PHYSIOLOGY SYMPOSIUM: Effects of heat stress during late gestation on the dam and its calf[1,2]

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ABSTRACT: Heat stress during late gestation in cattle negatively affects the performance of the dam and its calf. This brief exposure to an adverse environment before parturition affects the physiological responses, tissue development, metabolism, and immune function of the dam and her offspring, thereby limiting their productivity. During the dry period of a dairy cow, heat stress blunts mammary involution by attenuating mammary apoptosis and autophagic activity and reduces subsequent mammary cell proliferation, leading to impaired milk production in the next lactation. Dairy cows in early lactation that experience prepartum heat stress display reduced adipose tissue mobilization and lower degree of insulin resistance in peripheral tissues. Similar to mammary gland development, placental function is impaired by heat stress as evidenced by reduced secretion of placental hormones (e.g., estrone sulfate) in late gestation cows, which partly explains the reduced fetal growth rate and lighter birth weight of the calves. Compared with dairy calves born to dams that are exposed to evaporative cooling during summer, calves born to noncooled dry cows maintain lower BW until 1 yr of age, but display a stronger ability to absorb glucose during metabolic challenges postnatally. Immunity of the calves, both passive and cell-mediated immune function, is also impaired by prenatal heat stress, resulting in increased susceptibility of the calves to diseases in their postnatal life. In fact, dairy heifers born to heat-stressed dry cows without evaporative cooling have a greater chance leaving the herd before puberty compared with heifers born to dry cows provided with evaporative cooling (12.2% vs. 22.7%). Dairy heifers born to late-gestation heat-stressed dry cows have lower milk yield at maturity during their first and second lactations. Emerging evidence suggests that late-gestation heat stress alters the mammary gland microstructure of the heifers during the first lactation and exerts epigenetic alterations that might explain, in part, their impaired productivity.

Key words: calf, dairy cow, heat stress, late gestation

J. Anim. Sci. 2019.XX:XX-XX
doi: 10.1093/jas/skz061

[1]The authors thank the staff the Dairy Unit of the University of Florida (Hague, FL) for animal care and data collection.

[2]Based on presentation given at the Physiology Symposium: Postnatal Consequences of Heat Stress During Fetal Development titled "Effects of heat stress during late gestation on the dam and its calf" at the 2018 Annual Meeting of the American Society of Animal Science held in Vancouver, BC, Canada, 8 to 12 July, with publication sponsored by the *Journal of Animal Science* and the American Society of Animal Science.

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Received October 12, 2018.
Accepted February 10, 2019.

INTRODUCTION

Thermoneutrality is an essential requirement for animals to display their full genetic potential. Environments outside thermoneutral zone disrupt animals' homeostasis, compromising their performance. Thermal stress, particularly heat challenges above a cow's upper critical temperature, compromise dairy cow productivity, reproduction, health, and welfare, leading to economic burdens to dairy producers (St-Pierre et al., 2003; Key et al., 2014). Significant attention has been focused on understanding the direct impact of heat stress on physiology, immune function, and health of lactating dairy cows, and the development of preventive management strategies to alleviate it (West, 2003; Baumgard and Rhoads, 2013). Cows that are in the dry period, the nonlactating period between 2 adjacent lactations, produce less metabolic heat relative to lactating dairy cows (reviewed by Collier et al., 2017) and are thus theoretically less susceptible to heat stress. In studies using environmental chambers, heat-stressed dairy cows in early lactation or midlactation show increases in body temperature ranging from 1.6 to 2.1 °C (4.2% to 5.4%), compared with cows under thermoneutral condition, but pair-fed to match the intake of heat-stressed cows (Rhoads et al., 2009; Wheelock et al., 2010; Baumgard et al., 2011; Lamp et al., 2015). Using a similar experimental model, heat-stressed dry cows have 0.8 °C (2.1%) increase in body temperature compared with pair-fed thermoneutral cows (Lamp et al., 2015). The other widely used experimental model for studying heat stress is to compare the responses of cows provided with evaporative cooling (soakers, misters, and fans) to those that are not. Using this experimental model, lactating dairy cows without evaporative cooling have 0.91 °C (2.3%, 39.94 vs. 39.03 °C, respectively) greater vaginal temperature relative to cows provided with evaporative cooling (Weng et al., 2018). In contrast, when heat-stressed dry cows are deprived of evaporative cooling, their rectal temperatures increase by 0.3 to 0.5 °C (0.7% to 1.3%) relative to cooled herdmates. Even though dry cows have relatively modest physiological responses (e.g., increased body temperature) when exposed to heat stress relative to lactating dairy cows, the consequences of exposure to heat stress during the nonlactating period at the end of gestation are significant. When cooling is not provided during the dry period, the cow has lower milk yield in the subsequent lactation and gives birth to a lighter BW calf, reflecting the negative impacts on productivity of both the dam and her offspring. This review will highlight studies conducted in dairy cattle, illustrating the impact of late-gestation heat stress on the dam and her calf, and discuss potential mechanisms that explain the observed outcomes.

IMPACT OF LATE-GESTATION HEAT STRESS ON DAM PERFORMANCE

The most pronounced effect of late-gestation heat stress on dam's performance is the lower milk yield in the next lactation. In the study conducted by Wolfenson et al. (1988), providing evaporative cooling to dairy cows that are in the dry period increases the subsequent milk yield compared with cows without cooling. This improved lactational performance was associated with improved placental function as measured by increased placental production of estrone sulfate (Collier et al., 1982). Subsequently, many studies were performed to examine the impact of heat stress or evaporative cooling during the entire dry period on the performance of the cow and her calf (Table 1, Fig. 1). Although conducted at different geographic locations, these studies consistently report that providing evaporative cooling during the entire dry period increases the cow's milk yield in the subsequent lactation (Table 1). Results generated from these studies provide strong evidence that heat stress during late-gestation impairs cow productivity.

In heat-stressed lactating dairy cows, reduced DMI is the primary mechanism that explains the decreased milk yield. In early lactation, heat-stressed cows maintain similar milk yield compared with pair-fed cows under thermoneutrality, suggesting that the reduction of DMI by heat stress explains all the decrease in milk yield by heat stress in early lactation (Lamp et al., 2015). In contrast, heat-stressed midlactation cows have a further reduction of milk yield relative to pair-fed thermoneutral cows (Rhoads et al., 2009; Wheelock et al., 2010; Baumgard et al., 2011). These studies established that the decrease in DMI by heat stress in midlactation cows can only explain part (e.g., 50% to 65%) of the reduction of milk yield. Similar to lactating dairy cows, cows in the dry period have reduced DMI when exposed to heat stress. Relative to cooled dry cows, noncooled dry cows have an average of 13.4% (1.5 kg/d) reduction of DMI before calving (Table 1). However, it is not clear if this reduction of prepartum DMI would result in a significant decrease in milk yield observed in the subsequent lactation.

Table 1. Summary of studies on rectal temperature, DMI during the dry period, milk yield in the subsequent lactation, and gestation length of dairy cows that are provided with evaporative cooling (CL) or not (NC) during the dry period

	Rectal temperature, °C			DMI, kg/d			Milk yield, kg/d				Gestation length, d		
Citation	NC	CL	Diff., °C (%)	NC	CL	Diff., kg/d (%)	NC	CL	Length, d	Diff., kg/d (%)	NC	CL	Diff., d (%)
Wolfenson et al. (1988)	39.2	38.8	0.4 (0.9)**	—	—	—	37.2	40.7	150	3.5 (8.6)**	—	—	—
Avendaño-Reyes et al. (2006)	39.3	39.0	0.3 (0.7)**	—	—	—	25.4	28.1	56	2.7 (9.5)	—	—	—
Adin et al. (2009; Exp 1)	38.7	38.4	0.3 (0.8)**	9.1	10.7	1.6 (15)*	38.4	37.1	90	−1.3 (−3.5)	273.0	279.0	6.0 (2.2)
Adin et al. (2009; Exp 2)	38.8	38.5	0.3 (0.8)**	—	—	—	39.3	41.4	90	2.1 (5.1)*	274.0	278.0	4.0 (1.4)*
do Amaral et al. (2009)	39.2	38.8	0.4 (1.0)*	12.0	14.1	2.1 (14.9)**	26.2	33.7	210	7.5 (22.3)*	—	—	—
do Amaral et al. (2011)	39.4	39.0	0.4 (1.0)**	8.4	9.8	1.4 (14.3)	32.2	34.5	140	2.3 (6.7)†	—	—	—
Tao et al. (2011)	39.4	39.0	0.4 (1.0)**	8.9	10.6	1.7 (16.0)*	28.9	33.9	280	5.0 (14.7)*	274.1	277.4	3.3 (1.2)†
Tao et al. (2012a,b)	39.3	39.0	0.4 (0.9)**	10.2	11.4	1.2 (10.4)†	27.7	34.0	294	6.3 (18.5)**	272.0	276.0	4.0 (1.4)*
Tao et al. (2014)	39.0	38.7	0.3 (0.8)*	—	—	—	—	—	—	—	277.0	279.0	2.0 (0.7)
Thompson et al. (2014b)/Monteiro et al. (2014)	39.9	39.4	0.5 (1.3)**	10.4	12.3	1.9 (15.4)**	30.0	33.8	294	3.8 (11.2)†	271.5	275.4	3.9 (1.4)*
Monteiro et al. (2016a)	39.3	39.0	0.3 (0.9)**	—	—	—	—	—	—	—	276.3	276.1	−0.2 (−0.1)
Fabris et al. (2017a)	39.3	38.9	0.4 (1.0)**	9.8	10.6	0.8 (7.5)†	38.2	41.0	63	2.8 (6.8)†	275.2	278.9	3.7 (1.33)**
Average	39.2	38.9	0.4 (0.9)	9.8	11.4	1.5 (13.4)	32.3	35.8	—	3.5 (10.0)	274.1	277.5	3.3 (1.2)

**$P \leq 0.01$; *$P \leq 0.05$; †$P \leq 0.10$.

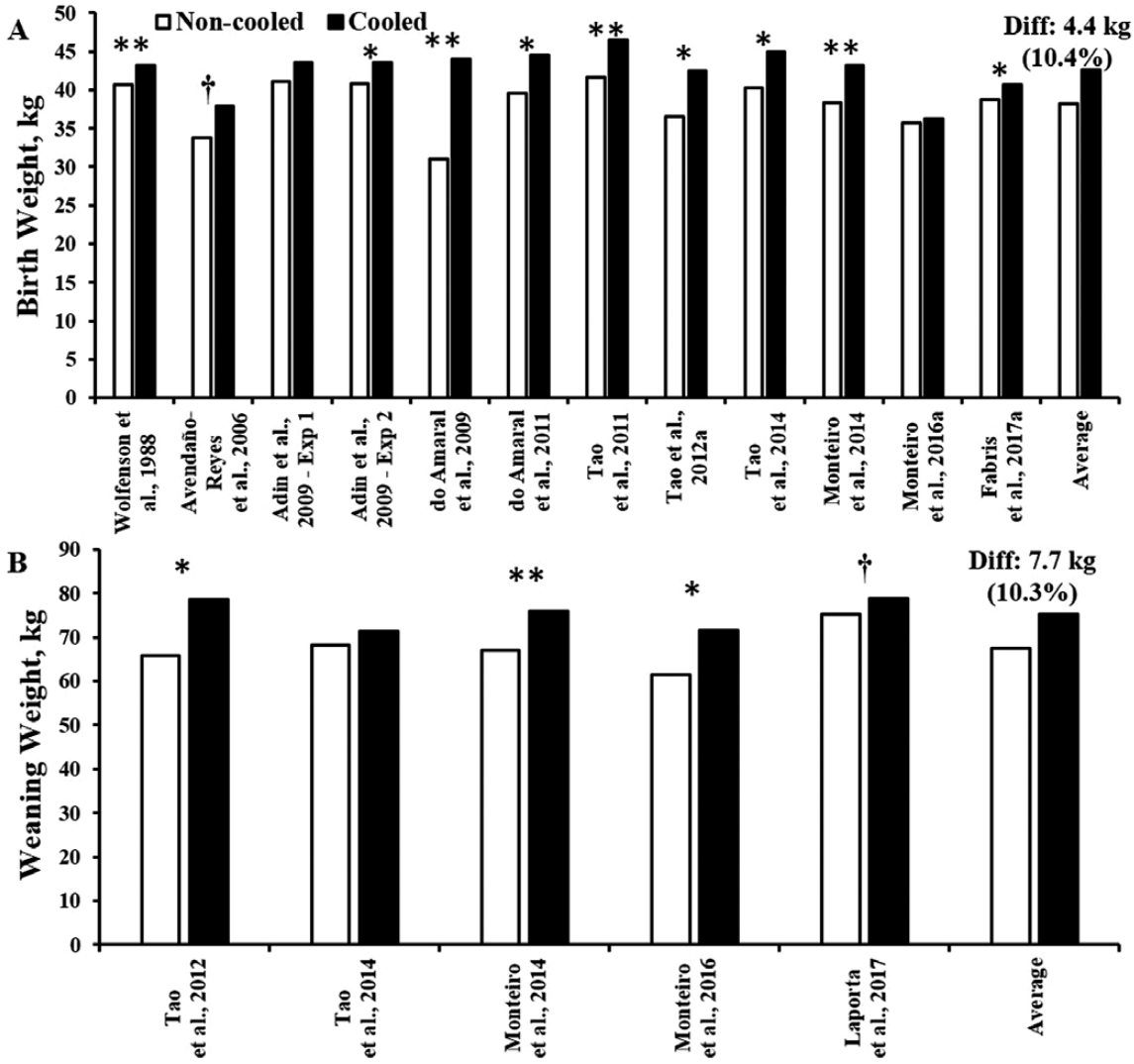

Figure 1. Summary of studies on birth weight (A) and weaning weight (B) of calves born to dairy cows that are provided with evaporative cooling (black bars) or not (open bars) during the dry period. $^{**}P \le 0.01$; $^{*}P \le 0.05$; $^{\dagger}P \le 0.10$.

Despite a reduction of DMI, prepartum heat stress does not have an influence on the glucose/insulin metabolism of dry cows. Deprivation of evaporative cooling during the dry period has no impact on blood concentrations of glucose, NEFA, β-hydroxybutyrate (**BHBA**), and insulin before calving (do Amaral et al., 2009; Tao et al., 2012b). Similarly, compared with pair-fed thermoneutral cows, heat-stressed dry cows have a similar trend of increase in plasma NEFA concentration (Lamp et al., 2015). Lamp et al. (2015) estimated the net carbohydrate and fat oxidation per unit of metabolic BW of dry cows using indirect calorimetry and showed that exposure to heat stress had no impact on either parameter, but the pair-fed thermoneutral dry cows had increased net fat oxidation and reduced net carbohydrate oxidation on a metabolic BW basis. In addition, Tao et al. (2012b) reported that heat-stressed cows without evaporative cooling had similar glucose and insulin responses to both glucose tolerance tests and insulin challenges compared with cows provided with evaporative cooling at 14 d before expected calving. These data indicate that heat stress during late gestation not only has no influence on carbohydrate and fat utilization, but also does not affect the insulin sensitivity of peripheral tissues of the dams. Therefore, it is unlikely that the decreased DMI from heat stress during late gestation is the primary reason for the reduced milk yield in the subsequent lactation.

Compared with prepartum cows under evaporative cooling, noncooled cows maintain a lower milk yield during the entire subsequent lactation (Table 1), suggesting altered mammary gland development before calving. In dairy cows, the dry period is a critical window for mammary gland development to replace senescent cells from the previous lactation with newly synthesized mammary epithelial cells via proliferation (Capuco et al., 1997, 2001). The extent of mammary cell renewal

before calving partially determines milk yield in the subsequent lactation. During the dry period, deprivation of evaporative cooling dramatically reduced mammary epithelial cell proliferation at 20 d before expected calving compared with cooled cows, indicating compromised mammary growth with prepartum heat stress (Tao et al., 2011); this leads to a reduction in milk yield in the subsequent lactation. However, the exact cellular mechanisms that mediate the impaired mammary growth by prepartum heat stress are not entirely understood.

Calf birth weight is positively correlated with the dam's milk yield in the subsequent lactation (Collier et al., 1982; Wolfenson et al., 1988), suggesting a synergy of tissue development between placenta and mammary gland during late gestation (Tao and Dahl, 2013). This synergy is probably mediated by the secretion of placental hormones which act on the mammary gland. In ewes, exposure to heat stress during late gestation decreases plasma concentrations of placental lactogen (Bell et al., 1989), but similar data have not been reported in dairy cattle. Placental lactogen possesses both lactogenic and mammogenic activities (Byatt et al., 1992, 1994; Byatt and Bremel, 1996). During the induced lactation in prepubertal dairy heifers, recombinant bovine placental lactogen exerts mammogenic responses resulting in increased milk yield (Byatt et al., 1994, 1997). However, its importance in mammogenesis of bovine mammary tissue during late gestation is still uncertain (Tao et al., 2018), as is any potential impact of heat stress to alter placental lactogen production in late gestation of dairy cattle. Compared with late-gestation dairy cows provided with shade, nonshaded cows have reduced placental production of estrone sulfate (Collier et al., 1982). Estrone sulfate is an estrogenic compound that serves as a potent mammogenic factor and enhances mammary cell proliferation (Tucker, 2000; Connor et al., 2007). However, the difference in the subsequent milk yield between nonshaded and shaded late-gestation cows did not reach statistical significance (Collier et al., 1982); therefore, the reduced placental production of estrone sulfate with heat stress may not be the only mechanism that mediates impaired mammary growth in late gestation.

Mammary gland development during the dry period can be functionally divided into 2 phases: mammary involution immediately after cessation of milking, and the subsequent mammary growth via cell proliferation until calving. Due to the concurrent pregnancy, mammary involution of dry cows is less extensive compared with cows that are not pregnant, but involves increased mammary autophagic activity (Zarzyńska et al., 2007) and enhanced apoptosis (Wilde et al., 1997; Sorensen et al., 2006). These cellular events during mammary involution have been recognized as primary mechanisms to eliminate or restore senescent mammary cells from previous lactation. However, whether the extent of mammary involution influences subsequent mammary growth is still not clear, and how environmental factors, such as heat stress, affect mammary involution is also not well understood. To examine the influence of heat stress during mammary involution on subsequent milk yield (Fabris et al., 2017b), cows are deprived of evaporative cooling during the first half (mammary involution) or the second half (mammary growth) of the dry period (and then cooled during the other half) or during the entire dry period. Compared with cows cooled during the entire dry period, deprivation of evaporative cooling during the first or second half of dry period or during the entire dry period has equally negative effects on milk yield in the next lactation. These data suggest that heat stress during any stage of the dry period has a negative impact on mammary growth and thus subsequent milk production.

Heat stress enhances the gene expression of heat shock proteins in mammary epithelial cells and mammary tissue (Collier et al., 2006; Orellana et al., 2017) and increases blood prolactin concentrations (do Amaral et al., 2010; Tao et al., 2011), both of which are reported to inhibit apoptosis in mammary cells (Accorsi et al., 2002; Collier et al., 2008). Furthermore, estrogen promotes mammary autophagy (Sobolewska et al., 2009), and heat stress during late gestation is related to reduced plasma concentration of estrone sulfate (Collier et al., 1982). Therefore, it is hypothesized that heat stress blunts mammary involution by inhibiting apoptosis and autophagy. To test this hypothesis, mammary biopsies were collected from dry dairy cows provided with or without evaporative cooling at 3, 7, and 14 d after dry-off. Compared with mammary tissue collected from cooled cows, mammary tissues collected from cows that were not cooled display lower protein expression of microtubule-associated protein light chain 3-I and -II (Wohlgemuth et al., 2016) and lower gene expression of autophagy-related protein 3 and 5 and Beclin 1 (Fabris et al., 2018), suggesting lower autophagic activity. Furthermore, the mammary gland of noncooled cows has reduced gene expression of caspase-3, which may indicate a lower extent of mammary apoptosis (Fabris et al., 2018).

These results partially support the hypothesis that heat stress during the early dry period blunts mammary involution, but the exact cellular mechanisms linking altered mammary involution with subsequent mammary growth and milk yield have not been established.

In addition to the potential influence on mammary apoptosis and autophagy, heat stress during the dry period affects the mammary gland transcriptome. A recent study (Dado-Senn et al., 2018) evaluated the transcriptome of mammary tissues collected from cooled and noncooled dry dairy cows using RNA-seq and revealed that deprivation of evaporative cooling significantly reduced the expression of a long noncoding RNA at 25 d after cessation of milking. This long noncoding RNA encompasses 7 miRNA seed regions that regulate more than 1,000 downstream genes including known markers of involution. Interestingly, the transcriptome analysis also identified upregulated genes involved in inflammation and immune activation in mammary gland of noncooled dry cows, suggesting potential connection between immune regulation and tissue development of the heat-stressed dry cow mammary gland.

Despite increased milk yield, cows that are provided with evaporative cooling during the dry period maintain a similar DMI in early lactation compared with cows without prepartum cooling (do Amaral et al., 2009, 2011; Tao et al., 2011, 2012b). With similar energy intake, prepartum cooled cows employ several metabolic adaptations in early lactation to support the increased energy output due to enhanced milk yield. Cows that are cooled during the dry period have greater plasma concentrations of NEFA and BHBA in early lactation compared with prepartum noncooled cows (do Amaral et al., 2009; Tao et al., 2012b). These data suggest greater adipose mobilization and hepatic ketone production of prepartum cooled cows to provide extra energy substrates in support of greater milk synthesis. Although a normal physiological response to support greater milk production, the increased NEFA and BHBA production in early lactation may pose a risk for the development of ketosis and fatty liver of prepartum cooled cows versus noncooled cows (Thompson et al., 2014a). Due to the greater milk yield, prepartum cooled cows have a greater lactose yield (do Amaral et al., 2009, 2011; Tao et al., 2011, 2012b), resulting in a greater glucose requirement for the mammary gland relative to prepartum noncooled cows. To meet this requirement, prepartum cooled cows alter glucose/insulin metabolism in early lactation as homeorhetic adaptations. Compared with cows without evaporative cooling when dry, prepartum cooled cows have reduced plasma glucose concentrations and tend to have decreased plasma insulin concentrations (Tao et al., 2012b). Tissue insulin action is also altered. Tao et al. (2012b) performed insulin challenges on cows that were cooled or not during the dry period at 7 d after parturition and showed that cows that received cooling during the prepartum period had weaker glucose response, but a similar insulin clearance with insulin challenge. These data, coupled with the lower basal insulin concentration, suggest that prepartum cooled cows have greater insulin resistance in peripheral tissues to shunt more glucose to mammary gland in early lactation relative to prepartum noncooled cows. Therefore, heat stress during the dry period has a profound influence on metabolism of the cow in early lactation, which is secondary to the milk yield response.

It is well understood that immune dysfunction occurs during the transition period and is partially responsible for the increased disease incidence in early lactation. Studies indicate that heat stress during late gestation exaggerates these dysfunctional immune effects during the transition period. Compared with prepartum cooled cows, cows without evaporative cooling have greater blood count of leukocytes but a smaller proportion of CD4+ T lymphocytes (Gomes et al., 2013), and weaker proliferative response and tumor necrosis factor-α production of peripheral blood mononuclear cells when they encounter a mitogen in vitro (do Amaral et al., 2010). In other studies, after challenge with the innocuous antigen ovalbumin, cows without evaporative cooling during the dry period have a weaker immunoglobulin (**Ig**) G production before calving (do Amaral et al., 2011) and in early lactation (Gomes et al., 2013) compared with prepartum cooled cows. Innate immunity is the first line of defense to pathogens and critical for disease resistance. Relative to dairy cows provided with evaporative cooling during the dry period, blood neutrophils of noncooled cows have a lower ability to phagocytize and destroy pathogens in early lactation (do Amaral et al., 2011). Therefore, heat stress during late gestation has negative influences on multiple arms of the immune system during the dry period and early lactation. With the lower immunity, it is expected that late-gestation heat stress would result in a greater disease incidence during early lactation. Indeed, compared with dairy cows dried during the cool season (December, January, and February in Florida), Thompson et al. (2011) reported that cows that were dried off in hot months (June, July,

and August) had greater incidences of mastitis, respiratory problems, and retained fetal membranes in the first 60 d of lactation on a Florida dairy farm. However, in controlled studies, Thompson et al. (2014a) reported that dairy cows that are not provided with evaporative cooling during the dry period have similar incidence of mastitis and survival rate in the first 2 mo of lactation, but a slightly lower incidence of metritis compared with prepartum cooled cows. The reduced metritis incidence is unexpected considering the impaired immunity of prepartum noncooled cows compared with cooled cows, but deserves further investigation.

IMPACT OF LATE-GESTATION HEAT STRESS ON OFFSPRING PERFORMANCE

Late gestation, particularly the dry period of dairy cattle, is not only a critical period for mammary development, but also a time of rapid fetal growth. Heat stress during late gestation has a direct impact on fetal development, which exerts carryover effects on the calf's future performance. It is well recognized that late-gestation cows exposed to heat stress give birth to lighter calves, suggesting fetal growth retardation resulting from maternal heat stress. For example, dairy calves born to cows that are not cooled during the dry period have an average of 10.4% (4.4 kg) lower BW at birth compared with those from cows exposed to evaporative cooling (Fig. 1). This retarded fetal growth by late-gestation heat stress results from multiple mechanisms. Fetal growth during late gestation relies on nutrient delivery through the placenta. When exposed to heat stress, late-gestation ruminants have lower blood concentrations of circulating placental hormones [estrone sulfate (cattle), Collier et al., 1982; placental lactogen (sheep), Bell et al., 1989; pregnancy-specific protein B (cattle), Thompson et al., 2013], reflecting an impairment of placental development. Indeed, the placental weight of ewes or cattle is reduced by exposure to heat stress during late gestation (Collier et al., 1982; Bell et al., 1989). This, coupled with the reduced placental blood flow with heat stress (Dreiling et al., 1991, Reynolds et al., 2006), creates a nutrient restricted environment in utero that limits fetal growth. The ruminant fetus also has increased body temperature when the dam is exposed to heat stress (Laburn et al., 1992, 2002; Faurie et al., 2001). Fetal hyperthermia may alter metabolism of the fetus and influence its development, but the extent to which it could affect overall fetal growth during late gestation is not clear. One consistent effect of heat stress during late pregnancy is a reduction in gestation length. Compared with dry cows provided with evaporative cooling, noncooled heat-stressed cows have approximately 3-d shorter gestation (Table 1). During the last week of gestation, the bovine fetus grows at a rate of 0.4 to 0.6 kg/d (Muller et al., 1975). Therefore, the shorter gestation length with late-gestation heat stress may account for part of the reduction of fetal growth by reducing the total time of fetal development.

Gestational insults also exert carryover effects on the offspring's metabolic responses and development. In ewes, exposure to heat stress during early gestation to midgestation reduces birth weight of newborn lambs compared with thermoneutral controls, but has no impact on growth rate of lambs during their early postnatal life (Chen et al., 2010; Yates et al., 2011). However, lambs that experience maternal heat stress during early pregnancy to midpregnancy had greater insulin secretion to glucose and weaker adipose tissue mobilization to adrenergic stimulation, suggesting altered pancreatic sensitivity and adrenergic physiology (Chen et al., 2010; Yates et al., 2011). In dairy cattle, the impact of maternal heat stress during the dry period on preweaning calf growth rate is inconsistently reported. Monteiro et al. (2014) reported that calves born to cooled or noncooled dry cows had similar ADG during the preweaning period. However, 2 recent studies (Monteiro et al., 2016a; Laporta et al., 2017) reported lower ADG (from birth to weaning) of calves born to noncooled dry cows compared with those born to cooled cows. It is important to note that all 3 studies were conducted at the same location where all calves were fed pasteurized whole milk. The day-to-day and study-to-study variations of nutrient and energy contents of liquid feed may result in inconsistent results among studies. Regardless of the preweaning ADG, studies consistently report an average of 10.3% (7.7 kg) lower BW at weaning of calves born to noncooled dry cows than those from cooled dry cows (Fig. 1). Interestingly, this lower BW of calves due to late-gestation maternal heat stress can persist up to 1 yr of age (Monteiro et al., 2016b).

Maternal heat stress during late gestation may also influence calves' metabolic responses. Monteiro et al. (2016a) performed glucose tolerance tests and insulin challenges on dairy calves born to dry cows provided with evaporative cooling or not during the preweaning period. Relative to calves born to cooled cows, calves from noncooled dry cows have a similar glucose response, but slower insulin clearance after insulin challenges, suggesting a weaker insulin action on muscle and adipose tissue.

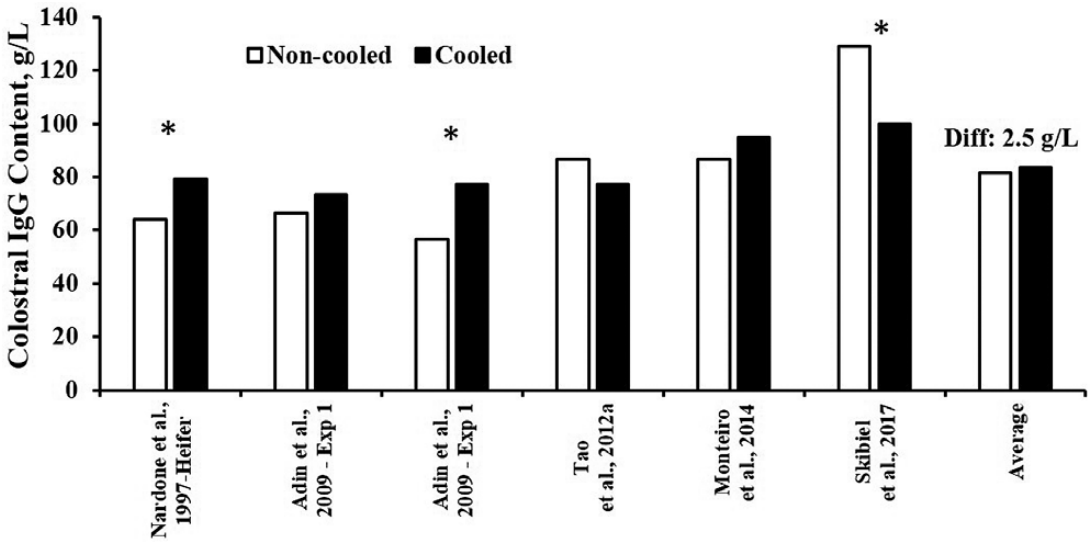

Figure 2. Summary of studies on colostral immunoglobulin G concentration of dairy cows that are provided with evaporative cooling (black bars) or not (open bars) during the dry period. $^{**}P \leq 0.01$; $^{*}P \leq 0.05$; $^{\dagger}P \leq 0.10$.

Interestingly, calves from the noncooled cows displayed a faster glucose clearance but a similar insulin response to glucose tolerance tests, indicating a greater glucose disposal but similar pancreatic sensitivity to glucose compared with those from cooled cows. Because glucose disposal after a glucose tolerance test is dependent on glucose uptake by both insulin dependent (muscle and adipose tissue) and independent tissues, these data may suggest that maternal heat stress during late gestation induces insulin resistance in peripheral tissues, but promotes a stronger glucose uptake through non-insulin-dependent tissues (Monteiro et al., 2016a). Although the cellular mechanisms mediating these observations are still unclear, these results provide preliminary evidence that late-gestation heat stress alters nutrient partitioning of calves in their early life. This could potentially influence the overall body growth and composition of calves during the preweaning period. However, whether the observed metabolic responses of preweaning calves due to late-gestation heat stress persist into maturity is still unknown and deserves further investigation.

Heat stress has profound negative impacts on immune function of lactating (Elvinger et al., 1991; Kamwanja et al., 1994; Lacetera et al., 2006) and transition dairy cows (do Amaral et al., 2010, 2011). It is not surprising then that maternal heat stress during late gestation has negative influences on the offspring's immune status. Successful passive transfer of colostral Ig is critical to neonatal survival and that transfer is negatively influenced by heat stress during late gestation. In 2 independent studies, Tao et al. (2012a) and Laporta et al. (2017) fed fresh colostrum collected from either cooled or noncooled dry cows to their respective newborns and reported that calves born to noncooled cows had lower serum IgG concentration at and after 24 h of birth and lower apparent efficiency of IgG absorption from colostrum compared with calves from cooled dry cows. These data suggest a compromised passive immunity with late-gestation heat stress. Successful passive immunity is partially dependent on the colostral IgG content and newborn's ability to absorb IgG (Quigley and Drewry, 1998). The data assessing impacts of heat stress during late gestation on colostral IgG concentration are inconsistent (Fig. 2). Compared with dairy heifers under thermoneutral condition during the last 3 wk of gestation, heat-stressed heifers produced colostrum containing lower concentration of IgG (Nardone et al., 1997). Similarly, Adin et al. (2009) reported that colostrum collected from dairy cows that were not provided with evaporative cooling during the dry period had lower IgG concentration compared with colostrum collected from cooled dry cows. However, others also report that deprivation of evaporative cooling during the dry period results in either greater (Laporta et al., 2017) or similar (Tao et al., 2012a; Monteiro et al., 2014) IgG content of colostrum compared with that collected from cooled dry cows. Therefore, it seems that the altered colostrum quality (more specifically, IgG content) is not the determining factor causing impaired passive immunity with late-gestation heat stress.

To further investigate the colostral and calf impacts, Monteiro et al. (2014) fed colostrum from the same pooled source to dairy calves born to either cooled or noncooled dry cows during summer, and

collected colostrum from both groups of cows and fed those pools of colostrum to calves that were born during winter. Compared with those from cooled dry cows, calves born to noncooled dry cows have a lower apparent efficiency of IgG absorption when fed the same colostrum; however, the sources of colostrum (from cooled vs. noncooled dry cows) did not affect the IgG absorption in calves born during winter (Monteiro et al., 2014). These data provide further evidence that the impaired passive immunity with late-gestation heat stress is due to compromised ability of the newborn that experienced maternal heat stress to absorb colostral IgG, rather than colostral Ig content. Cellular mechanisms of the reduced IgG absorption of newborns after late-gestation heat stress are not completely clear. Castro-Alonso et al. (2008) proposed that gut closure for IgG transfer in newborn goat kids was partially mediated by cell turnover, for example, apoptosis, of enterocytes and intestinal epithelial cells. To examine the impact of late-gestation maternal heat stress on intestinal apoptosis, bull calves born to either cooled or noncooled dry cows were sacrificed at birth before colostrum feeding, and 1 and 2 d after birth (after colostrum feeding at birth), and jejunal samples were assessed for apoptosis (Ahmed, 2017). Compared with bulls born to cooled dry cows, the jejunum collected from bulls born to noncooled dry cows had greater number of cells undergoing apoptosis, indicating a shift in the rate of gut closure (Ahmed, 2017). These data suggest that maternal heat stress accelerates gut closure of newborn calves through enhanced intestinal apoptosis, which in turn impairs passive immune transfer. It is also proposed that Fc receptor expression on enterocytes play a role in the passive immunity of newborn kids (Mayer et al., 2002). Maternal heat stress during late gestation may also impair the calves' ability to absorb IgG by directly reducing the enterocyte Fc receptor expression; however, direct evidence to support this hypothesis is lacking at present.

Cellular immunity of preweaning calves is also impaired by late-gestation heat stress. For example, peripheral blood mononuclear cells isolated from preweaning calves born to noncooled heat-stressed dry cows have a lower proliferation rate after mitogen stimulation ex vivo compared with those isolated from calves born to cooled dams (Tao et al., 2012a). Similarly, Monteiro et al. (2014) found that calves born to noncooled dry cows had lower whole blood proliferation ex vivo at 42 d after birth compared with those from cooled cows. This impaired cellular immunity may result from the under-developed immune organs by maternal heat stress during late pregnancy. In our preliminary studies, bull calves born to both cooled and noncooled dry cows were sacrificed either at birth, 1 and 2 d after birth (Ahmed et al., 2016) or at 8 d after birth (S.T. and G.E.D., unpublished data, University of Florida, Gainesville) to examine organ development. Consistent across studies, relative to calves from cooled cows, calves born to noncooled cows have a lower thymus weight adjusted for BW. These data suggest that maternal heat stress not only reduces overall fetal growth, but also selectively impairs the development of thymus during late gestation, which may, in turn, result in lower cellular immunity after birth.

In an attempt to quantify the carryover impacts of late-gestation heat stress on health, reproduction, and milk yield of offspring, Monteiro et al. (2016b) analyzed the records of 72 dairy heifers born to late-gestation heat-stressed dry cows that are provided with evaporative cooling or not during the course of 5 yr. After birth, all heifers were individually housed in hutches in a sand bedded barn and managed in an identical manner. Heifers born to noncooled dams had greater morbidity and mortality rates during the preweaning period compared with those born to cooled dams. Although no differences were observed for age at first breeding and calving, heifers born to noncooled cows required more services per pregnancy confirmed at day 30 after insemination. Also, fewer of the calves from noncooled dams completed their first lactation. Furthermore, heifers born to noncooled dry cows produced an average of 5 kg/d less milk throughout the first 35 wk of the first lactation (Monteiro et al., 2016b). This reduced milk yield of offspring by heat stress during late pregnancy is also related to lower alveolar area of mammary gland of lactating heifers (Mejia et al., 2017). Interestingly, a recent study (Laporta et al., 2018) using lactation records from previous experiments conducted during 9 summers at the University of Florida reported that the offspring born to late-gestation noncooled dry cows also produce less energy-corrected milk in their second lactation compared with those from dry cows under evaporative cooling. To further examine the impact of late-gestation heat stress on offspring's productivity, Laporta et al. (2018) evaluated the lactation performance of granddaughters of cooled or noncooled dry cows and showed that the granddaughters of noncooled dry cows produced less energy-corrected milk in their first and second lactation relative to granddaughters from cooled dry cows. Therefore, late gestation has

persistent influences on progeny's future productivity. Epigenetics, such as DNA methylation, may partially explain these long-term transgenerational impacts of heat stress. Skibiel et al. (2018) found that maternal heat stress during the dry period altered the methylation profile of the liver of the calves at birth and the mammary gland during their first lactation. Furthermore, there were 50 common differentially methylated genes between liver and mammary gland tissues that were involved in fundamental processes including cellular repair, oxidative defense, energy metabolism, and development. These epigenetic marks induced by late-gestation heat stress, regardless of animal sex, age, or tissue type, may contribute to the poor performance of the offspring postnatally.

CONCLUSION

Heat stress during late gestation has profound impacts on the productivity, metabolic responses, and health of the cow and her calf. To minimize these negative impacts, heat stress abatement is essential. Providing evaporative cooling to late-gestation dry cows improves milk yield of the cow and her offspring in their future lactations. Ferreira et al. (2016) estimated that the milk yield loss in the subsequent lactation of the dams caused by not cooling dry cows was approximately $800 million in the USA. Considering other positive impacts on offspring survival, health, and future productivity, heat stress abatement during late gestation is a management strategy that improves profitability of dairy producers.

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