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REPRODUCTIVE STATUS AND BLOOD BIOCHEMICAL PARAMETERS OF HOLSTEIN COWS WITH DIFFERENT MILK PRODUCTIVITIES IN CONNECTION WITH THE DYNAMICS OF LIPID METABOLISM DURING THE POSTPARTUM PERIOD

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Abstract

In the early period of lactation, the energy needs of high-yielding dairy cows sharply increase, which leads to a negative energy balance. For it compensation, the organism spends its internal resources, mainly lipid reserves. Normalization of cholesterol production at the beginning of the postpartum period is obviously associated with an increase in the animal reproductive ability. However, it remains unclear what role in the regulation of the reproductive function can play a change in the blood level of triglycerides. Here, we compared for the first time the duration of the calving to conception interval in Holstein cows with medium (MP) and high milk productivity (HP) depending on the increase or decrease in the blood concentration of triglycerides from the end of month 1 to the end of month 2 of lactation. Furthermore, we found a connection between the calving to conception interval, the serum content of triglycerides, and some other indexes of metabolism. Cows (*Bos taurus taurus*) of the Holstein breed of the 1st calving with milk yield of 6336±160 kg per 305-day lactation (n = 19; EKH Klyonovo-Chegodaevo, settlement Klyonovskoe, Moscow) and of the 2nd-3rd calving with milk yield of 10007±420 kg per 305-day lactation (n = 14; PZ Prinevskoe, Vsevolozhsk Region, Leningrad Province) were used in the experiments. In 3-4 and 7-8 weeks after calving, the blood samples were collected to assay the concentrations of triglycerides, total cholesterol, total protein and its fractions, urea, creatinine, glucose as well as the activity of aspartate aminotransferase (AST, EC 2.6.1.1) and alanine aminotransferase (ALT, EC 2.6.1.2). All cows were divided into 2 groups. Group I consisted of animals in which the blood level of triglycerides decreased by the end of the 2nd month of lactation (MP: n = 10, HP: n = 8). Group II consisted of animals in which no such decrease was observed (MP: n = 9, HP: n = 6). Twelve months after calving, the average values for the calving to conception interval and milk yield per 100-day lactation were determined in all groups. In cows with MP between the 3rd-4th and 7th-8th weeks of lactation, the blood triglycerides concentration decreased 1.2 times ($p < 0.001$) in group I and increased 1.1 times ($p < 0.01$) in group II. The total blood cholesterol content grew significantly (1.2-1.3 times) in animals of both groups. Meanwhile, the calving to conception interval was 1.6 times shorter in group I than in group II (86±12 vs. 140±21 days, $p < 0.05$). In cows with HP, by the end of the 2nd month of lactation, the concentration of triglycerides decreased 1.6 times ($p < 0.01$) in group I and increased 2 times ($p < 0.001$) in group II. The content of total cholesterol rose 1.2-1.5 times in the blood of animals of both groups. The calving to conception interval in group I was 1.5 times shorter than in group II, but this reduction was not reliable. In addition, in these animals, the milk yield per 100-day lactation in group I was 534 kg higher than in group II ($p < 0.05$). Correlation analysis revealed a negative relationship between the duration of the calving to conception interval and the triglyceride content in the blood of cows with HP at the end of the 1st month of lactation (r = 0.56 with $p < 0.05$). At the end of the month 2, a positive relationship between these indicators in cows with MP and HP

was observed ($r = 0.60$ with $p < 0.01$ and $r = 0.56$ with $p < 0.05$, respectively). In animals with MP, the duration of the calving to conception interval was also associated with biochemical parameters, which correlated with serum triglyceride concentrations. Thus, in cows of the Holstein breed, the dynamics of lipid metabolism in the middle of the first trimester of lactation was characterized by an increase in the total cholesterol content, whereas the blood level of triglycerides varied in different individuals differently. The decrease in the concentration of triglycerides from the end of month 1 to the end of month 2 of lactation, obviously, causes improving the reproductive function and leads to a reduction in the duration of the calving to conception interval, regardless of the milk productivity of animals. Concurrently, in animals with the high milk productivity, such a decrease is more pronounced and may be related to an increase in the milk yield.

Keywords: Holstein breed, cows, triglycerides, metabolism, reproductive ability, milk productivity

Low reproductive capacity in milk-type cows is a serious problem for contemporary cattle breeding [1, 2]. Weakened fertility (subfertility) in animals is the outcome of various reproduction disorders, mainly, elongation of post-calving anestrus, ovarian dysfunction, reduction of oocyte and embryonic viability, as well as deterioration of reproductive health due to decrease of immunity in general [1, 3]. Such disorders are mainly typical for Holstein cows and result in longstanding inter-calving interval, which significantly exceeds 400 days [4, 5]. At that, term of economic use of Holstein cows comprises in average no more than three lactations due to high culling of animals in herd [6].

It is known that reproductive function in cows with high genetic potential of milk production heavily depends on the intensity and trend of metabolic processes controlled by metabolic hormones [1, 7, 8]. At early period of lactation, energy needs drastically increase in animals, which is accompanied by gradual body adaptation to new metabolic state. Lack of nutritive substances could not be promptly replenished by high consumption of feed, especially in terms of low appetite in such cows [9]. Negative energy balance is formed, for compensation of which the body uses its internal, mainly lipid, resources [10, 11]. As a result of mobilization of fat depots, free fatty acids grow in the blood and further acidification results in increased number of ketone bodies, first of all, β-hydroxibutyrate [12-14]. Concentration of free fatty acids and β-hydroxibutyrate in blood points at negative energy balance in high yielding cows in post-calving period [15]. Besides, increase in concentration of such metabolites may negatively influence reproductive function and deteriorate reproductive health of animals due to total reduction of immunity [7, 13, 14].

Lipids including triglycerides, cholesterol, and phospholipids, as well as their derivatives, provide energy and play significant role in functioning of endocrine system and several intracellular signal ways [10].

Blood lipid level of Holstein cows varies, which, probably, becomes a consequence of body adaptation to new metabolic state. Reduction of cholesterol concentration was found immediately before calving and its gradual growth by the end of the 1st to 2nd month of lactation [16, 17]. Besides, concentration of triglycerides in the blood during post-calving period was lower than during the interlactation period. At that, growth of cholesterol concentration in blood in milk-type cows in post-calving period is related to earlier restoration of the sexual cycle and further decrease of the interval from calving to conception [18, 19].

Previously we had shown that upon injection of bovine placenta extract to Black Pied cows before calving, concentration of cholesterol in their blood grows in the first 3 weeks after calving, lutein ovarian activity is intensified in 2 months after calving, and then decreased in the next service period [20]. It means that regulation of cholesterol production at beginning of post-calving period evidently relates to the improved reproductive capacity of animals. Meanwhile, it is still unclear what role in regulation of reproductive function in cows may be played by change of concentration of blood triglyceride, the other component of

lipid metabolism.

Present paper introduces comparison between duration of the service period in Holstein cows with average and high milk production values (accordingly, 6336±160 and 10007±420 kg for 305 days of lactation) depending on the nature of changes in concentration of triglycerides in blood serum from the end of 1st until termination of the 2nd month of lactation. It was shown that reduction and increase in triglyceride concentration are especially expressed in animals with high milk production values. At that, duration of service period is associated with changes in concentration of triglycerides, as well as with changes of other metabolic values correlating with such concentration.

Purpose of research paper was to study relations between the reproductive function and protein and carbohydrate metabolism with changes in lipid metabolism during the post-calving period in cows with different milk yield values.

Techniques. Research was conducted in the Experimental Farm Klyonovo-Chegodaevo (Klyonovskoe Settlement, Moscow) and Production Farm Prinevskoye (Vsevolozhsk District, Leningrad Region) in 2016-2017. Cows (*Bos taurus taurus*) of Black Pied Holstein breed of the 1st calving with average milk yield (6336±160 kg for 305 days of lactation, Experimental Farm Klyonovo-Chegodaevo) and 2nd-3rd calving with high milk yield (10007±420 kg for 305 days of lactation, Production Farm Prinevskoye) were used. Animals were managed in loose housing conditions. Their diet was in line with zootechnical standards. All tests were conducted according to principles enclosed in Helsinki Declaration (World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects, 1964-2013), and best laboratory practices (National Standard of the Russian Federation GOST R 53434-2009).

A total of 19 cows with mean milk productivity (MP) and 14 cows with high milk productivity (HP) with restored sexual cycle were selected for research that was confirmed by normal manifestation of estrus after day 45 of lactation. Blood was collected from tail vein of animals in 3-4 and 7-8 weeks after calving (April-July) with the use of vacuum system Apexlab (Hebei Xinle Sci&Tech Co., Ltd, China) and delivered to the laboratory within 1-2 hours. Serum obtained by 15 min centrifuging at 2500 g was frozen and stored at –20 °C. Concentration of triglycerides, total cholesterol, total protein and its fractions, urea, creatinine, glucose, as well as activity of aspartate aminotransferase (AST, EC 2.6.1.2) and alanine aminotransferase (ALT, EC 2.6.1.2) enzymes was determined in blood serum samples with a biochemical analyzers ChemWell (Awareness Technology, USA), ACCENT 200 (PZ CORMAY S.A., Poland) by using reagents of Analyticon Biotechnology AG (Germany) and PZ CORMAY S.A. (Poland).

In 12 months after calving, mean values for service period and milk yield for 100 days of lactation were identified based on analysis of zootechnical and pedigree records in all groups of cows.

Obtained data was processed by one-way ANOVA test or two-way repeated measures ANOVA test with software SigmaStat (Systat Software, Inc., USA). Mean (*M*) and standard error of mean (±SEM) values are provided in table below. Statistical significance was measured by Tukey's test. Correlation coefficients (*r*) were calculated by Pearson's method and their statistical significance was assessed by SigmaStat.

Results. According to the nature of change in concentration of triglycerides in blood between weeks 3-4 and 7-8 of lactation, all animals were divided into two groups. This lactation period was chosen due to the fact that luteal activity of cow ovarium was increased during the aforesaid time interval [20]. Group I included species, triglyceride concentration in blood of which had decreased by the end of the 2nd month of lactation ($n = 10$ and $n = 8$, the cows with

mean and high milk productivity, respectively). No such decrease was noted in animals of group II (n = 9 and n = 6). Blood triglyceride concentration decreased 1.2 times in cows with mean productivity between weeks 3-4 and 7-8 of lactation ($p < 0.001$) in group I and increased 1.1 times ($p < 0.01$) in group II (Table 1). Consequently, by the end of month 2 such value was higher in cows with positive triglyceride concentration changes ($p < 0.001$). By weeks 7-8 of lactation, significant (1.2-1.3-fold) increase in the total blood cholesterol and 1.8-2.1-fold decrease of De Ritis ratio (AST/ALT) were in both groups, which may evidence of shifting metabolism towards anabolism. Besides, an increase in albumins (1.1-fold, $p < 0.01$), urea (1.4-fold, $p<0.01$), and ALT activity (1.7-fold, $p < 0.01$) occurred in group I. These results denote improvement of protein-synthesizing liver function caused by more intensive urea cycle and glucose-alanine cycle in animals with negative changes in blood concentration of triglycerides.

1. Blood biochemical indicators at the end of the 1st and 2nd months of lactation in Holstein cows of mean productivity depending on blood triglyceride concentration (M±SEM, n = 19; Experimental Farm Klyonovo-Chegodaevo, settlement Klyonovskoe, Moscow, 2016-2017)

Indicators	Time after calving			
	group I (n = 10)		group II (n = 9)	
	3-4 weeks	7-8 weeks	3-4 weeks	7-8 weeks
Triglycerides, μmol/l	0.206±0.006	0.175±0.007**[a]	0.189±0.006	0.213±0.007*[b]
Total cholesterol, μmol/l	3.89±0.19	4.90±0.14**	4.34±0.20	5.17±0.21*
Total protein, g/l	86.8±1.7	87.8±2.1	88.3±2.9	91.6±2.5
Albumins, g/l	24.6±0.8[c]	27.2±0.6*	27.5±1.1[d]	28.5±0.8
Globulins, g/l	62.2±1.6	60.6±2.4	60.7±2.4	63.0±2.5
Urea, μmol/l	4.90±0.43	6.91±0.43*	5.24±0.39	6.00±0.55
Creatinine, μmol/l	82.0±5.5	79.1±3.8	79.7±7.6	75.7±4.2
Glucose, μmol/l	2.08±0.36	1.79±0.25	1.62±0.21	2.02±0.17
AST, IU/l	70.1±3.4	62.2±4.6	87.7±14.9	66.7±4.6
ALT, IU/l	10.0±1.1	17.2±1.6*	11.9±1.6	15.2±0.8
AST/ALT	7.99±1.03	3.87±0.50*	8.29±1.44	4.55±0.50*

N o t e. Mean productivity — 6336±160 kg for 305 days of lactation. Animals were divided into groups by changes in blood triglyceride concentration. AST — aspartate aminotransferase, ALT — alanine aminotransferase.
[a, b, c, d] Differences between the groups are statistically significant at $p < 0.001$ and $p < 0.05$, respectively.
*, ** Differences between time intervals for one group are statistically significant at $p < 0.01$ and $p < 0.001$, respectively.

2. Blood biochemical indicators at the end of the 1st and 2nd months of lactation in Holstein cows of high productivity depending on blood triglyceride concentration (M±SEM, n = 14; CJSC "Pedigree Plant "Prinyevskoe", Vsevolozhsk District, Leningrad Region, years 2016-2017)

Indicators	Time after calving			
	group I (n = 8)		group II (n = 6)	
	3-4 weeks	7-8 weeks	3-4 weeks	7-8 weeks
Triglycerides, μmol/l	0.158±0.015[a]	0.096±0.013**[c]	0.082±0.015[b]	0.162±0.014***[d]
Total cholesterol, μmol/l	3.51±0.21	5.21±0.22***	3.80±0.11	4.64±0.24*
Total protein, g/l	72.3±1.2	76.0±0.7*	74.1±3.2	72.5±2.7
Albumins, g/l	34.4±0.9	35.8±1.2	32.7±1.8	32.6±0.9
Globulins, g/l	37.9±1.4	40.2±1.4	41.4±2.4	39.9±2.5
Urea, μmol/l	3.56±0.24	5.95±0.45***	3.97±0.37	5.36±0.33*
Creatinine, μmol/l	101.0±6.8	83.2±1.6	93.0±5.4	91.6±6.5
Glucose, μmol/l	2.89±0.17	3.10±0.09	2.95±0.14	2.82±0.18
AST, IU/l	96.3±5.1	85.2±1.8	81.2±5.4	82.2±4.4
ALT, IU/l	16.8±2.6	26.5±2.3*	18.8±2.2	21.0±4.4
AST/ALT	6.98±2.21	3.48±0.47	4.95±1.15	6.73±3.12

N o t e. High milk yield — 10007±420 kg for 305 days of lactation. Animals were divided into groups by changes in blood triglyceride concentration. AST — aspartate aminotransferase, ALT — alanine aminotransferase.
[a, b; c, d] Differences between the groups are statistically significant at $p < 0.01$ and $p < 0.01$.
*, **, *** Differences between time intervals for one group are statistically significant at $p < 0.05$; $p < 0.01$ and $p < 0.001$, respectively.

Changes in blood triglyceride concentration in cows with high productivity were more pronounced (Tables 2). By the end of the 1st month of lactation,

triglyceride concentration was 1.9 times higher ($p < 0.01$) in group I than in group II. By the end of the 2nd month it decreased 1.6 times ($p < 0.01$) in group I and increased 2 times ($p < 0.001$) in group II, due to which the values in group II were higher than in group I ($p < 0.01$). Trend of changes in other metabolism indicators between the 3-4th and 7-8th weeks of lactation also had a number of specificities. Both animal groups were characterized by significant increase in total blood cholesterol (1.2-1.5-fold) and urea (1.4-1.7-fold). At the same time, double decrease of De Ritis ratio in group I was insignificant due to high variability of such indicator, whereas slight increase thereof was in group II. Accordingly, shift of metabolic processes towards anabolism had not yet occurred in most cows with high productivity by the end of the 2nd month of lactation. Increase of blood ALT activity (1,6-fold, $p < 0.05$), as well as total protein (1.1-fold, $p < 0,05$) found in group I was mainly due to globulins.

The time from calving to conception in cows with mean productivity to a greater extent depended on the nature of changes in blood triglyceride level (Table 3). Service period of such animals in group with negative changes in triglyceride concentration was 1.6 times shorter than in group with positive changes ($p < 0.05$). Service period in cows with high productivity in group I was also 1.5 times shorter than in group II, however such decrease was insignificant due to high variability of the indicators. Besides, milk yield in such animals for 100 days of lactation in group I was higher than in group II ($p < 0.05$), whereas milk yield in cows with mean productivity slightly increased in group I.

3. Reproduction indicators and milk yield in Holstein cows of different productivity depending on changes in blood triglyceride concentration from the end of the 1st until the end of the 2nd month of lactation (M±SEM, $n = 33$)

Indicators	Milk productivity			
	mean		high	
	group I ($n = 10$)	group II ($n = 9$)	group I ($n = 8$)	group II ($n = 6$)
Service period, days	86±12[a]	140±21[b]	136±23	199±32
Milk yield for 100 days of lactation, kg	2452±115	2303±167	4342±155[c]	3808±118[d]

Note. Mean and high milk productivity values are 10007±420 and 6336±160 kg for 305 days of lactation. Animals were divided into groups by changes in blood triglyceride concentration.
[a, b; c, d] Differences between the groups are statistically significant at $p < 0.05$ and $p < 0.05$, respectively.

4. Correlation coefficients (r) between service period, blood triglyceride concentration and biochemical idicators at the end of the 1st and 2nd month of lactation in Holstein cows of different milk productivity

Pair of compared indicators	Time after calving			
	animals with MP ($n = 19$)		animals with HP ($n = 14$)	
	3-4 weeks	7-8 weeks	3-4 weeks	7-8 weeks
Service period—triglyceride concentration	0,25	0,60**	–0,56*	0,54*
Service period—cholesterol concentration	0.44	0.60**	0.42	0.12
Service period—total protein	0.26	0.50*	–0.13	0.23
Service period—glucose level	0.22	0.57*	0.18	–0.18
Service period—AST activity	–0.13	–0.53*	0.42	0.11
Service period—AST/ALT	–0.52*	–0.37	0.19	0.28
Triglyceride concentration—cholesterol concentration	–0.08	0.47*	–0.50	–0.19
Triglyceride concentration—glucose level	0.39	0.53*	0.13	0.05
Triglyceride concentration—AST activity	–0.55*	–0.11	0.19	–0.19

Примечание. Mean (MP) and high (HP) milk productivity are 10007±420 and 6336±160 kg for 305 days of lactation. AST — aspartate aminotransferase, ALT — alanine aminotransferase.
*, ** Statistical significance of r values ($p < 0.05$ and $p < 0.01$, respectively).

Correlation analysis revealed negative relationship between the service period and blood triglycerides in cows with high productivity ($p < 0.05$) at the end of the 1st month of lactation, and positive relationship between such values in cows with mean ($p < 0.01$) and high milk productivity ($p < 0.05$) at the end of 2nd month (Table 4). In 2 months after calving, service period in animals with

high milk productivity was also positively related to concentration of cholesterol ($p < 0.01$), total protein ($p < 0.05$) and glucose ($p < 0.05$) and negatively related to AST activity ($p < 0.05$). Besides, at the end of the 1st month of lactation the calving to conception interval correlated with De Ritis ratio ($p < 0.05$). It should be noted that service period was associated with the biochemical indicators related with blood level of triglycerides (only in case of total protein correlation coefficient $r = 0.39$ is insignificant). At the same time, dependence between the service period and cholesterol concentration or protein carbohydrate metabolism, which, in its turn, did not correlate with triglyceride concentration, was not found in cows with high milk productivity. Such results denote that association of service period with these blood indicators may be secondary and determined by their relationship with triglyceride concentration arising under the effect of total central regulator(s), for instance, one or several metabolic hormones [7, 8].

After calving, blood triglyceride level in cows is determined by two main factors: intensive hepatic accumulation during negative energy balance [21] and increased need of udder in milk fat synthesis [22]. Triglycerides enter into the blood as part of lipoproteins of very low density, formation of which requires cholesterol [10]. In our research, total cholesterol concentration increased by the end of the 2nd month of lactation in all cows, whereas triglyceride concentration only in group II. Besides, such concentration to a greater extent depended on the cholesterol synthesis in animals with mean milk productivity, which is confirmed by correlation between both indicators of lipid metabolism ($p < 0.05$) by the end of the 2nd month of lactation (see Table 4). Decrease of triglyceride concentration was especially manifested in group I with high productivity, in which milk yield for the first 100 days of lactation was increasing more significantly than in cows with mean productivity. Evidently, reduction of blood triglycerides in such animals mainly depends on intensity of synthesis of milk fat involved triglycerides. In general, blood triglycerides were also lower in animals with high milk yields. Lack of correlation between the milk yield for 100 days of lactation and blood concentration of triglycerides may evidence on nonlinear relationship between these indicators.

High genetic potential of milk productivity based on lactation dominant is considered as a factor negatively influencing reproductive performance of cows [1, 3]. In addition, the results we report here show that among animals from a herd with the same milk production, some individuals may have a higher milk yield, which may lead to a decrease in the concentration of blood triglycerides, and this decrease may be associated with a decrease in service period of this animal.

Service period in cows to a greater extent depends on early embryonic mortality, which, in its turn, depends on quality of oocytes and embryos [23, 24]. Changes in blood concentration of different metabolites cause relevant changes in follicle liquid and reproductive tract [25]. It means that metabolic status of mother cows impacts the micro environment where oocytes and embryos are developed. It is of particular importance for oocytes since growth of surrounding follicles from primordial to pre-ovulation stage takes nearly 180 days [26].

It is shown that concentrations of triglycerides in the blood of cows and in the liquid of dominant follicles correlate [27]. Although triglycerides supply important energy source, their excessive accumulation by oocytes and embryos deteriorates function of mitochondria and increases the risk of oxidation stress [10]. Thence, lower triglyceride concentration by the end of the 2nd month of lactation in group I could be related with quality preservation of oocytes (and/or embryos), which could result in a decrease of embryonic mortality and shorter service period. Nevertheless, increased total cholesterol during this period of lactation does not associate with higher reproductive function.

Previously we have shown that service period in Black Pied cows is related to parameters of protein-carbohydrate metabolism at the end of days in milk [28]. Therefore, in this research we have determined these biochemical parameters and their association with service period and blood triglycerides in Holstein cows. It was found that concentration of triglycerides is not the only factor associated with duration of the service period. Firstly, increased blood ALT activity characteristic of cows from group I regardless of milk yield at the end of the 2nd month of lactation is similar to that found on days 70-90 after calving in Black Pied cows with shorter service period [28]. Secondly, duration of the service period in animals with mean productivity is associated with concentrations of total protein and glucose, AST activity and De Ritis ratio, while associations of these parameters with protein-carbohydrate metabolism depende on correlation of the later with triglyceride concentration.

In present research, the service period in animals with high milk productivity was much longer than in animals with mean productivity, regardless of lower concentration of triglycerides in their blood. This is in line with the concept on determining rope of cow's genotype in reproductive function [29]. Besides, additional reduction of triglycerides in animals with high productivity, evidently, positively influences their reproductive performance and results in service period shorter than typical for the genotype.

Thus, lipid metabolism in the middle of the 1st trimester of lactation in Holstein cows is characterized by rising of total blood cholesterol in all tested animals, whereas triglyceride concentration varies among individuals in different ways. Reduction in triglycerides concentration from the end of the 1st until the end of the 2nd month of lactation, evidently, contributes to improvement of the reproductive function and results in shorted service period regardless of animal milk productivity. Herewith, such reduction is more expressed in animals with high milk production and could be related with an increase in milk yields.

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