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Morphological features of bovine placenta in case of viral, bacterial and protozoal infections

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SUMMARY
The problem of the intrauterine infection of fetus is one of the most critical ones in veterinary obstetrics and in perinatology due to the high level of infection in pregnant cows, the risk of developmental disorder of fetus and the birth of sick calves. Complications of pregnancy occur in case of viral, bacterial and protozoal infections, when the pathogen enters the uterus in an ascending or descending way with further transplacental infection of the fetus. Morphological studies of placenta of Black Pied cattle infected with bovine viral diarrhea, chlamydia and neosporosis were carried out. The presence of the pathogen was confirmed by serological and molecular genetic methods. The material used for histological studies was the fetal part of placenta. After sampling, the material was fixed in a 10% neutral formalin solution, then xylene-free method for histological preparation was used. Afterwards, samples were embedded in paraffin. In order to study morphological structures, samples were sectioned at 5–6 μm, and stained with hematoxylin and eosin. Histological sections were analyzed using a Leica DM 1000 light microscope at a magnification of 100×, 200×, 400×, 630×. On the basis of the conducted studies, it was established that bovine viral diarrhea-associated morphofunctional changes in the "mother – placenta – fetus" system are characterized by involutive-dystrophic changes with microcirculation disorders and the development of an immunity-associated inflammatory process. *Chlamydia abortus* intrauterine infection in the "mother – placenta – fetus" system in cows causes a complex of destructive morphological and functional changes of an infectious and toxic nature with a pronounced inflammatory reaction, involvement of blood vessels in the pathological process, and endothelial dysfunction development, alongside with tissue necrosis in case of a chronic process. The presence of cellular structures in the placenta and the inner part of the umbilical cord is a pathognomonic sign of chlamydia. The role of transplacental transmission of *Neospora caninum* in cattle was confirmed, the *Neospora* parasites subjected to basophilic staining were detected not only in the tissues of the placenta, but also in histological sections of the fetus heart and liver. The main characteristic diagnostic sign is the presence of basophilic stained *Neospora* parasites in the organs of the mother and fetus, placenta, and intervillous space. As part of the study morphological features of placenta, one of the most unique histohematic barriers and the basic element of the intrauterine infectious process, were determined.

Keywords: intrauterine infection, placenta, fetoplacental complex, bovine viral diarrhea, chlamydiosis, neosporosis, morphological changes

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Морфологические особенности плаценты крупного рогатого скота при вирусных, бактериальных и протозойных инфекциях

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РЕЗЮМЕ

Проблема внутриутробного инфицирования плода является одной из ведущих в акушерской практике и перинатологии в связи с высоким уровнем инфицирования беременных коров, опасностью нарушения развития плода и рождения больного теленка. Осложнения беременности возникают при вирусных и бактериальных инфекциях, а также внутриутробных протозоозах, когда возбудитель проникает в матку восходящим или нисходящим путем с дальнейшим трансплацентарным инфицированием плода. Проведены морфологические исследования плаценты коров черно-пестрой породы, инфицированных возбудителями вирусной диареи крупного рогатого скота, хламидиоза и неоспороза, наличие которых подтверждали серологическими и молекулярно-генетическими методами. Материалом для гистологических исследований служила плодная часть плаценты. Фиксацию материала после отбора осуществляли в 10%-м растворе нейтрального формалина, затем использовали метод проводки этиловый спирт – ксилол с последующим заключением в парафин. Для изучения морфологических структур изготовленные срезы толщиной 5–6 мкм окрашивали гематоксилином и эозином и проводили анализ на световом микроскопе Leica DM 1000 при увеличении 100×, 200×, 400×, 630×. Установлено, что морфофункциональные изменения в системе «мать – плацента – плод» при вирусной диарее крупного рогатого скота характеризуются инволютивно-дистрофическими изменениями с нарушениями микроциркуляции и развитием воспалительного процесса на иммунной основе. При внутриутробном инфицировании *Chlamydia abortus* в системе «мать – плацента – плод» у коров наблюдается комплекс деструктивных морфологических и функциональных изменений инфекционно-токсического характера с выраженной воспалительной реакцией, вовлечением в патологический процесс кровеносных сосудов и развитием эндотелиальной дисфункции с некротизацией тканей при хронизации процесса. Наличие ячеистых структур в плаценте и внутренней части пупочного канатика является патогномоничным признаком хламидиоза. Подтверждена роль трансплацентарной передачи *Neospora caninum* у крупного рогатого скота, базофильно окрашенные неоспоры выявлены не только в тканях плаценты, но и в гистологических срезах сердца и печени плодов. Характерным диагностическим признаком является наличие базофильно окрашенных неоспор в органах матери и плода, плаценте и межворсинчатом пространстве. В ходе исследований определены морфологические особенности плаценты, являющейся одним из самых уникальных гистогематических барьеров и основным звеном реализации внутриутробного инфекционного процесса.

Ключевые слова: внутриутробные инфекции, плацента, фетоплацентарный комплекс, вирусная диарея крупного рогатого скота, хламидиоз, неоспороз, морфологические изменения

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INTRODUCTION

The problem of the intrauterine infection of fetus is one of the most critical ones in veterinary obstetrics and in perinatology due to the high level of infection in pregnant cows, the risk of developmental disorder of fetus and the birth of sick calves [1–3]. Most infectious diseases causing intrauterine infection are subclinical or latent. However, the changes in the homeostasis parameters due to stress or other unfavorable environmental factors induce improper interaction in the "mother – placenta – fetus" system thus causing the disease manifestation [4]. According to modern concept, a combination of adverse external influences contributes to the disruption of the regulation of metabolic and immunological processes in the "mother – placenta – fetus" system, which leads to impaired adaptation to pregnancy, the formation of pathomorphological changes in the fetoplacental complex, the development of multiple organ pathology and a delay in intrauterine development of the fetus or transplant rejection [5–9].

To date, worldwide, the first and the second place in terms of reproductive losses of cattle and the economic damage caused to livestock is given to the protozoal parasites *Neospora caninum* and the causative agent of bovine viral diarrhea [10–17].

A special role in intrauterine infection of the fetus belongs to latent infections under conditions of pathogen-induced immunosuppression. Thus, for example, the causative agents of different infections can balance in the "pathogen – host" system for quite a long time. However, in case of the weakened immune system, *inter alia*, immediate disease clinical manifestation can be observed due to different stress factors.

Complications of pregnancy are associated with viral or bacterial infections, as well as intrauterine protozoal infection, when the pathogen enters the uterus in an ascending or descending way with further transplacental infection of the fetus. Such diseases include: a group of acute respiratory viral infections (infectious bovine rhinotracheitis, bovine viral diarrhea), chlamydia infection and neosporosis of cattle. As a rule, the infectious process affects the placenta, where a complex of degenerative-inflammatory changes develops. To reveal the pathogenetic mechanisms of intrauterine infection of the fetus, it is necessary

to study the complex of pathomorphological changes in the components "mother", "placenta" and "fetus" with different infectants, which will form a scientifically based approach to the development of a system for monitoring and biological protection of animals from pathogens of abortogenic infections.

In view of the above, the research was aimed at the study of morphological changes in the cow's placenta in case of viral (bovine viral diarrhea), bacterial (chlamydia) and protozoal (neosporosis) diseases.

MATERIALS AND METHODS

The tests were performed in the Department of Reproductive Technologies, Federal State Budgetary Scientific Institution "Ural Federal Agrarian Research Centre, Ural Branch of the Russian Academy of Sciences" and in agricultural organizations of the Ural Region.

The object of the study was the placenta of Black Pied cattle infected with pathogens of bovine viral diarrhea, chlamydia infection and neosporosis. Bovine viral diarrhea virus antigens were determined using the IDEXX Bovine Viral Diarrhoea Virus (BVDV) Antigen Test Kit/Serum Plus (IDEXX Laboratories, Inc, USA), antibodies to *Chlamydia abortus* were detected using the IDEXX Chlamydiosis Total Ab Test kit (IDEXX Laboratories, Inc, USA), determination of antibodies to *N. caninum* using the IDEXX *Neospora* X2 Ab Test kit (IDEXX Laboratories, Inc, USA). The results of enzyme immunoassay were evaluated using a SUNRISE reader (Tecan, Austria).

The pathogen DNA was isolated from the biological material and polymerase chain reaction (PCR) was performed in accordance with the manufacturer's instructions for the use of test systems. We used the Diatom™ DNA Prep 200 DNA extraction kit (Isogen Lab Ltd., Russia), the GenPak® DNA PCR test kit for determining the type of species-specific chlamydia infection in cattle for amplifying the DNA of *Chlamydia pecorum*, *Chlamydia abortus*, *Bovine herpes virus/type 1* (Isogen Lab Ltd., Russia), kits for the detection of bovine diarrhea virus (InterLabService Ltd., Russia). For amplification, an Applied Biosystems 2720 thermal cycler (Singapore) was used. The tests were performed by electrophoresis using an agarose gel and a Mini-Sub Cell GT mini-camera (Bio-Rad Laboratories, Inc., USA) with visualization under ultraviolet radiation in a CHEMIDOC XRS+ camera with interpretation of the results using Gel Doc XR+ Gel Documentation System (Bio-Rad Laboratories, Inc., USA). Tests for the DNA of the causative agent of bovine viral diarrhea were performed by PCR with real-time hybridization-fluorescence detection using a Rotor-Gene 3000 amplifier (Corbett Life Science, Australia).

The material for histological tests was the fetal part of the placenta at month 5–6 of gestation (the state of the stroma, chorion villus, intervillous space, vascular component were assessed), and the umbilical cord. After sampling, the material was fixed in a 10% neutral formalin solution, then the ethyl alcohol – xylene wiring method was used, followed by paraffin embedding. To study the morphological structures, the prepared sections 5–6 μm thick were stained with hematoxylin and eosin. Histological sections were analyzed using a Leica DM 1000 light microscope (Germany) at magnifications of 100×, 200×, 400×, 630×.

RESULTS AND DISCUSSION

The study of the relationship between local and general pathomorphological lesions in case of infectious diseases is one of the main conditions for revealing the pathogenetic mechanisms of the onset and development of infection, the characteristics of macro- and microorganism interaction, the immunological reactivity of the body and the course of compensatory-adaptive processes. The morphological assessment of the functional system "mother – placenta – fetus" is of particular interest when infected with pathogens of abortogenic infections and invasions that can pass through placental barrier. In our studies, such pathogens include bovine viral diarrhea, chlamydia, and neosporosis. In conditions where infection of the maternal organism occurs, the likelihood of infection of other components of the system, including the fetus, increases. At the same time, the organs of the animal reproductive system, as well as the placenta, are most susceptible to disruption of morphogenesis and the development of such a predisposition. The study of morphofunctional changes can help to identify the features of the interaction of infectious agents with the host's immune system and determine its role in the disease pathogenesis. In the future, this should become the basis for the development of methods for diagnosing and preventing the development of intrauterine infection.

Viral diarrhea-associated placental pathology in cattle. Histological examination of sections of the fetal part of the placenta revealed involutive-dystrophic changes with circulatory disorders. In the villous chorion there is a pronounced edema of the villous stroma, which has a diffuse character (Fig. 1). In this case, edema is observed both in the syncytiotrophoblast itself and in the perivascular space. The presence of lymphoid cell infiltration indicates the development of inflammatory process including the immunity-associated one. The villous stroma itself is denuded, the epithelial lining of the chorionic villi is disturbed, and in some areas of the placenta there are foci of fibrinoid deposition in the intervillous space and lime salts in the bloodless areas, indicating petrification of tissues in a state of ischemia (Fig. 2). Circulatory disorders are indicated by such characteristic lesions as avascular chorionic villi along with vascular thrombosis (Fig. 3) as well as lesions associated with the destruction of the vascular wall and disorders of cell membrane permeability. Erythrocyte slugging in small blood vessels is observed, as well as intravascular hemolysis (Fig. 4). In this case, hemosiderin deposition is observed both inside the vessels themselves and in the perivascular space (Fig. 5). The accumulation of ferric ions in areas of pathological accumulation of hemosiderin, which have a high catalytic activity, can have a direct damaging effect on the walls of blood vessels, aggravating the development of the pathological process (Fig. 6). The inclusion of reperfusion in the compensatory process against the background of hypoxic disorders contributes to the activation of lipid peroxidation and the formation of active radicals, which is important in the overall picture of the genesis of developing placental dysfunction.

Chlamydia associated placental pathology. During the morphological examination of the fetal part of the placenta from seropositive to *Chl. abortus* cows, the presence of a mesh structure, that is, the denuded stroma, was revealed.

The villous stroma denudation with desquamation of the syncytial epithelium was observed (Fig. 7). Villous syncytium is involved in direct contact with the stroma of the uterine mucosa, provides trophic, transport, gas exchange functions, and also produces a number of biologically active substances and vitamins. Thus, damage to the syncytium is directly detrimental to fetal development. In the intervillous space of the chorion, widespread formations of fibrinoid clots were detected (Fig. 8). Cellular structures with a basophilic crumbly substance, characteristic of chlamydia infection, were constantly encountered in the villous chorion (Fig. 9). These cellular structures are formed from the host cells after the release of elementary bodies as a result of the pathogen development cycle. The presence of such structures is a pathognomonic symptom associated with chlamydia infection. Kochetov V. V. et al. described similar changes [18]. With a long chronic course of the infectious process, focal and extensive necrotic lesions in placental tissues were detected, characterized by rejection of chorionic villi with single and multiple accumulations of lime salts, indicating petrification of necrotic areas (Fig. 10), focal inflammatory polymorphocellular

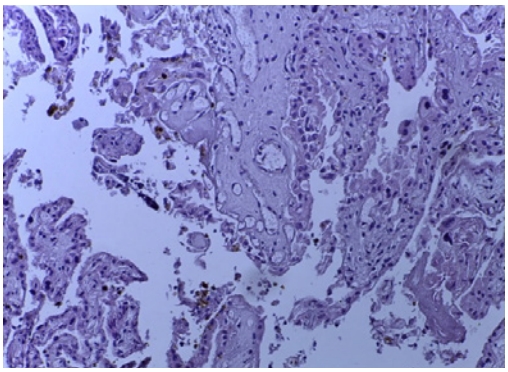

Fig. 1. Placenta. Viral diarrhea-associated edema of villous stroma (hematoxylin – eosin, magnification 200×)

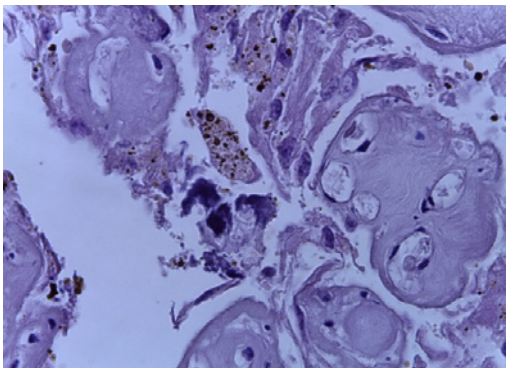

Fig. 2. Placenta. Viral diarrhea-associated lime salt deposition (hematoxylin – eosin, magnification 630×)

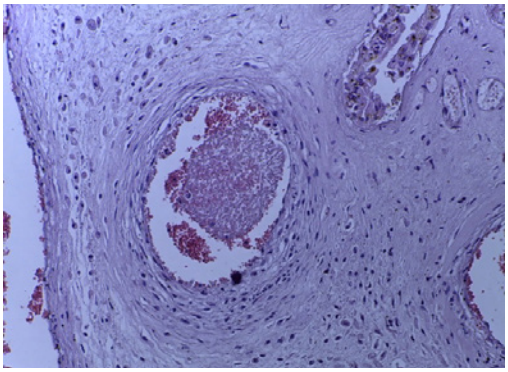

Fig. 3. Placenta. Viral diarrhea-associated thrombus formation in a vessel (hematoxylin – eosin, magnification 200×)

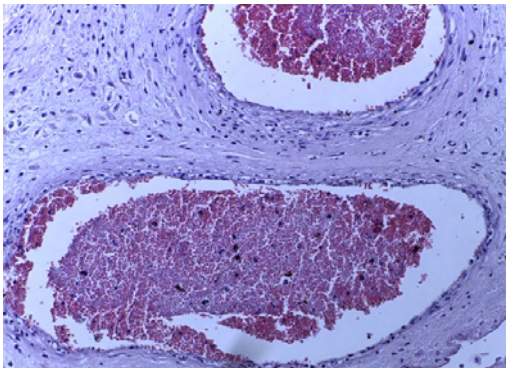

Fig. 4. Placenta. Viral diarrhea-associated hemolysis (hematoxylin – eosin, magnification 400×)

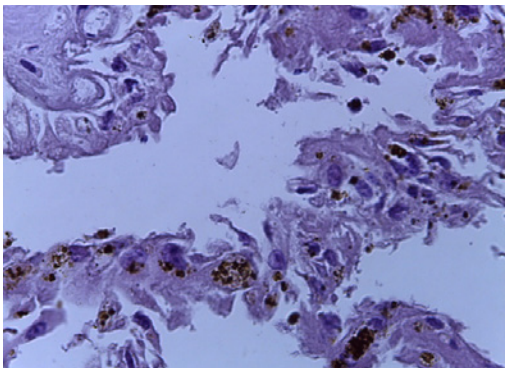

Fig. 5. Placenta. Viral diarrhea-associated deposition of hemosiderin (hematoxylin – eosin, magnification 400×)

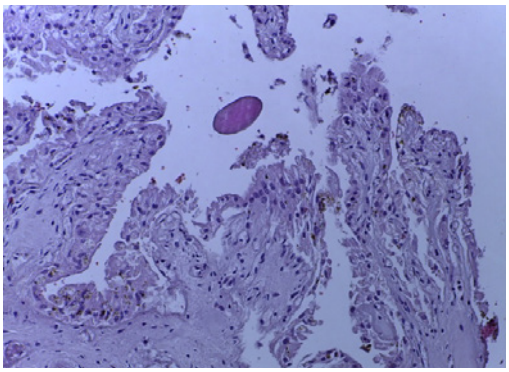

Fig. 6. Placenta. Viral diarrhea-associated fibrinoid deposition (hematoxylin – eosin, magnification 200×)

infiltrates and destruction of the epithelium. In case of improper compensatory-adaptive reactions in response to infection, purulent-necrotic disintegration of the placenta was observed.

To study the pathomorphological features of the development of an inflammatory reaction in case of chlamydia infection, the microvasculature was assessed. When examining the fetal part of the placenta of infected cows, uneven stromal vessel filling was observed. The blood vessels were mostly constricted or contained single erythrocytes. In some parts of the chorion, there was vessel hyperemia with diapedesis of erythrocytes due to the disorders of the vascular wall permeability. In some animals, hemodynamics disorders in the form of thrombosis of the villous capillary network were observed (Fig. 11). In the vascular network of the fetal part of the placenta, the breakdown of erythrocytes was expressed, leukocytes, macrophages, and desquamated endothelial cells were found in vessels of various calibers, which indicates a bacterial infection of the placenta and the development of endothelial dysfunction. There is perivascular polymorphocellular infiltration and

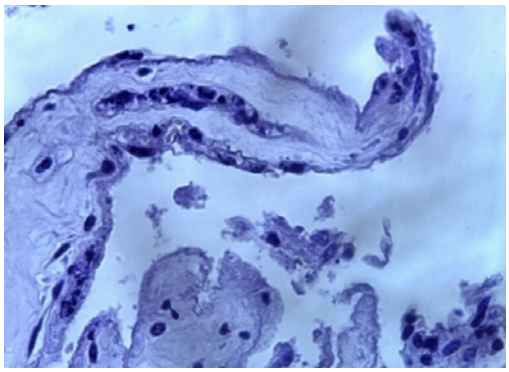

Fig. 7. Chorionic villi. Villus denudation in case of chlamydial infection in cattle (hematoxylin – eosin, magnification 630×)

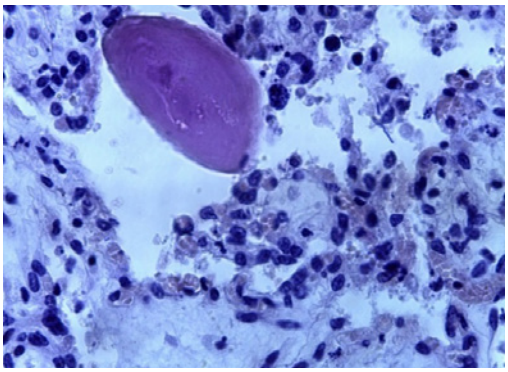

Fig. 8. Chorion. Intervillous space in case of bovine chlamydiosis. Fibrinoid clots (hematoxylin – eosin, magnification 630×)

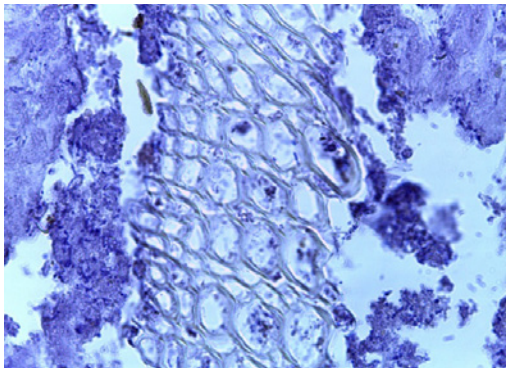

Fig. 9. Villous chorion. Cellular structures characteristic of chlamydia infection (hematoxylin – eosin, magnification 630×)

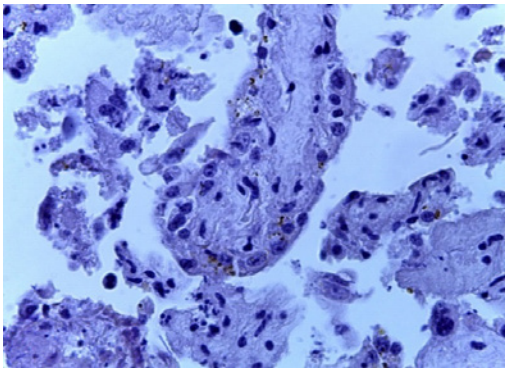

Fig. 10. Chorion. Bovine chlamydiosis-associated focal necrosis characterised by lime salt deposition. Fibrinoid clots (hematoxylin – eosin, magnification 630×)

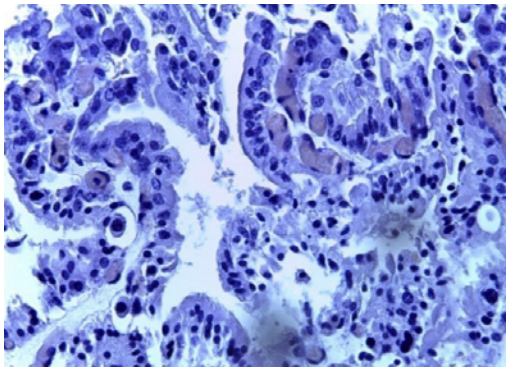

Fig. 11. The fetal part of the placenta. Thrombosis of the capillary network in case of bovine chlamydiosis (hematoxylin – eosin, magnification 400×)

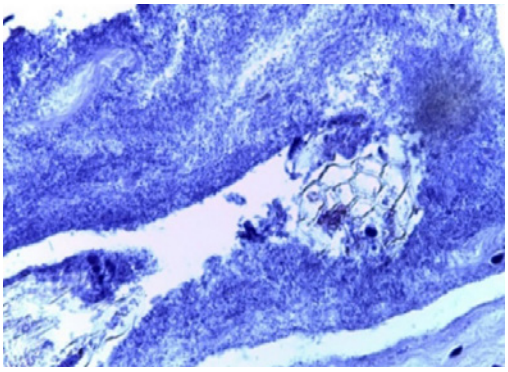

Fig. 12. Umbilical cord. Cellular structures characteristic of chlamydia infection (hematoxylin – eosin, magnification 630×)

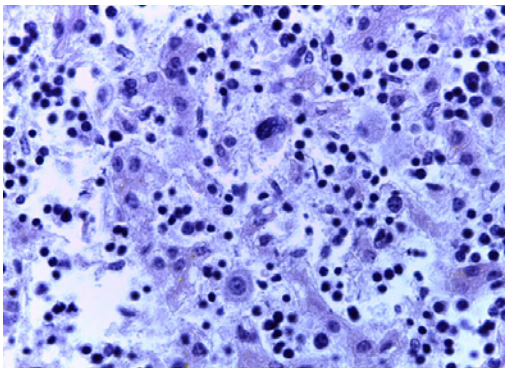

Fig. 13. Placenta. Loose villous stroma. Neospora (hematoxylin – eosin, magnification 400×)

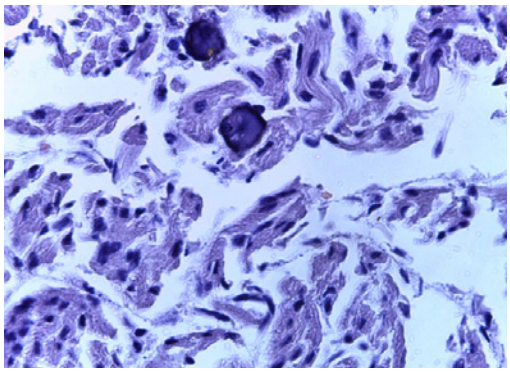

Fig. 14. Placenta. Epithelial layer. Neospora (hematoxylin – eosin, magnification 400×)

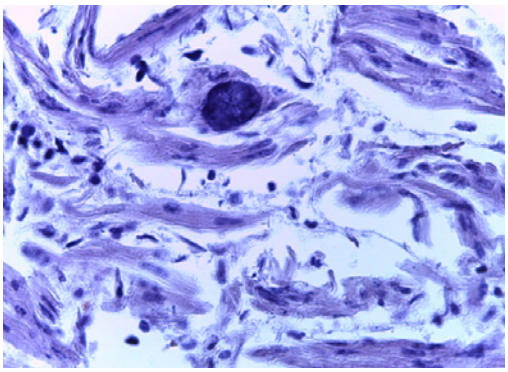

Fig. 15. Placenta. Intervillous space. Neospora (hematoxylin – eosin, magnification 400×)

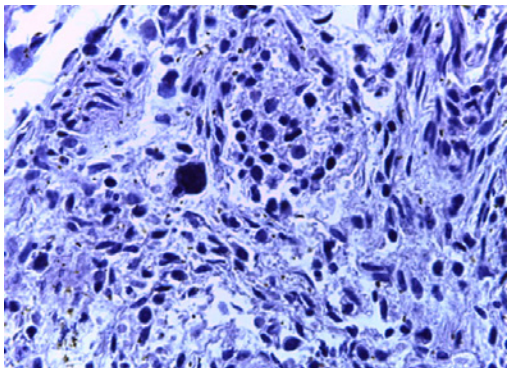

Fig. 16. Fetal part of the placenta. Epithelial layer. Neospora (hematoxylin – eosin, magnification 400×)

the presence of white blood elements in the lumen of the vessels, which is associated with the development of a classic inflammatory reaction in the placental tissues.

Histological examination of the umbilical cord tissue also revealed massive crumbly, basophilic masses with the presence of cellular structures on its inner part, which is typical for chlamydia infection (Fig. 12).

Thus, the conducted studies have convincingly shown that with chlamydia infection in cattle, all three components of the "mother – placenta – fetus" system are affected.

Neospora-associated placental pathology. The development of the placenta in *N. caninum* seropositive cows corresponded to gestation periods of 150–180 days. In the fetal part of the placenta, chorionic villi were preserved, which indicates the absence of a chronic inflammatory process. There were sharply crowded vessels of all calibers: from capillaries to large blood vessels, and some destruction of the surface epithelium connecting the fetal and maternal parts of the placenta, which is typical for spontaneous abortion [19]. Loose connective tissues of the villous stroma were observed in the cows' placenta infected with neospora (Fig. 13). The epithelial layer of the chorion was thickened and loosened. It contained basophilically stained rounded neospora parasites of different thickness (Fig. 14). Some of them were in a state of necrobacteriosis. The same neospora parasites were also found in the intervillous space (Fig. 15). In the epithelial layer of the fetal part of the placenta and the intervillous space, basophilically stained sarcosporidia were also found (Fig. 16), which is typical for neosporosis. In the placenta, signs characteristic of the spontaneous abortion, not associated with the development of a chronic inflammatory process, were observed. Neospora parasites were also found in the internal organs of the fetus, such as the heart and liver. At the same time, morphological signs of internal organ lesions in aborted fetuses were not detected. This is probably due to the fairly developed immune system of the fetuses, whose gestational age in the presented studies was 150–180 days, capable of competently responding to the effects of parasites and limiting their growth.

Thus, the cause of abortions in neospora-infected cows was not associated with the development of the inflammatory process as such, but, most likely, with the immune response of the mother to the invasion of the fetoplacental complex and/or the release of prostaglandins, provoked by the invasion of *N. caninum,* which led to the pregnancy termination. To sum it up the high abortion rate in *N. caninum*-associated pregnancies may be due to several factors. Reactivation of latent infection in seropositive animals is due to the suppression of cell-mediated immunity in mid-pregnancy. Unlike chlamydia, with neosporosis, pathological lesions of the placenta are not so pronounced, and therefore it is difficult to call these lesions the main cause of abortion. Most likely, being localized in the tissues of the placenta, neospora parasites trigger a cascade of reactions associated with the release of prostaglandins, which cause uterine contraction, and pro-inflammatory cytokines, which stimulate the synthesis of matrix metalloproteinases in the trophoblast, which

leads to the destruction of intercellular relationships and, as a result, rejection of the fetoplacental complex. In addition, in case of the general increased sensitization of the body an infested fetus can also induce the process of rejection by the mother's body.

CONCLUSION

On the basis of the studies performed, it was established that morphofunctional changes in the "mother – placenta – fetus" system in case of viral diarrhea of cattle are characterized by involutive-dystrophic changes with microcirculation disorders and the development of an immunity-associated inflammatory process.

In case of intrauterine infection with *Chl. abortus* in the "mother – placenta – fetus" system in cows, there is a complex of destructive morphological and functional changes of an infectious-toxic nature with a pronounced inflammatory reaction, involvement of blood vessels in the pathological process and the development of endothelial dysfunction with tissue necrosis during the chronic process. The presence of cellular structures in the placenta and the inner part of the umbilical cord is a pathognomonic sign of chlamydia infection.

The role of *N. caninum* transplacental transmission in cattle was confirmed; basophilically stained *Neospora* parasites were detected not only in placental tissues, but also in histological sections of the heart and liver of fetuses. Morphological and functional changes in the "mother – placenta – fetus" system in cows in case of *N. caninum* invasion are characterized by signs of microcirculation and hemodynamic disorders, and the development of sensitization. A characteristic diagnostic sign is the presence of basophilically stained *Neospora* parasites in the organs of the mother and fetus, placenta and intervillous space. Neosporosis-associated pregnancy termination, in our opinion, is not associated with the development of the inflammatory process as such, but, most likely, with the mother's immune response to invasion of the fetoplacental complex, which is consistent with the assumptions of a number of foreign authors [4, 17].

The performed studies made it possible to establish the morphological features of the placenta, which is one of the most unique histohematic barriers and the main link of the intrauterine infectious process, which explains the close attention of researchers to this temporary organ.

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