Comprehensive assessment of metabolic profile and dynamics of lipid metabolism alterations in calves with intrauterine growth restriction

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SUMMARY

One of the complications of pregnancy in cows is intrauterine fetal growth restriction (IUFR). In this condition, the fetus lags in size and weight relative to gestational age, negatively affecting the cow and its offspring. This study aimed to establish differences in blood parameters between calves born to dams with physiologically progressing pregnancies and those born to cows diagnosed with IUFR immediately after birth and to monitor changes in lipid metabolism parameters dynamically. The research was conducted on 30 Simmental calves: 16 with a history of IUFR (Group 1) and 14 animals without intrauterine developmental pathology (Group 2). The presence of IUFR was determined by clinical-ultrasonographic examination of mothers on days 38-47, 60-65, and 110-117 of gestation. Overall blood parameter assessment was conducted 24 hours after calf birth, and levels of total lipids and cholesterol were examined in serum collected on days 1, 3, 7, and 14 after birth. A decrease in glucose level, total protein, and immunoglobulin, and an increase in lactate, lactate/pyruvate ratio, and albumin-globulin ratio in blood collected one day after birth were identified. The dynamics of lipid metabolism changes indicate a persistent decrease in total lipids in serum from days 1 to 14 of life and cholesterol from days 1 to 3 of life. The obtained data contribute to the possibility of correctly selecting methods to correct the negative consequences in calves induced by IUFR development.

KEY WORDS

Clinical-ultrasonographic examination; dairy farming; cows; embryonic developmental delay; lipid metabolism; reproductive function.

INTRODUCTION

A current problem for modern animal husbandry is the reduction in the reproductive function of cattle. For efficient farm development, a cow must produce at least one calf per year, with the optimal range being 9-12 lactations. However, due to the increased productivity of cows, their reproductive system suffers, reducing the duration of their use to 1-2 lactations in some farms. Additionally, various diseases in animals may hinder the onset of pregnancy. Even in cases of productive insemination, pregnancy may occur with pathological deviations. One such deviation is intrauterine fetal growth restriction (IUFR), reaching up to 40% in some instances. IUFR is diagnosed when fetal growth and weight are below the established range for the gestational age. The occurrence of embryonic developmental delay is attributed to a combination of multiple random reactions between the fetus and the placenta (1-3).

IUFR has negative consequences both for the health of the mother and for the postnatal development of the offspring (4). Calves born with a diagnosis of IUFR often present with hypoglycemia, hypoxemia, lactic acidosis, dyslipidemia, underdeveloped antioxidant systems, and an increased frequency of respiratory diseases. From a physiological standpoint, the behavior and clinical condition of IUFR calves may initially appear normal; however, metabolic disorders are frequently diagnosed in these calves subsequently, adversely affecting their postnatal adaptation capabilities (5).

Common causes of fetal developmental retardation include stress, maternal diseases, especially disorders in the immune and endocrine systems, poorly organized nutrition, and unbalanced diets, which can lead to vitamin and mineral deficiencies and intoxication (6-8). An imbalance in concentrations

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of progesterone and estrogen hormones can be considered an endocrine system dysfunction (9,10). They are responsible for the proper implantation and placentation of the embryo (10,11). A deficiency in progesterone leads to disturbances in embryonic nutrition and autoimmune processes during the formation of the mother-placenta-fetus system (11). The immune reaction to the embryo increases, causing disruptions in its development, up to death (11). Another function of progesterone and estrogen hormones is to maintain the vaginal microbiota of the cow (10,12). Endocrine system dysfunction diagnosed with IUFR in cows has been associated with changes in vaginal bacterial flora during pregnancy: a decrease in the level of lactobacilli and bifidobacteria, and an increase in E. coli and Ent. faecalis (12). Shifts in vaginal flora towards conditionally pathogenic microorganisms reduce local immunity and may cause various diseases. Administration of gonadotropin-releasing hormone, gonadotropins, or progestins to cows promotes an increase in progesterone blood concentration, and secretory activity of the endometrium, and reduces immunological conflict in the developing mother-placenta-fetus system (11,13).

Another cause of IUFR development may be a disrupted diet of cows (14). Improper feed storage can lead to mold formation, which produces mycotoxins that can poison the organism, induce cancer development, and exhibit hepatotoxic, cytotoxic, and genotoxic properties. Examples include aflatoxins, secondary metabolites of Aspergillus species, which have teratogenic effects. The feed itself can also be a source of poisoning if it contains an unacceptable amount of plants harmful to animals (15).

An important factor in a well-composed diet is its balance of vitamins and minerals. The quantity of each microelement in the environment should be considered, as many regions exhibit deficiencies in certain elements. However, high soil content of elements does not always correlate with high content of those elements in fodder plants, due to the selectivity of the latter and the influence of some elements on the absorption of others (16). Among vitamins, deficiencies that negatively impact reproductive function, are vitamin A (carotene), and D, while vitamin C positively affects sexual function (15,17). The influence of vitamin E deficiency on the occurrence of IUFR has been demonstrated. Consequences of vitamin E deficiency in the diet of cows can lead to fetal developmental delay, fetal death, embryo abortion, and infertility (11,17).

A deficiency of minerals such as manganese, phosphorus, potassium, nickel, sodium, sulfur, selenium, iodine, zinc, copper, and cobalt leads to various disruptions in reproductive function (18,19). Research on the influence of trace elements on the development of IUFR has shown that calves born with this diagnosis exhibited intrauterine deficiencies of cobalt, manganese, copper, selenium, and zinc (20). In another study, a change in mineral ratios was observed: an increase in macroelements such as magnesium and potassium, and a decrease in sodium, along with a deficiency of manganese, copper, and selenium (21). In cows, intrauterine developmental delay is more strongly associated with copper and selenium deficiency, and to a lesser extent with zinc and manganese (22). Studies indicate that the deficiency of trace elements in calves adversely affects the antioxidant defense system (20). Consequently, there is a delay in the maturation of its enzymatic component, manifested by the accumulation of lipid peroxidation derivatives in the blood (20).

In the literature, the blood profile of calves with IUFR is characterized by decreased antioxidant activity, low levels of catalase, superoxide dismutase, glutathione peroxidase, L-ascorbic acid, glucose, protein, cholesterol, -tocopherol, and vitamin A, along with increased concentrations of malondialdehyde and diene conjugates (20,23). Accumulation of toxic products in their blood resulting from lipid peroxidation negatively affected the resilience of newborns to various diseases (5,20).

Research Objective: To evaluate the main plasma and blood parameters in calves with intrauterine growth retardation (IUFR) and calves developing without pathologies during pregnancy, within the first day after birth, and to track the dynamics of changes in serum concentrations of total lipids over 14 days after birth.

Research Tasks:

- Identify cows whose calves develop with IUFR;
- Analyze the metabolic profile of calf blood within the first day;
- Obtain data on serum concentrations of total lipids on the 1st, 3rd, 7th, and 14th days and analyze them.

METHODS AND MATERIALS

The subjects for the study were Simmental breed calves from the farm of G.A. Rogacheva in the Astrakhan region. A total of 30 calves were selected. To identify calves with IUFR, clinical and ultrasonographic assessment of pregnant cows was conducted using an ultrasound scanner Easi-Scan-3 (BCF Technology Ltd., United Kingdom) with a linear sensor of 4.5-8.5 MHz frequency on the 38th to 47th, 60th to 65th, and 110th to 117th days after productive insemination (corresponding to the 1st, 2nd, and 3rd examinations, respectively). For this purpose, the device covered with gel was inserted into the rectum of the cow, positioning it above the organs of interest (24).

The criteria for diagnosing IUFR were based on the established range of 12-16 mm for the coccygeal-crown size in the first examination and 26-48 mm for the second, and a body diameter of 6-9 mm on days 38-47 and 12-16 mm on days 60-65 (24). During the final (3rd) examination, the diagnosis was based on a fetal horn diameter of less than 15 cm and a placental diameter of up to 17 mm (24).

Based on the results of the clinical and ultrasonographic assessment of pregnant cows, all newborns were divided into two groups. Group 1 included 16 calves with a history of IUFR, Group 2 - 14 animals without pathology of intrauterine development. Blood samples were collected from the jugular vein of the calves into vacuum commercial systems with lithium heparin without the addition of anticoagulant, in the morning on an empty stomach on the 1st, 3rd, 7th, and 14th days after birth. For the comprehensive assessment of blood and serum parameters, blood from daily newborn calves was utilized. The indicators of carbohydrate metabolism (glucose, lactate, pyruvate) in whole blood, and protein (total protein, urea, creatinine, as well as albumins and total immunoglobulins) and lipid (total lipids, cholesterol) metabolism in serum were investigated using relevant methods (11,23) on a UV-1700 spectrophotometer (Shimadzu, Japan) and an Olympus-400 analyzer (Beckman Coulter, USA).

The results were presented as mean ± standard error of the mean (SEM). All obtained data underwent statistical analysis to identify significant differences ($p < 0.05$). For this purpose, IBM SPSS

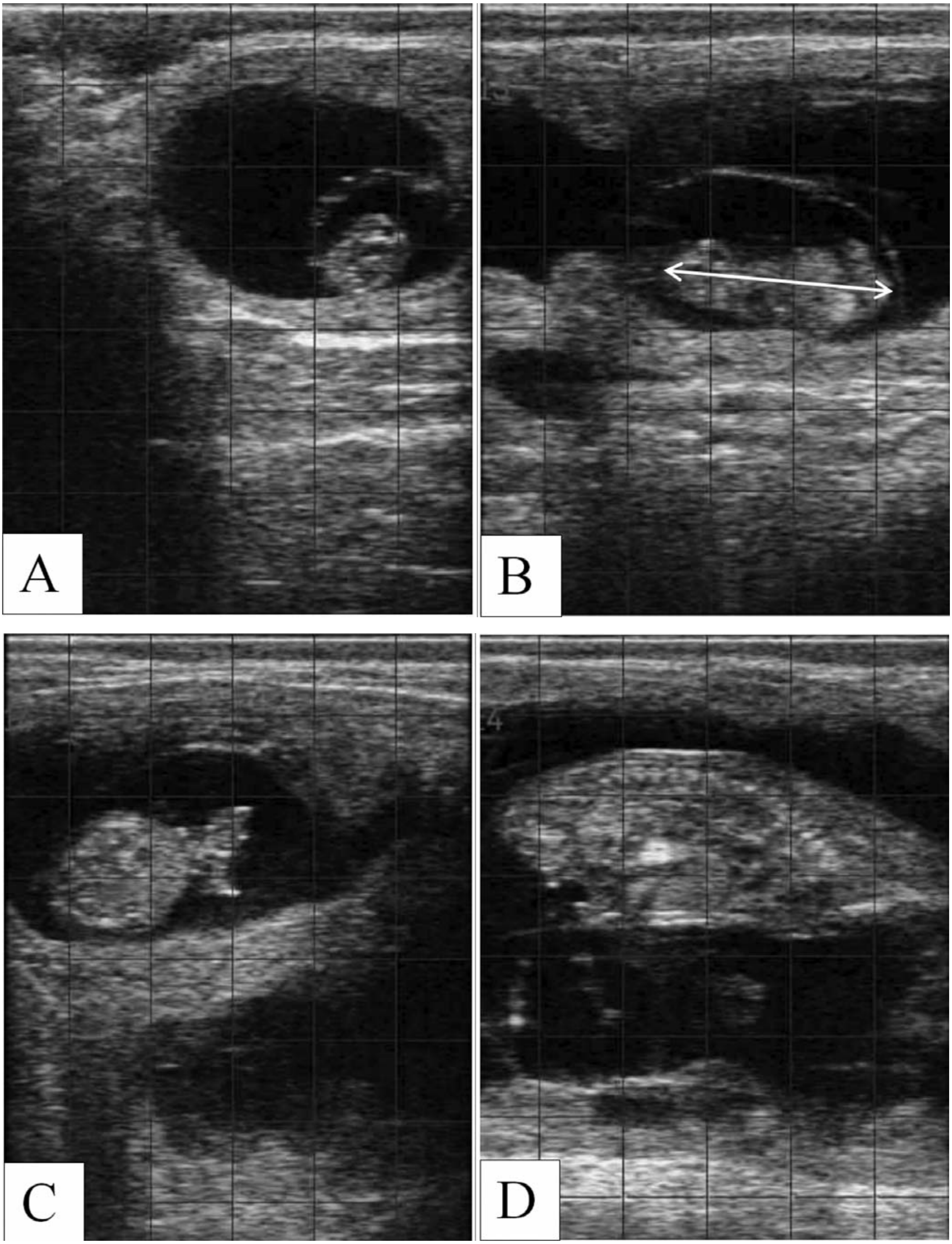

Figure 1 - Ultrasound images of embryos and fetuses obtained from cows on days 38-47 and 60-65 post-fertilization, respectively, are shown: 1A - with delayed embryo development (Group 1), 1B - with physiological gestation (Group 2), 1C - with delayed fetal development (Group 1), and 1D - with normal fetal development (Group 2). The crown-rump length of the embryo is indicated by the white line with arrows.

Statistics 20.0 software and the Mann-Whitney U test were employed.

RESULTS

Figure 1 illustrates typical ultrasound images of embryos and fetuses in cows from Group 1 and Group 2. Comparing the ultrasound images in Figures 1A and 1B, it is evident that the crown-rump length of the embryos (indicated by the white line with arrows) in cows from Group 1 was significantly smaller (in our study, 16 mm or less) compared to those in Group 2 (17-25 mm) during days 38-47 of gestation. The comparison of Figures 1C and 1D further reveals that the size delay of fetuses in cows from Group 1 compared to those in Group 2 persisted until days 60-65 post-fertilization. In our study, the crown-rump length and body diameter of fetuses in cows from Group 1 did not exceed 48 mm and 16 mm, respectively, during these gestational periods.

Figure 2 presents typical ultrasound images of the placenta in cows from Group 1 and Group 2 on days 110-117 of pregnancy. Comparing Figures 2A and 2B, it is evident that the anatomical connection between the cotyledon and the caruncle (denoted by a white asterisk) in cows from Group 1 is significantly smaller compared to that in Group 2.

The ultrasound images presented in Figures 1-2 show that the metric parameters of the embryo, fetus, and placenta in cows with IUFR in all three ultrasound examinations had characteristic differences from similar parameters in Group 2 without this pathology. Below we present the results of biochemical studies of the blood serum in calves of Group 1 and Group 2 1 day after their birth.

After obtaining the data, calculations were performed for the albumin-globulin ratio and the lactate/pyruvate ratio. Blood and plasma parameters showing significant differences using the Mann-Whitney U test were presented in Table 1.

The averaged results of the examination of calves without IUFR were taken as 100% when assessing the differences in parameters, and the resulting difference was rounded to two decimal places. This approach allows for a clear determination of the disparity in the values of the compared parameters.

Carbohydrate metabolism in calves is characterized by parameters such as glucose, glycogen, pyruvic acid, and lactic acid. Indicators indirectly indicating the quality of carbohydrate metabolism include changes in body mass, general well-being, and alterations in protein and lipid metabolism (25,26). Our obtained data on carbohydrate metabolism parameters in the blood of calves in the first group showed a glucose level of 28.60% lower and a lactate level of 80.43% higher compared to the second group. Consequently, the lactate/pyruvate ratio in calves with IUFR increased almost twofold, reaching 91.95%. The low glucose level in calves may indicate a decrease in its level in their mothers. The differences in urea and creatinine levels between the groups were not statistically significant: the concentrations of these metabolites in the serum of IUFR calves were 5.63±0.48 mmol/L and 115.6±10.5 μmol/L, respectively, while in newborns of Group 2, they were 4.97±0.21 mmol/L and 125.5±7.01 μmol/L.

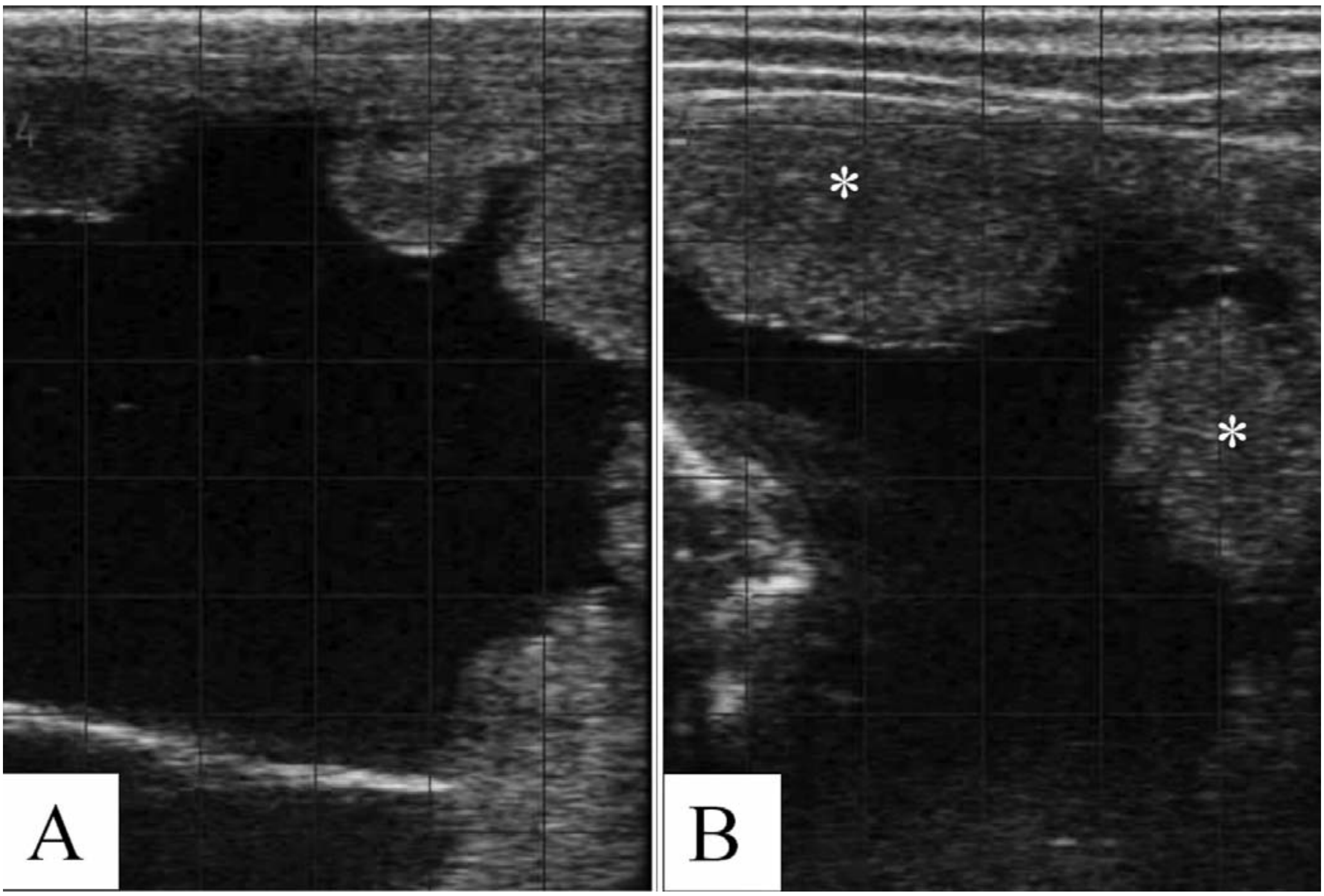

Figure 2 - Ultrasound scans of the placenta in cows on days 110-117 post-fertilization are shown: 1A - with delayed fetal development (Group 1), 1B - with physiological pregnancy progression (Group 2). The anatomical connection between the cotyledon and the caruncle of the placenta is marked with a white asterisk.

Table 1 - Significantly differing blood parameters of calves*, obtained within the first day after their birth.

Indicators	Data of calves from the Group 1	Data of calves from the Group 2
Blood		
Glucose (mmol/L)	3.47±1.83	4.86±1.27
Lactate (mmol/L)	2.49±0.96	1.38±0.30
Lactate/pyruvate ratio	18.6±0.48: 1	9.69±0.21: 1
Serum		
Protein (g/L)	50.1±1.83	63.7±2.27
Albumin-globulin ratio	2.40±0.18: 1	1.11±0.06: 1
Total immunoglobulins (g/L)	6.67±0.96	14.8±1.30
Total lipids (g/L)	1.05±0.07	2.21±0.04
Cholesterol (mmol/L)	0.83±0.04	1.23±0.04

Note: * Values were considered significantly different at $p < 0.05$.

Protein metabolism serves as an indicator reflecting the quality of growth and development in newborns, characterized by the content of albumins (approximately 60-70% of all blood proteins), globulins, and the total amount of blood proteins (26,27). In our study, the differences in serum albumin levels between the groups were not statistically significant: in 1-day-old IUFR calves, the value was 35.4±1.29 g/L, compared to 33.2±1.19 mmol/L in newborns without developmental pathology. However, in contrast to calves in the second group, calves with IUFR in the first days of life exhibit an increased albumin-to-globulin ratio and hypogammaglobulinemia. Additionally, a decrease in the total blood protein level in calves of the first group compared to the second 21.4% is noted.

Lipid metabolism undergoes significant alterations in metabolic pathologies (28) and affects body mass, the condition of organs and tissues, as well as the overall resilience of young animals. In the first days of life, newborn offspring exhibit a more than twofold decrease in the number of total lipids in the blood serum and a decrease in cholesterol by 32.52%, compared to the second group (Table 2).

The dynamics of tracking the levels of total lipids and cholesterol showed their stable increase in the blood plasma of calves born from cows with a physiological course of pregnancy, with both parameters within the normal range. The amount of lipids on the 3rd, 7th, and 14th days increased by 4.98%, 22.62%, and 23.53% (standard deviation $p < 0.05$), respectively, compared to the 1st day. The cholesterol content increased by 21.95%, 62.60%, and 78.86% (standard deviation $p < 0.05$) on the 3rd, 7th, and 14th days, respectively.

At the same time, calves with IUFR exhibited hypolipidemia and hypocholesterolemia. The cholesterol level in the blood serum was low until the 3rd day of life. The low lipid level persisted throughout the entire study period. Similar results are observed in hypotrophic calves.

DISCUSSION

The obtained data indicate immaturity of the enzymatic system in calves with IUFR. This can be observed in the shift of glucose oxidation from oxidative phosphorylation in the Krebs cycle towards anaerobic glycolysis. From a biochemical perspective, the decrease in glucose levels can be described as to reduced hepatic capacity to convert lactate into glucose and glycogen. This leads to a predominance of anaerobic glucose oxidation. As a result, lactate accumulates, altering the lactate/pyruvate ratio (29).

During pregnancy, the cow's placenta inhibits the penetration of immunoglobulins into the fetal bloodstream, resulting in very low levels of immunoglobulins in the calf after birth. An increase in its level occurs through the absorption of colostrum antibodies. The amount of immunoglobulins reflects the resilience of newborns to various diseases, so disruption of the digestive system significantly affects the overall condition of the calves (26,27).

In addition, the low level of immunoglobulins is associated with increased activity of anaerobic oxidation processes. Hypoxic conditions are confirmed by the level of lactate and its ratio to pyruvate (29). Under physiological conditions, biochemical processes in the body involve the breakdown of lactate in the liver to form pyruvate, followed by gluconeogenesis leading to glucose formation (29). In our case, lactate levels are elevated, while glucose levels are decreased. As a result, there is a shift in acid-base homeostasis: the accumulation of products of incomplete anaerobic metabolism stimulates oxygen-dependent reactions towards incomplete oxygen recovery (29). Active oxygen metabolites are formed, which participate in the accumulation of lipid peroxidation products (29,30). Oxidation also affects colostral immunoglobulins, the active absorption of which occurs during the first days of the calf's life (26,27). This

Table 2 - The dynamic changes of lipid metabolism in blood samples between calves with intrauterine growth retardation (Group 1) and without this diagnosis in the anamnesis (Group 2).

Time of sample collection	Total lipids content (g/L)		Cholesterol content (mmol/L)	
	Group 1	Group 2	Group 1	Group 2
The first day	1.05±0.07***	2.21±0.04	0.83±0.04**	1.23±0.04
The third day	1.73±0.07**	2.32±0.07	1.19±0.08*	1.50±0.10
The 7-th day	1.55±0.12***	2.71±0.19	1.86±0.14	2.00±0.12
The 14-th day	1.85±0.10**	2.73±0.09	2.25±0.19	2.20±0.13

Note: Statistical importance between Group 1 and Group 2: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

process may lead to oxidative modification of already absorbed immunoglobulins, disrupting their physicochemical and functional properties. The consequence of this is a reduction in the potential for offspring's anti-infective protection (27,30). The unstable state of the oxidative system in calves may be influenced by the condition of their mothers (20). Data analysis indicates that disruption in antioxidant defense and the occurrence of peroxidation reactions contribute to the development of oxidative stress. This provokes the development of various reproductive system diseases, negatively impacting pregnancy progression (31).

Many factors indicate the presence of oxidative stress in the calves of the first group. Its symptoms primarily manifest in the reduction of protein levels, and secondarily in the decrease of total lipids in the blood serum. The function of proteins in calves' bodies is significant; they are necessary for maintaining colloid osmotic pressure of blood, facilitating substance transport, and immune response. Therefore, it is important to evaluate the level of total protein and the specific ratio of albumins to globulins. This allows for a comprehensive assessment of the biochemical status of blood as physiologic and also suggests the presence of inflammation and protein metabolism in the body (27).

The ratio of albumins to globulins indicates the peculiarities of the physiological condition and the adequacy of their protein intake (27,32). Due to the specific metabolism in newborn calves, it becomes possible to assess the condition of their mothers (26). During the first days of life, calves absorb albumins and globulins into the bloodstream from colostrum through the lymphatic system without undergoing enzymatic hydrolysis (26,33). This occurs due to the high permeability of the intestinal mucosa as an adaptation mechanism to new environmental conditions (26,33). Thus, in newborn offspring, the formation of their immunity occurs through the utilization of maternal albumins and globulins as humoral antibodies (33,34).

Our results indicate a more than twofold change in the albumin-to-globulin ratio in calves born to mothers with IUFR compared to offspring from cows without this diagnosis in their medical history. Additionally, calves in the first group exhibited a lower protein concentration. It is presumed that calves in the first group experience an increase in albumins and a decrease in globulins in the blood. However, despite the difference in the quantity and quality of proteins, the urea level (a final product of protein metabolism) did not show significantly different values. This suggests that, at this stage, there is no active nitrogen metabolism occurring in the calves' livers. Therefore, the albumin-to-globulin ratio in calves is formed as a result of their direct absorption into the bloodstream from maternal colostrum. Thus, it can be concluded that cows with the diagnosis of IUFR experience an increase in the albumin-to-globulin ratio, indicating a disruption in their protein metabolism or the presence of inflammation (34).

Lipid metabolism influences weight, organ and tissue condition, and the overall resilience of young animals (35). To assess its quality, indicators of total lipids and cholesterol in the calves were compared over time. Low concentrations of total lipids and cholesterol in the serum of calves with IUFR may be associated with several factors. Firstly, insufficient intake of lipids from maternal colostrum, which may be due to a deficiency of lipids in colostrum, poor absorption by the calf's body, loss in feces, disruption in the formation of their components in the liver, and the cause may also lie in weak suckling reflexes and decreased appetite in calves with IUFR due to oxidative stress and acidosis (35). It is well-established that the concentration of total lipids in serum significantly changes in metabolic pathologies (28). Another reason could be increased expenditure to maintain thermoregulation (36). Additionally, hypolipidemia and hypocholesterolemia in newborns may be associated with increased cortisol secretion (14,23).

These results indicate problems with postnatal adaptation in calves with intrauterine growth retardation compared to calves born without this diagnosis in their medical history. One of the reasons for the occurrence of disruptions in the body's functioning is a deficiency of trace elements. Some studies show that the use of preparations containing trace elements such as cobalt, manganese, copper, selenium, and zinc for cows in the late stages of pregnancy and newborn calves contributed to reducing the manifestations of intrauterine fetal retardation (17,18,37,38). In addition to this, the application of certain trace elements, the deficiency of which directly affects the condition of the reproductive system, to cows before insemination contributes to an earlier onset of estrus, a reduction in the number of inseminations not resulting in pregnancy, a decrease in embryonic mortality, and the development of IUFR (18,22,37).

For diagnosing IUFR in the postnatal period, certain blood parameters of newborns can be considered. The most reliable indicators include immunoglobulins, total protein, glucose, and cholesterol levels. Literary sources also mention gamma-glutamyl transpeptidase, alkaline phosphatase, the de Ritis ratio, vitamin E, aspartate and alanine aminotransferases, total antioxidant activity, creatinine, and malondialdehyde (20). Among these, the most reliable indicator is the level of immunoglobulins.

One way to reduce the negative consequences of oxidative stress resulting from IUFR is the administration of supplements containing cobalt, manganese, copper, selenium, and zinc, the deficiency of which often triggers the development of IUFR (39-43). Another method to reduce the number of disturbances in early embryogenesis could be the use of prolonged progestin therapy, antioxidants and immuno-stimulants (44-48).

CONCLUSIONS

Modern animal husbandry faces the problem of deteriorating reproductive function in cows with increased productivity. This leads to increased loss of offspring at various stages of their life and development. One disease that increases the risks of calf loss in the early postnatal period is IUFR. The main economic damage is associated with the high morbidity and mortality of calves born to cows with this diagnosis.

We identified the main indicators characterizing the condition of calves with IUFR in the first days of their life. These indicators include decreased blood glucose levels, increased lactate content, hypoproteinemia, hypoglobulinemia, and dyslipidemia. These results indicate the presence of severe oxidative stress in newborns. It was also found that the serum lipid levels of calves with IUFR were decreased (by 25.4-52.5%, $p<0.05$) from day 1 to day 14, and cholesterol levels were decreased (by 20.7-32.5%, $p<0.05$) from day 1 to day 3 of life. The lipid level in the serum of calves indicates the persistence of disturbances in their enzymatic system in the first two weeks of life. An immature antioxidant system indicates a deficiency of certain micronutrients. The detected abnormalities require mandatory metabolic correction.

The obtained results indicate the further necessity of studying the difference in physiological processes between newborns with and without a history of IUFR. The data from our study can serve as a basis for developing a program to correct the condition of calves with IUFR at various stages of their development, as well as for developing a strategy to prevent these and similar disorders in the course of pregnancy in cows and for developing a forecasting program for computers.

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication and/or funding of this manuscript.

Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All methods were performed in accordance with the principles of the Declaration of Helsinki. The study was approved by Local Ethics Committees of Vernadsky Institute of Geochemistry and Analytical Chemistry of the Russian Academy of Sciences (Protocol 9 of 25.10.2023). Informed consent was obtained from all participants.

Consent for publication

Not applicable.

Authors contribution

Vladimir Safonov - Conceptualization, Methodology, Project administration, Writing - original draft. Anton Chernitskiy - Data curation, Investigation, Validation, Writing - review & editing. Tatiana Ermilova - Formal analysis, Supervision, Funding acquisition, Writing - review & editing. Emil Salimzade - Software, Visualization, Resources, Writing - review & editing.

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