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Abstract: Efficient production of heifers is fundamental to the productivity and sustainability of dairy farms. However, high pre-weaning morbidity and mortality risks are frequently reported worldwide, imposing substantial welfare and economic implications. A major contributing factor to disease susceptibility in the neonatal stage is the inability of calves to mount an effective immune response. There is now greater appreciation that exposure in utero to several stresses (nutritional, social, metabolic, etc.) during the last stages of pregnancy have downstream carry-over effects in calves' health, growth, and development. Suboptimal intrauterine conditions during critical periods of development lead to changes in tissue structure and function that may have long-term consequences on the offspring's physiology and disease susceptibility. Indeed, pre-weaning metabolic function and growth are associated with future milk production. Thus, late-gestation carry-over impacts span into the lactating stage of the heifers. Nevertheless, researchers have been studying how to minimize these impacts. This review will discuss the effects of maternal stress during late gestation on the offspring's growth, productivity, metabolism, and health. In addition, strategies focusing on maternal interventions to improve neonatal health will be discussed. A better understanding of the intrauterine conditions affecting calf health and growth may facilitate the design of management practices that could improve neonatal development and future cow productivity.

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INTERPRETIVE SUMMARY

Symposium review: **Late-gestation maternal factors affecting dairy calves' health and development.** *Abuelo.* Exposure to different stressors during gestation can have a marked effect on the development and health of the offspring. Such fetal programming can have a dramatic effect on the efficiency of production in livestock animals; paradoxically, late-gestating animals are often the most neglected in a management program, because they are not actively producing when pregnant. This review article discusses recent insights into stressors or other interventions that when imposed on the mother affect neonatal development, health, and lifetime production. Strategies focusing on maternal interventions to improve neonatal health are also discussed.

JOINT ANIMAL HEALTH AND GROWTH AND DEVELOPMENT SYMPOSIUM

Symposium review: Late-gestation maternal factors affecting dairy calves' health and development[1]

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ABSTRACT

Efficient production of heifers is fundamental to the productivity and sustainability of dairy farms. However, high pre-weaning morbidity and mortality rates are frequently reported worldwide, imposing substantial welfare and economic implications. A major contributing factor to disease susceptibility in the neonatal stage is the inability of calves to mount an effective immune response. There is now greater appreciation that exposure *in utero* to several stresses (nutritional, social, metabolic, etc.) during the last stages of pregnancy have downstream carry-over effects in calves' health, growth, and development. Suboptimal intrauterine conditions during critical periods of development lead to changes in tissue structure and function that may have long-term consequences on the offspring's physiology and disease susceptibility. Indeed, pre-weaning metabolic function and growth are associated with future milk production. Thus, late-gestation carry-over impacts span into the lactating stage of the heifers. Nevertheless, researchers have been studying how to minimize these impacts. This review will discuss the effects of maternal stress during late gestation on the offspring's growth, productivity, metabolism, and health. In addition, strategies focusing on maternal interventions to improve neonatal health will be discussed. A better understanding of the intrauterine conditions affecting calf health and growth may facilitate the design of management practices that could improve neonatal development and future cow productivity.

Keywords: Dairy Calf; Periparturient cow; Transition Period; Immunity; Developmental programming.

INTRODUCTION

The efficient rearing of replacement stock is essential for guaranteeing the sustainability of dairy farms and optimizing milk production. Diseases during the neonatal stage, however, significantly impact the economic viability of dairy operations, due to the costs associated with calf losses, treatments, and long-term effects on performance. Calf preweaning morbidity and mortality risks have been reported to be high (about 23-35% morbidity and 3.5-10.5% mortality) in several countries, including the US, Canada, and Australia (NAHMS, 2014; Windeyer et al., 2014; Abuelo et al., 2019b). Infectious diseases such as diarrhea or pneumonia are responsible for the majority of preweaned calf deaths at 56.5% and 22.5% respectively (NAHMS, 2007). The economic loss associated with calf mortality in Norway where calf production is 280,000 heads per year was estimated to be approximately $10 million in 2006 (Østerås et al., 2007).

A major contributing factor to this high disease incidence in the neonatal stage is the inability of calves to mount an effective immune response (Chase et al., 2008). Calves are born with a naïve and immature immune system, relying on passive transfer of immunity (primarily antibodies) for protection against pathogens (Godden et al., 2019). The calves' immune system, however, starts developing in utero as early as 42 days of gestation (Schultz et al., 1973), and can, therefore, be affected by maternal conditions during pregnancy. Moreover, the immune system is expected to have lower priority in fetal nutrient partitioning than other systems (Wu et al., 2006). Therefore, the immune system and, subsequently, the animals' ability to fight infectious diseases, are more one of the first affected systems when supply of nutrients to the fetus is limited.

Developmental programming, also referred to as fetal programming, refers to the concept that factors affecting fetal growth and development cause long-term changes in tissue structure, function, or both (Wu et al., 2006). This concept was first established using epidemiologic studies to show a strong association between adverse phenotypical characteristics (e.g., metabolic syndrome, growth alterations, and immune and reproductive dysfunction) and in utero exposure to various stressors (Barker, 2007). Subsequently, it has been shown in humans and livestock studies that every organ system and metabolic function can be affected by developmental programming (Reynolds et al., 2010).

In developmental programming, the timing and duration of insults or stressors will influence the observed effect, depending on which tissue or organs are developing at the time (Reynolds et al., 2010). Hence, there are different critical points or windows of susceptibility to stressors during developmental programming throughout the gestation: the peri-conception period, early, mid, and late gestation. Due to its focus on health and growth, this article will focus only on developmental programming during late gestation, given that it is the period of greatest fetal growth and fastest proliferation of immune cells in the bovine fetuses (Higgins et al., 1983). Adipogenesis is another process that, although initiated in mid-gestation, takes place to a greater extent in late gestation (Feve, 2005), and is susceptible to developmental programming (Du et al., 2010). It is important to highlight, however, that what occurred in previous pregnancy stages will also influence late gestational impacts. For example, the number of myocytes in muscle fiber is established in mid gestation, and late gestational insults will affect myocyte size and intramuscular adipocyte formation, but not change the number of myocytes in muscle fibers (Du et al., 2010). Similarly, liver mass is set during early pregnancy under the control of many genes

that are sensitive to nutritional and hormonal regulation in utero, whereas the regulation of liver maturation takes place during late gestation (Hyatt et al., 2008). Therefore, variations in the availability of nutrients to the fetus can result in long-lasting changes in the structure and/or function of key fetal tissues related to metabolism, growth, and health.

This review will discuss the effects of maternal nutritional and metabolic factors during late gestation on the offspring's growth, productivity, metabolism, and health; including interventions in the dam that result in improved neonatal health. Other factors known to influence fetal programming in cattle are beyond the scope of this review. For example, the readers are directed to other recent reviews summarizing the impact of late-gestational heat stress on the offspring (Dahl et al., 2016; Tao et al., 2019).

OVERVIEW OF DEVELOPMENTAL PROGRAMMING

Exposure of the fetus to different insults during critical periods of development may lead to adaptations that prove to be detrimental and associated with adult defects in several organ systems. In humans, it is recognized that a wide range of gestational events can alter the fetal developmental trajectory. These include, among others, maternal nutritional deficit/excess, disease states, environmental conditions, and exposure to toxicants (Padmanabhan et al., 2016); all of which are also relevant in dairy cattle.

Developmental programming takes place through various mechanisms. It is outside of the scope of this article to provide an in-depth review of all these factors. Depending on the type of insult, organ system affected, and the developmental window in which the insult occurs, several

106 mechanisms have been proposed linking these insults to unfavorable outcomes such as lower
107 survivability. Nonetheless, different insults can lead to offspring responses that converge on
108 common mechanistic pathways culminating in the development of similar adult outcomes
109 (Padmanabhan et al., 2016).
110
111 One of these mechanisms is through changes in the placenta. After implantation, the placenta
112 controls the exchange of substances between the dam and the fetus and any factor capable of
113 affecting the placenta can lead to altered fetal growth and organ development (Reynolds et al.,
114 2010), including among others, blood flow to the placenta and transporter changes that
115 ultimately change placental permeability and function. In cases of undernutrition, the transport of
116 nutrients to the fetus can be reduced and vice versa in cases of overnutrition, resulting in changes
117 in the availability of nutrients (e.g., glucose, fatty acids, amino acids, etc.) to the fetus that
118 ultimately can impact the growth and development of fetal tissues (Gaccioli et al., 2013).
119
120 In addition to changes in placental function, altered growth and development of fetal tissues can
121 lead to irreversible changes in tissue and organ structure as well as permanent changes in tissue
122 function (e.g., gene expression). An example of changes in function due to alterations in gene
123 expression are the epigenetic alterations. These are transgenerational heritable changes in gene
124 expression without alteration of the genetic code. Epigenetic alterations, such as DNA
125 methylation, histone modification, chromatin packing, and microRNA expression determine
126 whether a particular gene is available for transcription or not. There is ample evidence of several
127 maternal factors affecting the fetal epigenome, including nutrition and metabolic status, toxicants

(e.g., pesticides or herbicides), social interactions, and environmental stressors such as heat (Skibiel et al., 2018; Reynolds et al., 2019).

Another mechanism believed to be involved in prenatal programming is oxidative stress (**OS**); a deleterious process that results in damage of cell components, such as lipids, proteins, and DNA. However, it is unknown whether the developmental programming of OS may be through directly modulating gene expression or indirectly through the effects of certain oxidized molecules (Luo et al., 2006).

EFFECT OF MATERNAL NUTRITION

Maternal nutritional status during pregnancy is a major factor in developmental programming events and ultimately offspring outcomes (Reynolds and Caton, 2012). Maternal nutrition can alter the fetal and postnatal epigenome and transcriptome, often leading to measurable alterations in metabolism and growth (Elolimy et al., 2019). Also, placental function is altered to match fetal growth to the ability of the maternal supply line (nutrient restriction or excess) to allocate resources to the fetus, thereby resulting in changes of nutrients available to the fetus and affecting fetal growth and the long-term health of the offspring (Gaccioli et al., 2013).

Maternal Undernutrition

Most developmental programming research in ruminants has focused on nutrient restriction in pregnant animals (Chavatte-Palmer et al., 2015). In cattle, probably the best example of the impact of maternal undernutrition are birth defects in calves that are associated with deficiencies in nutrients in the dam during pregnancy, such as chondrodystrophy in calves associated with

manganese deficiency (Valero et al., 1990). However, maternal nutrient supply below requirements is also associated with decreased pre- and post-natal growth, altered immune responses, and increased morbidity and mortality risks not only during the neonatal stage but also during the productive life of cows (Cooke, 2019). For example, Moriel et al. (2016) reported that restricting energy supply of beef cows to 70% of daily NE_m requirements during the last 40 d of gestation resulted in calves that had lower titers after bovine diarrhea virus vaccination at 306 days of life. Hence, even short-term restrictions have long-term implications, as calves born to cows fed the restricted diet showed decreased humoral responses to vaccination 10 months after birth (Moriel et al., 2016).

In dairy cows, survival to second parity and milk yield were reduced, and SCC was increased in the offspring of dams with greater milk yield preconception and during gestation (Berry et al., 2008). In dairy farms, cows are pregnant and lactating for most of the pregnancy, meaning that the fetus competes for nutrients with the requirements for milk production – with cows producing more milk likely providing less nutrients to the fetus. Heifers born to dams that were lactating while pregnant produced 53 kg less milk, lived 16 d shorter and were metabolically less efficient than those born to non-lactating dams during pregnancy (Gonzalez-Recio et al., 2012). Furthermore, the reduced milk production, survivability, and metabolic efficiency of the offspring were increased according to the cow level of milk production. Thus, calves born to the more productive cows can be precluded from fully expressing their genetic merit. Despite these potential effects on the offspring, maintaining tight calving intervals is critical for ensuring the economic efficiency of the dairy farms (Dalcq et al., 2018). Hence, ensuring adequate nutrition of lactating pregnant cows is critical to avoid the negative impacts of reduced nutrient

availability during pregnancy on the health and productivity of offspring. Fortunately, in most modern dairy farms, dry cows are fed a TMR diet designed to meet the dietary requirements. However, it is important to consider that other housing, social, and environmental factors that might impact feed intake could potentially affect fetal development. For example, management factors such as overstocking, inadequate heat abatement, or health status (e.g., lameness) that result in decreased feed intake in the late dry period will not only affect the cow in early lactation but also potentially have a negative impact on the offspring development.

Maternal Overnutrition

In commercial dairy farms is arguably more common nowadays to find overconditioned cows at dry-off than underconditioned, as have been shown in some farms (Chebel et al., 2018). In humans, maternal obesity has been linked to increased adiposity and metabolic syndrome (i.e., type 2 diabetes, high blood pressure, etc.) in the offspring (Alfaradhi and Ozanne, 2011). Maternal obesity upregulated the expression of genes related to lipogenesis and adipogenesis in adipose tissue of rats (Borengasser et al., 2011). Metabolic syndrome in humans has many similarities with the fat cow syndrome (De Koster and Opsomer, 2012) and therefore it is likely that similar links between overconditioned pregnant cows and increased risk of metabolic disease in the offspring also exist in dairy cows (Opsomer et al., 2016). The impact of maternal overnutrition in fetal programming in cattle has not been as extensively studied as undernutrition. Nevertheless, there is evidence of its existence in beef cattle, where maternal overnutrition during gestation resulted in increased mRNA expression of intramuscular adipogenesis and collagen deposition in skeletal muscle (Duarte et al., 2014). Therefore, late gestation overnutrition plausibly affects tissue structure in dairy calves. Dairy cows with high BCS at dry-

off are more likely to lose BCS during late gestation whereas cows with low BCS at dry-off will likely gain BCS in the dry period (Chebel et al., 2018). Changes in body composition during late gestation can potentially negatively affect the calves' development (discussed below in the maternal metabolic status section). However, further research is needed to elucidate and quantify the impact of maternal overnutrition and adiposity during gestation on dairy calf growth and health outcomes.

Dietary Cation Anion Difference Diets

Dairy cows are usually fed a negative dietary cation anion difference (**DCAD**) diet during the last weeks of gestation as a strategy to prevent clinical hypocalcemia (Lean et al., 2006). In fact, a recent meta-analysis revealed that feeding a negative DCAD resulted in decreased risks of clinical hypocalcemia, retained placenta, metritis and overall disease during the early postpartum period (Lean et al., 2019). Diets with a negative DCAD aim to create a compensated metabolic acidosis in the cows, which decreases their blood pH and activates different homeostatic mechanisms that result in increased mobilization and absorption of Ca (Goff, 2006). However, it is possible that this maternal metabolic acidosis induced by negative DCAD prepartum diets could also acidify the calves' blood in utero, because of the highly vascularized nutrient transfer system that occurs during the last trimester (Collazos et al., 2017). Metabolic and respiratory acidosis in newborn calves has been associated with reduced efficiency of colostral Ig absorption, leading to increased risk of mortality in dairy calves (Besser and Gay, 1994). Hence, it was initially hypothesized that feeding a negative DCAD to dams could have negative downstream implications for calf health and development postnatally.

Some early studies reported decreased IgG absorption in calves born to dams fed acidogenic diets (Quigley and Drewry, 1998). However, contradictory results were found in more recent controlled studies. For example, the efficiency of IgG absorption and the concentrations of Ig were similar between calves whose dams received a diet with a DCAD of −100 mEq/kg and those born to dams fed a DCAD of +77 mEq/kg during the last 21 d prepartum (Morrill et al., 2010). Collazos et al. (2017) also found no effect of the level of negative DCAD (–70 or –180 mEq/kg) or feeding duration (last 21 d or 42 d prepartum) on IgG efficiency of absorption and serum concentrations. However, a more evident metabolic acidosis was identified at birth in the calves born to dams fed the –70 mEq/kg DCAD diet, although differences in acid-base status were not present at 3 d of life and there were no associations between measures of metabolic acidosis and efficiency of IgG absorption. Tucker et al. (1992) also reported that the DCAD level of the diet (–30 or +90 mEq/kg) did not affect the acid-base status or the plasma mineral content of their calves. Similar results were recently confirmed, where feeding an acidogenic diet to cows prepartum did not alter blood mineral or gas concentrations in their calves compared with calves born to dams fed a nonacidified diet (Diehl et al., 2018). In addition, the level of negative DCAD was not associated with differences in calf BW at birth or ADG up to 62 d of age; however, heifers born to dams fed a DCAD diet during the last 42 d prepartum had lower BW at birth and 62 d of life compared with calves born to dams fed the last 21 d prepartum (Collazos et al., 2017). This difference, however, was not present at 3 and 6 mo of age, indicating that the differences in birth BW were compensated during the first months of life. The study of Collazos et al. (2017) is the only one to the author's knowledge that also examined calf morbidity across maternal treatments, not finding any statistical difference in the percentage of calves treated for diarrhea. Collectively, these data indicate that the changes in acid-base balance observed at birth

in calves whose dams received a negative DCAD diet prepartum are transient in nature and do not affect passive transfer of immunity, disease risk, or growth.

Colostrum composition and volume

In addition to in utero effects, nutrition during late pregnancy can also affect calves' development and immunity through changes in colostrum production. Colostrum intake is critical not only for transfer of passive immunity and disease resistance but also for other long-term implications such as improved feed efficiency, reduced age at first calving, and higher milk production in the first lactations (Jones et al., 2004; Faber et al., 2005; Godden, 2008; Godden et al., 2019). Colostrogenesis takes place during the last several weeks prepartum (Brandon et al., 1971), and therefore is conditioned by the dam's status during this time.

Several factors affect the colostrum concentration of Ig; including, among others, dry period length, time from calving to milking, dam's vaccination status, parity, late-gestation nutrition, and season of calving (Godden, 2008). An in-depth review of all the factors associated with colostral Ig concentration is beyond the scope of this article. Nevertheless, it is important to highlight how maternal nutrition might influence calf development and immunity through changes in colostrum composition. Approximately 19.7% of calves in the US receive pooled colostrum (Urie et al., 2018), which can potentially compensate for individual cows producing insufficient or low-quality colostrum. However, herd-level factors influencing colostrum composition are still relevant.

Concentration of CP in the dry diet has not been associated with the IgG concentration of colostrum (Blecha et al., 1981; Quigley and Drewry, 1998). Conversely, the absorption of IgG was reduced by 21.8% in calves that received colostrum obtained from cows fed restricted amounts of energy and CP (Hough et al., 1990). On the other hand, compared to cows that received a dry period diet formulated to meet the energy requirements, those receiving a high energy diet had lower colostral IgG concentrations, higher concentrations of insulin compared, and increased colostrum concentration of de novo fatty acids compared to cows fed a controlled diet (Mann et al., 2016). This study also showed that changes in colostrum composition beyond IgG concentration, such as insulin and fatty acids, are achievable through dietary interventions. The provision of hormones and growth factors through colostrum impact the maturation of the neonatal gastrointestinal tract (Hammon et al., 2013). Nevertheless, research is still needed to quantify the impact of the differences in colostral components caused by different dry period feeding strategies on gut maturation, metabolism, and growth of the newborn calf.

Another important factor to consider is the volume of colostrum produced. Farms need to collect a enough high-quality colostrum to ensure an optimal colostrum management plan. However, colostrum yield has been traditionally negatively associated with Ig concentration (Pritchett et al., 1991). In addition, several dairy herds have reported a deficiency of colostrum production by cows during fall and winter (Gavin et al., 2018), which limits the ability of farms to feed sufficient high-quality colostrum to all their calves. Unfortunately, there is not much evidence regarding the factors influencing the volume of colostrum produced by dairy cows. In the aforementioned study by Mann et al. (2016), there were no statistical differences in colostrum volume among the different dietary plane of energy treatments, although cows fed energy-

controlled diet produced numerically less colostrum than those fed the high-energy diet. Also, cows with persistently infected mammary glands produced less colostrum volume than matched healthy animals (Maunsell et al., 1998). Collectively, these data suggest that prepartum maternal nutrition can impact colostrum production. Clearly, the relationship between prepartum diet, colostrum composition and yield, and calf health and development merits further investigation.

EFFECT OF MATERNAL METABOLIC STATUS

Despite identical housing and feeding conditions, dairy cows exhibit considerable individual variation on a variety of metabolic and endocrine variables (Kessel et al., 2008). Thus, this review article considers metabolic status during late pregnancy separately to maternal nutrition.

Late Gestation Metabolic Stress

Dairy cows experience metabolic stress during the transition period when they fail to physiologically adapt to the profound increase in nutrient requirements associated with fetal growth and milk production (Sordillo and Mavangira, 2014). Metabolic stress is characterized by altered nutrient utilization, OS, and dysfunctional immune and inflammatory responses (Abuelo et al., 2015b). The negative impact of metabolic stress on the immune function, health, and production of dairy cattle during the periparturient is well established (Kehrli et al., 1989; Sordillo and Aitken, 2009). Metabolic stress is initiated several weeks before calving (Grummer, 1993; Sordillo and Raphael, 2013) and therefore can potentially affect the fetus.

Evidence from other species also support the fact that exposure to metabolic stress during pregnancy impacts the robustness of immune response of the offspring to a challenge during the

neonatal stage. For example, rats exposed to a pro-inflammatory stimulus during late gestation produced offspring with a significantly lower TNFα response to lipopolysaccharide stimulation (Hodyl et al., 2007; Hodyl et al., 2008; Beloosesky et al., 2010). Furthermore, high maternal inflammation during gestation was positively associated with development of wheezing and recurrent respiratory tract infections in infants during the first 14 months of life (Morales et al., 2011). Also, maternal markers of OS in humans were positively associated in the offspring with the umbilical cord blood concentration of the pro-inflammatory cytokines IP-10 and IL-5; and negatively with that of the anti-inflammatory cytokine IL-4 (Hernandez-Trejo et al., 2017).

In vitro exposure of bovine oocytes and embryos to elevated NEFA concentrations results in differences in methylation and gene expression of networks associated with gene networks affected were related to lipid and carbohydrate metabolism, cell death, immune response and metabolic disorders (Desmet et al., 2016). Hence, it is possible that greater maternal circulating NEFA during late gestation might impact calf development in utero. We recently studied in dairy cattle the association of late gestation maternal metabolic stress with the immune and metabolic responses of their calves (Ling et al., 2018). Our results suggest that exposure to maternal metabolic stress (altered nutrient utilization, dysregulated inflammation, and OS) may adversely impact some metabolic and inflammatory responses of the offspring that could influence disease susceptibility. We monitored the dams' serum oxidant status, NEFA, and haptoglobin concentrations during the last month of gestation. For each of these biomarkers, cows were classified in low and high groups based on the median value of the average concentration of the prepartum samples. Calves born to cows with higher NEFA or oxidant status showed lower BW at birth and throughout the first month of life. However, no association between the degree of

334 maternal metabolic stress and ADG at 4 wk. of age was identified. Thus, indicating that
335 compensatory growth did not occur postnatally in the first 4 wk. However, this study did not
336 explore whether BW matched later in life, making it not possible to know the persistence of the
337 effect in time.
338
339 Exposure to higher maternal concentrations of NEFA was also associated with greater serum
340 concentrations of reactive oxygen and nitrogen species that resulted in higher values of oxidant
341 status index in the calves throughout their first month of life. To the authors' knowledge, the
342 effect of maternal NEFA concentration during late gestation on the oxidative status of the
343 offspring in postnatal life has not yet been investigated. The mechanism by which prenatal
344 exposure to high maternal NEFA concentrations in late gestation leads to an increased oxidant
345 status is unknown. However, *in vitro* studies demonstrate that fatty acids may induce cellular
346 ROS production directly (Inoguchi et al., 2000; Listenberger et al., 2001) and indirectly by
347 stimulating inflammatory pathways (Ohtsu et al., 2017). Furthermore, *in vitro* studies in bovine
348 oocytes and blastocysts demonstrate that elevated NEFA concentrations alter gene expression
349 related to oxidative metabolism (Van Hoeck et al., 2013; Van Hoeck et al., 2015). However, it is
350 yet to be determined whether prenatal exposure to high maternal NEFA concentrations during
351 late gestation influences the expression of genes related to redox homeostasis. Further research is
352 required to determine whether offspring exposed to high maternal NEFA concentrations during
353 late gestation are at increased risk of diseases associated with OS, such as diarrhea, pneumonia
354 and mastitis (Ranjan et al., 2006; Lykkesfeldt and Svendsen, 2007).
355

Calves exposed to high maternal oxidant status also had higher circulating concentrations of haptoglobin and TNFα, indicating greater basal inflammatory responses when compared to calves born to cows with a lower oxidant status. The clinical significance of elevated TNFα and haptoglobin concentrations during the first month of life is unknown. Further research is warranted to determine whether an elevated basal inflammatory status during this period is associated with adverse health and production outcomes. Murray et al. (2014) reported that serum haptoglobin concentrations in dairy calves during the first week of life are positively associated with morbidity and mortality during the first 4 months of life. Furthermore, elevated TNFα concentrations contribute to impaired metabolic function in dairy cattle (McCarthy et al., 2016) and may adversely affect growth rates by inhibition of insulin like growth factor-1 (Suda et al., 2003; Borghetti et al., 2009). The relationship between the level of basal inflammation during the neonatal period and the development of dysregulated inflammatory responses later in life is also unknown. This is of particular interest because dysregulated inflammation in dairy cattle is highly implicated in the pathogenesis of metabolic stress during the transition period and inflammatory-based diseases, such as mastitis and endometritis (LeBlanc, 2014; Sordillo and Mavangira, 2014)

In contrast, LPS-induced inflammatory responses were less robust in calves exposed to higher maternal biomarkers of inflammation or oxidant status, suggesting compromised immune responses to microbial agonists (Ling et al., 2018). However, it is unknown whether the resulting differences in immune responses in these calves is substantial enough to actually increase their risk of infectious disease. Hence, further studies should evaluate the effect of late-gestation inflammation and OS on neonatal calf disease susceptibility.

Oxidative Stress in Developmental Programming

Oxidative stress, a component of metabolic stress, plays an important role in developmental programming (Thompson and Al-Hasan, 2012). Oxidants can induce genetic changes by oxidation of DNA (Thompson and Al-Hasan, 2012) and epigenetic alterations by DNA methylation and histone modification (Ziech et al., 2011). Studies in rats and guinea pigs have also demonstrated that phenotypic alterations resulting from suboptimal intrauterine environments can be prevented by prenatal antioxidant supplementation (Cambonie et al., 2007; Evans et al., 2012). In addition to changes in gene/protein expression, OS can also contribute to the creation of an abnormal environment for the fetus to develop through changes in maternal metabolic function (Alfaradhi and Ozanne, 2011). In humans, maternal OS results in obesity, insulin resistance, and diabetes through interference of insulin signaling (Urakawa et al., 2003; Furukawa et al., 2004). Exposure to these conditions during gestation increases the risk of developing metabolic syndrome in the offspring (Alfaradhi and Ozanne, 2011). In fact, altered insulin signaling in offspring of obese or overfed mothers has been reported with increased inflammation and OS in various models (Bruce et al., 2009; McCurdy et al., 2009). Nevertheless, reducing the degree of OS results in the reversal in the metabolic syndrome phenotype of the offspring. Sen and Simmons (2010) reported that vitamin C antioxidant supplementation to pregnant rats fed a high-fat diet decreased adiposity, normalized glucose tolerance, and reduced OS and inflammation in their offspring. Thus, in this model of human disease, maternal OS negatively impacts the growth and health of the offspring.

Studies performed in the last decade clearly indicate that dairy cows experience OS around the time of calving (Castillo et al., 2003; 2005; Sordillo and Aitken, 2009; Abuelo et al., 2013;

2015a). OS during this time diminishes functional capabilities of immune cell populations, increases the cows' susceptibility to several diseases (Sordillo and Aitken, 2009; Abuelo et al., 2019a), and also results in altered immune responses in the offspring (Ling et al., 2018). Furthermore, as in humans, an association between insulin sensitivity and OS has also been reported in periparturient cattle (Abuelo et al., 2016a), with antioxidant supplementation resulting in improved insulin sensitivity (Abuelo et al., 2016c). Therefore, it is possible that OS in dairy cattle also affect developmental programming through both changes in gene/protein expression and insulin signaling. Thus, controlling prepartum OS through micronutrient antioxidant supplementation might help ameliorate the phenotypical changes associated with different maternal stressors given the central role of OS in key mechanisms of developmental programming.

SUPPLEMENTATION STRATEGIES

Supplementation of specific nutrients above requirements during gestation is common practice in humans and livestock species (Cooke, 2019). In dairy cows, supplementation strategies during late gestation are usually implemented on farms to promote transition cow health. Some of these strategies, however, have shown to impact offspring development and health, and are discussed below.

Trace Minerals

Trace minerals are essential for the adequate development of fetal nervous, immune, and reproductive systems; and the fetus depends completely on the dam for supply of these elements (Hidiroglou and Knipfel, 1981). Many trace minerals can cross the placenta in ruminants.

Furthermore, recent evidence analyzing dam and fetal liver mineral content suggest a high maternal to fetal transfer at low maternal mineral concentration but a more limited transfer as maternal mineral content increases (Van Saun, 2019). The impact of supplementing dams during late gestation with trace minerals has been examined in beef and dairy cattle. Marques et al. (2016) compared the supplementation of inorganic and organic sources of Cu, Co, Mn, and Zn during the last trimester of gestation in beef cows. They found no differences in birth BW among treatment (organic and inorganic trace minerals) and control groups. However, the calves born to cows that received the organic-complexed source of trace minerals had increased weight at 205-d weaning and lower incidence of respiratory disease during the feedlot phase. Organic sources of trace minerals are more bioavailable than inorganic ones. Therefore, cows receiving organic sources of trace minerals likely had more trace minerals available to supply the fetus. This study did not report feed intake and therefore it is not possible to evaluate whether the differences in growth observed are due to increased feed intake or feed efficiency. Nevertheless, it clearly documents how maternal nutritional interventions can have relative long-term implications in the growth and health of the offspring.

Supplementation of organic sources of trace minerals to dairy cows during late gestation also resulted in no differences in calf birth BW compared to cows receiving inorganic sources (Jacometo et al., 2015). However, in contrast to the study in beef cows, there were no differences in BW between the two groups throughout the first 8 weeks of life. Nevertheless, it is possible that the differences in growth associated with greater in utero trace mineral supply take place later in life. Maternal nutrition with organic trace minerals also resulted in decreased pro-oxidant load, greater expression of key redox transcription factors, and changes in neutrophil mRNA and

449 miRNA expression (Jacometo et al., 2015). Further studies are still needed, however, to
450 determine the impact of maternal trace mineral supplementation on the calves
451 immunocompetence and susceptibility to diseases. Also, as discussed above, it is important to
452 clarify if the observed effects of trace minerals are due to their role in redox balance (Abuelo et
453 al., 2016b) or other biological functions.
454
455 ***Fatty acids***
456 During gestation, ω-3 and ω-6 are transferred to the fetus through the placenta (Noble et al.,
457 1978). In general terms, the derivatives of ω-6 fatty acids are considered pro-inflammatory
458 whereas ω-3 derivatives are inflammation pro-resolving (Sordillo, 2018). In humans, children
459 born to woman supplemented with ω-3 fatty acids during pregnancy showed less cases of
460 allergies and asthma (Olsen et al., 2008). Similarly, supplementation of ω-3 fatty acids to
461 pregnant sows resulted in increased piglet viability and pre- and post-weaning growth (Tanghe
462 and De Smet, 2013).
463
464 In ruminants, maternal supplementation of ω-6 fatty acids to beef cows enhanced calves' cold
465 tolerance by improving storage and thermogenic capacity of brown adipose tissue (Lammoglia et
466 al., 1999). However, it reduced survival to second parity and increased milk somatic cell count in
467 ewes (Encinias et al., 2004). Research in dairy cows also showed that feeding moderate amounts
468 (1.7% of DM) of saturated or unsaturated long-chain fatty acids during the last 8 wk of gestation
469 improved apparent efficiency of absorption of IgG, and changed the fatty acid profile of
470 colostrum and plasma of calves to reflect that of the supplements (Garcia et al., 2014). The
471 mechanism behind the differences in apparent efficiency of absorption of IgG associated with

fatty acid supplementation are unknown. The authors speculated that it could be attributed to faster gastric emptying associated with a greater fatty acid content of the colostrum in supplemented cows, or to changes in the fatty acid profile of the enterocyte membrane that facilitate the IgG pinocytosis process. Thus, strategic fatty acid supplementation during late gestation has the potential to be used to improve calf survivability, but further research is still needed to optimize the amount of ω-6 and ω-3 fatty acids needed for improved calf health.

Rumen-protected Methionine

Another supplementation strategy that has been extensively studied in the last years is the administration of rumen-protected methionine during late gestation. Methionine is an essential amino acid and its metabolism can generate the antioxidants taurine and glutathione (Zhou et al., 2016); and the provision of amino acids to the dam can ameliorate the effects of fetal growth restriction due to undernutrition and improve health and growth of offspring (Lin et al., 2014). Methionine supply during late gestation resulted in changes in placental metabolism and DNA methylation in a calf sex-specific manner (Batistel et al., 2019). Calves born to cows that received methionine during late gestation were heavier at birth (+2 kg) and at 9 wk. of age (+3.1 kg), also exhibiting greater ADG (+0.05 kg/d) despite no differences in feed intake compared to the control group (Alharthi et al., 2017). Thus, maternal methionine supplementation resulted in improved feed efficiency during the 9 wks of duration of the study.

Calves born to cows supplemented cows also showed higher plasma concentrations on insulin and lower plasma concentrations of glucose, along with decreased glucose-to-insulin and fatty acids-to-insulin ratios (Jacometo et al., 2016), which is suggestive of improved insulin sensitivity

in these animals. Hepatic gene transcriptomic analyses also revealed a faster maturation of key metabolic pathways in calves born to supplemented dams, as shown by the upregulation of genes related to gluconeogenesis and fatty acid oxidation along with insulin sensitivity earlier in life. However, the supplementation had no effect on the inflammatory or oxidant status of calves throughout the first 9 wks of life. More recently, the same authors also reported changes in the calf leukocyte mRNA expression of some genes related to cell adhesion and chemotaxis and the toll-like receptor pathway (Jacometo et al., 2018). This indicates changes in the immune function of calves born to supplemented cows. However, there were no differences in the lipopolysaccharide-induced cytokine-release response between calves born to supplemented and unsupplemented cows (Jacometo et al., 2018). Hence, it remains unclear whether the changes observed in gene expression translate in an increased ability to fight infections. Thus, further work should evaluate the impact of these interventions in calf disease susceptibility.

CONCLUSIONS

In summary, there is substantial evidence in dairy cattle supporting the effect of late gestation maternal stressors or other interventions that, when imposed on the mother, affect neonatal development, health, and lifetime production. In this line, given the central role of OS in the various processes implicated in developmental programing, further studies are needed to investigate the short- and long-term impact that ameliorating late gestation OS might have on the development of immune and metabolic function of the offspring. Thus, increasing our understanding of the underlying mechanisms developmental programming will lead to dry cow management programs aimed at improving not only early lactation cow health but also neonatal

517 calf growth and immunity. Also, more research is still needed to evaluate the impact of different
518 interventions in the calves' immunocompetence and disease resistance.
519
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525
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