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Diselementosis as a risk factor of embryo loss in lactating cows

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Abstract: The aim of this research was to reveal the impact of bioelemental status of dairy cows on intrauterine growth restriction and embryo death at early gestation stages. The research included 22 Holstein cows with average annual dairy productivity of 6400–7600 kg. All animals were subjected to transrectal ultrasonography to determine corpus luteum and pregnancy status, and their blood was sampled for biochemical analyses on the 19th–22nd, 28th–32nd, and 38th–45th days of gestation. Zinc, copper, manganese, and selenium blood contents were determined by atomic absorption spectrophotometry. Serum levels of calcium, phosphorus, and magnesium were determined with an automatic biochemistry analyzer. Protein-bound iodine was determined spectrophotometrically. Analysis of results was realized based on the character of embryo development: physiological formation (Group I, n = 9), growth restriction (Group II, n = 8), and death (Group III, n = 5). Serum concentrations of Ca, P, and Mg were 2.76–2.84 mmol/L, 1.77–1.92 mmol/L, and 1.13–1.36 mmol/L in range; blood contents of Zn, Cu, Mn, and Se were 40.8–52.7 μmol/L, 15.9–18.7 μmol/L, 2.50–3.43 μmol/L, and 1.23–1.41 μmol/L in range; and protein-bound iodine was 0.32–0.36 μmol/L in Group I. Serum concentration of the studied trace elements was lower in Groups II and III in comparison with Group I. Cows of Group II demonstrated the following indices: calcium content, 2.72–2.79 mmol/L; phosphorus content, 1.79–1.97 mmol/L; magnesium, 0.98–1.09 mmol/L; zinc, 33.8–36.8 μmol/L; copper, 13.9–15.3 μmol/L; manganese, 2.50–2.89 μmol/L; selenium, 1.04–1.11 μmol/L; protein-bound iodine, 0.29–0.37 μmol/L. The difference according to the level of serum Ca reached 4.2%, P 6.8%, and Mg 23.5% ($P < 0.01$), while according to blood concentration Zn was 30.2% ($P < 0.001$), Cu 21.6%, Mn 15.2%, Se 26.2% ($P < 0.05$), and protein-bound iodine 21.3% ($P < 0.01$). Cows of Group III demonstrated the following indices: calcium content, 2.48–2.56 mmol/L; phosphorus content, 1.74–1.93 mmol/L; magnesium, 0.99–1.02 mmol/L; zinc, 31.2–34.0 μmol/L; copper, 12.2–15.4 μmol/L; manganese, 2.24–3.06 μmol/L; selenium, 1.00–1.03 μmol/L; protein-bound iodine, 0.24–0.30 μmol/L. The differences in comparison with cows of Group I reached 11.4% ($P < 0.05$), 9.4%, 27.2% ($P < 0.001$), 35.5% ($P < 0.001$), 20.6% ($P < 0.05$), 15.2% ($P < 0.05$), 29.1% ($P < 0.05$), and 33.3% ($P < 0.001$), respectively. Disorders of trace elements in cows are one of the main reasons for intrauterine growth restriction and embryo death. Primarily it is connected with magnesium, zinc, copper, selenium, and iodine deficits that have direct or indirect effects on growth, generation, and differentiation of the cells of the developing embryo. Lactating cows with a high level of milk production demonstrate high risk of diselementosis and consequently embryopathy development. Correction of diselementosis in lactating cows should be considered as one of the ways for solving the problem of their fertility.

Key words: Cow, lactation, trace elements, embryo development

1. Introduction

An important place among the causes of decreasing fertility and efficiency of breeding is occupied by reproductive losses connected with intrauterine growth restriction of the embryo and fetus and their sudden death at early gestation stages. The spread of these pathologies in high-producing dairy herds reaches 30%–40% and more (1–4). Therefore, it is not accidental that in practical conditions under the growth of dairy productivity the clinically registered conception rate has decreased from 60%–65% to 35%–40% during the last years. Meanwhile, some researchers continue to assert that actual fertility of ovulated cells is preserved at the level of 90%–95%. It was shown that intrauterine growth restriction and embryo death at early stages of formation are connected with endocrine, immune, and metabolic disorders in the organisms of inseminated animals and formation of the "mother-embryo-fetus" system (3,5,6).

Macro- and microelements play an important role in providing reproductive functions in animals and humans (7–12). Calcium, phosphorus, and magnesium together provide the course of energetic and plastic processes in the organs of the reproductive system, activity of uteroplacental and fetoplacental blood flows, and development of the fetus's bone tissue. Zinc, copper, manganese, selenium, and iodine in the composition of enzymes, hormones, and

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vitamins participate in the processes of hematogenesis, tissue respiration, growth, proliferation, differentiation of cellular structures, regulation of free-radical oxidation, and provision of the functional activity of the endocrine and immune systems. Disorders of bioelemental composition of the organism (excess, deficit, imbalance), defined as "diselementosis" in the biological literature (13), are always accompanied by the development of various latent or clinically evident pathological states. Diselementosis is one of the main causes for decreasing productivity and reproductive capacity of animals (11).

The aim of this research was to study the impact of diselementosis in lactating dairy cows on intrauterine growth and embryo death at early gestation stages.

2. Materials and methods

2.1. Animal materials and study design

The research included 22 lactating black-motley Holstein cows with an average annual dairy productivity of 6400–7600 kg. The animals' ration included corn silage at 25 kg, sainfoin hay at 3 kg, barley straw at 3 kg, a mixture of grains at 7 kg, and sunflower oil cake at 1 kg. Daily consumption of feed on a dry basis was 17.6 kg with the content of 5.5 g of calcium, 4.0 g of phosphorus, 2.3 g of magnesium, 7.2 mg of copper, 33.0 mg of zinc, 34.5 mg of manganese, 0.18 mg of selenium, and 0.37 mg of iodine in 1 kg of dry matter.

All animals were subjected to transrectal examination with the use of ultrasound scanner Easi-Scan-3 with a linear encoder of 4.5–8.5 MHz (BCF Technology Ltd., UK). Corpus luteum size was determined at every examination and the presence/absence of pregnancy was checked on the 28th–32nd and 38th–45th days. Embryo visualization on the 28th–32nd days after insemination under its physiological formation was 92.3%, under growth restriction was 66.7%, and under its subsequent death was 42.9%. Coccygeal-parietal size and the embryo's body diameter were measured after the establishment of pregnancy. Evaluating echometric values, we followed generalized data of the scientific literature and our own studies (1,2). Blood samples from all cows were obtained for biochemical analysis after every ultrasonic scanning of the genitals.

All cows were retrospectively divided into 3 groups. Group I consisted of animals with physiological formation of an embryo (n = 9). Group II contained cows with growth restriction (n = 8) and Group III contained cows with embryo death (n = 5). Intrauterine embryonic death was diagnosed when it was present in the uterus on the 28th–32nd days after conception and absent on the 38th–45th days. Embryo's coccygeal-parietal size of 18–25 mm and body diameter of 10–13 mm were the criteria for physiological formation of pregnancy on the 38th–45th days after insemination and conception. Embryo's growth restriction was diagnosed when its coccygeal-parietal size and body diameter were 12–16 and 7–9 mm, respectively. Cows with physiological gestation course had a corpus luteum with a diameter of 18.2 ± 0.28 mm, under embryo's growth restriction it was 13.8 ± 0.28 mm, and under its death it was 12.9 ± 0.56 mm. Average daily dairy productivity of the animals was considered during the trial.

2.2. Collection of samples

Blood samples from all cows were obtained from coccygeal vein puncture and were collected into sterile vacuum tubes without anticoagulant. Sterile vacuum EDTA tubes were used to obtain whole blood. After clotting for 1 h at room temperature, blood samples without anticoagulant were centrifuged (UC-1612, ULAB, China) at 4000 × *g* for 10 min at room temperature, and sera were carefully harvested and stored at –20 °C until biochemical analysis.

2.3. Analysis of mineral substances

Blood mineral substance levels, including those of zinc, copper, manganese, and selenium, were determined by using an atomic absorption spectrophotometer (AA6300, Shimadzu, Japan). Serum calcium, magnesium, and phosphorus levels were determined by an automated biochemistry analyzer (Hitachi 902, Roche Diagnostics, Japan). The quantitative analysis of serum protein-bound iodine (PBI) levels in the samples was conducted by spectrophotometry (UV-1700, Shimadzu, Japan) according to the procedure modified from the relevant literature (14). Quantitative analysis of progesterone in blood serum samples was conducted by immune-enzyme analysis with the use of a test system (Xema-Medica Co. Ltd., Russia), validated for the cattle, and with the use of immunoenzyme reaction analyzer (Uniplan, AIFR-1, Pikon, Russia).

2.4. Statistical analysis

For statistical analysis, the independent sample t-test was used to determine the differences among Groups I, II, and III. Statistical evaluations of differences between cows with gestation periods of 19–23, 28–32, and 38–45 days were done by using the paired t-test in STATISTICA 8.0 (StatSoft. Inc., USA). Statistical significance was set at $P < 0.05$. All data were expressed as mean ± standard error of the mean (SEM).

3. Results

Research results are represented in the Table. Statistically significant differences for serum calcium and phosphorus levels in cows with physiological gestation course (Group I) and with fetal growth restriction (Group II) were not found during any research period. However, for embryo death (Group III) the serum concentration of calcium was lower in comparison to animals of Group I on the 19th–

Table. Content of macro- and microelements in serum and blood of cows with physiological gestation course, fetal growth restriction, and embryo death (mean ± SEM).

Parameter	Days of gestation		
	19–23	28–32	38–45
Ca, mmol/L	2.76 ± 0.09 2.79 ± 0.07 2.56 ± 0.09	2.84 ± 0.09 2.72 ± 0.12 2.60 ± 0.10	2.80 ± 0.08 2.73 ± 0.09 2.48 ± 0.11[a]
P, mmol/L	1.77 ± 0.11 1.97 ± 0.16 1.93 ± 0.07	1.92 ± 0.07 1.79 ± 0.12 1.74 ± 0.11	1.90 ± 0.09 1.79 ± 0.11 1.84 ± 0.13
Mg, mmol/L	1.26 ± 0.01 0.98 ± 0.03[c] 1.02 ± 0.03[c]	1.36 ± 0.03 1.04 ± 0.02[c] 0.99 ± 0.02[c]	1.13 ± 0.05 1.08 ± 0.03 1.02 ± 0.03
Zn, µmol/L	52.7 ± 2.51 36.8 ± 2.77[c] 34.0 ± 3.24[c]	40.8 ± 2.83 33.8 ± 1.18[b] 31.2 ± 3.03[b]	41.2 ± 1.91 36.7 ± 2.54[a] 31.7 ± 2.42[b]
Cu, µmol/L	17.5 ± 0.84 13.9 ± 0.81[a] 13.9 ± 0.33[b]	18.7 ± 0.71 15.3 ± 0.83[b] 15.4 ± 1.44	15.9 ± 0.72 13.9 ± 0.93 12.2 ± 0.96[b]
Mn, µmol/L	2.64 ± 0.11 2.50 ± 0.09 2.24 ± 0.14[a]	3.43 ± 0.07 2.89 ± 0.14[a] 3.06 ± 0.18	2.50 ± 0.07 2.60 ± 0.16 2.58 ± 0.14
Se, µmol/L	1.27 ± 0.08 1.11 ± 0.10 1.00 ± 0.11	1.41 ± 0.13 1.04 ± 0.07[a] 1.00 ± 0.08[a]	1.23 ± 0.10 1.09 ± 0.08 1.03 ± 0.09
PBI, µmol/L	0.32 ± 0.01 0.29 ± 0.02 0.30 ± 0.02	0.36 ± 0.01 0.29 ± 0.02[b] 0.24 ± 0.01[c]	0.34 ± 0.02 0.37 ± 0.02 0.29 ± 0.01

The first line – physiological formation of embryo (Group I), the second line – fetal growth restriction (Group II), the third line – embryo death (Group III). [a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$ in comparison with animals of Group I.

23rd days of gestation by 7.2%, on the 28th–32nd days by 8.5%, and on the 38th–45th days by 11.4% ($P < 0.05$). Cows of Group I with physiological gestation course under the increase of gestation periods demonstrated an increase of phosphorus serum level by 7.3%–8.5% ($P < 0.05$). On the contrary, phosphorus serum level decreased by 9.1%–9.8% ($P < 0.05$) in Group II and by 4.7%–9.8% ($P < 0.05$) in Group III in comparison with the initial level.

Under fetal growth restriction in cows of Group II on the 19th–23rd and 28th–32nd days of gestation the magnesium serum level was 22.2% and 23.5% lower ($P < 0.001$), but for embryo death (Group III) it was lower by 19.0% and 27.2% ($P < 0.001$), respectively, in comparison with the control group.

Zinc serum level in cows of Groups II and III on the 19th–23rd days of gestation was lower by 30.2% ($P < 0.001$) and by 35.5% ($P < 0.001$) in comparison with Group I. Zinc blood level in cows (Group II) on the 28th–32nd and 38th–45th days of gestation was lower by 17.2% ($P < 0.01$) and 10.9% ($P < 0.05$), while for those with embryo death (Group III) it was lower by 25.5% ($P < 0.01$) and 23.1% ($P < 0.01$), respectively, in comparison with Group I.

Copper blood level in cows of Groups II and III on the 19th–23rd days of gestation was lower by 21.6% ($P < 0.05$) and 21.6% ($P < 0.01$), respectively, in comparison with Group I. The zinc/copper blood ratio changed in all cases of embryonic development disorders during these periods of gestation. Under fetal growth restriction (Group II) it decreased by 12.0% ($P < 0.05$) and under embryo death (Group III) by 18.6% ($P < 0.05$) in comparison with Group I.

Under fetal growth restriction (Group II) on the 28th–32nd and 38th–45th days of gestation copper blood level was lower by 18.2% ($P < 0.01$) and 12.5%, while under

embryo death (Group III) it was lower by 17.6% and 23.3% ($P < 0.01$), respectively, in comparison with Group I.

Manganese blood level was by 15.2% ($P < 0.05$) lower in cows with embryo death (Group III) on the 19th–23rd days after conception in comparison with Group I. Manganese blood level decreased by 15.8% ($P < 0.05$) in cows with fetal growth restriction (Group II) on the 28th–32nd days of gestation in comparison with Group I.

The zinc/manganese ratio under embryonic development disorders (Groups II and III) during the first study appeared to be lower by 23.8%–26.3% ($P < 0.01$) and during the second one by 14.6%–25.5% ($P < 0.05$) in comparison with animals of Group I.

Selenium blood level in cows of Group II decreased by 26.2% ($P < 0.05$) on the 28th–32nd days of gestation and in animals of Group III by 29.1% ($P < 0.05$) in comparison with the control group. During the same period the PBI level in serum of cows of Group II decreased by 21.2% ($P < 0.01$) and in cows of Group III by 33.4% ($P < 0.001$) in comparison with Group I.

When analyzing the dairy productivity of experimental animals it was stated that daily yield of milk in cows of Group I was 20.2 ± 1.21 kg, while in animals of Groups II and III it was 22.6 ± 0.96 kg and 24.6 ± 1.03 kg, respectively, 11.9% and 21.8% higher than in Group I ($P < 0.05$). Moreover, the period from calving to conception or lactation on average was 83.7 days in cows of Group I, 96.2 days in cows of Group II, and 139.6 days in cows of Group III. This suggests that diselementosis development in cows of Group II and especially Group III under the same level of feeding as in animals of Group I is greatly connected with an increased excretion of bioelements with milk out of their organisms. Increase of daily yield of milk from 20.2 ± 1.21 kg to 24.6 ± 1.03 kg resulted in 7.2%–11.4%, 23.1%–35.5%, 17.6%–21.6%, 10.8%–15.2%, 16.3%–29.1%, and 14.1%–33.4% decrease of calcium serum concentration, blood content of zinc, copper, manganese, selenium, and PBI.

4. Discussion

The problem of intrauterine fetal death in dairy cows at early gestation stages is important because of significant economic losses connected with the decrease of fertility and dairy productivity. In this work we have studied the role of diselementosis in dairy cows for fetal growth restriction and embryo death. It has been discovered that intrauterine growth restriction and embryo death were registered against the background of magnesium serum level decrease. It is known (15,16) that under magnesium deficit there is a decrease of energetic potential of cells and activity of detoxication processes, and an increase of thrombogenesis that leads to uteroplacental and fetoplacental blood flow disorders. Magnesium deficiency is also accompanied by the increase of prostaglandin E_2 and prostaglandin $F_{2\alpha}$ synthesis (16), decrease of progesterone synthesis function of the corpus luteum, and increase of uterine contractility, which has a negative impact on the character of the gestation course.

Current results indicated that corpus luteum diameter on the 28th–32nd days of gestation in cows of Group I was 15.1 ± 0.18 mm, while in animals of Groups II and III it was 11.3 ± 0.28 mm and 10.1 ± 0.56 mm, respectively, 25.2% and 33.1% lower than in Group I. Serum progesterone concentration in cows during this period in Group I was 8.6 ± 1.39 ng/mL, while in Groups II and III it was 8.2 ± 1.51 and 4.10 ± 1.12 ng/mL, respectively.

Based on the current results, definite differences could be revealed in calcium-phosphorus metabolism in cows with physiological embryo development and death. There is no definite proof of a specific effect of calcium and phosphorus deficit on animals' reproductive system. Disorder of calcium-phosphorus metabolism in cows has a negative effect on embryo formation, probably as a consequence of a negative effect of a general metabolic and energy disorder on the balance of other trace elements.

The present results showed that fetal growth restriction and embryo death in dairy cows are directly connected with zinc deficiency. This element plays the most important role in the protection of DNA and transcriptional proteins from free-radical oxidation (by the induction of Cu,Zn-superoxide dismutase), and it participates in inhibition of proteinase and neutralization of lipopolysaccharides and toxic metals. Zinc is an essential element in the processes of DNA synthesis and repair, growth, proliferation, differentiation, and migration of cells and embryo- and immunogenesis (17,10,18). Zinc deficiency provokes the decrease of sex and corticosteroid hormones, somatomedin secretion, intensification of proinflammatory cytokine expression, and inhibition of the processes of cell proliferation and embryo growth (18). Therefore, developmental delay and embryo death in dairy cows at early gestation stages are the consequences of zinc deficiency and disorders of its metabolism in the organism. Experiment in vivo (19) showed that additional introduction of zinc to animals effectively protected them from lipopolysaccharide-induced intrauterine growth restriction and embryo and fetus death.

The current findings showed that the negative impact on embryo development is caused by the decrease of copper level and zinc/copper blood ratio in cows. It is known (10,20,18) that under copper deficiency the hormone-producing function of the hypothalamus decreases and the frequency of early mortality and embryo resorption increases. Essential trace elements such as copper and zinc are inorganic components of the main enzyme managing the free-radical oxidation of Cu,Zn-superoxide dismutase.

Copper is the main oxidase agent of ceruloplasmin. Support of the balance between oxidative processes and endogenous antioxidants is one of the important defense mechanisms of a developing embryo's cell structure.

Though there was no evidence for a relationship between embryonic development and manganese blood level in cows in the current study, the role of this trace element deficiency cannot be ruled out in embryonic and fetal mortality in lactating dairy cows. In the works of other researchers (20,21), in which the key role of manganese for the formation of cartilaginous and bone tissues during organogenesis in the embryo and fetus was studied, stimulation of cholesterol synthesis and sex steroids was shown. This bioelement, by entering the composition of mitochondrial superoxide dismutase (Mn-SOD), determines the differentiation of cellular structures of the forming embryo.

Among the essential trace elements, selenium possesses a rather wide spectrum of biological action. Selenium as a component of glutathione peroxidase catalyzes reduction of hydrogen peroxide and organic hydroperoxides, preventing cell membrane oxidative damage. In addition, this trace element is a part of iodothyronine deiodenase, controlling the level of the local and systemic presence of triiodothyronine and by means of it the activity of cellular growth and apoptosis, tissue differentiation of hormonopoiesis, and immunogenesis (18,22–24). Selenium is also an antidote for toxic metals. It is stated that selenium supplementation in bovine rations provided a progesterone blood concentration increase of 22.0% (25). It is thought that this is connected to the fact that selenium, as a component of glutathione peroxidase, destroys peroxide compounds in the corpus luteum and activates ovarian hormone-synthesizing function. The results of our research proved that under fetal growth restriction selenium blood level decreased by 26.2% ($P < 0.05$) on the 28th–32nd days and under embryo death it decreased by 29.1% ($P < 0.05$) in comparison with the physiological gestation course. In all cases of fetal growth restriction and embryo death, a low level of selenium was accompanied by iodine deficiency. It is known that low iodine level in cows leads to the decrease of thyroid hormone synthesis (11). In previous research (5) we showed that under fetal growth restriction in dairy cows a significant decrease of the serum triiodothyronine level was registered. The deficiency of this hormone has a negative effect on the processes of cellular growth and tissue differentiation. The connection of a high frequency of embryonic death and fetal abortions with selenium and iodine deficiency was also shown in the works of other authors (26,27).

Thus, the most important bioelements determining embryo formation and development in animals are zinc, copper, and manganese that are accumulating in the embryo in increased amounts (20), and also magnesium, selenium, and iodine. In the experiments of Sales et al. (28) it was demonstrated that parenteral introduction of zinc, copper, selenium, and manganese salts to recipient animals 17 days before transplantation of embryos promoted an increase of their survival rate by 13%. The studies of Mundell et al. (29) on meat cows stated that an injection of trace elements (copper, manganese, and zinc) 30 days before a fixed time of artificial insemination increased animals' conception rate from 51.2% to 60.2%, or by 9%. Hawkins (30) also reported about fertility improvement in dairy cows after an injection of the drug Multimin, containing selenium, manganese, zinc, and copper.

The results of our research on determining the role of the bioelemental status of cows in embryo development conform with the reports of Hostetler et al. (20), stating that embryonic and fetal storage of trace elements and other nutrients necessary for normal embryo and fetus formation and development is fully determined by the level of consumption and maternal organism provision of these substances.

The current research shows that the high level of milk production in lactating cows during fertilization and early embryogenesis causes a deficit of microelements in the maternal (and embryo) organism as a consequence of their increased excretion of microelements through milk and thereby has a negative effect on assimilation processes of all necessary nutrients, embryo formation, and survival rate.

Considering the world experience of organizing dairy animal husbandry, it is possible to affirm that an increase of cows' dairy productivity significantly decreases their fertility. Thus, according to Butler (31) an increase of average annual dairy productivity of cows from 4000 to 10,000 kg led to the decease of their conception rate from the first insemination from 65% to 38%. Yániz et al. (32) reported that the increase of average annual dairy productivity of cows from 8300 kg to 9660 kg was accompanied by the decrease of their conception rate from 39.1% to 34.8%, and when their productivity reached 11,221 kg, their conception rate was 32.3%. These researchers also attributed negative tendencies in fertility decrease in high-yielding cows to the difficulties in balancing their rations with energy, vitamins, and microelements because of physiological restrictions of the gastrointestinal system with possibilities in high-yielding animals for supplying biologically active substances, spent on milk production, at the expense of roughages. The results of our studies have demonstrated that a high level of milk production, increase of lactation period duration before insemination, and conception of animals and at the same time the forming deficit and imbalance of trace elements cause both the decrease of conception

rate and embryo loss at early gestation stages. Of cows with physiological formation of embryo (Group I), 55.5% conceived at the first insemination in 32–84 days after calving. The conception rate of the whole group was 1.89. Embryo death was registered in cows under the excess of average daily productivity by 22.4% in animals of Group I, lactation duration by 55.9 days, and conception rate by 0.51. It was 22.7%.

In conclusion, this research has studied the role of the deficit and imbalance of the main macro- and microelements in embryonic development in lactating cows at early gestation stages. The results demonstrate that magnesium, zinc, copper, and selenium, which have direct or indirect impacts on growth, proliferation, and differentiation of the developing embryo's cells, are the most important trace elements in the process of the formation and survival of embryos. Primary or secondary deficiency of these bioelements should be considered as one of the main risk factors of fetal growth restriction and embryo death in lactating cows. The risk of these bioelement deficiencies and imbalances in lactating cows rises with an increase in their dairy productivity level and reduction of terms of their insemination and conception after calving to best values. The search for methods of diselementosis correction in the organisms of lactating cows, forming embryos, and fetuses under the impact of destabilizing factors and lactation duration by the moment of insemination and conception should be considered as one of the ways for minimizing fertility problems in animals.

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