Impact of Heat Stress on the Cow and Her Progeny

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Abstract

Maternal (F_0) exposure to heat stress during late gestation has profound and lasting effects on her mammary gland regeneration during the dry phase of lactation and on her developing calf (i.e., daughters), influencing its physiology and productivity throughout life. Late-gestation heat stress derails maternal mammary gland regeneration, reducing production capacity in her subsequent lactation. In the short term, heifers subjected to intrauterine hyperthermia exhibit impaired growth and immune function, which may compromise early-life health and development. Long-term consequences extend well beyond early life, as these animals demonstrate reduced survival rates, shorter lifespans, and diminished milk production, all of which have significant economic and welfare implications for the dairy industry. The impact of late-gestation heat stress is not confined to a single generation of F_1 daughters, rather, its effects extend to the granddaughters (F_2), suggesting a multigenerational transmission of compromised phenotypes. This generational inheritance may be driven, in part, by organ-specific macro- and microstructural alterations and epigenetic modifications (i.e., methylation changes) that have been identified in tissues like the mammary gland. Such alterations could disrupt normal mammary development, leading to suboptimal lactational performance, further compounding the adverse effects of intrauterine heat stress. The economic burden of these physiological disruptions in the F_1 progeny has been quantified and it is substantial with annual financial losses in the U.S. dairy industry exceeding $500 million due to decreased productivity and increased culling rates and this does not account for the loss associated with the F_2 generation. Given the scale of these consequences, implementing effective heat abatement strategies for dry-pregnant cows is critical to mitigating the long-term effects of intrauterine hyperthermia and ensuring the sustainability of dairy production in an era of rising global temperatures.

Introduction

Heat stress, defined by prolonged exposure to high ambient temperatures and elevated relative humidity, represents a major challenge to dairy cattle worldwide, including those raised in temperate regions. As global temperatures continue to rise, the negative consequences of heat stress on livestock production and animal welfare are becoming increasingly evident. According to NASA, the five warmest years on record have all occurred since 2016 (NOAA, 2021). This ongoing climatic trend underscores the urgency of implementing strategies to mitigate heat stress to protect dairy cattle from its detrimental effects. While the impact of heat stress on lactating cows has been extensively studied and is widely recognized as

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a major economic and welfare concern (West et al., 2003), the effects on non-lactating members of the herd, including dry-pregnant cows and youngstock, have received significantly less attention in both scientific literature and on-farm management practices. However, emerging research highlights that these groups are also vulnerable to heat stress, with potential long-term consequences for their health, productivity, and overall herd performance. One of the most critical yet underappreciated periods of susceptibility to heat stress occurs during the dry period, a time essential for mammary gland regeneration and the establishment of optimal conditions for the next lactation. During this phase, extensive cellular remodeling takes place in the mammary tissue, allowing for the replacement of old epithelial cells and the development of new secretory cells necessary for peak milk production in the subsequent lactation. However, exposure to heat stress during the dry period disrupts this regenerative process, leading to impaired mammary cell turnover and reduced secretory capacity. As a result, cows that experience heat stress in late gestation often exhibit lower milk yields in the following lactation, with studies indicating persistent production losses even after calving.

The dry period of dairy cows coincides with the final trimester of gestation. This phase is characterized by exponential fetal growth, making the developing fetus highly vulnerable to external environmental insults, including maternal heat stress. Through the intrauterine environment, the fetus is exposed to the physiological consequences of maternal hyperthermia, which can result in long-lasting alterations in their developmental trajectories. Despite increasing scientific evidence highlighting the adverse phenotypic outcomes associated with heat stress in dry-pregnant cows and youngstock (Ouellet et al., 2020; Dado-Senn et al., 2020), these effects remain largely overlooked in both research and industry discussions. This proceedings will explore how environmental heat stress at key developmental stages, particularly during the last trimester of fetal development, can lead to persistent, multi-lactational, and even multigenerational phenotypic consequences. We will present a novel body of research investigating the long-term impacts of chronic intrauterine heat stress exposure on early-life mammary development and ultimately its function of at least three generations (F_0, F_1, and F_2). By integrating findings from multiple disciplines, this work aims to shed light on the far-reaching consequences of heat stress exposure during critical windows of development, emphasizing the need for proactive mitigation strategies to ensure the sustainability and welfare of dairy cattle in a warming world.

Impact of Dry Period Heat Stress on the Cow (F_0)

In lactating dairy cattle, exposure to elevated temperature and humidity induces heat stress, which negatively impacts milk production. However, non-lactating pregnant animals, including dry cows and growing heifers, are also highly susceptible to environmental hyperthermia. Our research has established that heat stress during late gestation in both nulliparous and multiparous dams results in significant reductions in milk yield, with first-lactation heifers producing approximately 3.9 kg/day less milk (Davidson et al., 2021) and multiparous cows experiencing losses of up to 5 kg/day in subsequent lactations (Tao et al., 2011; Figure 1A).

In multiparous cows, hyperthermia experienced during the dry period not only impairs mammary development at the structural level but also disrupts mammary function. Specifically, heat stress during the dry period

alters mammary gland microstructure, leading to reductions in alveolar size, increased stromal connective tissue deposition, and modifications in epithelial cell turnover (Fabris et al., 2020). At the functional level, heat stress affects gene expression and regulatory pathways critical for mammary involution and regeneration, as revealed through transcriptomic analyses (Dado-Senn et al., 2018). These immediate impairments during the dry period are followed by lasting carryover effects into the subsequent lactation, well after the initial insult.

Subsequently, Dado-Senn et al. (2019) sought out to investigate the carry over effects of dry period heat stress on the microstructure of the mammary gland during the subsequent lactation. Specifically, cows exposed to heat stress during the dry period exhibited microstructural alterations in their mammary tissue during the following lactation, including reduced alveolar size and luminal area, changes in epithelial cell composition, and increased stromal connective tissue deposition. These alterations suggest impaired mammary epithelial cell function and reduced secretory capacity. Additionally, there were disruptions in cell turnover, with decreased proliferation and increased apoptosis, further compromising mammary gland efficiency (Dado-Senn et al., 2019). The molecular consequences of this altered development are also profound, with proteomic analysis revealing distinct differences in mammary gland protein expression profiles between heat-stressed and control animals (Skibiel et al., 2022).

Collectively, these findings emphasize the profound and lasting consequences of dry period heat stress on mammary development and function. The structural and molecular alterations in the mammary gland contribute to compromised lactational performance, underscoring the importance of implementing heat abatement strategies during late gestation to safeguard future milk production potential.

Impact of In Utero Heat Stress on the Daughter's (F_1)

Growth and immune function

The dry period in dairy cows aligns with the final trimester of gestation, a critical stage marked by rapid fetal growth. During this time, the developing fetus is particularly susceptible to maternal heat stress and will undergo several physiological and metabolic adaptations to cope with the adverse in utero environment. For example, dairy heifers exposed to intrauterine hyperthermia exhibit lower birth weights (average reduction of 5 kg) and reduced weaning weights (average reduction of 8 kg), indicating early-life growth retardation. Additionally, these calves experience compromised immune development and function, including impaired apparent efficiency of immunoglobulin **(IgG)** absorption (15 to 20% less), reduced circulating IgG levels, and lower lymphocyte counts, which may increase susceptibility to disease (Monteiro et al., 2014). Heifers exposed to in utero heat stress require more veterinary assistance and treatment administration pre-weaning, relative to counterparts gestated under thermoneutrality (Dado-Senn et al., 2020) A more detailed description of the effects of in utero heat stress on immune function across the lifetime of these animals has been reviewed by our group (see Dahl et al., 2017).

Growth deficits extend beyond simply birth body weight, affecting stature (hip height) ,and head circumference all the way to weaning (approximately 2 month of age, Dado-Senn et al., 2021). Interestingly, this growth retardation is not transient, and remains evident until 12 months of age (Monteiro et al., 2016, Davidson et al., under review) further underscoring the developmental delays induced by heat stress. Emerging evidence from our research suggests that intrauterine hyperthermia programs key

organs, tissues, and physiological systems that are critical for future productivity. Notably, mammary gland development is disrupted by in utero hyperthermia, potentially impairing future lactational performance. In a similar manner, immune related organs, such as the thymus and spleen are smaller (Ahmed et al., 2021), and the adrenal glands are enlarged in in utero heat stressed animals compared to those gestated under thermoneutrality (Guadagnin et al., 2024). For a more detailed discussion of the short-term consequences of intrauterine hyperthermia, with an emphasis on immune function and organ development, please refer to comprehensive reviews from our group (Dahl et al., 2017; Dado-Senn et al., 2020).

Calves exposed to in utero hyperthermia experience not only immediate growth deficits but also lasting consequences that extend well into adulthood. Notably, growth retardation (reduced stature and lower body weigh) is not merely a temporary setback; instead, it continues until at least 12 months of age (Monteiro et al., 2016; Davidson et al., under review), highlighting the prolonged developmental delays induced by heat stress and their potential long-term consequences on heifer performance. Yet, the most striking long-term impact is the substantial decline in milk production. Heifers gestated under heat stress produce approximately 4.5 kg/day less milk in their first lactation, a trend first identified in a retrospective study summarizing five years of research at the University of Florida (Monteiro et al., 2016). However, an even more extensive 10-year analysis conducted by our group (Laporta et al., 2020) revealed that the negative effects of late-gestation heat stress extend far beyond first lactation, influencing survivability and productivity across multiple lactations. On average, a dairy cow in the United States born to a heat-stressed dam will have a productive lifespan that is five months shorter and will produce 120 kg/year less milk for three consecutive lactations compared with a cow born to a cooled dam. Additionally, more nulliparous heifers from heat-stressed pregnancies fail to reach their first lactation, and overall lifespan is reduced by approximately 11 months. These findings underscore the profound and lasting consequences of in utero hyperthermia, not only for individual animals but also for herd productivity and farm profitability. A more detailed discussion of these long-term effects can be found in Ouellet et al. (2020) and Cattaneo et al. (2022).

Mammary gland development postnatally: birth to lactation

The development of the mammary gland is highly plastic, shaped by both genetic and environmental factors from fetal life through postnatal growth. Early-life programming, influenced by maternal nutrition and environmental conditions, plays a critical role in establishing the structural and functional capacity of the mammary gland, ultimately impacting future lactational performance. In utero exposures to stressors, such as heat stress or suboptimal nutrition, can induce lasting developmental changes, altering mammary epithelial proliferation, differentiation, and tissue composition. Understanding the interplay between nutrition and environmental plasticity in shaping mammary gland development is essential for optimizing lifetime milk production and improving dairy herd efficiency. Foundational work has demonstrated the significance of nutritional programming on mammary growth during the pre-weaning (Geiger et al., 2016) and pre-pubertal periods (Sejrsen et al., 1982; Meyer et al., 2006) and subsequent milk production potential (Soberon et al., 2012), yet the potential influence of maternal hyperthermia during late gestation on the mammary development of the offspring remains an emerging area of study and will be summarized below.

Research by Dado-Senn et al. (2020) highlights that intrauterine hyperthermia disrupts normal mammary growth trajectories, leading to impaired mammary parenchyma development before weaning. Calves gestated under heat stress exhibit reduced epithelial proliferation and altered cellular composition, which may limit the mammary gland's capacity for milk synthesis later in life. These developmental changes suggest that the mammary gland's ability to fully differentiate and prepare for lactation is compromised before birth, setting the stage for long-term production deficits.

Beyond early-life (pre-weaning) developmental disruptions, in utero heat stress also exerts long-term effects on mammary gland growth and development, particularly during the peripubertal and gestational periods (Davidson et al., under review; Davidson et al., in preparation). Peripubertal mammary glands from heat-stressed heifers exhibit fewer mammary epithelial cells and alveoli, reduced estrogen receptor expression, and lower proliferative capacity compared to their in utero-cooled counterparts (Davidson et al., under review). Similar signs of delayed udder growth and glandular development persist into mid and late gestation (6 and 9 months of pregnancy, data not published; Davidson et al., in preparation), further suggesting that these heifers enter their first lactation with compromised mammary tissue structure and function, predisposing them to reduced milk yield.

These structural and functional deficiencies translate into significant lactational deficits (see Figure 1B). Skibiel et al. (2018) demonstrated that cows exposed to in utero heat stress produce less milk during their first lactation, likely due to the impaired development of the mammary parenchyma. At the microstructural level, mammary tissue from these cows contains fewer and smaller alveoli, as well as a lower abundance of mammary epithelial cells, reducing the gland's overall capacity for milk synthesis. These findings collectively underscore the lasting consequences of in utero heat stress on mammary gland development, affecting both the structure and molecular function of the tissue. The developmental delays observed throughout critical growth windows suggest that prenatal heat exposure programs the mammary gland for suboptimal performance, highlighting the urgency of implementing effective heat abatement strategies for dry-pregnant cows to protect future lactational outcomes.

Impact of In Utero Heat Stress on the Granddaughters (F_2)

Multigenerational (also referred to as intergenerational) effects can occur when a pregnant dam (the maternal generation, F_0) is exposed to a stressor (i.e., any factor that disrupts homeostasis, such as heat stress) that can have direct effects on the developing fetus (F_1) and the germ line of the fetus (that will give rise to the F_2), leading to altered phenotype of the resulting offspring (Figure 2). Yet, a true transgenerational will reveal in the F_3 generation - the first "unexposed transgenerational offspring" (Skinner, 2008). The conjunct analysis of 10 controlled heat stress studies by Laporta et al. (2020) allowed us to follow the records of granddaughters (F_2, born to F_1 daughters of the dam exposed to heat stress). This study revealed negative carryover effects on the F_2's survival and milk production, including reduced survival through puberty and decreased milk yield during their first lactation. However, it remains unknown if these effects are transgenerational in nature as we lack information on the F_3 generation, which would be the first unexposed transgenerational offspring.

Notably, our group (Larsen and Laporta, 2024) has recently reported early-life changes in the microstructure and cellular turnover of the mammary gland in F_2 granddaughters, born to F_1 daughters of dams exposed to heat stress. These changes may partly explain the reduced lactational performance of these offspring at maturity (Laporta et al., 2020; Figure 1C). Specifically, we observed alterations in ductal development, a lower number of proliferating cells, an increased proportion of cells undergoing apoptosis, and reduced expression of estrogen receptors - key factors that regulate mammary growth and proliferation in a developing/growing tissue. Interestingly, these microstructural changes occurred without any evident phenotypic differences at the mammary level, such as teat size, length, or distances between teats. Additionally, there were no apparent differences in feed intake or growth trajectory. This suggests that while the granddaughters of heat-stressed cows may appear phenotypically identical to those born to cooled dams in late gestation, their mammary gland development is significantly altered. These findings reveal that the long-term consequences of heat stress extend beyond visible traits and may affect the organ and tissue development in ways that are not immediately apparent, but could have profound impacts on future milk production.

Summary and Conclusions

Dry period heat stress disrupts the progression of critical cellular processes taking place in the mammary gland, beginning with involution and continuing with redevelopment as cows prepare for parturition. Disruption of these processes ultimately reduces milk synthesis capacity in the subsequent lactation. In addition to direct effects of dry period heat stress on the cow, the adverse effects of intrauterine hyperthermia on fetal development extend beyond early life, leading to lower survival and lifetime productivity of the daughters. Daughters exposed to in utero heat stress produce significantly less milk across multiple lactations, and the reduced survivability and productivity phenotype is further perpetuated across generations. Through germline exposure in the fetal daughter, these effects can extend to the granddaughters, emphasizing the lasting biological and economic consequences of prenatal heat stress. Given the cumulative impact of these developmental disruptions, implementing proactive heat abatement strategies for dry-pregnant cows is essential to safeguard mammary development and ensure the sustainability of future dairy generations.

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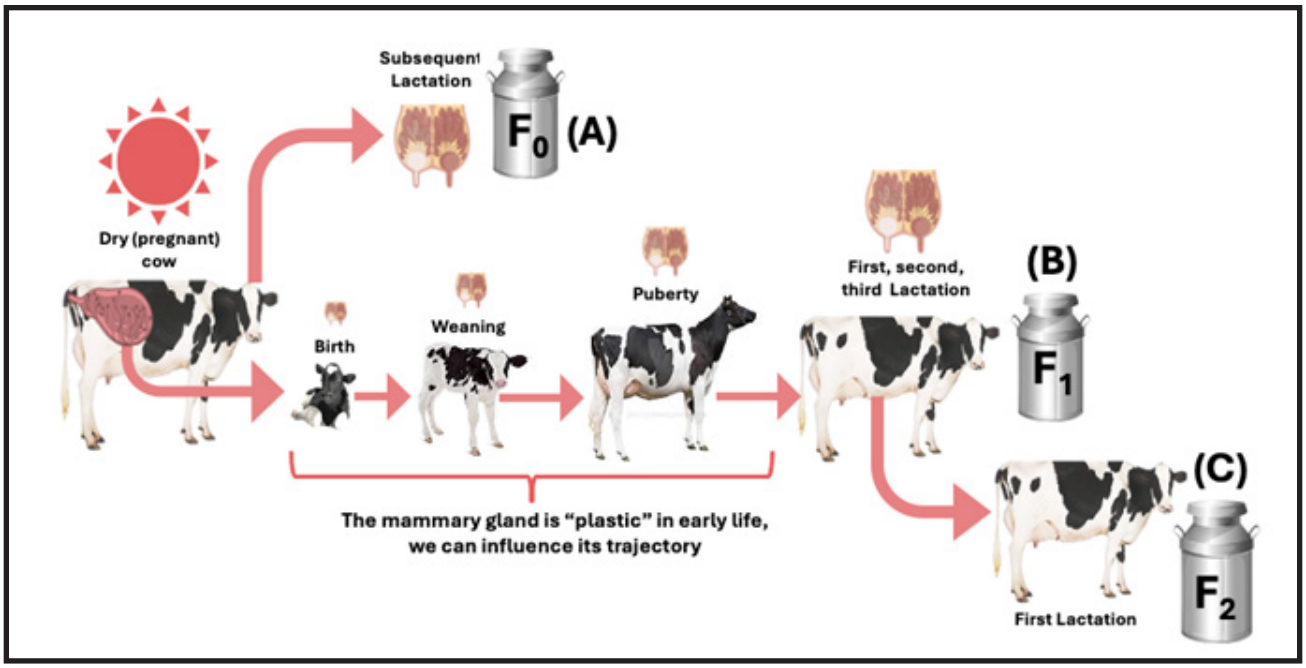

Figure 1. Impact of dry period (late-gestation) heat stress on mammary developmental trajectory of: (A) the dam (F_0, key references: Tao et al., 2011), (B) her Daughter (F_1, key references: Monteiro et al., 2016; Laporta et al., 2020) and (C) her granddaughter (F_2, key references: Laporta et al., 2020; Larsen and Laporta, 2024). Exposure to heat stress during the dry period (6 to 8 weeks prepartum) can derail the developmental progression of the mammary gland of at least three generations of cows.

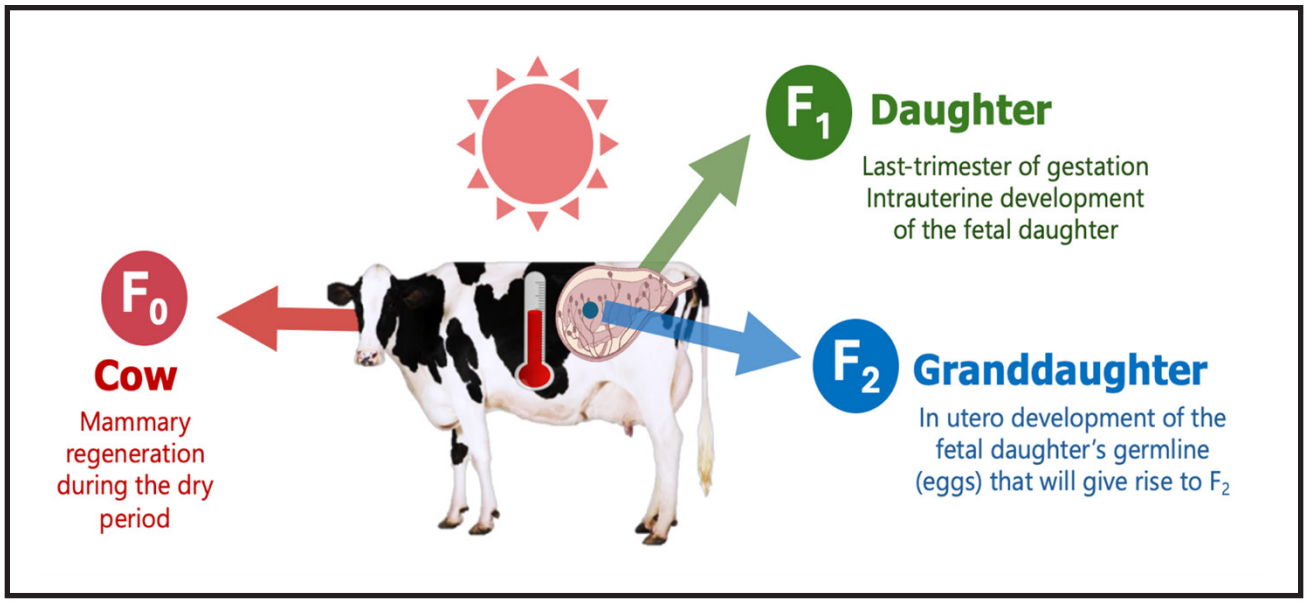

Figure 2. Multigenerational effects of late-gestation heat stress. The dry period of dairy cows (F_0) coincides with a critical window of fetal development during the last trimester of gestation, when the daughters (F_1) are developing in utero. Within these fetal daughters, the female germline that will give rise to the granddaughters (F_2) is also forming. Exposure to heat stress during this sensitive developmental stage can induce lasting physiological and epigenetic changes, potentially impacting all three generations (F_0, F_1, and F_2).