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Maternal late-gestation metabolic stress is associated with changes in immune and metabolic responses of dairy calves

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ABSTRACT

Metabolic stress in periparturient dairy cows is characterized by excessive lipid mobilization, inflammation, and oxidative stress that is associated with immune dysfunction. Thus, metabolic stress around the time calving is linked to the development of various early-lactation health disorders. Maternal status during late pregnancy can have carryover effects on several health and production variables of neonatal calves. However, the effects of metabolic stress during gestation on metabolic and immune responses of newborn calves remain unknown. Thus, we aimed to investigate whether metabolic stress in late-gestation dairy cows is associated with changes in the metabolic and immune responses of their offspring during the first month of life. Holstein-Friesian cows (n = 12) were blood sampled at 28 and 15 d before expected calving. The average between these 2 sampling points in the serum concentrations of nonesterified fatty acids (NEFA), haptoglobin (Hp), and oxidant status index (OSi)—defined as the ratio between reactive oxygen and nitrogen species and total antioxidant potential—were calculated as indicators of the degree of lipid mobilization, inflammation, and oxidant status (OS), respectively. Calves were subsequently divided into groups (n = 6 each) according to their dams' high or low degree of lipid mobilization, inflammation, and OS. The metabolic responses of calves in each of these groups were compared weekly throughout their first month of life by assessing serum concentration of NEFA, Hp, and OSi. Additionally, whole blood was obtained from calves at each sampling period and subjected to a lipopolysaccharide (LPS)-stimulated tumor necrosis factor-α (TNF-α) production assay to assess cell-mediated innate immunity against induced inflammatory responses, using high (5 μg/mL of blood) and low (10 ng/mL) concentrations of LPS. Calves born to cows with higher NEFA or OSi showed lower body weight at birth and throughout the study, whereas no association between any of the maternal groups and average daily gain at 4 wk of age was identified. Serum concentrations of reactive oxygen and nitrogen species were higher in calves exposed to higher maternal NEFA concentrations or OSi when compared with calves born to cows with lower values of these biomarkers. Calves exposed to high maternal OS also had higher circulating concentrations of Hp and TNF-α, indicating greater basal inflammatory responses when compared with calves born to cows with a lower OSi. In contrast, LPS-induced inflammatory responses were less robust in calves exposed to higher maternal biomarkers of inflammation or OS, suggesting compromised immune responses to microbial agonists. Collectively, these data suggest that prenatal exposure to maternal parameters of metabolic stress may adversely affect some metabolic and inflammatory responses of the offspring that could influence disease susceptibility.
Key words: calf health, dairy cow, lipid mobilization, oxidative stress, transition period

INTRODUCTION

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 excessive lipid mobilization, oxidative stress, and inflammatory dysfunction (Abuelo et al., 2015). The negative effect of metabolic stress on the immune function, health, and production of dairy cattle during this period is well established (Kehrli et al., 1989; Sordillo and Aitken, 2009). Metabolic stress starts several weeks before calving (Grummer, 1993; Sordillo and Raphael, 2013), and therefore can potentially affect the fetus.

Evidence exists in other nonruminant species that maternal stress during gestation influences fetal devel-

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opment and exerts carryover effects on the offspring (McMillen and Robinson, 2005; Merlot et al., 2008). Studies in humans and murine models demonstrated that suboptimal intrauterine conditions during critical periods of development lead to changes in tissue structure and function (Fowden et al., 2006), which may have long-term consequences on offspring physiology and disease susceptibility (McMillen and Robinson, 2005; Merlot et al., 2008). Studies in dairy cattle have also demonstrated that exposure to heat stress and restricted or excessive energy intake during late gestation affect the immune and metabolic function of the offspring (Gao et al., 2012; Tao et al., 2012, 2014; Osorio et al., 2013). Moreover, Monteiro et al. (2016) demonstrated that the detrimental effects of in utero exposure to heat stress on milk yield and reproductive performance extend to at least the first lactation of offspring. Thus, prenatal conditions have the potential of significantly affecting the productivity and health status of replacement heifers.

The first month of life is a time when the greatest neonatal morbidity and mortality rates are observed on dairy farms (Windeyer et al., 2014); hence, maternal carryover effects can have a significant effect on calf health during this time. Unfortunately, no information exists on how metabolic stress in the dam can affect immune responses in the newborn calf when they are at risk for succumbing to health disorders. Therefore, we hypothesized that calves born to cows experiencing increased metabolic stress will exhibit altered metabolic status and immune responses in the first month of life. The objective of our preliminary observational study was to compare metabolic status and LPS-induced whole blood tumor necrosis factor-α (**TNF-α**) release between calves born to cows that experienced different degrees of maternal metabolic stress. As an index for quantification of metabolic stress is yet to be established (Sordillo and Mavangira, 2014; Abuelo et al., 2015), the carryover effects of the 3 components of metabolic stress triad (lipid mobilization, inflammation, and oxidative stress) were separately assessed.

MATERIALS AND METHODS

Animals

The Charles Sturt University Animal Care and Ethics Committee approved all procedures involving animals before the commencement of the study (Protocol 15/120). During October and November 2016, 12 multiparous Holstein-Friesian dairy cows and their calves were monitored for the last month of gestation and the first month of life, respectively. Given the lack of previous studies investigating the effect of maternal metabolic stress on the calves immune and metabolic status, this sample size was selected to create 2 groups ($n = 6$) for comparison. Cows entering their 2nd to 4th lactation were selected based on the proximity of their calving dates from a 180-head commercial pasture-based dairy farm located in Ladysmith, New South Wales, Australia, with an average 305-d normalized milk production of 8,513 kg/cow.

Further selection criteria included a variation in BCS lower or equal to 0.5 points during the last month of gestation for cows and adequate passive transfer of immunoglobulins in the calves. For this, cows were body condition scored to the nearest quarter point using the 5-point (1 = lean, 5 = obese) system described by Edmonson et al. (1989) at each sampling point and within the first week after calving. To assess passive transfer of immunity, the serum sample collected in the first week of age was analyzed for IgG using a radioimmunodiffusion assay (Bovine IgG test, Triple J Farms, Bellingham, WA). The first 12 cow/calf pairs met both criteria, with all calves being singletons born from an unassisted eutotic calving and having an IgG concentration higher than the 10 g/L cutoff commonly used to define failure of passive transfer of immunity (Godden, 2008). Hence, no further animals were enrolled. Additionally, all animals underwent a weekly veterinary clinical exam throughout the study period to rule out any clinical disease. In calves, the exam included assessment of appetite, rectal temperature, heart and respiratory rate, umbilical and joint swelling, and the presence or absence of diarrhea. None of the animals enrolled in the study showed clinical signs of disease; hence, the data from all cows and calves was included in the statistical analyses. Calf weights were estimated with a heart girth tape (Holstein Calf Weigh Tape; The Coburn Company Inc., Whitewater, WI) placed vertically at the point of the elbow (Heinrichs et al., 2007).

Cows and calves in the study were each managed under identical conditions. Cows were housed outdoors on pasture, and calves were housed in individual calf shelters for the first 2 wk of life and then housed in a straw-bedded shed in groups of 6 to 8 calves. Cows were dried off 60 d before the expected calving date. During the first 4 wk of the dry period, cows grazed a ryegrass and clover pasture with an estimated supply of 2.5 kg of DM/d per cow and were offered oaten hay ad libitum. For the last 30 d of the dry period, cows received 2 kg of concentrate and 1 kg of anion salts once daily in addition to the same supply of pasture and ad libitum access to oaten hay. Calves were removed from dams within 12 h after birth. Calves received 4 L of colostrum from their respective dams within the first 12 h of life and then twice daily for the first 2 d at a rate of 10% BW/d. Thereafter, they received 2.5 L of