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ORIGINAL ARTICLE

Separate indices of homeostasis and the balance of the prooxidant–oxidant system in sheep for fetoplacental insufficiency

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Our research is aimed at solving one of the primary problems of sheep farming – receiving a viable lambs, as the level of neonatal mortality of lambs is 15% and above, which significantly reduces the profitability of the livestock industry. One of the reasons for this is the fetoplacental insufficiency, which causes the violation of antenatal development and, as a consequence, decline of the clinical condition and potential of development of newborns. Solving the problem of fetoplacental malnutrition is primarily due to issues of diagnosis and prevention, which are difficult even for humane medicine. In veterinary obstetrics this direction remains insufficiently investigated. There are only a few publications, especially for sheep, but they are devoted to the study of several other aspects of fetoplacental insufficiency. Fetoplacental malnutrition is a multifactorial pathology, but in livestock production, ecologically deficient factors and defective/unbalanced feeding are the leading ones, which negatively affect the structure and function of the fetoplacental complex in particular. In particular, the concentration of free radical oxyslides increases while simultaneously reducing the antioxidant defense of the organism. According to the results of studies of individual homeostasis and the balance of the prooxidant–antioxidant system, their differences in the sheep breed are clinically healthy, compared with the animals for fetoplacental insufficiency. The results obtained will be used by us in the further development of the method of objective diagnosis and the program of rational prevention of fetoplacental insufficiency in sheep.

Keywords: Viable lambs; Antenatal pathology; Diagnosis; Antioxidant defense; Fetoplacental complex

Introduction

Fetoplacental insufficiency is one of the most common causes of antenatal pathology and a factor in perinatal death of the fetus. In particular, fetal hypoxia develops, retention of its pre-natal growth and development, increases the likelihood of preterm birth, various anomalies of birth activity, birth traumas of the fetus; in newborns, it is more difficult to re-run the adaptation process, to detect growth and development disorders more often, they are more prone to diseases (Bardien et al., 2016; Camacho et al., 2017; Lees et al., 2013; Makatsariya et al., 2016; Voevodin et al., 2017).

The morphological picture of the placenta with fetoplacental insufficiency is characterized by degenerative and dystrophic processes, changes in permeability of the villous stroma, signs of impaired maturation, and a number of other pathological changes. In particular, with fetoplacental insufficiency, structural changes associated with circulatory disorders, involuntary-dystrophic changes, as well as compensatory processes are revealed. Among the pathomorphological changes that occur in the placenta for fetoplacental insufficiency, there are decreases in the number of blood vessels in the stem and terminal villi, fibrinoid re-degeneration of the epithelium of the villi, stroma and vascular walls, deposition of fibrinoid in the space between the villi, collagenization of the stroma, reduction in the space between the villi, infarcts, enlargement of symplastic kidneys with signs of dystrophy, morphological immaturity of the placenta, dominance of the intermediate villi. These processes represent the result of the complicate reaction of the fetoplacental system to the pathological condition of the maternal organism and cause changes in its function. With preserved compensatory reactions in the placenta, its insufficiency has a relative character, in these cases, pregnancy ends with a viable and healthy fetus. However, the presence of a viable and healthy fetus indicates favorable conditions for pre-natal development and, therefore, excludes clinically significant structural and functional insufficiency of the placenta. At emergence of pathological conditions from the placenta, unlike compensatory and adaptive changes, the return to its normal function can no longer be, as there are pathological changes of its histological structure. (Basistij, 2016; Sehgal, 2018; Van der Linden et al., 2013; Veropotvelyan et al., 2016; Zhang et al., 2015).

The pathogenesis of fetoplacental insufficiency plays a major role in the reduction of uterine and placental perfusion, resulting in impaired placental function, including transport, trophic, respiratory, and endocrine (Longo, 2018; Pahomova & Komilova, 2016; Sebire, 2017; Wesolowski & Hay, 2016). Placental dysfunction leads to disruption of the normal functioning of the mother-placenta-fetal system with significant changes in its major metabolic processes (Bekmukhambetov et al., 2016; Romanenko, 2017; Zanardo et al., 2008). Due to the expansion of diagnostic capabilities for the detection of disorders of the placental function, and in connection with the acquisition of new data on the mechanisms of regulation of blood circulation in the placenta for physiological and complicated pregnancy, it was possible to make some additions to the pathogenesis and tactics of treatment of placental insufficiency. In recent decades, there has been a growing interest in the medical aspects of the effects of free radicals, an increase in the latter, changes the balance between them and antioxidant protection, which causes the development of pathophysiological conditions (Forman et al., 2014; Mirończuk–Chodakowska et al., 2018; Murphy, 2014; Pisoschi & Pop, 2015; Simioni et al., 2018). Free radical oxidation is a vital process, since reactive oxygen species are participants in the metabolism of proteins, nucleic acids, lipids, and other normal phenomena, due to the functioning of the antioxidant protection system, the process of peroxidation does not lead to dysfunction of the body. The reactions of peroxidation are universal in nature, serve as a source of the bulk of energy required for vital activity, and an indicator of the stability of metabolic transformations in the body. Free radical and peroxide reactions are an integral part of such important biological processes as protein modification, electron transport in the respiratory chain, synthesis of prostaglandins and leukotrienes, cell proliferation and differentiation, metabolism and synthesis of catecholamines, phagocytosis, metabolism some xenobiotics (Gubskij et al., 2005; Liang et al., 2008).

Formed lipid peroxides are involved in the synthesis of prostaglandins and steroid hormones that determine the functional activity of the reproductive system, and their excessive accumulation leads to damage to cell membranes, reducing the process of protein synthesis and the development of organ pathology. Ischemic changes in organs and tissues are accompanied by hyper activation of free radical processes and impaired functional and structural integrity of biomembranes (Liu et al., 2013). That is, free radical oxidation of lipids is one of the dominant metabolic processes that provide regulation of the functional activity of the organism's physiological systems, as well as an inducer of oxidative stress of free radical pathology. In general, the inability of the antioxidant defense system to resist the intensification of free radical oxidation processes leads to a significant weakening of the metabolic and detoxification functions of the placenta (Agarwal et al., 2006; Lykkesfeldt & Svendsen, 2007; Papa Gobbi et al., 2014; Perrone et al., 2016).

It is well known that any adaptive or pathological process runs against the background of the formation of reactive oxygen species and the intensification of free radical oxidation of biosubstrates. In response, the organism's antioxidant system is activated. It is represented by low molecular weight compounds - the traps of radicals which include vitamins (A, C, E, D and K), bioflavonoids, low molecular weight thiols (glutathione and ergothionein), as well as antiperoxidase enzymes: superoxide dismutase, glutathione peroxidase, glutathione reductase, catalase, etc. The end result of the adaptation process is the adaptation of the organism to new environmental conditions or the disruption of adaptive mechanisms. The consequence is the development of a pathological condition, which is determined as a result of one of the main factors in the regulation of metabolism - the relationship of antioxidant and prooxidant mechanisms, in other words, the ability of the antioxidant system to protect the cell from free radicals and peroxides (Dröge, 2002; Halliwell & Gutteridge, 2015).

Oxidative stress can be approximately divided into three stages: the initiation of reactive oxygen species - free radical oxidation, the formation of free radicals and the formation of lipid peroxides and hydroxides - lipid peroxidation (Husain et al., 2008).

The most important role in the development of oxidative stress is played by the first stage - the initial stage, because it is directly related to metabolic disorders in pathological conditions and the pharmacy correction is easiest (Costa et al., 2011; Galenko–Jaroshevskij et al., 2001). The formation of reactive oxygen species (the initial stage) is promoted by free radical reactions. They can be both enzymatic and non-enzymatic in nature. The first include respiratory chain reactions, synthesis of prostaglandins, cytochrome, phagocytosis, increased metabolism of adenyl nucleotides, etc. For the second - catalyzed by copper and zinc ions, oxidation processes of organic compounds, reactions induced by various toxic factors, ionization, etc. Feature of free radical reactions is their chain character and obligatory participation of free radicals in their realization. (Costa et al., 2011; Krichkovskaja L.V. et al., 2001; Serviddio et al., 2013).

A free radical is a molecule or part thereof having an unpaired electron in the molecular or external atomic orbit. The presence of such an electron is the initial link of oxidative stress and gives the system high reactivity in chemical transformations and in this connection the possibility of damage to biologically important molecules (Serviddio et al., 2013).

The formation, accumulation and recycling of free radical oxidation products is controlled by a system of antioxidant protection, including enzymatic and non-enzymatic chains. The antioxidant protection system limits the processes of free radical lipid oxidation in almost all its chains and maintains this class of reactions at a relatively constant level. It controls the content of reactive oxygen species, free radicals, molecular products of lipid peroxidation in the body and plays an exceptional role in maintaining homeostasis (Foyer & Noctor, 2005; Lü et al., 2010).

In recent years, the role of oxidative stress in the manifestation of the reproductive function of females has been studied. In particular, it was found that its occurrence is due to the overproduction of reactive oxygen species, which not only play an important role in secondary messengers in many intracellular signaling cascades, but also have an indispensable effect on pathological processes in the genital organs. An imbalance between oxidants and antioxidants can lead to a number of female reproductive diseases (Lu et al., 2018).

This issue has been sufficiently covered in veterinary medicine (Gutyj et al., 2017; Lee et al., 2017; Omidi et al., 2017; Perfil'ev et al., 2017), but poorly understood in animal reproduction (Alonso–Alvarez et al., 2017; Talukder et al., 2017; Wang et al., 2017), particularly in the case of antenatal pathology. These changes are indicative of the state of pre-natal development, timely detection of which allows to predict the risk of adverse results in fetoplacental insufficiency.

Diagnosis and evaluation of pregnancy severity, choice of term and method of parturition, prevention of adverse perinatal consequences for fetoplacental insufficiency remains one of the most pressing problems in modern obstetrics (Redline, 2015; Tezikov et al., 2016). In this regard, the purpose of the study was to study individual indices of homeostasis and balance of the prooxidant - oxidative system of sheep with fetoplacental insufficiency as a component in the development of diagnostic methods and prevention programs.

Materials and Methods

The experiments were conducted in the conditions of laboratories and clinical base of the Department of Veterinary Reproductology and Training and Production Center for Animal Husbandry and Crop Production of Kharkiv State Veterinary Academy, Department of Nanocrystalline Materials of the Institute of Scintillation Materials of NAS of Ukraine (Kharkiv), Laboratory of Immunorehabilitation. I.I. Mechnikov NAMS of Ukraine (Kharkiv).

The subject of the study was sheep of the breed of precocus, live weight 40–45 kg and age 3–5 years. In total, 10 animals were selected, which were divided into two groups of analogues - 5 each. The animals of the control group were clinically healthy, the experimental group - with fetoplacental insufficiency.
To make a diagnosis of fetoplacental insufficiency, conventional methods of clinical and obstetric and gynecological examination were performed, as well as special methods of colpos cytoscopy and ultrasonography (Skljarov, 2013).
In all experimental animals, individual indices of homeostasis and balance of the prooxidanly – anioxidant system (the content of total protein, vitamin A and zinc in serum, malondialdehyde, catalase, superoxide dismutase, reduced glutathione, erythrocyte, hemoglobin, 2,3-diphosphoglycerate) were determined.
The content of vitamin A and carotene in the serum was determined by the Bessie method in the modification V.I. Levchenko et al., hemoglobin - hemoglobincyanide method, total protein - refractometrically, zinc and malondialdehyde - by spectrophotometry, erythrocyte count - by counting in Goryaev's chamber (Levchenko, 2010).
The level of reduced glutathione was determined spectrophotometrically by the method of F.I. Gimmerh (Gimerh, 1967).
The activity of catalase was determined by the colorimetric method according to the method of M.A. Koroljuk et al (Koroljuk et al., 1988). The activity of superoxide dismutase was evaluated by the method of T.V. Sirota (Sirota, 1999).
The concentration of 2,3-diphosphoglycerate was determined by spectrophotometry (Stein, 1999).
To determine the statistical probability of the difference between the group averages we used the parametric method of statistics - Student's t-criterion. The difference between the group averages was considered statistically significant at P >0.95. Data were processed using Microsoft Excel 2010, Office (X15–74884) for Windows® 7. The results are presented as mean (M) and sample mean error (± m).

Results

According to the results of researches on the study of individual indices of homeostasis and the balance of the prooxidant – antioxidant system, their differences in sheep of clinically healthy compared to animals with fetoplacental insufficiency were revealed (Table 1). Thus, in ewes of the control group (clinically healthy) the content of vitamin A in the serum was 0.79 µmol/l, whereas in experimental animals (with fetoplacental insufficiency) - 0.68 µmol/l, ie 0.11 µmol/l or 13.9% lower (P>0.99).

Table 1. Individual indices of homeostasis and balance of the prooxidant – antioxidant system in ewes with fetoplacental insufficiency.

Indices	Groups of animals		P *	+/–	%
	Control (n=5)	Experimental (n=5)			
Serum Content:					
- Vitamin A, µmol/l	0,79 ± 0,03	0,68 ± 0,02	>0,99	–0,11	13,9
- zinc, µmol/l	14,73 ± 0,68	11,91 ± 0,82	>0,95	–2,82	19,1
- total protein, g/l	46,41 ± 2,43	41,59 ± 2,21	>0,99	–4,82	10,4
State of the prooxidant – antioxidant system					
Serum Content					
- malondialdehyde, µM/l					
- catalase, µM/H_2O_2/l – min	0,94 ± 0,08	1,13 ± 0,09	>0,95	+0,19	20,2
- superoxide dismutase, conditional. units/mgHb	22,14 ± 1,96	17,51 ± 1,22	>0,95	–4,63	20,9
Content in erythrocytes:	9,22 ± 0,69	7,71 ± 0,80	>0,95	–1,51	16,4
- malondialdehyde, µM/l					
- catalase, µM/H_2O_2/l – min	46,82 ± 3,34	34,71 ± 2,89	>0,999	–12,11	25,9
- reduced glutathione, µM/l	8,82 ± 0,75	6,71 ± 0,69	>0,95	–2,11	23,9
- prooxidant – antioxidant ratio (conditional. units)	5,22 ± 0,55	4,39 ± 0,71	>0,95	–0,83	15,9
	2 : 1	3 : 1	–	–	–
Oxygen metabolism system status:					
- the number of erythrocytes, T/l	5,81 ± 0,66	4,74 ± 0,77	>0,95	–1,07	16,4
- hemoglobin content, g/l	8,41 ± 0,82	6,82 ± 0,83	>0,95	–1,59	18,9
- the concentration of 2,3-diphosphoglycerate, mmol/l	0,66 ± 0,07	0,51 ± 0,07	>0,999	–0,15	22,7

Note: * P >0,95 – low probability criterion; P >0,99 – average probability criterion; P >0,999 – high probability criterion

In clinically healthy ewes, the zinc content in the serum was 14.73 µmol/l, and in the experimental ones - 11.91 µmol/l, ie 2.82 µmol/l or 19.1% lower (P>0.95).
The content of total protein in the serum of clinically healthy ewes was at the level of 46.41 g/l, whereas in the experimental - 41.59 g/l, ie 4.82 g/l or 10.4% lower (P>0, 99).
In the animals of the control group the content of malondialdehyde was 0.94 µM/l, and the experimental - 1.13 µM/l, ie 0.19 µM/l or 20.2% more (P>0,95).
The content of catalase in the serum of clinically healthy ewes was at the level of 22.14 µM/H_2O_2/l-min, whereas in the experimental - 17.51 µM/H_2O_2/l-min, ie 4.63 µM/H_2O_2/l-min or 20.9% lower (P>0.95).
In the animals of the control group, the content of superoxide dismutase was 9.22 conditional. units/mgHb, and experimental - 7.71 conditional. units/mgHb, that is, at 1.51 conditional. units/mgHb or 16.4% less (P>0.95).
The content of malondialdehyde in the erythrocytes of clinically healthy ewes was at the level of 46.82 µM/l, while the experimental - 34.71 µM/l, ie 12.11 µM/l or 25.9% lower (P>0,999).

In the animals of the control group, the catalase content was 8.82 μM/H_2O_2/l-min, and experimental - 6.71 μM/H_2O_2/l-min, ie 2.11 μM/H_2O_2/l-min or 23.9% less (P>0.95).
The content of reduced glutathione in erythrocytes of clinically healthy ewes was at the level of 46.82 μM/l, while the experimental - 34.71 μM/l, ie 12.11 μM/l or 25.9% lower (P>0,999).
Compared with the control group, the prooxidant – antioxidant ratio changed from 2:1 in experimental animals. units up to 3:1 conditional units. In clinically healthy ewes, the number of erythrocytes was at the level of 5.81 T/l, and in the experimental ewes - 4.74 T/l, ie 1.07 T/l or 16.4% lower (P>0.95).
The content of hemoglobin in clinically healthy ewes was 8.41 g/l, while in experimental - 6.82 g/l, ie 1.59 g/l or 18.9% lower (P>0.95). In control animals, the concentration of 2.3 – diphosphoglycerate was 0.66 mmol/l and of the experimental group - 0.51 mmol/l, ie 0.15 mmol/l or 22.7% more (P>0.999).

Discussion

With our research we are trying to solve one of the primary tasks of sheep breeding - obtaining viable young animals, because the level of neonatal mortality of lambs reaches 15% and above, which significantly reduces the level of profitability of the livestock industry (Dwyer & Morgan, 2006; Liege Cristina Garcia Silva et al., 2018; Skljarov, 2013; Crempien, 2001; Vasylieva, 2017). One reason for this is fetoplacental insufficiency, which causes impaired intrauterine development and, as a consequence, impaired clinical status and developmental potential of newborns. Fetoplacental insufficiency is one of the most important problems of obstetrics, neonatology and perinatology today (Duttaroy, 2014; Sidorova & Makarov, 2005). Its frequency varies, according to various authors, from 22% to 45% of all pregnancies (Ajlamazjan et al., 2013; Burkitova et al., 2017; Roos et al., 2009; Sidorova & Makarov, 2005), increasing significantly with concomitant extragenital pathology.
The solution to fetoplacental insufficiency is, above all, related to diagnostics and prevention issues that are difficult even for humane medicine (Diner et al., 2016; Ordiyants et al., 2018; Tezikov et al., 2016). In veterinary obstetrics, this area remains poorly understood (Audette & Kingdom, 2018; Murashko et al., 2016). There are only a few publications, including those on sheep, but they are devoted to some other aspects of fetoplacental insufficiency (Galan et al., 1999; Limesand et al., 2007; Monson et al., 2017; Rozance et al., 2015; Rozance et al., 2017).
Fetoplacental insufficiency is a multifactorial pathology, however, environmental factors and defective/unbalanced feeding are leading in animal husbandry, which negatively affect in particular the structure and function of the fetoplacental complex. In particular, the concentration of free radical oxides increases while reducing the organism's antioxidant protection (Agarwal et al., 2012; Li et al., 2018; Mohebbi–Fani et al., 2012; Perrone et al., 2016).
We conducted a research to study the individual indices of homeostasis and the balance of the prooxidant – antioxidant system in ewes with fetoplacental insufficiency. It was found that compared to clinically healthy animals, fetoplacental insufficiency reduced the serum content of vitamin A by 0.11 μmol/l (13.9%), zinc by 2.82 μmol/l (19.1%), total protein - by 4.82 g/l (10.4%), catalase - by 4.63 g/l (20.9%) and superoxide dismutase - by 1.51 conditional. units/mgHb (16.4%) and the content in erythrocytes of malondialdehyde - by 12.11 μm/l (25.9%), catalase - by 2.11 μm/H_2O_2/l – min (23.9%), reduced glutathione - by 12.11 μm/l (25.9%), as well as hemoglobin - by 1.59 g/l (18.9%), the concentration of 2.3-diphosphoglycerate - by 0.15 mmol/l (22.7%) and erythrocyte count - by 1.07 T/l (16.4%). The prooxidant and antioxidant ratio also changed from 2:1 conditional. units up to 3:1 cond. units in accordance. Higher compared to the control group in the experimental animals was only an indicator of the serum content of malondialdehyde - by 0.19 μm/l (20.2%).
The most important function of the placenta is the exchange of nutrients and oxygen between the mother and her fetus. The physiological function of the placenta should occur with adequate remodeling of the spiral arteries by extravascular trophoblasts. When this process is disrupted, resulting suboptimal and inadequate placental function leads to the manifestation of pregnancy complications. Impaired placental function can cause preeclampsia and lead to restriction of fetal growth due to hypoxia. The presence of hypoxia leads to oxidative stress due to the imbalance between active oxygen species and antioxidants, thereby causing damage to proteins, lipids and DNA. In the placenta, you may find signs of morphological adaptation in response to hypoxia. Various placental lesions, such as maternal or fetal vascular malperfusion, lead to a decrease in oxygen exchange between mother and fetus. Clinically, some biomarkers suggestive of oxidative stress, such as malonic dialdehyde and reduced levels of free thiols (Schoots et al. 2018).
Reactive oxygen species are formed as by-products of aerobic respiration and metabolism. Mammalian cells have developed various enzyme mechanisms to control the production of reactive oxygen species, one of the central elements signal transmission paths involved in cell proliferation, differentiation and apoptosis. Antioxidants also provide protection against induced reactive oxygen species, damage to lipids, proteins and DNA. Reactive oxygen species and antioxidants are involved in the regulation of reproductive processes in both animals and humans, such as changes in the luteal cycle and endometrium, follicular development, ovulation, fertilization, embryogenesis, embryonic implantation, differentiation and growth of the placenta. In contrast, the disproportions between the production of reactive oxygen species and antioxidant systems cause oxidative stress, which negatively affects reproductive processes. High levels of reactive oxygen species in embryonic, fetal and placental development are a special feature of pregnancy. Thus, oxidative stress occurs as a likely promoter of many pregnancy-related disorders such as miscarriage, embryopathy, preeclampsia, fetal growth retardation, preterm birth, and low birth weight. Forage and environmental factors can contribute to such adverse pregnancy outcomes and increase offspring susceptibility to the disease. It happens, at least in part, due to the deterioration of antioxidant defense systems and increased generation of reactive oxygen species, which alters cellular signaling and/or damage to cellular macromolecules. Relationships between oxidative stress, the reproductive system of females, and the development of adverse pregnancy outcomes are important problems in human and animal reproductive medicine. In this direction, studies by Al-Gubory et al. (2010) summarized the role of reactive oxygen species in the reproductive processes of females and the state of knowledge about the relationship between reactive oxygen species, oxidative stress, antioxidants, and pregnancy in mammals of different species.
Considerable evidence points to oxidative stress in the pathophysiology of many complications of pregnancy, and this topic has become central to both clinical and fundamental scientific research. Oxidative stress occurs when the production of reactive oxygen species overloads internal antioxidant protection.. Reactive oxygen species play an important role as second messenger in many intracellular signaling cascades aimed at supporting a cell in homeostasis with its immediate environment. At higher levels, they can

cause indiscriminate damage to biological molecules, resulting in loss of function and even cell death. It is investigated how the active oxygen components in the placenta are generated and detoxified, and what role they play in homeostatic concentrations (Burton & Jauniaux, 2011).

It is known that reactive oxygen species have a two-phase effect, because their adequate concentration is necessary for the development of the embryo, implantation, protection of the fetus against infections, steroidogenesis, preservation of pregnancy. On the other hand, uncontrolled generation of reactive oxygen species can lead to embryo resorption, placental degeneration with subsequent alteration of maternal-fetal metabolism, delayed fetal growth, termination of pregnancy, stillbirth (Mutinati et al., 2013).

Hypoxia and oxidative stress due to alimentary factors and, to a large extent, multiple pregnancies have been shown to play an important role in the development of fetal hypotrophy. Thus, twins had higher plasma concentrations of malondialdehyde and decreased total antioxidant activity compared to single (Sales et al., 2018).

Hussein Ali Naji (2017) shows changes in malonic dialdehyde concentration, glutathione levels and overall antioxidant activity associated with zinc and copper supply to the organism of sheep.

Yuksel & Yigit (2015) investigated in the blood of mothers during various trimesters of pregnancy and in the umbilical cord blood of neonates the content of malondialdehyde and the level of nitric oxide, as well as catalase, superoxide dismutase and glutathione peroxidase. The level of malondialdehyde was found to be lower in the third trimester than in the first and second trimesters. Nitrogen oxide levels were higher in the third trimester than in the first and second trimesters. Catalase activity was lower in the second and third trimesters than in the first trimester. Glutathione peroxidase activity was significantly higher in the second and third trimesters compared to the first. The activity of superoxide dismutase decreased during pregnancy. There was no significant difference in superoxide dismutase activity in the third trimester between maternal and umbilical cord blood.

Erisir et al. (2009) evaluated the oxidant and antioxidant status by determining the concentration of glutathione peroxidase, catalase, malondialdehyde and glutathione before and during pregnancy in sheep. It was established that the concentration of malondialdehyde for 2 and 3 months of pregnancy were lower than at 1, 4, 5 months of pregnancy and in non-pregnant sheep. Glutathione concentration and glutathione peroxidase activity during pregnancy were increased. Glutathione concentration and glutathione peroxidase activity were highest at 2 and 3 months of gestation. Catalase content decreased after 1 month of pregnancy and was lowest at 2 months and 3 months of pregnancy. These changes may indicate a tendency to oxidative stress at 2 and 3 months of pregnancy.

Kandiel et al. (2016) aimed to test a hypothesis regarding the effect of reproductive status on the hormonal state of an animal and its metabolic status. The results showed significant changes in some biochemical parameters of sheep blood serum during pregnancy as compared to luteal and/or follicular stages. Pregnancy was associated with significantly higher levels of progesterone, glutathione peroxidase, malondialdehyde, and nitric oxide. Cyclic animal samples showed higher levels of insulin, T3, T4, superoxide dismutase and glucose. From these results, it can be concluded that the effects of the reproductive state, including lipid peroxidation and organism metabolism, can have long-lasting effects and should therefore be taken into account in the early prediction and/or diagnosis of metabolic diseases related to energy balance disorders and/or oxidative stress in sheep.

Rios et al. (2017) conducted studies to evaluate changes in some indicators of sheep oxidation status during pregnancy and lactation. It has been established that the level of antioxidants has two terms of reduction – during the second month of pregnancy and at the 5th day of lactation. It is concluded that the susceptibility to lipid oxidation decreases with the number of fetuses during pregnancy and lactation. There is a mechanism for preventing lipid oxidation, including changes in the antioxidant capacity of glutathione peroxidase and ascorbic acid.

Liege Cristina Garcia Silva et al. (2018) examined the relationship between antioxidant enzyme levels and oxidative profile and viability of neonatal lambs born prematurely (135 days) and on time (145 days). The authors found a positive correlation between glutathione peroxidase and superoxide dismutase levels, the occurrence of oxidative stress and the clinical condition of neonatal animals.

Nawito et al. found changes in the oxidant/antioxidant balance of sheep during pregnancy under different feeding conditions. The level of malondialdehyde was found to be significantly increased in pregnant animals fed concentrates or grazed on pastures with low-quality forage and was accompanied by low levels of total antioxidant capacity. The activity of catalase and superoxide dismutase is reduced in pregnant animals by feeding concentrates compared to the consumption of low-nutrient feeds. These data suggest that animals may have experienced some degree of oxidative stress and lipid peroxidation, as well as homeostasis disorders in pregnant creatures grazed on pastures with low-quality forage.

Gür et al. (2011) studied the effect of one- and two-fold pregnancy on oxidative and antioxidant balance. Malondialdehyde was found to be higher in two-fold pregnancies than in non-pregnant and single-born sheep. Serum glutathione levels and glutathione peroxidase activity in two-fold pregnancy were lower than in non-pregnant sheep. In addition, the activity of glutathione peroxidase in two-fold pregnancy was lower than that of pregnant sheep with a single fetus.

Al-Gubory et al. (2004) investigated the antioxidant enzymatic systems of the yellow body of sheep during pregnancy. In particular, copper, zin-superoxide dismutase, manganese, glutathione peroxidase, glutathione reductase, and glutathione-S-transferase at 15th, 40th, 60th, 80th, and 128th – gestation days. There was a significant increase in the enzymatic activity from the 15th to the 40th day of pregnancy. These results showed that the activity of antioxidant enzymes undergoes radical changes during early pregnancy and suggests that the yellow body of early pregnancy may be rescued from luteolysis by increasing the activity of key antioxidant enzymes and inhibiting apoptosis. Supported levels of antioxidant enzymes in the yellow body throughout pregnancy may be associated with reactive oxygen species that are constantly generated in steroidogenically active luteal cells and may be involved in maintaining lutein steroidogenic activity and cell integrity.

Durmuș et al. (2017) concluded that the metabolic profiles of blood and the oxidant/antioxidant balance of sheep vary depending on the time after feeding. The authors conclude that for the maximum diagnostic value of these metabolic blood profiles, the most appropriate time for blood sampling is just before feeding. Antunovic et al. (2004) significant changes in sheep blood indicators due to age and reproductive status, and in particular the parameters of the metabolic profile during lactation compared with non-pregnant and lactating animals. Therefore, changes in individual indices of homeostasis and the balance of the prooxidant-oxidant system may be diagnostic markers for the pathological course of pregnancy, in particular for fetoplacental insufficiency and to be taken into account when developing diagnostic and preventive measures (Perrone et al., 2016).

Conclusion

According to the results of researches on the study of individual indices of homeostasis and the balance of the prooxidant-antioxidant system, their differences in ewes of clinically healthy compared to animals with fetoplacental insufficiency were revealed. It was found that compared to clinically healthy animals, fetoplacental insufficiency reduced the serum content of vitamin A by 0.11 µmol/l (13.9%), zinc by 2.82 µmol/l (19.1%), total protein - by 4.82 g/l (10.4%), catalase - by 4.63 g/l (20.9%) and superoxide dismutase - by 1.51 conditional. units/mgHb (16.4%) and the content in erythrocytes of malondialdehyde - by 12.11 µm/l (25.9%), catalase - by 2.11 µm/H_2O_2/l-min (23.9%), reduced glutathione - by 12.11 µm/l (25.9%), as well as hemoglobin - by 1.59 g/l (18.9%), the concentration of 2.3-diphosphoglycerate – by 0.15 mmol/l (22.7%) and erythrocyte count - by 1.07 T/l (16.4%). The prooxidant and antioxidant ratio also changed from 2:1 conditional. units up to 3:1 conditional. units in accordance. Higher compared to the control group in the experimental animals was only an indicator of the serum content of malondialdehyde - by 0.19 µm/l (20.2%). The results obtained will be used by us in the future to develop a method of objective diagnosis and a program for the rational prevention of fetoplacental insufficiency in sheep.

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