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Carry over effects of late-gestational heat stress on dairy cattle progeny

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ABSTRACT

The impacts of late gestation heat stress on the dam and her subsequent lactation are well-recognized. However, more recent research has demonstrated the long-lasting and severe negative consequences on the in-utero heat-stressed progeny. Dairy calves born to late gestation heat-stressed dams weigh less at birth and up to one year of age and have compromised metabolism and immune function. In-utero programming of these offspring may coordinate alterations in thermoregulation, mammary development, and milk synthetic capacity at different developmental windows. Thus, prenatally heat-stressed dairy heifers will produce less milk across multiple lactations and have a lower herd survival rate, potentially negatively impacting the U.S. dairy economy. Dry period heat stress abatement strategies should be considered not only for the productivity and welfare of the pregnant dam but also for the developing calf.

1. Introduction

The negative consequences of environmental heat stress on dairy cattle productivity and welfare are long-lasting and seem to extend over multiple generations. It is well-recognized that direct exposure to heat stress in lactating dairy cows will impair animal health, fertility, and milk production. However, there are negative productive consequences even when cows are exposed to heat-stress during the dry period. This period is a non-lactating state initiated during the last six to eight-weeks of gestation and completed at calving (i.e. the beginning of the next lactation cycle). We have previously shown that cows exposed to heat stress during the dry period have decreased milk production by 3–7.5 kg/d and increased incidences of health disorders in the next lactation [1], compared with cows cooled during the dry period. If cows are not provided heat stress abatement during the dry period, milk production losses could cost the US dairy industry $810 million annually [2].

The dry period coincides with late gestation, an important period for fetal growth and development. Exposure to heat stress through the intrauterine environment can cause negative, long-term productive consequences in dairy heifers through a concept known as in-utero programming. It is proposed that experiences early in development can program structural and functional changes in the fetus that persist to alter adult physiological function and health [3]. This is relevant as recent literature supports the concept that prenatal and early life stressors can greatly impact growth and development of cattle with long-term consequences on health and production [4–6]. Indeed, research from our group and others demonstrates that prenatal heat stress exposure can alter growth and productivity in key developmental windows including fetal development, the preweaning period, and through pregnancy and lactation (Fig. 1). The specific negative outcomes and physiological processes that explain the effects of late gestation heat stress in dairy cattle are the focus of the following sections.

2. In-utero heat stress impacts the progeny

2.1. Impact of late-gestational heat stress on the fetus

A developing fetus cannot control its body temperature independent of the dam, nor can it escape the influence of and changes in the maternal environment [7]. In-utero fetal thermoregulation is constrained to fetal metabolic heat production and dam-offspring heat transfer. Fetal heat exchange with the dam occurs largely through the fetal-placental circulation, accounting for approximately 85% of total fetal heat loss with the remaining exchange through fetal membranes, amniotic fluid, and the uterine wall [7,8].

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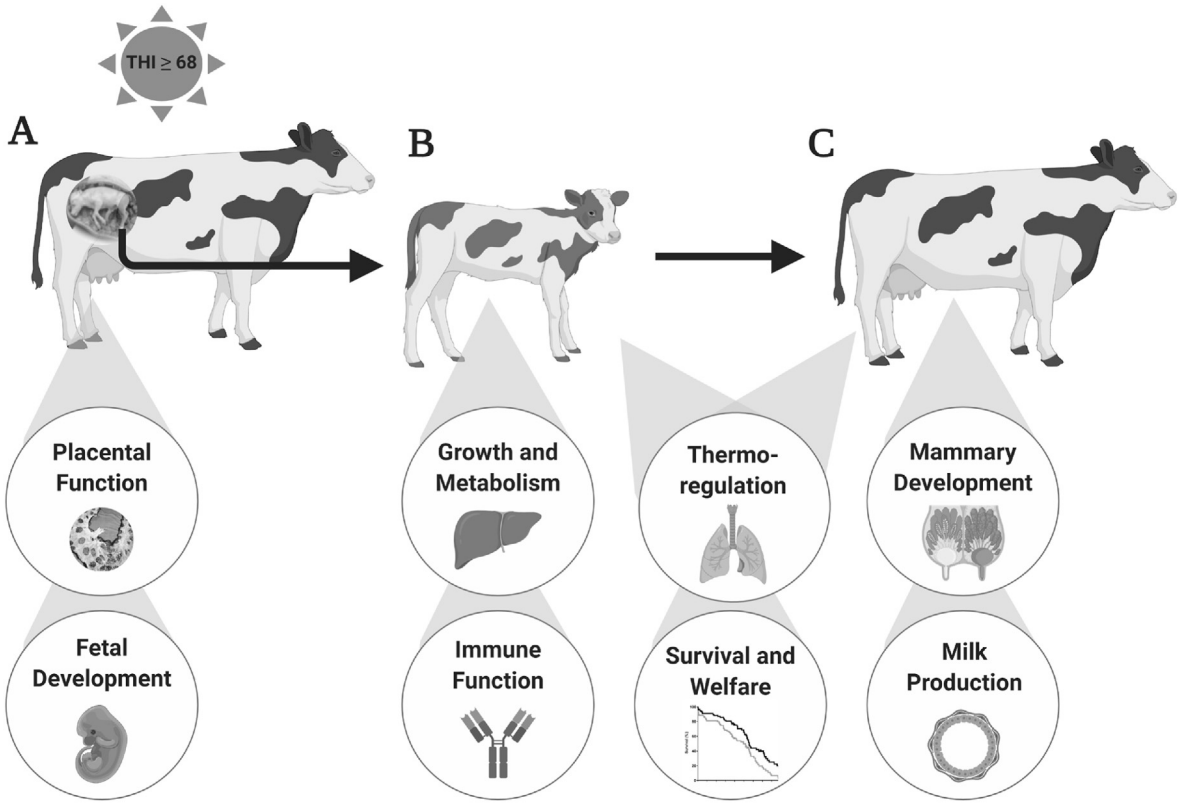

Fig. 1. A summary of the impact of in-utero heat stress on offspring outcomes as a (**A**) developing fetus, (**B**) postnatal calf, and (**C**) mature cow.

Thus, alterations in maternal core temperature can impact fetal temperature. However, the extent to which fetal hyperthermia may alter fetal metabolism and development requires further investigation.

Late gestation heat stress in dairy cattle coincides with a period of rapid fetal growth, where the fetus draws nutrients through the placenta to accrue 60% of its birth weight [9]. Dry period heat-stressed cows have lower blood concentrations of circulating placental hormones such as estrone sulfate and pregnancy-specific protein B reflecting an impairment of placental function [10,11]. Indeed, the placental weight is reduced by exposure to heat stress during late gestation [10]. Additionally, heat stress reduces placental blood flow [12], and a combination of these factors creates a nutrient restricted environment in utero that limits fetal growth.

Beyond alterations to gross placental weight, emerging research from our group has identified specific morphological characteristics of placentae that differed between dry period heat stressed or cooled cows with potential to impact placental function and calf growth [13]. Dams exposed to dry period heat stress had an increased incidence of placental teratomas and a higher cotyledonary weight/placental weight ratio compared with cooled dams, leading to a reduced calf birth weight. In addition, these heat-stressed dams had a higher placental weight, cotyledonary weight, cotyledonary surface area, cotyledonary number, and membrane weight. Discrepancies between studies reporting lighter versus heavier placentae after late gestation heat stress may be attributed to differences in study design, potential compensatory growth to combat reduced blood flow and hypoxia, or the large number of placental abnormalities in the present study, which increased placenta weight but inhibited effective nutrient delivery to the calf [10,13].

2.2. Impact of late-gestational heat stress on the postnatal calf

2.2.1. Calf birth weight and weight gain

Calves exposed to late gestation heat stress are born weighing on average 4.0 kg less (9% reduction) compared with calves born to cows provided heat abatement during the dry period (Table 1). Differences between in-utero heat-stressed and cooled calf birth weights vary from a 0.6 kg (n.s.) to a 13 kg difference ($p < 0.001$) [14,15]. Disparities among studies may be attributed to severity and duration of heat stress during late gestation exposure, slight differences in gestation length, or other unknown physiological discrepancies such as genetic and epigenetic regulation during conception and gestation. However, there is consistency across studies in the observation of a reduced birth weight following in utero heat stress.

Indeed, the reduced birth weight of in-utero heat-stressed calves is attributed to a combination of the direct effect of heat stress on fetal hyperthermia and impaired placental function, previously discussed above, as well as a shorter gestation length. Compared with dry cows provided with evaporative cooling, heat-stressed cows have a reduced gestation length of on average 2 d (Table 1). During the last week of gestation, the bovine fetus grows at a rate of 0.4–0.6 kg/d [16]. Therefore, this shorter gestation length may partially contribute to the reduction of fetal weight by decreasing time for fetal growth. Whereas most literature confirms that dry period heat stress induces a shorter gestation length, a few studies found no difference in gestation length between cattle exposed to heat stress or evaporative cooling [14,17,18]. This discrepancy insinuates that late gestation heat stress might alter

Table 1
Summary of published studies that determine the impact of late gestation heat stress and cooling on progeny gestation length and birth weight.

Period	IUHT[a]	IUCL		IUHT	IUCL		Reference
	Gestation length (d)			Body weight (kg)			
Birth	281	281		36.6	39.7	*	Collier et al. (1982b) [10]
Birth	–	–		40.6	43.2	**	Wolfenson et al. (1988) [47]
Birth	–	–		33.7	37.9		Avendaño-Reyes et al. (2006) [48]
Birth	274	278	*	40.8	43.6	*	Adin et al. (2009) [33]
Birth	–	–		31	44	**	do Amaral et al. (2009) [15]
Birth	–	–		39.5	44.5	*	do Amaral et al. (2011) [49]
Birth	274	277		41.6	46.5	*	Tao et al. (2011) [50]
Birth	272	276	*	–	–		Tao et al. (2012a) [51]
Birth	–	–		36.5	42.5	**	Tao et al. (2012b) [21]
Birth	277	279		40.2	45	*	Tao et al. (2014) [17]
Birth	272	275	*	38.3	43.1	**	Monteiro et al. (2014) [23]
Birth	277	278		40.7	43.4	*	Karimi et al. (2015) [24]
Birth	276	276		35.7	36.3		Monteiro et al. (2016a) [14]
Birth	–	–		39.8	42.6		Guo et al. (2016) [26]
Birth	275	279	**	39	41.9	*	Laporta et al. (2017) [20]
Birth	275	277	*	38.3	42.6	*	Fabris et al. (2019) [52]
Birth	275	276		40.1	42.5	*	Dado-Senn et al. (2020) [18]
Birth Average	**275**	**277**		**38.2**	**42.4**		

* indicates $p < 0.05$; ** indicates $p < 0.01$.
[a] IUHT = in-utero heat stress; IUCL = in-utero cool.

Table 2
Summary of published studies that determine the impact of late gestation heat stress and cooling on progeny weaning and post-weaning weights.

Period		IUHT[a]	IUCL		Reference
	Month	Body weight (kg)			
Weaning	2	65.9	78.9	*	Tao et al. (2012b) [21]
Weaning	2	68.2	71.3		Tao et al. (2014) [17]
Weaning	2	67	76	**	Monteiro et al. (2014) [23]
Weaning	2	61.4	71.7	**	Monteiro et al. (2016a) [14]
Weaning	2	75.3	78.9		Laporta et al. (2017) [20]
Weaning	1.5	68.3	73.6		Skibiel et al. (2017) [19]
Weaning	2	75.0	81.6	*	Dado-Senn et al. (2020) [18]
Weaning Avg		**68.7**	**76.0**		
Post-weaning	3 to 7	146.4	154.6		Tao et al. (2012b) [21]
Post-weaning	3 to 12	200.2	190.9	*	Monteiro et al. (2016b) [22]

* indicates $p < 0.05$; ** indicates $p < 0.01$.
[a] IUHT = in-utero heat stress; IUCL = in-utero cool.

several physiological events that, in combination, lead to a lower calf birth weight.

Late gestation heat stress can cause carry-over effects on progeny growth and development. Research from our group reported lower preweaning ADG of in-utero heat-stressed calves compared with in-utero cooled calves [14,18–20]. Indeed, Dado-Senn et al. (2020) assessed the impact of both prenatal and postnatal heat stress exposure on calf productivity, including ADG, and found that postnatally cooled calves had a greater dry matter intake that did not translate to improved body weight gain. Instead, ADG was driven entirely by prenatal heat stress abatement whereby in-utero heat-stressed calves weighed 2.4 kg less at birth and 6.6 kg less at weaning with a 10% decrease in ADG compared with in-utero cooled calves [18]. These results suggest that in-utero heat stress exerts a strong and persistent influence over calf postnatal body weight gain. Further work must be conducted to determine the mechanisms by which body weight gain persists from birth to weaning; hypotheses include alterations in metabolic pathways through organ developmental differences, endocrine perturbation, or in-utero programming of organs and tissues.

Body weights at more advanced stages of development also differed between in-utero thermal exposure. On average, calves born to late gestation heat-stressed dams weighed 7.3 kg less at weaning compared with calves born to cooled dams (Table 2). There are fewer reports determining the effect of in-utero heat stress on heifer body weight after weaning (Table 2) [21,22]. In a retrospective study by Monteiro et al. (2016b), the impact of in-utero heat stress on heifer body weight persisted through 1 year of age, such that in-utero heat stressed heifers weighed less every month up to 12 months of age relative to in-utero cooled heifers. At the time of calving and through the first lactation, however, there were no differences in body weight between in-utero exposure [22]. Additional investigation is warranted to determine if the reduced body weight gain from birth to the first year of life contributes to the loss in productivity of in-utero heat-stressed dairy cattle.

It is also important to recognize that calf sex may play a role in animal birth weight and growth outcomes, as dairy bull calves are commonly born heavier than heifers. Studies reviewed here often included bulls in birth weight outcomes but did not follow bull calves after birth due to farm management procedures. Further, while some studies report a sex distribution with a higher number of heifer calves [21,23], others did not report the sex distribution for calf outcomes [15,24]. However, a recent study from our group followed both bull and heifer calves after birth with approximate equal distributions per treatment. In-utero heat stressed calves weighed less at birth and weaning with gender included in the statistical model as a covariate [17]. Further examination is warranted to determine if there are sex-dependent outcomes to in-utero heat stress exposure in dairy cattle.

2.2.2. Calf metabolism

Preweaned calf metabolism is also impacted by late gestation heat stress. The influence of prenatal heat stress on feed intake is difficult to ascertain, as reports show either no difference in feed intake between in-utero heat-stressed and cooled calves or a reduction in feed intake for in-utero heat-stressed calves relative to in-utero cooled calves [14,18]. Although feed intake did not differ, Dado-Senn et al. (2020) found that prenatal heat-stressed calves required additional esophageal tube feeding events to meet daily minimum intake requirements, which has obvious welfare, health, and nutritional implications [18,25]. We postulate that in-utero heat stress may program the calf to have an altered metabolism

that could reduce feeding motivation.

There are further implications of late gestation heat stress on the calf metabolic profile. Indeed, calves exposed to in-utero heat stress have lower plasma concentrations of insulin, prolactin, and insulin-like growth factor-I but no change in glucose, non-esterified fatty acid (NEFA), or β-hydroxybutyrate (BHBA) plasma concentrations within 2 h after birth [26]. After colostrum consumption, calves born to heat-stressed dams have greater circulating insulin in the first week of life relative to those born to cooled dams [1]. As the in-utero heat-stressed calf develops postnatally, it shows no difference in basal plasma concentrations of insulin and glucose but higher NEFA and BHBA concentrations after 32 d of age relative to in-utero cooled calves [14].

Further, glucose tolerance tests (**GTT**) and insulin challenges (**IC**) were conducted before and after weaning in calves exposed to late gestation heat stress or cooling [14,17]. In utero heat-stressed calves had a faster glucose clearance after the GTT and a slower decline in insulin concentration after IC; after weaning in-utero heat-stressed calves had faster glucose clearance during GTT and IC. Similar results in the ovine model demonstrate elevated glucose utilization rates, inhibited insulin secretion, and variable glucose stimulated insulin secretion in lambs exposed to in-utero heat stress (i.e. intrauterine growth restricted; IUGR) [27–29]. Enhancement of the whole-body insulin response after in-utero heat stress in dairy calves could be indicative of metabolic adaptations to accumulate energy in peripheral tissues such as adipose and muscle tissues and diminish lean growth [1]. These adaptations may contribute to alterations in and composition of body weight gain up to 1 year of age, accelerating pubertal adiposity with consequences on milk yield and mammary growth [30]. Thus, the adaptive responses of metabolism and ultimately body composition are consistent with lower productivity at maturity.

2.2.3. Calf immune response

Late gestation heat stress negatively impacts the dairy calf immune status, particularly through failed passive transfer of immunoglobulins (**Ig**), a process vital to neonatal survival. Studies from our group demonstrate that in-utero heat-stressed calves fed either fresh dam or frozen pooled colostrum had lower serum IgG concentrations at 24 h after birth and/or lower apparent efficiency of IgG absorption compared with in-utero cooled calves [18,20,21]. Successful passive immune transfer can be attributed to the dam's colostral IgG component and calf's IgG absorption ability component [31]. Whereas previous literature suggests that compromised IgG absorption in the in-utero heat-stressed calf could arise from lower colostrum IgG content [32,33], other work indicates that in-utero heat stress does not impact colostral IgG concentration [18,21,23] or actually leads to an increased colostrum IgG, potentially due to lower colostrum volume [20,34].

Indeed, Monteiro et al. (2014) conducted a crossover study to isolate the impact of late gestation heat stress colostral and calf IgG absorption factors by (1) feeding pooled colostrum from thermoneutral dams to dairy calves exposed to either late gestation heat stress or cooling through the intrauterine environment or (2) feeding colostrum from late gestation heat-stressed or cooled dams to calves born in thermoneutral conditions [23]. Calves born under in-utero heat stress had a lower apparent efficiency of IgG absorption compared with in-utero cooled calves, whereas colostrum sourced from heat-stressed or cooled dams did not affect IgG absorption in thermoneutral calves. These data further support the idea that impaired passive immunity in the calf after late gestation heat stress exposure is caused by impaired IgG absorption. We posit that the reason for this impaired ability for IgG absorption after in-utero heat stress is caused by altered rates of intestinal gut closure. A study by Ahmed et al. (2016) demonstrated that calves born to late gestation heat-stressed dams had an increase in jejunal enterocyte apoptotic rate both before and after colostrum ingestion, indicative of accelerated gut closure and impaired passive immune transfer [35].

Beyond early-life passive immune transfer, late gestation heat stress can impact cell-mediated immunity of the postnatal calf. In-utero heat-stressed calves had lower peripheral blood mononuclear cell proliferation relative to in-utero cooled calves after mitogen stimulation ex vivo that persisted up to 56 d of age [21]. Further, calves exposed to late gestation heat stress had increased whole blood leukocyte proliferation, evidenced by higher neutrophil and lymphocyte percentage at 42 d of age compared with calves exposed to late gestation cooling [23]. Alterations in cell-mediated immunity may be derived from compromised organ development after in-utero heat stress, particularly the thymus [35], but further work is required to characterize immune organ development and altered endocrine signaling after in-utero heat stress exposure.

2.3. Impact of late-gestational heat stress on the lactating cow

2.3.1. Production outcomes

Two retrospective analyses were performed across a 5-year period (2007-2011) and a 10-year period (2008-2018) from studies of the same experimental design conducted at the University of Florida to assess the impact of maternal late gestation heat stress on progeny performance across multiple generations and lactations [22,36]. Animals from these studies were managed identically after birth and cooled upon calving. Heifers born to heat-stressed dams produce less milk across the first 35 weeks in milk in their first (1.3–5.1 kg/d), second (1.9 kg/d) and third lactations (6.7 kg/d) compared with heifers born to cooled dams [22,36,37]. Milk fat, protein, and lactose yields were decreased across lactations for in-utero heat stressed cows. The decrease in milk yield was not associated with lower body weight at calving or through the first lactation or differences in gestation length. Further, when measured, rectal temperatures, respiration rates, and calf birth weights were similar between in utero heat-stressed and cooled heifers [22,37].

2.3.2. Mammary development

It is evident that maternal late gestation heat stress has a long-lasting, permanent effect on the development and function of the progeny's mammary gland, as demonstrated by the lower milk production across multiple lactations of in-utero heat-stressed cows. Impaired mammary development from in-utero heat-stress is coordinated, in part, by alterations in mammary microstructure, cellular processes, and epigenetic regulation [37,38]. Our group first determined whether in-utero heat stress could alter mammary tissue structure and cellular processes in the mammary gland by collecting mammary biopsies from in-utero heat-stressed and cooled primiparous heifers at 21 and 42 days in milk [37]. Histology and immunohistochemistry revealed that in-utero heat-stressed heifers had smaller mammary alveoli comprised of fewer mammary epithelial cells and a lower rate of mammary epithelial cell proliferation relative to in-utero cooled heifers. This is indicative of reduced milk secretory capacity from aberrant mammary development that persists more than two years after the gestational insult.

Beyond cellular structure, gestational heat stress exposure can impact progeny phenotype through epigenetic modifications, particularly related to mammary cell development and milk synthesis gene expression [39]. Further, key metabolic organs such as the liver can be epigenetically regulated and play a role in milk synthesis. Thus, we set to evaluate the epigenetic profiles of first-

lactation mammary tissue and newborn liver from in utero heat-stressed and cooled heifers and bulls, respectively [38]. More than 300 differentially methylated genes were identified, related to functions such as *transcription and translation*, *innate immune defense*, *cell signaling*, *enzyme activation*, *cell proliferation and apoptosis*, and *development*, in line with our histological evidence of reduced mammary function. Additionally, 50 differentially methylated genes were conserved across the heifer mammary tissue and the bull liver tissue, which suggests a similar pattern of heat-stress induced epigenetic regulation of metabolic organs. Although liver tissue was collected from bulls, it is possible that these outcomes could be similar in the liver of heifer calves, leading to epigenetic alterations in organs crucial to lactation with potential impact on production outcomes for multiple lactation cycles and perhaps even multiple generations.

2.4. Impact of late-gestational heat stress on progeny thermoregulation

While the impact of in-utero heat stress on progeny postnatal thermoregulation has been studied in the porcine model [40,41], little literature has addressed this phenomenon in the dairy calf. From birth to 28 d of age, in-utero heat-stressed calves have a higher rectal temperature relative to in-utero cooled calves [20]. We also investigated the impact of similar or opposing postnatal thermal environments on calf thermoregulation. In a study by Dado-Senn et al. (2020), calves born to heat-stressed or cooled dams during late gestation were exposed to heat stress or cooling postnatally for 56 d. Thermoregulatory responses (respiration and heart rate; and rectal, body and skin temperature) were recorded thrice daily in the morning (0700 h), afternoon (1300 h), and evening (1900 h). Whereas thermoregulatory responses were primarily elevated under the sole influence of postnatal heat stress, there were notable prenatal by postnatal interactions (Fig. 2A). For example, in the afternoon, calves exposed to both prenatal and postnatal heat stress had the highest respiration rate, whereas calves prenatally heat-stressed then postnatally cooled had the lowest respiration rate throughout the day [18]. Further, continuously heat-stressed calves had elevated rectal temperatures in the afternoon, congruent with the porcine model [40], and calves exposed to prenatal cooling then postnatal heat stress had the lowest heart rate compared with other treatment groups. These data suggest that in-utero heat stress leads to in-utero programming to prepare the calf for a similar or opposing postnatal environment. Further research is needed to understand how in-utero heat stress might program organ systems to promote thermal homeostasis in the calf after birth.

Interestingly, the interactions between prenatal and postnatal environments were observed in pre-weaned calves were incongruous with a study in dairy cattle whereby heifers exposed to prenatal heat stress were subjected to a heat stress challenge as lactating cows (Fig. 2B) [42]. This study found that cattle exposed to prenatal heat stress and then heat-stressed as mature lactating cows had reduced rectal temperature and sweating rates and elevated skin temperature compared with prenatally cooled heifers under heat stress challenge. The rise in skin temperature suggests greater conductive cooling that would reduce core body temperature and sweating rate. These results support the hypothesis that heat stress in utero in late gestation may improve thermotolerance at maturity by improving heat dissipation capacity to maintain core body temperature, but perhaps at the cost of lactational performance. Discrepancies between Ahmed et al. (2017) and the previous study may be attributed to duration of postnatal heat stress exposure, animal age at the challenge, surface area at postnatal heat stress exposure, or differences in physiological state [42–44].

2.5. Progeny survival

Retrospective analyses previously mentioned demonstrate that heifers born to heat-stressed dams survive for a shorter period of time in the dairy herd [22,36]. The in-utero heat-stress calf stillborn rate was around 4%, but there were no stillborn cases among in-utero cooled calves. There were specific developmental windows in which these in-utero heat-stressed heifers had a reduced chance of survival including before puberty [22], before breeding [36], and after the first lactation [22]. Therefore, abatement of in utero heat stress represents a significant opportunity to improve herd lifespan in dairy cattle.

While reasons for leaving the herd vary, much can be attributed to heifer health, reproduction, and milk production. First, the early life immune challenges experienced by in-utero heat-stressed heifers contribute to immune dysfunction and increased morbidity. As such, the reasons for calf death or euthanasia before weaning include malformation, septicemia, navel infection, pneumonia, and

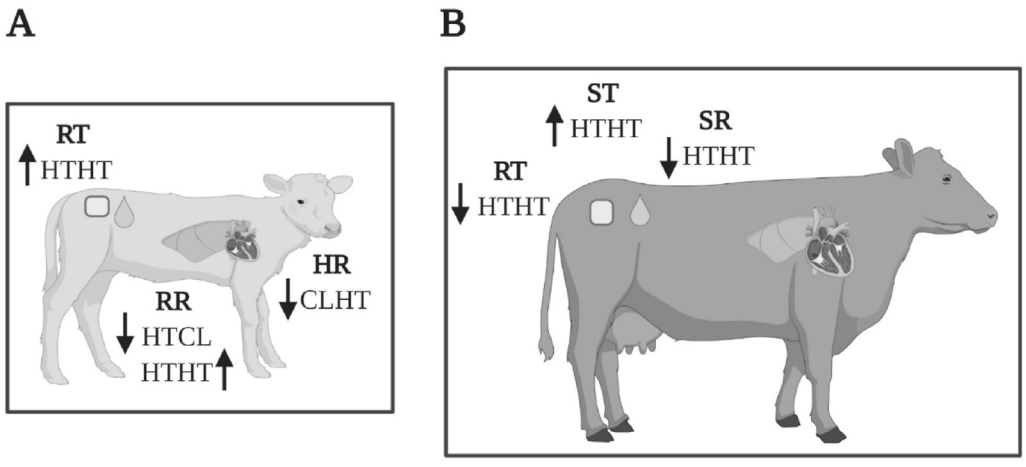

Fig. 2. A summary of the impact of in-utero heat stress on offspring thermoregulatory response of the pre-weaned calf (**A**, Dado-Senn et al., 2020) and mature cow (**B**, Ahmed et al., 2017). (A) Calves exposed to in-utero heat stress then postnatal heat stress (**HTHT**) had a higher rectal temperature (**RT**) and respiration rate (**RR**), while calves exposed to in-utero heat stress but then cooled postnatally (**HTCL**) had the lowest RR. Calves exposed to in-utero cooling then heat stressed postnatally had the lowest heart rate (**HR**). (B) Heifers exposed to in-utero heat stress and then subjected to a heat stress challenge as a lactating cow had a lower RT and sweating rate (**SR**) but a higher skin temperature (**ST**).

growth retardation [22]. Further, the 5-year retrospective analysis found in-utero heat-stressed heifers had a greater number of services per conception and increased age at pregnancy confirmation [22]. Reasons cited for heifers leaving the herd around puberty include genetic culling, growth retardation, mastitis, and infantile ovaries, many of which are indicative of impaired reproductive performance. Finally, although not included in the retrospective analyses, it is logical to postulate that heifers born to heat-stressed dams may be culled earlier from the lactating herd due to a reduction in productive performance.

3. Conclusions

Whereas previous literature has highlighted the impact of late gestation heat stress on the dam's subsequent lactation, more recent data demonstrates long-lasting and severe negative consequences on the in-utero heat-stressed progeny [1,45,46]. Indeed, prenatal heat stress exposure can alter growth and productivity in key developmental windows including fetal development, the preweaning period, and through pregnancy and lactation. Primary adverse outcomes include a reduction in offspring growth, impaired immune function and welfare, and reduced milk production, all of which may be coordinated by developmental programming and epigenetic regulation with potential repercussions across multiple lactations and generations.

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