



Review Article

Influence of maternal nutrition and heat stress on bovine oocyte and embryo development

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ABSTRACT

The global population is expected to increase from 7.6 to 9.6 billion people from 2017 to 2050. Increased demand for livestock production and rising global temperatures have made heat stress (HS) a major challenge for the dairy industry. HS been shown to have negative effects on production parameters such as dry matter intake, milk yield, and feed efficiency. In addition to affecting production parameters, HS has also been shown to have negative effects on the reproductive functions of dairy cows. Mitigation of HS effects on dairy cow productivity and fertility necessitate the strategic planning of nutrition, and environmental conditions. The current review will discuss the potential nutriepigenomic strategies to mitigate the effect of HS on bovine embryo.

1. Introduction

The global human population is expected to increase from 7.6 to 9.6 billion people from 2017 to 2050 [1]. In order to meet the nutritional needs of the growing population, there is a critical demand for more efficient livestock production, especially in developing countries [1]. Heat stress (HS) is a major challenge to livestock producers in many countries across the world, especially to those located in desert and tropical climates. As reported by the United States' Environmental Protection Agency (US EPA) [2], the average global temperature is expected to increase by 0.3 °C to 4.8 °C by the year 2100 which may have a negative impact on animal production efficiency if effective heat abatement strategies are not implemented. Together, harsh geographical climates and rising global temperatures make heat stress a critical concern for animal production.

The upper critical limit of the thermo-neutral zone for dairy cattle is approximately 25 °C; thus, dairy cows are at risk of HS when exposed to temperatures above 25 °C [3]. In addition to ambient temperature alone as an indicator of HS, the temperature humidity index (THI), which combines temperature and humidity to create an index score, can also be used to estimate the effect of environmental conditions on dairy cattle [4]. As described by Armstrong [5], THI values can be divided into four categories according to the degree of HS experienced by dairy cows: no HS (≤ 71), mild HS (72–79), moderate HS (80–90), and severe HS (> 90).

2. Heat stress negatively impact animal production

HS has many negative effects on dairy cow welfare and productivity such as increased rate of respiration, sweating, and peripheral blood flow. HS has also been shown to cause decreased dry matter intake which limits nutrient supply to the mammary gland and results in decreased milk yield and overall feed efficiency [6–8]. Additionally, increased THI results in imbalanced cooling ability of the cow, resulting in heat load that negatively affect DMI and milk production [9,10].

In addition to altering production, HS also alters metabolic pathways including those involved in acid-base homeostasis. Elevated respiration rate decreases the level of circulating carbon dioxide (CO₂), which disrupts the blood carbonic acid to bicarbonate equilibrium. As a result, urinary bicarbonate excretion increases and blood pH becomes unstable which can lead to a number of metabolic issues for the dairy cow [11].

3. Heat stress and altered maternal nutrition impair reproduction capacity

In addition to its negative effects on production, HS impairs the reproductive functions of dairy cows [12]. Elevation of maternal body temperature negatively affects several aspects related to reproduction capacity either directly through effects on oocyte quality, success of fertilization, and/or embryo development [13,14] or indirectly by

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limiting nutrient supply to support reproductive function and/or effects on reproductive hormones secretion and level [15–17].

3.1. Impairment of reproductive hormones

The gonadotropin releasing hormone (GnRH) released from hypothalamus that stimulates the release of Gonadotropins; Luteinizing hormone (LH) and Follicle stimulating hormone (FSH); from anterior pituitary gland are main regulators of ovarian functions [12]. Research on the effect of HS on peripheral blood LH is not giving a consistent picture yet, since some studies recorded increase [18], decrease [19,20] and even no effect [21,22] of HS on LH. However, the decreased LH level could be more reasonable, since low LH level could result in decrease estradiol secreted from the dominant follicle, and thus, decrease fertility by poor expression of estrus, poor follicle maturation, and ovarian inactivity [23]. Moreover, steroid production by cultured granulosa and thecal cells was low when cells were obtained from cows exposed to heat stress 20–26 days previously [24]. Implantation failure and early embryonic death resulted from decreased blood progesterone level during HS condition has been reported in dairy cow [25]. Yet, more research is needed to unravel the mechanism by which heat stress alters the levels of circulating reproductive hormones.

3.2. Altering oocyte quality and embryonic development

During hot seasons, cows showed a high incidence of early embryonic mortality due to several reasons. One of these reasons is the direct effect of elevated temperature on follicular development and oocyte competence [26]. In addition, HS negatively affects the super-ovulation response of cows and subsequently recovered embryos number, and quality [27]. A recent study on pigs reported that gilts exposed to HS during the follicular phase showed a clear induction of ovarian autophagy, and that HS increases anti-apoptotic signaling in oocytes and early follicles [28]. Ultrasonography studies revealed that, the size of the first- and second-wave dominant follicles were reduced under HS conditions [29,30]. This affects the development of other follicles and leads to ovulation problems [31]. HS was also correlated with lower steroid concentrations in the follicular fluid obtained from large follicles and reduced granulosa cell viability [32]. Deleterious effect on follicular development and follicular fluid contents directly reflects on the oocyte quality and affects its developmental competence [26,33,34]. On the molecular level, HS seems to alter the maternal RNA stored at the oocyte. This was observed at subsequent developmental stages before embryonic genome activation which can explain the lower quality blastocysts obtained from oocytes collected in hot season than those from oocytes collected in cold season [35]. However, more researches are still needed to elucidate this point. Embryos are highly susceptible to maternal HS during the first early stages of development and this susceptibility reduced as the development proceeds. Exposure of lactating cows to heat stress at day 1 after oestrus (1–2 cell stage embryos), reduced the proportion of embryos that developed to the blastocyst stage at day 8 after oestrus. However, heat stress in later stages had no effect on the proportion of embryos that were blastocysts at day 8 [36].

In vitro studies indicated that exposure of cultured oocytes to physiologically relevant heat shock (41 °C) during the first 12 h of maturation decreases their cleavage rate and blastocyst rate by 30 to 65% [37–39]. Recently, it has been reported that HS during oocyte maturation is associated with reduced cytoplasmic events and apoptosis of the cumulus cells and therefore compromise the survival of the oocyte itself [40]. The mechanisms by which elevated temperature affects oocyte and embryo physiology are not completely understood. However, several studies elucidated this effect from different prospective. Based on the gene expression patterns, it has been reported that HS stimulates the apoptosis signaling pathway in oocyte by upregulation of *BAX* and *ITM2B* (apoptotic genes) [27] and in early stage embryo by

down-regulate genes associated with embryonic survival, such as *CDX2*, a transcription factor involved in the regulation of embryo implantation and placental development [41]. In another studies, expression of growth/differentiation factor-9 (*GDF9*) associated with oocyte maturation was downregulated when oocyte was exposed to HS both *in vivo* [42] and *in vitro* [43]. Furthermore, the apoptotic pathway of Caspases 2, 3, and 7 were upregulated when bovine oocytes were exposed to HS in *in-vitro* model leading to mitochondrial damage and nuclear fragmentation [44]. On the other hand, impaired micro-tubulin and microfilaments, which are involved in nuclear and organelles transport have been reported as consequences of oocyte exposure to HS [45,46]. The sensitivity of these cytoskeletal elements to HS affects other cytoplasmic organelles including mitochondria, essential element for oocyte developmental competence. Differences in mitochondrial distribution and shape have been recorded in oocytes isolated in hot season compared to cold season [47]. Mitochondrial functions are also influenced by HS with low membrane potential in association with apoptotic pathway activation [48].

It is also possible that HS directly affects embryonic development via epigenetic regulation, or indirectly through decrease DMI and alter the metabolic status of the animal [49,50]. Dobbs et al. [51] showed that DNA methylation was low during the early stages of embryonic development but increased between the six-to-eight-cell-stage to the blastocyst stage. Additionally, in rat model, low protein diet altered the *de novo* methylation process in early stage embryo [50]. However, the direct effect of HS on bovine embryo DNA methylation- de-methylation mechanistic is not well established.

3.3. Altering maternal DMI and energy balance

Short term HS has been shown to induce negative energy balance (NEB) [52,53], and even exacerbate the existing NEB by prolonging the period of decreased DMI in highly producing dairy cow [12]. Highly producing dairy cows suffer from NEB which usually occurs after calving due to the disparity between dry matter intake (DMI) and an increase demand for milk production [54]. During HS, cows mobilize adipose reserves which results in elevated non-esterified fatty acids (NEFA) [52,53] that have been shown to decrease oocyte and embryo quality in *in vitro* studies [54–57].

Blood glucose level was reduced during short term (7 days) [52] and long term (during the hot season) exposure to HS [35]. However, in another *in vivo* short term (4 days) study [53] blood glucose was not affected by HS. This could be due to the short term exposure to HS which could not predict well the impact of HS on blood glucose level. Even more, elevated blood NEFA concentration is also associated with decreased glucose concentration in ovarian follicular fluid [43,54,58]. This reduction of glucose level can significantly impact oocyte development because glucose serves as the main energy source and provides the necessary elements for oocyte maturation including pyruvate, ATP, and reducing agents such as NADPH and glutathione that neutralize the reactive oxygen species (ROS) [59]. Therefore, HS can have indirect negative effects on oocyte and subsequent embryonic development via this reduction in available glucose [54]. In addition, increased NEFA concentrations affect the expression of genes involved in lipid metabolism in various tissues, such as the mammary gland [60], oocytes [54], and the embryo itself [61]. The mRNA abundance of DNMT3A (regulating embryonic DNA methylation), IGF2R (growth factor), and SLC2A1 (glucose transporter) were up-regulated in blastocysts resulting from NEFA exposed oocytes [61,62] resulting in an imbalance embryonic DNA methylation [41].

3.4. Altering anti-oxidant capacity

During HS, maternal total plasma anti-oxidant capacity decreased [42]. Additionally, ROS such as hydrogen peroxide, superoxide anion, and hydroxyl radical are elevated when both the bovine oocyte [43]

and bovine embryo [63] exposed to HS *in vitro*, which impairs pre-implantation embryonic development [64]. Nevertheless, maternal HS resulted in early embryonic mortality and poor embryo quality in dairy cow model [13,36]. Additionally, in mice model, maternal HS resulted in early embryonic mortality and decreased the rate of embryo development to morula stage and increase level of embryonic hydrogen peroxide concentration [65]. This impairment could be explained by the fact that early stage embryo cannot synthesis glutathione [65,66]. Furthermore, elevated blood NEFA during HS is associated with reduced embryonic REDOX (intra-cellular oxidation reduction) [62].

On the other side, when embryo development advances (> 8 cells) the embryo acquires resistance to HS [63], this could be explained, in part, by improved oxidative status via a reduction in the level of ROS and an increase in glutathione anti-oxidant activity, and the *de novo* synthesis of embryonic cells glutathione [63,66,67]. On the other part, before activation of embryonic genome, the embryonic cells are fully dependent on maternal transcripts formerly stored in their growing oocytes, thus, impairment of maternal transcripts during HS will be affecting the performance of embryonic cells until EGA (EGA; embryonic genome activation; embryonic genome becomes active and massive embryonic gene expression begins to take place) [21,51,52].

4. Nutritional strategies to improve reproduction during HS conditions

4.1. Dietary cation-anion difference

There is insufficient data on the direct effect of dairy cattle nutrition on bovine embryo quality and development during HS. However, there are several nutritional strategies that may be implemented to mitigate the effect of HS on maternal energy balance and thus, embryo quality and development. One potential dietary modification that may be used to minimize the negative effects of HS on dairy cows is the manipulation of the dietary cation-anion difference (DCAD; mEq/kg of DM) [68,69]. DCAD is an index of the acid-base status of the animal as it is the relative balance between the principle cations (potassium, K; sodium, Na) and the principle anions (chloride, Cl; sulfur, S) in the cow's diet [70]. Studies suggest that DCAD can be used as a strategy to improve feed efficiency (3.5% fat-corrected milk per unit DMI) through altering rumen environment and pH [69,71,72] which could stimulate DMI. Greater DMI could increase the supply of essential nutrients to support embryonic growth and development. Reduced DMI is associated with downregulation of metabolic biomarkers Na⁺/K⁺ ATPase mRNA and sodium/glucose co-transporter1 (SLC5A1) in ewe oocytes [73], that might indicate the role of DCAD in modulating the nutrigenomic mechanism regulating oocyte quality and hence, embryo quality however, the exact nutri-epi-genomic role of DCAD on embryo growth is not yet established.

4.2. Epi-nutrients supplementation

Epi-nutrients are a subset of nutrients such as folate, vitamin B-12, and choline, which are necessary for epigenetic regulation of the genome, through DNA methylation and histone modifications [74,75]. Proper supplementation of such nutrients during HS may play a role in regulating embryonic development; however, the extent to which such epi-nutrients could regulate embryo epigenome during HS is not yet investigated. These nutrients play a role in peri-conceptual DNA methylations which affect embryonic development, subsequent growth, and health status of the offspring [76]. Most epi-nutrients, such as folate, vitamin B-12, methionine, choline, and betaine, can modulate the 1-carbon metabolism pathways responsible for generating the major methyl donor, S-adenosylmethionine (SAM), which can directly affect DNA methylation [77]. Additionally, Folate is involved in *de novo* nucleotide synthesis [78].

During early embryonic development, the epi-nutrients choline and

folate are essential for DNA methylation re-programming [79]. The mRNA of folate–methionine cycle enzymes are expressed in mouse heat stressed pre-implantation embryos, when incubated in folate containing medium [78]. In *in vivo* study, [80] folic acid was supplemented in diet of heat stressed female mice, at the beginning of gestation, and was successfully reduced the heat stress induced neural tube defects.

Vitamin B-12 is required for the function of methionine synthase, an enzyme required for the regeneration of methionine from homocysteine, making it an important participant in one-carbon metabolism [77].

4.3. Long term supplementation of anti-oxidants

As aforementioned HS negatively affects the anti-oxidant scavenging activity of the cow, oocytes and the resulting embryos, therefore anti-oxidant supplementation might play a role in relieving the oxidative action of HS. Short-term supplementation of anti-oxidants like vitamin A, E, and C could not scavenge either the maternal or embryonic ROS developed during HS [81–83]. However, long term effect of these anti-oxidants on the cow and the embryos is not yet investigated. Additionally, long term (90 days) supplementation of β-carotene starting 15 d before calving increased the pregnancy rate by 14 percentage units [84], on the other side, the effect of β-carotene supplementation for long term on bovine embryo still needs to be investigated.

Another potent anti-oxidant is the green tea flavonoid compound epigallocatechin gallate (EGCG) which was previously investigated in mouse embryo model [85]. EGCG exerted an anti-oxidant, and anti-apoptotic action on preimplantation mouse embryos. Further investigations are needed to investigate if EGCG has similar effects on bovine embryos during HS.

4.4. Balancing maternal diet for proper protein metabolism

Since HS increased blood urea nitrogen (BUN) and plasma creatinine by 71% and 13.2%, respectively in heat stressed lactating dairy cows [52,86], indicating alteration in protein metabolism and increase in skeletal muscle protein catabolism [52]. In a recent study by Kaufman *et al.* [87], the reduction of rumen degradable protein (RDP) and rumen un-degradable protein (RUP) levels during hot summer climate was an efficient strategy to increase the use of amino acids to limit protein catabolism in heat stressed dairy cow. However, the extent to which how such an approach can improve bovine gamete and embryo quality is not been yet established, therefore, such area of research of relating amino acid profile balancing to reproduction performance during heat stress needs to be investigated.

5. Other non-nutritional approaches

Other environmental measure could be taken into consideration to alleviate the negative HS effect on reproduction is to provide dairy farms with proper cooling system during hot summer seasons, however, poor areas and small scale farms might not be able to provide such an expensive facilities, therefore, having proper nutritional strategy to alleviate the deteriorating HS effect on animal reproduction and future production is essential.

6. Future perspectives

More in-depth studies using genomic and metabolomic technologies are needed to clearly investigate the genomic and epigenetic mechanism of action of HS on bovine embryonic development. Most of the literature discussing the effect of HS and/ or NEB on bovine embryo are based on *in vitro* embryo and oocyte maturation models; however, the *in vivo* effects are not well understood. Furthermore, the effect of nutrigenomic and nutri-epigenetic diets interaction on bovine embryos and oocytes during HS is a new area that should be considered for

future research.

Another future consideration is proper attention for breeding program, for selection of HS tolerant breeds, instead of only selection for high milk production breeds.

7. Conclusions

The rapidly changing climate, global warming, and the parallel rapidly growing population size, ringing the alarm for critical strategies to manage livestock productivity and reproducibility. As shown in this current review, the effect of HS on maternal nutritional metabolic, and anti-oxidant status is reflected on the oocytes, resulting embryos and the fertility status of the cow. Therefore, long term programming of maternal nutrition is the key factor to mitigate the HS effect on the oocytes and the developing embryos. Additionally, proper nutritional managing of the transition cow to keep the energy balance, could play a positive effect on the oocytes and the resulting embryo, and hence, the future progeny and production.

Competing interests

The authors declare no competing interests.

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References

- Thornton PK. Livestock production: recent trends, future prospects. *Philos Trans R Soc Lond B Biol Sci* 2010;365:2853–67. <http://dx.doi.org/10.1098/rstb.2010.0134>.
- US EPA O. Future of Climate Change n.d.
- Berman A, Folman Y, Kaim M, Mamen M, Herz Z, Wolfenson D, et al. Upper critical temperatures and forced ventilation effects for high-yielding dairy cows in a subtropical climate. *J Dairy Sci* 1985;68:1488–95. [http://dx.doi.org/10.3168/jds.S0022-0302\(85\)80987-5](http://dx.doi.org/10.3168/jds.S0022-0302(85)80987-5).
- Polsky L, von Keyserlingk MAG. Invited review: effects of heat stress on dairy cattle welfare. *J Dairy Sci* 2017;100:8645–57. <http://dx.doi.org/10.3168/jds.2017-12651>.
- Armstrong DV. Heat stress interaction with shade and cooling. *J Dairy Sci* 1994;77:2044–50. [http://dx.doi.org/10.3168/jds.S0022-0302\(94\)77149-6](http://dx.doi.org/10.3168/jds.S0022-0302(94)77149-6).
- Bernabucci U, Lacetera N, Baumgard LH, Rhoads RP, Ronchi B, Nardone A. Metabolic and hormonal acclimation to heat stress in domesticated ruminants. *Animal* 2010;4:1167–83. <http://dx.doi.org/10.1017/S175173111000090X>.
- West JW. Effects of heat-stress on production in dairy cattle. *J Dairy Sci* 2003;86:2131–44. [http://dx.doi.org/10.3168/jds.S0022-0302\(03\)73803-X](http://dx.doi.org/10.3168/jds.S0022-0302(03)73803-X).
- Lough DS, Beede DL, Wilcox CJ. Effects of feed intake and thermal stress on mammary blood flow and other physiological measurements in lactating dairy cows. *J Dairy Sci* 1990;73:325–32. [http://dx.doi.org/10.3168/jds.S0022-0302\(90\)78677-8](http://dx.doi.org/10.3168/jds.S0022-0302(90)78677-8).
- Holter JB, West JW, McGilliard ML. Predicting ad libitum dry matter intake and yield of Holstein cows. *J Dairy Sci* 1997;80:2188–99. [http://dx.doi.org/10.3168/jds.S0022-0302\(97\)76167-8](http://dx.doi.org/10.3168/jds.S0022-0302(97)76167-8).
- Holter JB, West JW, McGilliard ML, Pell AN. Predicting ad libitum dry matter intake and yields of Jersey cows. *J Dairy Sci* 1996;79:912–21. [http://dx.doi.org/10.3168/jds.S0022-0302\(96\)76441-X](http://dx.doi.org/10.3168/jds.S0022-0302(96)76441-X).
- Benjamin MM. Outline of veterinary clinical pathology. Kalyani Pub; 1985.
- De Renzis F, Scaramuzzi RJ. Heat stress and seasonal effects on reproduction in the dairy cow—a review. *Theriogenology* 2003;60:1139–51.
- Putney DJ, Drost M, Thatcher WW. Embryonic development in superovulated dairy cattle exposed to elevated ambient temperatures between days 1 to 7 post insemination. *Theriogenology* 1988;30:195–209.
- Hansen PJ, Drost M, Rivera RM, Paula-Lopes FF, al-Katanani YM, Krininger CE, et al. Adverse impact of heat stress on embryo production: causes and strategies for mitigation. *Theriogenology* 2001;55:91–103.
- De Renzis F, Lopez-Gatius F, García-Ispierto I, Morini G, Scaramuzzi RJ. Causes of declining fertility in dairy cows during the warm season. *Theriogenology* 2017;91:145–53. <http://dx.doi.org/10.1016/j.theriogenology.2016.12.024>.
- Sartori R, Rosa GJM, Wiltbank MC. Ovarian structures and circulating steroids in heifers and lactating cows in summer and lactating and dry cows in winter. *J Dairy Sci* 2002;85:2813–22. [http://dx.doi.org/10.3168/jds.S0022-0302\(02\)74368-3](http://dx.doi.org/10.3168/jds.S0022-0302(02)74368-3).
- Wise ME, Armstrong DV, Huber JT, Hunter R, Wiersma F. Hormonal alterations in the lactating dairy cow in response to thermal stress. *J Dairy Sci* 1988;71:2480–5. [http://dx.doi.org/10.3168/jds.S0022-0302\(88\)79834-3](http://dx.doi.org/10.3168/jds.S0022-0302(88)79834-3).
- Roman-Ponce H, Thatcher WW, Wilcox CJ. Hormonal interrelationships and physiological responses of lactating dairy cows to a shade management system in a subtropical environment. *Theriogenology* 1981;16:139–54.
- Wise ME, Armstrong DV, Huber JT, Hunter R, Wiersma F. Hormonal alterations in the lactating dairy cow in response to thermal stress. *J Dairy Sci* 1988;71:2480–5. [http://dx.doi.org/10.3168/jds.S0022-0302\(88\)79834-3](http://dx.doi.org/10.3168/jds.S0022-0302(88)79834-3).
- Madan ML, Johnson HD. Environmental heat effects on bovine luteinizing hormone. *J Dairy Sci* 1973;56:1420–3. [http://dx.doi.org/10.3168/jds.S0022-0302\(73\)85376-7](http://dx.doi.org/10.3168/jds.S0022-0302(73)85376-7).
- Gauthier D. The influence of season and shade on oestrous behaviour, timing of preovulatory LH surge and the pattern of progesterone secretion in FFPN and Creole heifers in a tropical climate. *Reprod Nutr Dev* 1986;26:767–75.
- Gwazdauskas FC, Thatcher WW, Kiddy CA, Paape MJ, Wilcox CJ. Hormonal patterns during heat stress following PGF(2)alpha-tham salt induced luteal regression in heifers. *Theriogenology* 1981;16:271–85.
- Roman-Ponce H, Thatcher WW, Buffington DE, Wilcox CJ, Van Horn HH. Physiological and production responses of dairy cattle to a shade structure in a subtropical environment. *J Dairy Sci* 1977;60:424–30. [http://dx.doi.org/10.3168/jds.S0022-0302\(77\)83882-4](http://dx.doi.org/10.3168/jds.S0022-0302(77)83882-4).
- Roth Z, Meidan R, Shaham-Albalancy A, Braw-Tal R, Wolfenson D. Delayed effect of heat stress on steroid production in medium-sized and preovulatory bovine follicles. *Reproduction* 2001;121:745–51.
- Khodaei-Motlagh M, Zare Shahneh A, Masoumi R, Derensis F. Alterations in reproductive hormones during heat stress in dairy cattle. *African J Biotechnol* 2011;10:5552–8. <http://dx.doi.org/10.5897/AJB09.033>.
- Al-Katanani YM, Paula-Lopes FF, Hansen PJ. Effect of season and exposure to heat stress on oocyte competence in Holstein cows. *J Dairy Sci* 2002;85:390–6.
- Bényei B, Gáspárdy A, Cseh S. Effect of the El Niño phenomenon on the ovarian responsiveness and embryo production of donor cows. *Acta Vet Hung* 2003;51:209–18. <http://dx.doi.org/10.1556/AVet.51.2003.2.9>.
- Hale BJ, Hager CL, Seibert JT, Selsby JT, Baumgard LH, Keating AF, et al. Heat stress induces autophagy in pig ovaries during follicular development. *Biol Reprod* 2017;97:426–37. <http://dx.doi.org/10.1093/biolre/iox097>.
- Badinga L, Thatcher WW, Diaz T, Drost M, Wolfenson D. Effect of environmental heat stress on follicular development and steroidogenesis in lactating Holstein cows. *Theriogenology* 1993;39:797–810.
- Wilson SJ, Kirby CJ, Koenigsfeld AT, Keisler DH, Lucy MC. Effects of controlled heat stress on ovarian function of dairy cattle. 2. Heifers. *J Dairy Sci* 1998;81:2132–8. [http://dx.doi.org/10.3168/jds.S0022-0302\(98\)75789-3](http://dx.doi.org/10.3168/jds.S0022-0302(98)75789-3).
- Wolfenson D, Roth Z, Meidan R. Impaired reproduction in heat-stressed cattle: basic and applied aspects. *Anim Reprod Sci* 2000;60–61:535–47.
- Roth Z. Heat stress, the follicle, and its enclosed oocyte: mechanisms and potential strategies to improve fertility in dairy cows. *Reprod Domest Anim* 2008;43(Suppl 2):238–44. <http://dx.doi.org/10.1111/j.1439-0531.2008.01168.x>.
- de S Torres-Júnior JR, de F A Pires M, de Sá WF, de M Ferreira A, Viana JHM, Camargo LSA, et al. Effect of maternal heat-stress on follicular growth and oocyte competence in Bos indicus cattle. *Theriogenology* 2008;69:155–66. doi:10.1016/j.theriogenology.2007.06.023.
- Gendelman M, Aroyo A, Yavin S, Roth Z. Seasonal effects on gene expression, cleavage timing, and developmental competence of bovine preimplantation embryos. *Reproduction* 2010;140:73–82. <http://dx.doi.org/10.1530/REP-10-0055>.
- Chambers I, Tomlinson SR. The transcriptional foundation of pluripotency. *Development* 2009;136:2311–22. <http://dx.doi.org/10.1242/dev.024398>.
- Ealy AD, Drost M, Hansen PJ. Developmental changes in embryonic resistance to adverse effects of maternal heat stress in cows. *J Dairy Sci* 1993;76:2899–905. [http://dx.doi.org/10.3168/jds.S0022-0302\(93\)77629-8](http://dx.doi.org/10.3168/jds.S0022-0302(93)77629-8).
- Schrock GE, Saxton AM, Schrick FN, Edwards JL. Early in vitro fertilization improves development of bovine ova heat stressed during in vitro maturation. *J Dairy Sci* 2007;90:4297–303. <http://dx.doi.org/10.3168/jds.2007-0002>.
- Edwards JL, Saxton AM, Lawrence JL, Payton RR, Dunlap JR. Exposure to a physiologically relevant elevated temperature hastens in vitro maturation in bovine oocytes. *J Dairy Sci* 2005;88:4326–33. [http://dx.doi.org/10.3168/jds.S0022-0302\(05\)73119-2](http://dx.doi.org/10.3168/jds.S0022-0302(05)73119-2).
- Lawrence JL, Payton RR, Godkin JD, Saxton AM, Schrick FN, Edwards JL. Retinol improves development of bovine oocytes compromised by heat stress during maturation. *J Dairy Sci* 2004;87:2449–54. [http://dx.doi.org/10.3168/jds.S0022-0302\(04\)73368-8](http://dx.doi.org/10.3168/jds.S0022-0302(04)73368-8).
- Ahmed JA, Nashiruddullah N, Dutta D, Biswas RK, Borah P. Cumulus cell expansion and ultrastructural changes in in vitro matured bovine oocytes under heat stress. *Iran J Vet Res* 2017;18:203–7.
- Silva CF, Sartorelli ES, Castilho ACS, Satrapa RA, Puelker RZ, Razza EM, et al. Effects of heat stress on development, quality and survival of Bos indicus and Bos taurus embryos produced in vitro. *Theriogenology* 2013;79:351–7. <http://dx.doi.org/10.1016/j.theriogenology.2012.10.003>.
- Ferreira RM, Chiaratti MR, Macabelli CH, Rodrigues CA, Ferraz ML, Watanabe YF, et al. The infertility of repeat-breeder cows during summer is associated with decreased mitochondrial DNA and increased expression of mitochondrial and apoptotic genes in oocytes. *Biol Reprod* 2016;94:66. <http://dx.doi.org/10.1095/biolreprod.115.133017>.
- Roth Z. Effect of heat stress on reproduction in dairy cows: insights into the cellular and molecular responses of the oocyte. *Annu Rev Anim Biosci* 2017;5:151–70. <http://dx.doi.org/10.1146/annurev-animal-022516-022849>.

- [44] Roth Z, Hansen PJ. Involvement of apoptosis in disruption of developmental competence of bovine oocytes by heat shock during maturation. *Biol Reprod* 2004;71:1898–906. <http://dx.doi.org/10.1095/biolreprod.104.031690>.
- [45] Ju J-C, Jiang S, Tseng J-K, Parks JE, Yang X. Heat shock reduces developmental competence and alters spindle configuration of bovine oocytes. *Theriogenology* 2005;64:1677–89. <http://dx.doi.org/10.1016/j.theriogenology.2005.03.025>.
- [46] Ju J-C, Tseng J-K. Nuclear and cytoskeletal alterations of in vitro matured porcine oocytes under hyperthermia. *Mol Reprod Dev* 2004;68:125–33. <http://dx.doi.org/10.1002/mrd.20054>.
- [47] Gendelman M, Roth Z. Incorporation of coenzyme Q10 into bovine oocytes improves mitochondrial features and alleviates the effects of summer thermal stress on developmental competence. *Biol Reprod* 2012;87:118. <http://dx.doi.org/10.1095/biolreprod.112.101881>.
- [48] Soto P, Smith LC. BH4 peptide derived from Bcl-xL and Bax-inhibitor peptide suppresses apoptotic mitochondrial changes in heat stressed bovine oocytes. *Mol Reprod Dev* 2009;76:637–46. <http://dx.doi.org/10.1002/mrd.20986>.
- [49] Sinclair KD, Allegrucci C, Singh R, Gardner DS, Sebastian S, Bispham J, et al. DNA methylation, insulin resistance, and blood pressure in offspring determined by maternal periconceptual B vitamin and methionine status. *Proc Natl Acad Sci U S A* 2007;104:19351–6. <http://dx.doi.org/10.1073/pnas.0707258104>.
- [50] Kwong WY, Miller DJ, Ursell E, Wild AE, Wilkins AP, Osmond C, et al. Imprinted gene expression in the rat embryo-fetal axis is altered in response to periconceptual maternal low protein diet. *Reproduction* 2006;132:265–77. <http://dx.doi.org/10.1530/rep.1.01038>.
- [51] Dobbs KB, Rodriguez M, Sudano MJ, Ortega MS, Hansen PJ. Dynamics of DNA Methylation during Early Development of the Preimplantation Bovine Embryo. *PLoS One* 2013;8:e66230. <http://dx.doi.org/10.1371/journal.pone.0066230>.
- [52] Wheelock JB, Rhoads RP, Vanbaale MJ, Sanders SR, Baumgard LH. Effects of heat stress on energetic metabolism in lactating Holstein cows. *J Dairy Sci* 2010;93:644–55. <http://dx.doi.org/10.3168/jds.2009-2295>.
- [53] Garner JB, Douglas M, Williams SRO, Wales WJ, Maret LC, DiGiacomo K, et al. Responses of dairy cows to short-term heat stress in controlled-climate chambers. *Anim Prod Sci* 2017;57:1233. <http://dx.doi.org/10.1071/AN16472>.
- [54] Leroy JLMR, Valckx SDM, Jordaens L, De Bie J, Desmet KLJ, Van Hoeck V, et al. Nutrition and maternal metabolic health in relation to oocyte and embryo quality: critical views on what we learned from the dairy cow model. *Reprod Fertil Dev* 2015;27:693–703. <http://dx.doi.org/10.1071/RD14363>.
- [55] Van Hoeck V, Bols PEJ, Binelli M, Leroy JLMR. Reduced oocyte and embryo quality in response to elevated non-esterified fatty acid concentrations: a possible pathway to subfertility? *Anim Reprod Sci* 2014;149:19–29. <http://dx.doi.org/10.1016/j.anireprosci.2014.07.015>.
- [56] Van Hoeck V, Rizos D, Gutierrez-Adan A, Pintelon I, Jorssen E, Dufort I, et al. Interaction between differential gene expression profile and phenotype in bovine blastocysts originating from oocytes exposed to elevated non-esterified fatty acid concentrations. *Reprod Fertil Dev* 2015;27:372–84. <http://dx.doi.org/10.1071/RD13263>.
- [57] Wathes DC, Fenwick M, Cheng Z, Bourne N, Llewellyn S, Morris DG, et al. Influence of negative energy balance on cyclicity and fertility in the high producing dairy cow. *Theriogenology* 2007;68(Suppl 1):S232–41. <http://dx.doi.org/10.1016/j.theriogenology.2007.04.006>.
- [58] De Bie J, Marei WFA, Maillou V, Jordaens L, Gutierrez-Adan A, Bols PEJ, et al. Differential effects of high and low glucose concentrations during lipolysis-like conditions on bovine in vitro oocyte quality, metabolism and subsequent embryo development. *Reprod Fertil Dev* 2017;29:2284–300. <http://dx.doi.org/10.1071/RD16474>.
- [59] Sutton-McDowall ML, Gilchrist RB, Thompson JG. The pivotal role of glucose metabolism in determining oocyte developmental competence. *Reproduction* 2010;139:685–95. <http://dx.doi.org/10.1530/REP-09-0345>.
- [60] Abdelatty AM, Iwaniuk ME, Garcia M, Moyes KM, Teter BB, Delmonte P, et al. Effect of short-term feed restriction on temporal changes in milk components and mammary lipogenic gene expression in mid-lactation Holstein dairy cows. *J Dairy Sci* 2017;100:4000–13. <http://dx.doi.org/10.3168/jds.2016-11130>.
- [61] Van Hoeck V, Sturmeijer RG, Bermejo-Alvarez P, Rizos D, Gutierrez-Adan A, Leese HJ, et al. Elevated non-esterified fatty acid concentrations during bovine oocyte maturation compromise early embryo physiology. *PLoS One* 2011;6:e23183. <http://dx.doi.org/10.1371/journal.pone.0023183>.
- [62] Desmet KLJ, Van Hoeck V, Gagné D, Fournier E, Thakur A, O'Doherty AM, et al. Exposure of bovine oocytes and embryos to elevated non-esterified fatty acid concentrations: integration of epigenetic and transcriptomic signatures in resultant blastocysts. *BMC Genomics* 2016;17:1004. <http://dx.doi.org/10.1186/s12864-016-3366-y>.
- [63] Sakatani M, Kobayashi S-I, Takahashi M. Effects of heat shock on in vitro development and intracellular oxidative state of bovine preimplantation embryos. *Mol Reprod Dev* 2004;67:77–82. <http://dx.doi.org/10.1002/mrd.20014>.
- [64] Guérin P, El Moutassim S, Ménézo Y. Oxidative stress and protection against reactive oxygen species in the pre-implantation embryo and its surroundings. *Hum Reprod Update* n.d.; 7:175–89.
- [65] Ozawa M, Hirabayashi M, Kanai Y. Developmental competence and oxidative state of mouse zygotes heat-stressed maternally or in vitro. *Reproduction* 2002;124:683–9.
- [66] Gardiner CS, Reed DJ. Synthesis of Glutathione in the Preimplantation Mouse Embryo. *Arch Biochem Biophys* 1995;318:30–6. <http://dx.doi.org/10.1006/abbi.1995.1200>.
- [67] Lim JM, Liou SS, Hansel W. Intracytoplasmic glutathione concentration and the role of beta-mercaptoethanol in preimplantation development of bovine embryos. *Theriogenology* 1996;46:429–39.
- [68] West JW, Haydon KD, Mullinix BG, Sandifer TG. Dietary cation-anion balance and cation source effects on production and acid-base status of heat-stressed cows. *J Dairy Sci* 1992;75:2776–86. [http://dx.doi.org/10.3168/jds.S0022-0302\(92\)78041-2](http://dx.doi.org/10.3168/jds.S0022-0302(92)78041-2).
- [69] Wildman CD, West JW, Bernard JK. Effect of dietary cation-anion difference and dietary crude protein on performance of lactating dairy cows during hot weather. *J Dairy Sci* 2007;90:1842–50. <http://dx.doi.org/10.3168/JDS.2006-546>.
- [70] Erdman R, Iwaniuk M. DCAD: It's not just for dry cows. *Tri-State Dairy Nutr Conf*; 2017.
- [71] Razzaghi A, Aliarabi H, Tabatabaei MM, Saki AA, Valizadeh R, Zamani P. Effect of dietary cation-anion difference during development and postpartum periods on performance, blood and urine minerals status of Holstein Dairy Cow. *Asian-Australasian J Anim Sci* 2012;25:486–95. <http://dx.doi.org/10.5713/ajas.2011.11325>.
- [72] Alfonso-Avila AR, Charbonneau É, Chouinard PY, Tremblay GF, Gervais R. Potassium carbonate as a cation source for early-lactation dairy cows fed high-concentrate diets. *J Dairy Sci* 2017;100:1751–65. <http://dx.doi.org/10.3168/jds.2016-11776>.
- [73] Pisani LF, Antonini S, Pocar P, Ferrari S, Brevini TAL, Rhind SM, et al. Effects of pre-mating nutrition on mRNA levels of developmentally postpartum genes in sheep oocytes and granulosa cells. *Reproduction* 2008;136:303–12. <http://dx.doi.org/10.1530/REP-07-0394>.
- [74] Kussmann M, Van Bladeren PJ. The Extended Nutrigenomics – Understanding the Interplay between the Genomes of Food, Gut Microbes, and Human Host. *Front Genet* 2011;2:21. <http://dx.doi.org/10.3389/fgene.2011.00021>.
- [75] DelCurto H, Wu G, Satterfield MC. Nutrition and reproduction: links to epigenetics and metabolic syndrome in offspring. *Curr Opin Clin Nutr Metab Care* 2013;16:385–91. <http://dx.doi.org/10.1097/MCO.0b013e328361f96d>.
- [76] Sinclair KD, Allegrucci C, Singh R, Gardner DS, Sebastian S, Bispham J, et al. DNA methylation, insulin resistance, and blood pressure in offspring determined by maternal periconceptual B vitamin and methionine status. *Proc Natl Acad Sci U S A* 2007;104:19351–6. <http://dx.doi.org/10.1073/pnas.0707258104>.
- [77] Mazzio EA, Soliman KFA. Epigenetics and nutritional environmental signals. *Integr Comp Biol* 2014;54:21–30. <http://dx.doi.org/10.1093/icb/ucu049>.
- [78] Koyama H, Ikeda S, Sugimoto M, Kume S. Effects of folic acid on the development and oxidative stress of mouse embryos exposed to heat stress. *Reprod Domest Anim* 2012;47:921–7. <http://dx.doi.org/10.1111/j.1439-0531.2012.01992.x>.
- [79] Choi S-W, Friso S. Epigenetics: a new bridge between nutrition and health. *Adv Nutr* 2010;1:8–16. <http://dx.doi.org/10.3945/an.110.1004>.
- [80] Shin JH, Shiota K. Folic acid supplementation of pregnant mice suppresses heat-induced neural tube defects in the offspring. *J Nutr* 1999;129:2070–3.
- [81] Paula-Lopes FF, Al-Katanani YM, Majewski AC, McDowell LR, Hansen PJ. Manipulation of antioxidant status fails to improve fertility of lactating cows or survival of heat-shocked embryos. *J Dairy Sci* 2003;86:2343–51. [http://dx.doi.org/10.3168/jds.S0022-0302\(03\)73827-2](http://dx.doi.org/10.3168/jds.S0022-0302(03)73827-2).
- [82] Ealy AD, Howell JL, Monterroso VH, Aréchiga CF, Hansen PJ. Developmental changes in sensitivity of bovine embryos to heat shock and use of antioxidants as thermoprotectants. *J Anim Sci* 1995;73:1401–7.
- [83] Ealy AD, Aréchiga CF, Bray DR, Risco CA, Hansen PJ. Effectiveness of short-term cooling and vitamin E for alleviation of infertility induced by heat stress in dairy cows. *J Dairy Sci* 1994;77:3601–7. [http://dx.doi.org/10.3168/jds.S0022-0302\(94\)77304-5](http://dx.doi.org/10.3168/jds.S0022-0302(94)77304-5).
- [84] Aréchiga CF, Staples CR, McDowell LR, Hansen PJ. Effects of timed insemination and supplemental beta-carotene on reproduction and milk yield of dairy cows under heat stress. *J Dairy Sci* 1998;81:390–402. [http://dx.doi.org/10.3168/jds.S0022-0302\(98\)75589-4](http://dx.doi.org/10.3168/jds.S0022-0302(98)75589-4).
- [85] Roth Z, Aroyo A, Yavin S, Arav A. The antioxidant epigallocatechin gallate (EGCG) moderates the deleterious effects of maternal hyperthermia on follicle-enclosed oocytes in mice. *Theriogenology* 2008;70:887–97. <http://dx.doi.org/10.1016/j.theriogenology.2008.05.053>.
- [86] Shwartz G, Rhoads ML, VanBaale MJ, Rhoads RP, Baumgard LH. Effects of a supplemental yeast culture on heat-stressed lactating Holstein cows. *J Dairy Sci* 2009;92:935–42. <http://dx.doi.org/10.3168/jds.2008-1496>.
- [87] Kaufman JD, Pohler KG, Mullinix JT, Rius AG. Lowering rumen-degradable and rumen-undegradable protein improved amino acid metabolism and energy utilization in lactating dairy cows exposed to heat stress. *J Dairy Sci* 2018;101:386–95. <http://dx.doi.org/10.3168/jds.2017-13341>.