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Review paper

Metabolic disorders in cows and the level of immunity in calves

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Abstract

Metabolic diseases in cows have a significant influence on their health status, milk production, and the health and immune parameters of newborn calves. One of the most critical periods in the lactation cycle of dairy cows is the transition period, which covers the last three weeks before and the first three weeks after calving. It is characterized by the occurrence of metabolic and endocrine adaptations resulting from the increased demand for nutrients to support future lactation and avoid metabolic dysfunction. Metabolic stress is a hypermetabolic and catabolic response to homeostatic imbalance which affects the development and maturation of foetus. Lipid mobilization is a typical feature of a negative energy balance (NEB), whereby non-esterified fatty acids (NEFA) are released into the bloodstream and used as a source of energy.

The aim of this review was to present results of our research and research of other authors on the impact of metabolic disorders in dairy cows on the immune and health status of calves.

Keywords: calves, dairy cows, immune status, metabolic diseases

Introduction

Metabolic diseases in cows are an important health and economic problem in dairy cattle farming. During the transition period, about 3 weeks before and 3 weeks after calving, cows are at risk of immune and metabolic dysregulation, which makes them highly vulnerable to various infectious and non-infectious diseases (Vlasova and Saif 2021). A particular risk for the cow is the higher demand for energy and nutrients for the synthesis of colostrum and later milk, which in combination with reduced feed intake during the transition period causes microelement deficiencies and a tendency towards a negative energy balance (NEB) after calving. The energy deficiency during the last weeks of the prepartum stimulates cows to mobilize the lipid tissue in the form of non-esterified fatty acids (NEFA), followed by accumulation of beta-hydroxybutyric acid (BHBA) in blood. Although these changes are a normal adaptive process in high-producing dairy cows, failure to adapt leads to metabolic disturbances that affect yield and reproductive performance after parturition (Wankhade et al. 2017). A reduction in dry matter intake (DMI) causing nutrient deficiencies can be a risk factor for changes in colostrum composition and quality (Ling et al. 2018) and also poses a threat to normal prenatal development in calves.

The results have confirmed the correlation between the metabolic stress in cows during pregnancy and the immune status of calves, which determines their development and maturation, and increases incidence of failure of passive transfer and health status (diarrhoea, sepsis, and respiratory disease).

Immunological and metabolic changes in cows during the transition period

Metabolic disturbances in the peripartum period in dairy cows, largely determined by reduced feed intake, involve excessive lipid mobilization, inflammation, and oxidative stress associated (increase of production and releasing of ROS and RNS) with reduced immunity (Kushibiki et al. 2003, Tufarell et al. 2023). Anorexia observed in cows before calving is an important factor determining an energy deficiency, which results from the inflammatory response induced during this period. Released inflammatory mediators induce a strong anorectic effect, resulting in reduced feed intake during the transition period preceding calving. Observed in the transition period negative energy balance (NEB) contributes to the occurrence of inflammation in structures of the adipose tissue induced by spontaneous lipolysis. The catabolism occurring in adipocytes also initiates the remodeling of the adipose tissue. With a negative energy balance developing in late pregnant and early lactated cows, the oxidative stress is also activated. This state begins to increase in the formation of pro-inflammatory proteins, including cytokines (IL-6) and plasminogen. It is likely that NEB can indirectly contribute to synthesis of plasminogen, as this pro-inflammatory protein is produced in the liver parenchyma and adipocytes, sites which are closely associated with changes caused by NEB (Tufarell et al. 2023, Wnorowska et al. 2024). According to Horst et al. (2021), the inflammation in combination with a significant reduction in feed intake by cows stimulates mobilization of the adipose tissue and causes additional glucose drainage, activating the production and release of ketone compounds. Anorexia in the final period before calving together with an increased NEFA and hyperketonaemia may also be consequences of immune activation, but don't need themselves be the cause of disturbances in the transition period. Nevertheless, the occurrence of a prepartum inflammatory reaction in cows is an important element of preparation for parturition, and activation of the immune system by non-pathogenic factors is the basis for tissue remodelling (mammary gland and uterus) during the change in the cow's physiological status in the peripartum period (Horst et al. 2021). Therefore metabolic and immunological stress, which is characterized by excessive lipid mobilization, inflammation, and oxidative stress in the peripartum period, is linked to the development of various disturbances in health parameters. Improvement of cows' health during the transition period can be modified by using nonsteroidal anti-inflammatory drugs (NSAID) which could positively affect milk production and health parameters by controlling the inflammation status, but it has its limitations. These NSAIDs that act as preferential inhibitors of cyclooxygenase-1 (COX-1) activity show important side effects (e.g., increased risk of retained placenta, culling, or metritis) even if milk production is, on average, ameliorated. In contrast, preferential inhibitors of cyclooxygenase-2 (COX-2) activity have overall positive effects on cows' health, with potential beneficial effects on milk production. Furthermore, it is important to note that with certain NSAID treatments, milk discarding is mandatory to prevent contamination with drug residues, but increased milk production can compensate for the loss of milk revenue during the withdrawal period (Trimboli et al. 2020).

Changes in oxidative metabolism result from increased energy requirements for foetal development and decreased dry matter intake by the cow. High production of reactive oxygen species (ROS) exceeds the capacity of antioxidant defences to neutralize pro-oxidants (tocopherols, ascorbic acid, carotenoids, lipoic acid, glutathione – GSH), resulting in oxidative damage to lipids, DNA, proteins and other molecules, and can potentially affect future productivity and health status (Ling et al. 2018). Metabolic stress, is a hypermetabolic and catabolic response to homeostatic imbalance that results in a significantly reduced glucose concentration in blood. Energy deficiency and metabolic disorders could be a crucial cause of oxidative stress in dairy cows. When energy is not obtained from the diet, the cow begins to exploit its own energy reserves. Lipid mobilization is a typical feature of energy deficiency during the transition period, whereby NEFA are released into the bloodstream and used as a source of energy (Sordillo and Raphael 2013). An increase in NEFA and BHBI concentrations was also found in cow sera 21 d before calving in a study by Mikuła et al. (2021). However, a recent study (Horst et al. 2021) has shown that changes in circulating NEFA, ketones, and calcium can also be a reflection of normal homeorhetic adaptations used by healthy, high-producing cows in order to increase milk production after delivery, or may be the result of immune activation (increase in production of pro-inflammatory cytokines IL-1, TNFα) and its consequences during the peripartum period. An example is an increase in TNFα, which plays a major role in inducing fatty liver and insulin resistance in dairy cattle. Increased production and release of TNFα influence metabolic functions in dairy cows, which is conducive to accumulation of hepatic triglycerides, particularly

Table 1. Selected examples of the effects of metabolic disorders in dairy cows on their immune parameters and health status.

Type of disorder	Mechanism of effect on immune functions	Health risk	References
High NEFA concentration	Increased production of pro-inflammatory cytokines IL-1, IL-6, and interferon-γ; massive neutrophil necrosis; inhibition of PMBC proliferation; overproduction of TNF-α.	Mastitis; metritis	Ster et al. 2012, Sundrum 2015 Khan et al. 2022
Subclinical ketosis	Decreased chemotaxis and microbial killing of neutrophils; decreased respiratory burst activity of bovine neutrophils; reduction in IL-8 production; decrease in number or function of T-cells (CD3, CD4, CD8); decreased percentage of PBMC	Mastitis; milk fever; metritis; cystic ovarian disease	Itle et al. 2015
Subclinical hypocalcaemia	Reduced total circulating neutrophil number; neutrophil phagocytosis and changes in oxidative burst activity	Displaced abomasum; milk production losses; culling; risk of mastitis in early lactation; metritis; retained placenta	Roberts et al. 2012, Žekić-Stošić et al. 2018
Parturient paresis	Decrease in neutrophil count; decrease in PMBC activity (chemotaxis and phagocytosis)	Retained foetal membranes; left displaced abomasum; uterine diseases; clinical mastitis; digestive and respiratory disorders	Piñeiro et al. 2019
Fat cow syndrome, fatty liver syndrome	Decreased phagocytic activity of milk polymorphonuclear leukocytes; leukopenia; increased production of pro-inflammatory cytokines TNF-α and IL-6; production and release of IFNγ; inhibition of proliferation of PBMCs	Retained placenta; metritis; lameness; infertility.	Mordak et al. 2017

Legend: PMBC – peripheral blood mononuclear cells, APP – acute phase proteins, NEFA – non esterified fatty acids.

during late lactation (Martel et al. 2018). In cows with a substantial NEB, a significant reduction in the leukocyte count and a prolonged recovery period following uterine infection have been observed as well (Sheldon et al. 2019). As demonstrated by Ingvartsen and Moyes (2013), a high NEFA concentration during the transition period in dairy cows can also impair neutrophil activity and suppresses phagocytosis. Their effect arises from activation of toll-like receptor 4 (TLR4), the main lipopolysaccharide (LPS) receptor, which activates nuclear factor κβ (NF-κβ) and leads to secretion of tumour necrosis factor α (TNFα) and interleukins 1 and 8 (IL-1 and IL-8), increasing inflammation and insulin resistance (LeBlanc 2020). These changes also reduce regulation of macrophage-specific expression of IL-15, which stimulates activation of the proliferation of T and NK cells and increases B cell activity and antibody production, while interference in the production and release of IL-8 is an important factor affecting neutrophil function in the development of placental retention in post-partum cows. The immune system uses available energy for oxidative phosphorylation, and thus in the case of NEB the immune system (e.g. macrophage function) shows disturbances in the efficiency of defence mechanisms (LeBlanc 2020). The most important health problem with high blood NEFA and BHBA concentrations is the development of immunosuppression, which is associated with decreased immunoglobulin production by B cells and high susceptibility to infectious diseases immediately after delivery (mastitis or uterine diseases). A low IgG concentration was also observed in the colostrum of cows exposed to oxidative stress, which confirms the relationship between maternal oxidant/antioxidant enzymes, colostrum quality, passive calf immunity and increases the risk of infection in newborn calves (Çolakoğlu et al. 2021). Examples of the effects of immune disorders on the immune and health status of dairy cows are presented in Table 1.

Disturbances in calves

The condition of cows in the final period of gestation can also influence a number of health and production parameters, both during the prenatal period and in neonatal calves, mainly through disturbances in colostrum intake. Colostrum is a food source for calves that takes part in the development of digestion and is an important stimulator of digestive tract function. It also provides newborn calves with immunoglobulins, large amounts of vitamins (mainly fat-soluble), and minerals, as well as a number of factors of the humoral non-specific immune response (interferon, lactoperoxidase or lactoferrin) and cells taking part in the immune response, which enhance the immune functions of the neonate in various ways (Lopez and Heinrichs 2022). The most common clinical forms of diseases in calves arising from impaired colostrum intake are diarrhoea and sepsis. There have been few studies assessing the consequences of metabolic stress in cows during pregnancy on the metabolic and health status of neonatal calves. More than 20 years ago, Quigley and Drewry (1998) demonstrated that metabolic changes in dairy cows resulting from a poor diet (a deficiency or excess of specific nutrients) have a significant effect on the survival rate of calves and the incidence of diarrhoea, diseases of osteoarticular system, neurological disfunction.

The quality of colostrum consumed by newborn calves not only guarantees effective immunoglobulin transfer, which determines passive transfer of immunity, but also has a crucial influence on the formation of the calf's digestive tract, which determines its growth and development. Substances contained in colostrum significantly modulate the development of the alimentary tract in neonatal calves, including specific and non-specific local defence mechanisms associated with mucous membranes, e.g. promoting intestinal epithelial cell growth and differentiation, activating secretion of mucus, antimicrobial peptides (mainly lysozyme), secretory phospholipase, increasing production of secretory IgA. It's the result of intake of colostrum with suitable parameters, containing antibacterial and antiviral substances. These include lysozyme and lactoferrin, growth factors such as insulin-like growth factors (IGF 1 and 2), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor β-2 (TGF-β2), and growth hormone (GH), cytokines, such as interleukin-1 β (IL-1 β), and microbiota, including probiotic bacteria from genera *Lactobacillus*, *Lacticaseibacillus*, *Bifidobacterium* and *Enterococcus*. (Hyrslova et al. 2020). Poor colostrum quality could also have a potential negative effect on the development of digestive processes, including villus length and width, crypt depth, villus height to crypt depth ratio, and mucosal thickness, which are associated with local mucosal defence mechanisms in neonatal calves (Yang et al. 2015). Perinatal changes have long-lasting ripple effects in newborn calves, and proper intestinal development is crucial for their growth (Osoiro 2020).

Other effects of colostrum components include stimulation of the specific proliferative response of mononuclear blood cells and activation of pro-inflammatory cytokine production. In calves fed high-quality colostrum, the development of pathogenic Gram-positive and Gram-negative bacteria has been shown to be limited by the production of substances inhibiting their growth, mainly organic acids, hydrogen peroxide and bacteriocins (Vlasova and Saif 2021). Probiotic bacteria present in colostrum compete with pathogens, including *E. coli* and *Salmonella* in adhesion to the mucous membrane, in part by creating a specific acidic environment associated with the production of lactic acid (Puppel et al. 2019). Through their direct effect on metabolism in rumen and stimulation of the activity of its microbiota, they play an important role in preventing and combating gastrointestinal disorders and also inhibit the development of metabolic acidosis through their natural buffering capacity in rumen, increasing utilization of lactic acid by the rumen microbiota (Corcionivoschi et al. 2010). In a study Ling et al. (2018), calves born to Holstein-Friesian cows with metabolic problems and elevated concentrations of NEFA and haptoglobin (Hp) had significantly lower body weight. However, there were no significant differences ($p \leq 0.05$) in the number and differentiation of specific types of blood cells (lymphocytes, neutrophils, monocytes). In the case of exposure of calves to higher oxidative stress resulting from metabolic disorders in cows during pregnancy, higher plasma concentrations of TNF-α were observed in calves following stimulation with 10 ng/ml or 5 μg LPS. This indirectly indicates subclinical inflammation in neonates and a higher inflammatory response in comparison with calves born to healthy cows. Moreover, calves exposed to a high concentration of lipids in the cows, particularly in late pregnancy, had much higher serum oxidative stress parameters, including ROS and acute phase markers, mainly Hp. Calves born to cows with higher serum Hp in the second trimester of pregnancy had lower plasma concentrations of TNF-α following stimulation with any concentration of LPS. Windeyer et al. (2014) hypothesized that calves would have metabolic and immune disorders in the first month of life. They observed higher morbidity and mortality in neonates in the first four weeks of rearing, and the values of selected immune parameters were statistically significant in comparison to calves from cows without health disorders (Table 2).

Table 2. Comparative analysis of selected parameters in calves from Holstein-Friesian dairy cows with symptoms of metabolic diseases.

Parameter	Calves from healthy cows	Calves from cows with health disorders	P value	References
Hp concentration (g/L)	0.22	0.49	0.0039	Windeyer et al. 2014
Body weight (kg)	40.6	38.7	0,004	Ling et al. 2018
Mean feed conversion (kg/d)	0.61	0.58	0.27	
Mortality (%)	9.3	12.3	0.003	Windeyer et al. 2014
% occurrence of diarrhoea	≤ 15	> 20%	nd	Walker et al. 2012
IgG concentration (g/L)	≥10 (21%)	≤10(45%)	0.048	Godden et al. 2008
IgA concentration (g/L)	1.96	1.45	0.008	Alomari et al. 2016
Concentration of probiotic bacteria, CFU/mL	3.2×10^{10}	3.2×10^{8}	0.046	Berge and Vertenten, 2018
Concentrations of selected parameters of oxidative stress ROS, µmol/L TBARS, mmol/L FRAP, mmol/L	 33 0.86 0.74*	 44 0.82 0.40	 0.04 0.05	Urban-Chmiel et al. 2011
Concentrations of selected biochemical parameters GLU, mmol/L SOD, U/ml TBIL, µmol/L	 4.82 70.52 6.60	 5.62 66.54 6.21	 0.09 0.35 0.76	Wang et al. 2019

Legend: GLU – glucose, SOD – superoxide dismutase, TBIL – total bilirubin, CFU – Colony-forming unit, Hp – haptoglobin, ROS – reactive oxygen species, TBARS – thiobarbituric acid reactive substances, FRAP – ferric reducing antioxidant power assay.

The impact of placental transport on foetal energy, nutrient supply and neonatal immunity

Nutrition in cows during late gestation significantly influences foetal development and the postnatal condition of calves. Higher energy intake (1.47 Mcal/kg of DM) during the last 21 days of prepartum can affect birth weight and the immune competence of newborn calves (Osorio et al. 2013). While immunoglobulins in calves are ingested with the colostrum immediately after parturition, nutrients essential to normal development are provided to the foetus through active placental transport. Research (Gao et al. 2009, Batistel et al. 2017) underscores that the main energy substrate essential to foetal growth and metabolism is glucose. Due to limited glycogenesis in the foetus, it depends mainly on glucose obtained from the cow by placental transport. This is made possible by glucose transporter proteins (GLUTs), including GLUT1 (SLC2A1), (SLC2A3) and (GLUT 4:SLC2A4), which in addition to glucose are also involved in the transport of fructose, galactose, mannose and maltose via facilitated diffusion along the concentration gradient (Lucy et al. 2012). Batistel et al. (2017) showed an increase in the plasma concentration of insulin and GLUT4: SLC2A4 regulation in response to increased methionine intake in cows in the prepartum period. This demonstrates, that amino acid concentrations are linked to an increase in insulin secretion and glucose transport through the placenta into the foetal bloodstream. The authors confirmed that the body weight of newborn calves born to cows with higher plasma insulin and insulin-regulated glucose transporters was about 4 kg higher. A significant effect of maternal methionine (Met) supply during late pregnancy on the calf's condition at birth and on its growth has been also confirmed by Alharthi et al. (2018), who showed significantly higher birth weight (44.1 kg) in comparison to the control (42.1 kg), as well as greater hip and wither height.

The diet of cows, especially in the second half of gestation, plays an important role not only in foetal development but in colostrogenesis as well. Mann et al. (2016) found that IgG concentration was not dependent on the level of dry matter in the diet. However, the study showed differences in the effects of a standard diet and a diet exceeding the energy requirements of dairy cows on the fatty acid composition and IgG and insulin concentrations of the colostrum. Excessive intake of high-energy feedstuffs during the dry period reduced the IgG concentration in the colostrum and increased levels of insulin and fatty acids. Nardone et al. (1997) confirmed the effect of heat stress on feed conversion efficiency by heifers in the final period of gestation, resulting in changes in colostrum composition and quality. Selected values of physiological parameters of calves are presented in Table 3.

Table 3. Analysis of selected parameters in calves from cows with metabolic and stress disorders in comparison to calves from normal cows.

Parameter	Calves born to cows with metabolic or deficiency disorders	Calves from healthy cows	References
Cases of reduced vitality	52%	19%	Berry et al. 2007
Birth weight (kg)	40.4	38.7	
Postnatal mortality correlated with IgG concentration	~32	~23	Waldner and Rosengren, 2009
% diarrhoea within 10 d of age	49.1	33.3	Stanek et al. 2014 Carvalho et al. 2020
Predisposition to disease in the neonatal period (<30 days of age)	~22	~28	Waldner and Rosengren, 2009
Mean serum IgG concentration in calves (g/L)	21.6	30.1*	Hunter, 2015, Wilhelm et al. 2017
Percentage of calves with failure of passive transfer	2.1	2.5	
Average reduction in weaning weight	16.5	10.7	Hunter et al. 2015

BCS of cows and health status of calves

Efficient nutrient utilization by the foetus, and later the neonate, may also be determined by the cow's body condition score (BCS), partly due to increased nutrient bioavailability. The higher level of NEFA and BHBA in calves born to cows with an adequate BCS supports the hypothesis that they potentially have a more mature metabolism, capable of easily utilizing fat stores as a source of fatty acids for oxidation and ketogenesis (Altharti et al. 2021). This is in line with the findings of earlier research (Girard et al. 1990) indicating that lipolysis, glycogenolysis, and gluconeogenesis must be activated in newborn calves in order to maintain an adequate blood glucose concentration. There is a strong correlation between malnutrition or excessive nutrition in the mother in the final period of gestation and susceptibility to chronic metabolic disorders in later rearing period of calves, particularly after they reach maturity (Altharti et al. 2019).

Analysis of health and immune parameters is significantly impeded by the scarcity of studies dealing with aspects of immune parameters in calves subject to metabolic stress due to metabolic disorders in pregnant cows. Lopes et al. (2021) showed a correlation between the functionality of the innate immune system in neonatal calves and the BCS of cows before calving. This was demonstrated by ex vivo LPS challenge of whole blood to stimulate the immune system of calves during the first weeks of life, followed by evaluation of mRNA abundance and concentrations of interleukins IL1B, IL6, IL10, and TNF. High BCS in cows during pregnancy could increase the newborn calf's susceptibility to disease, including infectious diseases causing diarrhoea and bovine respiratory disease. According to Lorenz et al. (2011), one way to control the mortality rate of calves due to metabolic disorders is to prevent excessive body condition (BCS) in cows and heifers before calving (target BCS 2.75-3,0 on a scale of 1-5). BCS, in both dairy and beef cows, is important in the transfer of colostral immunity to newborn calves, which is influenced by the concentration of antibodies in the colostrum, the half-life of antibodies (resulting in part from the pH of the colostrum), suckling activity of calves, and the absorption capacity of the neonate, determined by the readiness of the gut environment for absorption. Low suckling activity in calves may also be the result of difficult parturition in cows and weakening of the newborn by the prolonged delivery (Filteau et al. 2003). Low content of immunoglobulins in the colostrum is a key factor determining impairment of passive resistance in newborn calves (Table 4).

A high BCS before calving predisposes cows to health disorders such as inflammation and oxidative stress, which may affect the immune response in newborn calves. Lopes et al. (2021) observed greater mRNA expression of IL1B, NFKB1, and GSR and lower GPX1 and CBS expression in calves born to cows with BCS >3.75 following LPS challenge. High BCS (≥4) in cows has an influence on colostrum quality i.e. immunoglobulin levels and composition, the content of lactoprotein and fatty acids (Singh et al. 2015) The body condition of the cow during pregnancy can affect immunity in the calf, because the immune system begins to devel-

Table 4. Incidence of failure of passive transfer in newborn calves of beef breeds (Charolais, Simmental, Hereford, Limousin, and Angus) and dairy breeds (Holstein-Friesian) in relation to body condition (BCS) in cows in the peripartum period

Body condition score (BCS)	Percentage of calves with failure of passive transfer (%) Concentration of serum IgG < 10.0 g/L				References
	Beef	P value	Dairy	P value	
≥1 and < 2	nd		6.0	0.003	Filteau et al. 2003, Waldner and Rosengren, 2009, Urban-Chmiel et al. 2019
≥2 and < 3	21.2	0.04	nd		
≥3 and < 4	16.2	0.05	3.9	0.05	
≥4 and < 5	25	0.029	nd		
≥5	33.4	0.033	5.8 0.03		

Legend: nd – not detected

op in utero as early as 42 d of gestation (Zhao et al. 2019). The authors reported a significant influence of prepartum BCS in cows on colostrum density, immunoglobulin levels, and lactoprotein content. In cows with BCS >4.25 these estimated parameters were even 10% higher than in the case of 'normal' BCS between 3.0 and 3.75. Zhao et al. (2019) found that losses of calves were correlated with the BCS of cows. Losses amounted to 23.62% of calves born to cows with BCS 4.5-5.0, 14.36% for BCS 4.0-4.25, 13.33% for BCS 3.73-4.0, and 5.53% for BCS 3.0-3.5. The high losses in calves were often correlated with suppression of immune response and low birth weight, which translated into increased mortality. Calves born to cows with a high BCS ≥ 3.75 had lower birth weight by 2.15 kg, while height at the withers and body length were not statistically significant in comparison with calves born to cows with a normal BCS (Alharthi et al. 2021). Reduced immunity in calves during the peripartum period is also believed to be associated with significant changes in the level of circulating metabolites (Sordillo and Mavangira 2014). In calves born to cows with a high BCS, significant changes in the biochemical parameters were observed, i.e. reduction in plasma levels of ceruloplasmin, albumin, urea, NEFA and BHBA. The BCS of the cow also reduced the total bilirubin concentration and increased activity of paraoxonase in the calf for the first 50 days of life. Indicators of antioxidant potential (FRAP) in the plasma of calves from cows with a high BCS also showed a tendency to be lower in calves in the first 9 weeks after birth (Alharthi et al. 2021).

Effect of vitamin, mineral and energy deficiencies in cows on calves

Vitamin and mineral deficiencies in prepartum cows may result in calves born with reduced metabolic rates, vigour, and immune activity, which decreases their chances of survival (Quigley and Drewry 1998). One of the most important microelements, which influenced peripartum activity of immune system in cows is selenium (Se). Selenium determines the proper functioning of the immune system by regulating humoral immune mechanisms, including increasing the level of Ig M and G (Avery and Hoffmann 2018). Selenium supplementation in animals, enhances the phagocytic activity of neutrophils, granulocytes and macrophages, and after stimulation with mitogens causes an increase in the number of T lymphocytes (Kamada et al. 2007). Se is essential for the production of lymphocyte migration inhibitory factor and IL 2 (Wintergerst et al. 2007), which accelerates the proliferation, maturation and activity of T cells (Shrimali et al. 2008). T cells are particularly sensitive to selenium deficiency because their cell membrane contains lipids that are more easily oxidized than the lipid membrane of B cells (Arthur et al. 2003). Se deficiency reduces the number and cytotoxic activity of T cells, which leads to reduced lymphotoxin production (Carlson et al. 2010). Studies conducted by Cao et al. (1992) showed that in cows selenium deficiency leads to a reduced level of lymphocyte proliferation (stimulated by concanavalin A). Se supplementation also increases blast transformation of spleen lymphocytes and prevents the reduction of lymphocyte proliferation (Hefnawy and Tórtora-Pérez 2010). Use of sodium selenate affects the expression of IL 2 α and β subunits on the surface of activated T , B and NK cells and so-called LAK cells. However, it does not affect the endogenous concentrations IL-1, IL-2 or IFN-γ. By binding to IL-2 receptors, IL-1 induces a signal for the transition of activated cells from the G1 (post-mitotic) phase to the S phase (DNA synthesis) of the cell cycle (József and Filep 2003). Selenium deficiency inhibits neutrophil migration and disrupts the function of receptors on their surface. This mechanism is most likely based on the oxidation of tubulin by excess H_2O_2 and the resulting damage to neutrophil microtubules (Haddad et al. 2002). Neutrophils from Se-deficient animals have an impaired ability to produce and release

Table 5. Effect of calcium ion level in prepartum dairy cows on incidence of stillbirths, total serum protein concentration, and incidence of diarrhoea in calves up to 10 days of age (Hunter 2015, Wilhelm et al. 2017).

Parameter in calves	Calves from cows with calcium deficiency (n=113)	Calves from cows with normal calcium levels (n=660)	P value
% of calves stillborn or dead within 24 h after birth	2.0	2.5	0.32
% of calves with failure of passive transfer	2.1	2.5	0.87
% of calves with symptoms of diarrhoea	49.1	33.3	0.04
% of calves with respiratory diseases	4.1	5.3	nd

Legend: Calcium deficiency was identified in cows when the calcium level was below 2 mmol/l and normocalcaemia above 2 mmol/l.

free radicals within the cell (Yang et al. 2004). Studies conducted on calves and cows demonstrated the high effectiveness of Se in activating their immune system. Kamada et al. (2007) showed that the use of colostrum with 1 ppm of sodium selenate immediately after parturition increased the absorption of IgG in calves by 20%, while with 3 ppm by 42%. A higher concentration of Se in colostrum (5 ppm) reduced the absorption of these immunoglobulins. It should be remembered that the recommended selenium content in cow colostrum is at the level of 0.3 ppm. The increase in IgG absorption from colostrum with Se supplementation observed by the above authors is probably related to the formation of Se-IgG complexes, which are more easily absorbed in the mechanism of pinocytosis occurring in the calves' intestine. In other studies (Hall et al. 2014), selenium yeast (105 mg daily) and sodium selenate (0.3 mg Se/kg dry matter feed) were administered from 8 weeks to 1 week before parturition to pregnant cows. Calves from mothers receiving Se supplementation showed higher serum IgG concentration at 48 h of life (by 50%) compared to the control group, and this effect was extended in time, because at 14 days of life the IgG concentration of these calves was higher by up to 75%. The majority symptoms of vitamin and energy deficiencies are non-specific and characterized by increased susceptibility to disease in calves. In contrast with vitamins (mainly fat-soluble), most minerals easily penetrate the placenta to enter the blood of the foetus, and the developing foetus is even able to utilize the compounds present in its mother's blood.

A common health problem in dairy cows in postpartum period is clinical hypocalcaemia, also known as milk fever, which predisposes to foetal membrane retention, ketosis, metritis, abomasum displacement, and mastitis (Curtis et al. 1984). The incidence of clinical hypocalcaemia increases with age: it accounts for 1% in cows in their first lactation and 4%, 7% and 10% in the second, third, fourth or subsequent lactation respectively (Reinhardt et al. 2011). A serious problem, is the occurrence of subclinical hypocalcaemia in cows in the peripartum period, the frequency of which increases with age from about 20% in the first lactation to 41% in the second and 54% in subsequent production cycles. Subclinical calcium deficiencies commonly result in suppression of cellular and humoral immune response leading to an increased risk of metritis. A few studies have also shown that these health problems in cows affect the survival rate, health, and production parameters of calves. Planski and Abrashev (1987), showed that incidence of diseases with diarrhoea and of respiratory diseases was twice as high in calves born to hypocalcaemic cows as in calves born to cows with normal calcium levels. A similar study (Wilhelm et al. 2017) also found higher morbidity with symptoms of diarrhoea in calves from cows with hypocalcaemia (Table 5). In chronic disorders in which a zinc deficiency is accompanied by increased glucocorticoid levels, significant changes were observed in T cell activity, reducing the effectiveness of the immune response (Paul and Dey, 2015).

A particular risk for newborn calves is the occurrence of energy deficits in cows in late pregnancy. Energy deficiencies in cows, in the transition period, not only have a decisive influence on the production, composition and quality of the colostrum, but also immune parameters of calves. Mann et al. (2016) have confirmed that nutrition during late pregnancy in cattle has an influence on the colostrum quality; the colostrum of cows fed high-energy diets had a lower IgG level and a higher insulin concentration. The lower colostrum IgG level could be an effect of high glucose concentrations, which cause a reduction in secretion of Ig from B-1 lymphocytes. Another study (Janovick-Peterson et al. 2011, Graugnard et al. 2012) found that overfeeding of cows in the prepartum dry period leads to higher blood glucose concentrations. Lower IgG concentration in colostrum could affect the humoral immune response and susceptibility to infections in calves, especially when they obtain the colostrum directly form the udder, in the case of both beef and dairy cows. Nowak et al. (2012) have revealed differences in chosen parameters of the colostrum of cows and the sera of calves (Table 6).

The influence of the greater energy intake in cows in late pregnancy on the birth weight and neonatal immunocompetence of newborn calves was confirmed

Table 6. Serum concentrations of immunoglobulins, albumins (mg/mL), and insulin-like growth factor IGF-1 (ng/mL) and birth weight of calves born to calves with a correct energy balance and cows receiving energy-deficient feed (Nowak et al. 2012).

Parameter	Calves from cows fed with a normal energy concentration during the dry period – 0.69 UFL/kg DM	Calves from cows fed with a lower energy concentration during the dry period – 0.61 UFL/kg DM	P value
Total Ig concentration, mg/mL	20.5	19.4	0.6
IgG, mg/mL	17.3	16.2	0.61
IgM, mg/mL	2.7	2.76	0.86
IgA, mg/mL	0.359	0.356	0.96
Albumins mg/mL	29.1	28.1	0.12
IGF-1, ng/mL	130.6	99.3	0.24
Birth weight (kg)	45.1	46.3	0.57

Legend: 1 kg DM (dry matter) of grass is the equivalent of 1 UFL/kg DM, DM – dry matter, IGF-1 – insulin growth factor, UFL – unit of energy used in Ireland. One UFL is equivalent to 1kg of barley.

Table 7. Selected health parameters of HF calves born to primiparous cows and cows in subsequent lactation cycles that received supplements of saturated acids (SAT) and esterified (ESS) fatty acids in their feed from 8 weeks before parturition (Garcia et al. 2014 with our own modification).

Parameter	Groups of calves				
	From primiparous cows	From control cows	From cows receiving SAT supplement	From cows receiving ESS supplement	P≤0.01
	At birth				
Birth weight, kg	37.2	39.8	43.7	43.8	0.06
Total protein, g/dl	48.3	48.2	46.2	48.0	0.75
Serum IgG, g/L	0.20	0.20	0.30	0.20	0.66
	24 h after birth				
Total protein, g/dl	63.5	61.6	65.8	62.3	0.9
Serum IgG, g/L	24.0	22.1	44.6*	37.3	0.04
Mean immunoglobulin absorption, %	23.7	23	28.6*	25.1	0.03

Legend: * statistically significant differences at P≤0.01, SAT – supplements of saturated acids, ESS – esterified fatty acids.

in another study (Osorio 2020). The use of two different energy doses (1.24 and 1.47 Mcal/kg dry weight) in the diet of cows in the transitional period significantly reduced the birth weight of newborn calves (by 5 kg), suppressed PMN phagocytosis (difference of 23 p.p.) and influenced the Hp concentration at 7 d after birth (Osorio et al. 2013). Garcia et al. (2014), showed that supplementation with esterified or non-esterified long-chain fatty acids in cows during pregnancy significantly influenced immune parameters in calves immediately after birth and on subsequent days of rearing. The results indicate that feeding pregnant cows moderate amounts (1.7% of DM) of saturated (SAT) or unsaturated long-chain fatty acids (ESS) during the last eight weeks of pregnancy increases the IgG absorption by newborn calves and influences the fatty acid profile of the colostrum and of the plasma in the calves. It is particularly worth noting the significant (p≤0.05) negative correlation between the IgG absorption in calves and the concentration of NEFA in cows, indicating that metabolic disorders manifested as increased NEFA significantly affect humoral immune mechanisms in calves (McGee et al. 2006, Chigerwe et al. 2009). Selected parameters of calves born to cows receiving SAT and ESS are shown in Table 7.

Heat stress as a factor inducing metabolic changes in cows and neonatal calves

The metabolism of pregnant cows is also influenced by environmental stress factors, such as those associated with the microclimate in their housing. Numerous studies have confirmed that cows exposed to heat stress, especially in the third trimester of pregnancy, exhibit significant changes in biochemical parameters associated with increased of NEFA, beta-hydroxybutyrate (BHB), and oxidation markers in the blood (Hulbert and Moisá 2016, Guo et al. 2016). These changes in the

Table 8. Values of selected biochemical parameters in calves from cows subjected to heat stress (Monteiro et al. 2016 with own modification).

Average concentration of parameters	Age of calves in weeks						P≤0.05
	1		3		8		
	K	HS	K	HS	K	HS	
Insulin, ng/mL	0.51	0.54	0.44	0.45	0.46	0.45	0.02
Glucose, mg/dL	81	71	84	82	78	72	0.09
NEFA, µEq/dL	452	503	418	447	483	512	0.05
TBARS µmol/L	0.52	0.72*	0.49	0.56	0.51	0.56	0.05

Legend: K – control, HS – calves from cows exposed to heat stress, TBARS – thiobarbituric acid reactive substances (markers of oxidative status), NEFA – non esterified fatty acids.

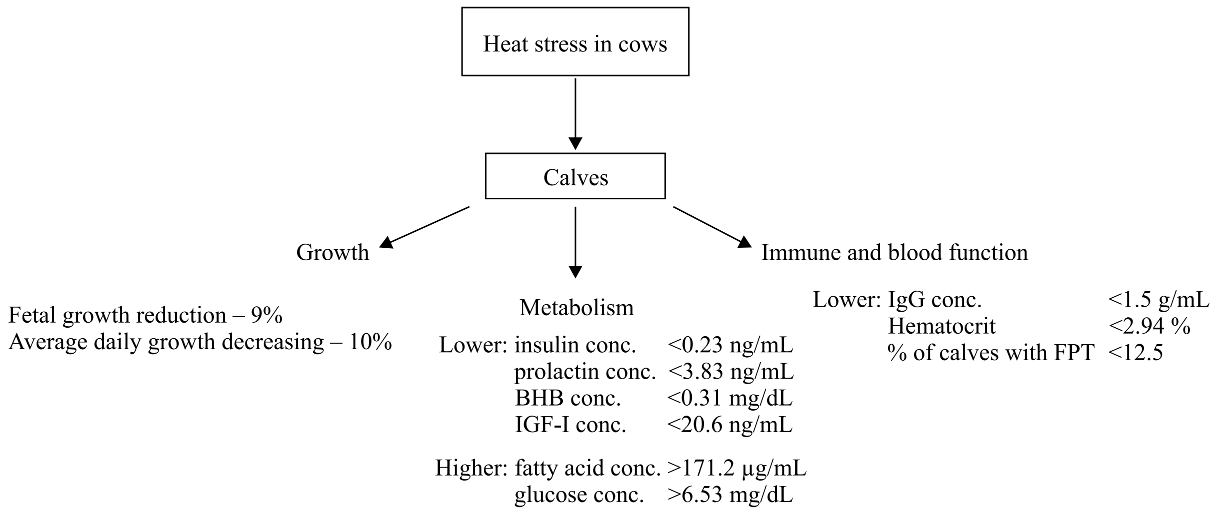

Fig. 1. Effect of heat stress in dairy cows during pregnancy on growth, metabolism and immune parameters in calves.

biochemical profile of pregnant cows are also reflected in an increase in NEFA and BHB level in neonatal calves. Exposure of calves to higher level of NEFA in cows during pregnancy was also associated with higher concentrations of ROS and NOS and a higher oxidant status in calves throughout their first month of life (Abuelo 2020). These changes also largely coincided with lower consumption of starter feed on successive days of rearing, which suggests increased utilization of glucose and decreased utilization of fatty acids relative to calves whose mothers were not subjected to heat stress (Table 8). Tao et al. (2012) revealed significant changes in immunological parameters i.e. reduction in IgG level in calves born to heat-stressed cows (in utero heat stress) in comparison to non utero-stressed calves due to low absorption (1.058 ± 173 mg/dL vs. 1. 577 ± 149 mg/dL), significantly lower average apparent efficiency of IgG absorption (32 *vs* 20 %), and lower rates of PBMC proliferation. Calves born to cows with high oxidant stress after exposure to heat stress have clinical symptoms of oxidative stress during the first months of life (Fig. 1). High oxidant stress significantly increased the level of inflammation in calves, as evidenced by higher serum Hp and basal TNF-α concentrations (Ling et al. 2018). Furthermore, studies analysing selected blood parameters in calves have shown a lower haematocrit level and reduced plasma concentrations of insulin, prolactin, and IGF (Monteiro et al. 2016). In the case of cows exposed to heat stress during pregnancy, a significant (about 10%) reduction has been observed in the foetal growth rate and average weight gains in calves during the first few weeks of rearing (Dade-Senn et al. 2020). In addition, Guo et al. (2016) observed failure of passive transfer in a significant proportion of such calves at 24 h after birth, mainly due to insufficient colostrum immunoglobulin absorption. Disturbances of immune mechanisms in calves from cows with metabolic problems involve the inhibition of the antiviral response resulting from reduced proliferation of Tc cells, IFNγ, inhibition of phagocytosis due to suppression of proliferation of Th cells, and release of IL-8 (Table 9). A decrease in the effectiveness of humoral response has been observed as well, as a consequence of reduced IgG concentration and shorter time that antibodies remain in the sera of calves. These changes resulted in inhibition of mechanisms of post-vaccination immunity as a consequence of oxidative stress.

Table 9. Selected immune and health parameters in calves born to cows with metabolic or stress problems (Tao et al. 2012, Monteiro et al. 2014, Urban-Chmiel 2019, Skibel et al. 2017, Zou et al. 2017).

Estimated parameter	Age (weeks) and origin of calves coming from healthy or stressed cows					
	1 week of age		2 weeks of age		3 weeks of age	
	healthy cows	stressed cows	healthy cows	stressed cows	healthy cows	stressed cows
Phagocytic activity (%)	~48	~48	~48	~55	~39	~62
Concentration of probiotic strains CFU/g	3.9×10^6	2.7×10^5	3.6×10^7	3.9×10^6	3.9×10^8	3.7×10^8
Total plasma protein g/dL	~6.2	~6.8	~6.2	~5.5	~6.3	~5.8
Total IgG g/L	~25	~16	~16	~10	~17	~10
% proliferation of PMNC	52	40	nd	nd	12	10
% proliferation of CD14 (Th)	5.9	4.9	11.7	8.9*	13.8	11.8
% proliferation of CD18 (Tc)	1.6	0.59*	13.2	7.9*	15.9	12.4
Respiratory score ≥4 (%)	12.50	43.75				
BRSV antibodies (titre)	6.1	6.0	8.1	7.5	6.4	5.9
BHV-1 antibodies (titre)	5.2	5.1	5.9	4.9*	4.9	3.8*
BVD antibodies (titre)	1.3	1.1	7.2	3.9*	7.6	5.9
Haptoglobin (mg/L)	~6.5	~6.5	~6.5	~7.5	~6.5	~6.5
Serum Amyloide A (mg/L)	~0-12	~20	~20	~40*	~30	~30

Legend: nd – not detected, BRSV – bovine respiratory syncytial virus, BHV-1 – bovine herpes virus, BVD – bovine viral diarhoea, PMNC – polymorphonuclear cells, Th – T helper cells, Tc – cytotoxic T cell; * significant differences, P≤0.05.

Conclusions

The occurrence of metabolic problems in cows during pregnancy can significantly affect immune status determining the development and maturation of the calf, resulting in an increased incidence of FPT and health problems (diarrhoea, sepsis, respiratory disease) during the first few weeks of life. Bearing in mind the presented examples, as well as the small number of scientific studies dealing with the effect of metabolic disorders in cows on the immune status of calves, it seems advisable to conduct further research on this topic.

An optimum calving BCS before parturition should be between 3.0-3.5. A lower BCS may be associated with lower production and reproductive performance, while a higher BCS may reduce feed intake and increase risk for metabolic diseases.

Feed intake should be relatively constant during the initial phase of the dry period (days 60-21 prepartum) but can decline quite dramatically thereafter, especially during 7 - 10 days prior to calving The major animal factors that influence dry matter intake (DMI) during this time are body weight (BW), day of gestation, parity, body condition, and health. Cows with excess body condition (>4 on a 5-point scale) consumed about 8 percent less DM than cows with similar BW but lower body condition scores.

Both male and female calves should be fed at least 4 L of high-quality colostrum within 12 hr after birth. Optimally, calves shouldn't be fed at least 10%-12% of their birth weight at the first feeding. The best practice is to feed the first meal of colostrum within 1-2 hours after birth.

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