-month-old of prenatal development, the absolute mass of all lymph nodes was increased: superficial cervical by 83.3%, popliteal by 46.8%, mandibular by 15.4%, caudal mediastinal by 28.6%. The relative mass was increased only in the superficial cervical, moderately was decreased in the popliteal and caudal mediastinal, and significantly in the mandibular.

In 6-month-old fetuses, the absolute weight was increased mostly in the superficial cervical (by 43.9%), and least in the popliteal (by 7.8%). The absolute weight of the mandibular and caudal mediastinal lymph nodes was increased by 13.3 and 35.2%, respectively. The relative mass of the superficial cervical lymph node increased, the popliteal and mandibular lymph node decreased, and the caudal mediastinal lymph node practically did not change.

By the age of 7-month-old fetus, the absolute weight of all lymph nodes maximally increased: superficial cervical by 60.5%, popliteal by 61.9%, mandibular by 55.2%, caudal mediastinal by

**Table 3.** Possible dependencies of changes in the mass of some lymph nodes on the mass of fetuses in the prenatal period of cattle ontogenesis (n = 66).

| Lymph node | Statistical relationship | Regression equation | $R^2$ |
|---|---|---|---|
| Superficial cervical *(ln. cervicalis superficialis)* | linear | $y = 0.2705 + 0.0002 \cdot x$ | 0,8621 |
| | quadratic | $y = -9E\text{-}09x^2 + 0.0004x - 0.2854$ | 0,9296 |
| | cubic | $y = -3E\text{-}13x^3 + 2E\text{-}09x^2 + 0.0003x - 0.1227$ | 0,9336 |
| Popliteal *(ln. popliteus)* | linear | $y = -0.0437 + 0.0001 \cdot x$ | 0,8904 |
| | quadratic | $y = 2E\text{-}09x^2 + 0.0001x + 0.0768$ | 0,8974 |
| | cubic | $y = -4E\text{-}13x^3 + 2E\text{-}08x^2 - 2E\text{-}05x + 0.2785$ | 0,9108 |
| Mandibular *(ln. mandibularis)* | linear | $y = 0.1262 + 6.799E\text{-}5 \cdot x$ | 0,8154 |
| | quadratic | $y = 3E\text{-}10x^2 + 6E\text{-}05x + 0.148$ | 0,8164 |
| | cubic | $y = -2E\text{-}13x^3 + 8E\text{-}09x^2 - 1E\text{-}05x + 0.2674$ | 0,8373 |
| Caudal mediastinal *(ln. mediastinales caudales)* | linear | $y = 0.1033 + 0.0001 \cdot x$ | 0,8094 |
| | quadratic | $y = -2E\text{-}10x^2 + 0.0001x + 0.0909$ | 0,8095 |
| | cubic | $y = -3E\text{-}14x^3 + 9E\text{-}10x^2 + 0.0001x + 0.107$ | 0,8096 |

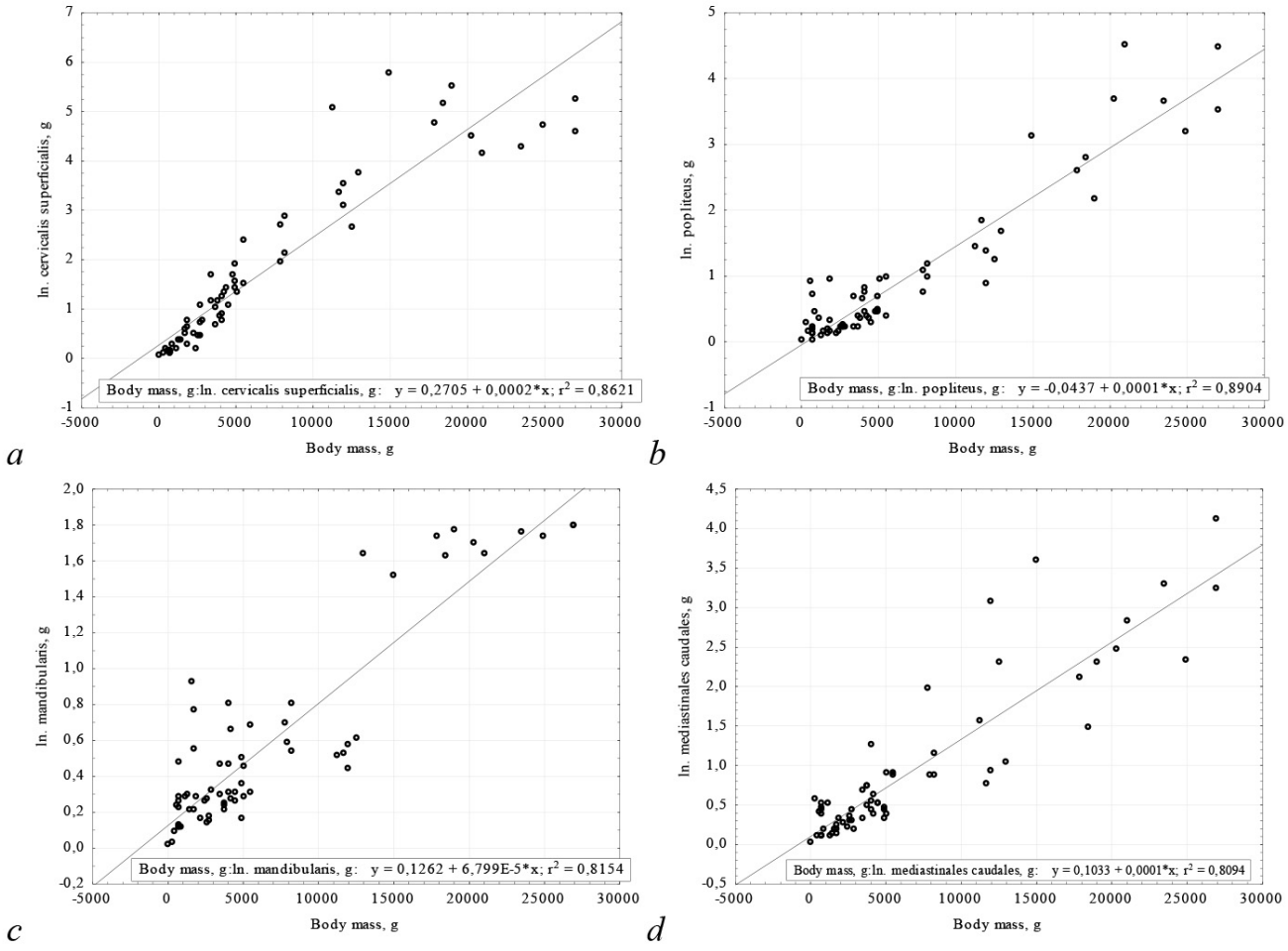


**Figure.** Dependence of the dynamics of some lymph nodes mass (*a – ln.cervicalis superficialis, b – ln.popliteus, c – ln. mandibularis, d – ln. mediastinales caudales*) on the bovine fetal mass during the prenatal period of ontogenesis: (n = 66)

59%. The relative mass was increased in all, without exception, lymph nodes, maximally in the superficial cervical, and minimally in the mandibular. In the fetal lymph nodes of this age, the components of lymphoid lobules were actively developing, mainly due to the expansion of the lymphocytes transit zones and clonal proliferation of T- and B-lymphocytes (Gavrilin et al, 2018).

Until the age of 8-month-old, the absolute weight of the superficial cervical lymph nodes has been increased by 26.3%, popliteal by 53.9%, mandibular by 31.6%, and caudal mediastinal by 43.3%. At the same time, the relative mass of almost all lymph nodes was slightly decreased, with the exception of the popliteal.

By the end of prenatal development, the absolute weight of all lymph nodes was increased moderately. At the time of birth, the superficial cervical lymph node had the maximum absolute mass, and the mandibular one had the minimum. The absolute weights of the popliteal and caudal mediastinal lymph nodes were almost the same. Up to the age of 9-month-old in fetuses, the relative weight of the superficial cervical and mandibular lymph nodes practically did not change, the popliteal lymph node was decreased, and the caudal mediastinal lymph node was slightly increased.

In comparison with 3-month-old fetuses, 9-month-old cattle fetuses most significantly was increased the absolute weight of the mediastinal (by 6 400%), superficial cervical (by 4 269.2%) and popliteal (by 2 566.7%) lymph nodes, and less mandibular one (by 445%).

When determining the dependence of the change in the mass of some lymph nodes on the weight of the fetuses, it was found that the change in the mass of the superficial cervical could be better described by the cubic ($R^2 = 0.9336$) and quadratic ($R^2 = 0.9296$) equations. The growth of the popliteal lymph node could be also better described by the cubic equation in which $R^2 = 0.9108$. For the mandibular and caudal mediastinal growth could be described by any of the equations, $R^2$ does not exceed 0.837.

A direct relationship between the lymph node mass and the fetal mass was observed only during the first third of the fetal period. Further growth in the mass of the lymph nodes did not directly depend on the body weight of the fetus.

## Discussion

It is known that peripheral lymphoid organs in 2-month-old fetuses of mammals are in their infancy, and the maximum potential for the realization of their immunological reactivity according to the data of some researchers (Sapin et al., 1978; Hlystova, 1987) is formed before the period of sexual and physiological maturity. When studying the morphogenesis of human lymph nodes, it was

noted that the period of lymph nodes formation begins at the end of the 2nd month of fetal development and ends only over a number of years after birth (Karpocheva & Galeeva, 2017).

In cattle, there are about 300 lymph nodes, which are divided into somatic, visceral and mixed. In mammals, according to different authors, the volume of lymphatic tissue ranges from 0.14% to 1% of body weight, and in humans, the lymphatic complex, which is grouped into 500–1000 lymph nodes, accounts for 600–800 g, approximately 1/100 of body weight (Policard, 1965).

The timing of the appearance of definitive structure signs of the lymph node parenchyma in mammals is controversial. In the works of different authors, it varies from the middle of the fetal period to the initial stages of postnatal ontogenesis (Grigor'ev & Moljanova, 2009; Chernenko et al., 2020).

It is known that antigenic loading by any antigen causes reactivity of the fetal immune system, which leads to anergy or an increase in its reactivity. Also, endo- and exogenous factors acting on the maternal organism during pregnancy can lead to a disruption in the morphogenesis of internal organs, which is expressed by an imbalance in the formation of a clearly determined spatial tissue structure. It was experimentally determined that intrafetal antigenic load (administration of the Vaxigrip split vaccine, human γ-immunoglobulin) to rats led to an acceleration of the morphogenesis of the lymph nodes (mediastinal), which was manifested by high morphometric parameters, an earlier formation of the parenchymal cortical layer, the appearance of lymph nodules, a more pronounced functional state of the medulla sinuses compared to intact animals (Kusch & Vasilchuk, 2014).

But for ungulates, including cattle, a special desmochorial type of placenta structure is inherent, which is normally absolutely impervious to macromolecules with potential antigenic properties. In this regard, the main factor of antigenic stimulation of the peripheral lymphoid organs parenchyma is antigens of endogenous origin, the concentration of which in the fetus' body increases in proportion to the scale of growth and development of somatic systems (Sapin et al., 1978; Aagaard et al., 2014; Parker & Makori, 2018).

In addition, the spectrum of immunocompetent morphological markers studied in fetal lymph nodes is mainly limited by such indicators as the total amount of lymphoid parenchyma, signs of its differentiation into cortical and medullary matter, the presence of lymph nodules in the parenchyma (Jeklova et al., 2007; Grigor'ev & Moljanova, 2009; Balogh, 2010; Cupedo et al., 2011; Chuchkova et al., 2016).

Asynchrony in the dynamics of the lymph nodes mass and the mass of the fetuses themselves, starting from the second third of the fetal period, in our opinion, is associated with the active differentiation of their lymphoid parenchyma and the beginning of the formation of the main structural and functional units - lymphoid lobules and the development of the main functional zones. Previous studies have determined that at this time in the lymph nodes lymphoid lobules became separated and their main zones started to be formed (lymphocytes transit, clonal proliferation of T- and B-lymphocytes, accumulation of plasma cells and antibody formation) (Lieshchova, 2007; Gavrilin et al., 2013; 2018).

The mechanisms of morphogenesis, and, accordingly, changes in their mass indicators in connection with the formation of the zonal lobular structure of the lymphoid parenchyma in the lymph nodes of mammals under conditions of extremely limited antigenic exposure, which is primarily characteristic of autonomous intrauterine development, is practically not described in the scientific literature. And above all in mature-bearing species of ungulates, in which, due to the high degree of maturity during the development of the movement apparatus, the interaction of the body's reactive structures with environmental factors increases like an avalanche from the first hours of postnatal ontogenesis, which requires an appropriate level of development and competence of antigen-reactive structures.

## Conclusion

The dynamics of the lymph nodes absolute mass in cattle during the prenatal period of ontogenesis was characterized by: a moderate increase in the first third of the fetal period (3–4 months), followed by a sharp increase during the second third (maximum at 7 months) and a gradual increase by the time of birth (8–9 months). The relative mass at the beginning of the fetal period in the superficial cervical and mandibular lymph nodes was decreased, and increased in the popliteal and caudal mediastinal lymph nodes. In the second third of the fetal period, it was sharply increased in almost all the studied lymph nodes, and by the time of birth, it was decreased moderately. A direct relationship between the lymph node mass and the mass of the fetus was observed only during the first third of the fetal period. Further growth in the lymph nodes mass did not directly depend on the weight of the fetus.

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