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Review Article

Selecting Thermotolerant Animals as a Strategy to Improve Fertility in Holstein Cows

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ABSTRACT

The objective of this review is to approach current information on the effects of heat stress on the embryo and cow´s fertility and the selection of heat tolerant animals as a strategy to improve fertility and diminish the deleterious effects of heat stress. Heat stress decreases fertility by diminishing quality of oocytes and embryos through direct and indirect effects. Furthermore cows submitted to heat stress show decreased hormone secretion, reduced folliculogenesis, endometrial alterations and increased secretion of cytokines. These effects are exacerbated in high producing lactating cows due to their intense metabolism. The identification of molecular markers to thermotolerance in high producing lactating cows would allow an improvement in fertility without relinquishing on their milk production. Several single nucleotide polymorphisms (SNPs) have been identified and associated to heat tolerance. These SNPs could be the key to divert from the reduction on fertility and economical losses that the milk industry is suffering due to heat stress.

Keywords: cow, heat stress, reproduction, single nucleotide polymorphisms.

INTRODUCTION

Most high producing dairy cows are subfertile. The reproduction of these animals can be depreciated by health problems (Hernandez *et al.,* 2012), nutrition (Chapinal *et al.,* 2012), heat stress (Hansen, 2009) or a combination of these factors. The association of an intense lactation metabolism and heat stress is at present the largest problem encountered by the dairy industry in Brazil and most of the world. Oocytes of cows exposed to high temperatures lose their competence for fertilization (Gendelman & Roth, 2012a) and development to the blastocyst stage (Gendelman & Roth, 2012b). Furthermore, these cows may exhibit impaired folliculogenesis (Badinga *et al.,* 1993), hormone secretion (Wolfenson *et al.,* 1995; Roth *et al.,* 2000), endometrial function (Malayer *et al.,* 1988) and blood flow to the uterus (Roman-Ponce *et al.,* 1978).

The deleterious effects of heat stress in the embryo are most evident when it is in the early stages of its development (Ealy *et al.,* 1993; Demetrio *et al.,* 2007). However, recent studies (Demetrio *et al.,* 2007; Silva *et al.,* 2012) demonstrated that once subjected to heat stress the embryos chances of developing will be decreased even after post-implantation stages. Embryos that suffered heat-stress up until the 7th day of development, *in vitro* or *in vivo* showed lower pregnancy rates on day 30 and higher rates of embryonic loss on day 42 of gestation.

It is undeniable that the *Bos indicus* (zebu) have greater capacity for thermoregulation than *Bos taurus* (European). However, studies with Holstein cows (*Bos taurus*) have shown that some individuals of the same race can experience heat stress without presenting severe fertility damage (Vasconcelos *et al.,* 2011). This thermal resistance has been attributed to single nucleotide polymorphisms (SNPs) in genes involved in response to heat stress or genes responsible for homeostasis (Basiricò *et al.,* 2011; Li *et al.,* 2011; Liu *et al.,* 2011; Charoensook *et al.,* 2012). It is noteworthy that the daughters of selected high-producing dairy bulls are also more heat sensitive, so the continued selection for milk production can result in high susceptibility to heat stress (Bohmanova *et al.,* 2005). Keeping that in mind, cross-breeding with more specific characteristics determined by quantitative gene studies and polymorphisms (SNP) should be included in selection programs.

Influences of Heat Stress on Reproduction

The reduction in fertility has been documented in a number of mammalian species when females are subsequently exposed to high temperatures. In dairy cows, conception rates in artificial insemination can vary from 55% during the months of low temperatures and humidity, to less than 10% during the months of high temperatures and humidity. The adverse environment causes a reduction in the duration and intensity of estrus, besides increasing the incidence of anestrus and silent ovulation (Badinga *et al.,* 1993; Kadokawa *et al.,* 2012).

High ambient temperatures can lower the LH plasma concentration, which is necessary for the full development of the dominant follicle. Dominant follicles developed in an environment with low levels of LH possibly have their final development and differentiation stage negatively affected (Guzeloglu *et al.,* 2001). The growth and development of ovarian follicles, which can be accurately monitored by ultrasound, are also affected by heat (Badinga *et al.,* 1993). Existing an additive effect of heat stress and higher milk production in decreased conception rates.

The pre-ovulatory follicle is an important component of the reproductive system and the deterioration of this function may affect other reproductive events, such as the secretion of gonadotropins and subsequent development of the corpus luteum and embryo (Guzeloglu *et al.,* 2001). Heat stress affects follicular development by reducing the number of receptors for FSH in the granulosa cells (Shimizu *et al.,* 2005) and by suppressing aromatase activity in these cells, resulting in a low production capacity of estradiol by the follicles (Wolfenson *et al.,* 1997; Shimizu *et al.,* 2005). The dominant follicle of the first follicular wave is smaller in diameter and usually has less follicular fluid in lactating dairy cows under heat stress (Badinga *et al.,* 1993; Guzeloglu *et al.,* 2001).

The follicles that are developing in the ovaries of cows suffering heat stress, even when damaged, continue to grow. Subordinate follicles showed a decrease in size in cows under heat stress during the first follicular wave (Wilson *et al.,* 1998; Roth *et al.,* 2000). Apparently, these damaged follicles ovulate subfertile oocytes for several months after the reduction of thermal stress (Roth *et al.,* 2001; Al-Katanani *et al.,* 2002).

Besides affecting the ovarian follicles, heat stress is also able to affect the corpus luteum causing longer luteal phases. This delay is caused by the reduction of estradiol secretion by the dominant follicle. After stress interruption, cows exhibit luteolysis and the follicles resume their normal development, but oocyte recovery occurs much later (Roth *et al.,* 2002).

The effects of high ambient temperatures on reproductive functions are exacerbated by increased metabolic heat production associated with lactation (Sartori *et al.,* 2002) and the increase in relative humidity (West, 2003). Lactating cows are more susceptible to thermal stress than heifers and an explanation would be the fact that the metabolic heat produced by lactating cows promotes hyperthermia during the summer, while in heifers the metabolic heat production is lower, and they probably don't show hyperthermia at the same environmental temperatures as cows (Wilson *et al.,* 1998). This reduction in the reproductive capacity of dairy cows during the summer is associated with decreased body thermoregulation and genetic selection of these animals for high milk production (Roth, 2008).

In the United States, fertility declined with the increase in milk production from 4500 to 7500 kg / day, decreased conception rates were associated with an increase in demand in milk production postpartum (Butler & Smith, 1989; Huang *et al.,* 2008).

Heat Stress and Embryo Survival

A determining factor for embryonic development is the microenvironment formed in the oviduct and uterus. Disturbances in these environments can lead to changes in cell function and development errors. In lactating dairy cows in which the metabolic demands of lactation exacerbate decreased fertility (Al-Katanani *et al.,*1999) heat stress disrupts embryonic development *in vivo* (Putney *et al.,* 1988; Ealy *et al.,* 1993). There are probably many causes for reduction in embryo survival during stress, such as a reduction in the uterine vasculature and decreased hormonal secretion (Wolfenson *et al.,* 2000). Furthermore, heat stress may act directly on the embryo, compromising its development (Edwards & Hansen, 1997; Sugiyama *et al.,* 2003; Sakatani *et al.,* 2004). The importance of embryonic commitment compared to the environment in which it develops has been demonstrated by a study using reciprocal transfers in sheep (Alliston & Ulberg, 1961). Three days of thermal stress compromised the proper embryo, and to a smaller extent, the capacity of the uterus to maintain embryo development. In contrast, recent studies in mice suggested that maternal stress compromises embryo survival by affecting the oviduct far more than the embryo directly (Ozawa *et al.,* 2002).

Cows under heat stress after insemination exhibit a lower pregnancy rate (Putney *et al.,* 1988; Ealy *et al.,* 1994). The effects of heat stress on the embryos are not apparent until the later stages of development. Fertilized oocytes of sheep and cows, when placed in high temperatures, both *in vitro* and *in vivo*, are impaired; however, continue to develop; only dying during critical stages of implantation (Thatcher *et al.,* 2001). Heat stress is more detrimental to embryo survival when it occurs up to the blastocyst stage (Ealy *et al.,* 1993; Demetrio *et al.,* 2007). It has been demonstrated *in vitro* that the embryos are especially sensitive to high temperatures while at the 2-cell stage, showing an intermediate effect on 4-8 cell embryos, and little or no effect when in the morulae stage (Ealy *et al.,*1995; Edwards & Hansen, 1997; Loureiro *et al.,* 2007). However, when embryos are subjected to high temperatures *in vitro* or *in vivo* until day 7 of development (blastocyst), they show lower pregnancy rates at day 30 (Demetrio *et al.,* 2007; Silva *et al.,* 2012) and higher rates of embryonic loss on day 42 of gestation (Demetrio *et al.,* 2007), evidencing the residual effect of temperature on embryonic and fetal survival.

Compared to most cells, embryos are particularly sensitive to temperature changes. A rise in temperature to 41 ° C for 4.5 hours is sufficient to reduce the proportion of embryos that develop in culture medium (Krininger *et al.,*2002; Hernández-Cerón *et al.,* 2004). Other effects that do not directly affect the embryo however undertake their survival; include reduction in blood flow in the uterus (Roman-Ponce, 1978), compromising the amount of nutrients and hormones being sent to this organ (Howell *et al.,* 1994).

Cows that evolved in warm climates have acquired genes that protect the embryos from high temperatures. Brahman, Nelore and Romosinuano embryos suffer less stress than embryos from Angus and Holstein cows (Paula-Lopes et al. 2003; Hernández-Cerón *et al.,*

2004; Barros *et al.*, 2006). The differences continued after transfers, cows receiving an Angus embryo subjected to temperatures of 41°C had lower pregnancy rates compared to cows that received non-stressed Angus embryos. However, there was no difference in cows receiving stressed or non-stressed Nelore embryos (Silva *et al.,* 2013).

Conflicts exist regarding maternal and paternal genotype in thermotolerance. Studies developed by Block *et al.*, (2002) with embryos on day 4 of development showed that the genotype of the oocyte is the determinant factor for embryonic resistance to heat stress. Embryos produced by insemination of Brahman oocytes with Angus sperm were more thermotolerant than embryos produced from Holstein oocytes and Angus sperm. In contrast, no difference was observed when Holstein oocytes were inseminated with Brahman or Angus sperm. These results may suggest that genes that confer thermotolerance are imprinted on the paternal side, or that embryo thermotolerance depends on some genetic factor produced in the oocyte which remains active in the embryo.

Thermotolerance in Holstein Cows

Body temperature is regulated by modulation of metabolic heat production, and heat loss from the body. The mechanism of evaporation occurs by loss of water by respiration and by evaporation of water through the sweat glands. The heat stress tolerance depends on the maximum and minimum temperatures that define the thermal comfort of the animal. The maximum temperature for dairy cows is 25 to 28.4 ° C, above this the animal's body temperature begins to rise (Berman *et al.,* 1985; Dikmen & Hansen, 2009).

The effect of the characteristics of the fur in the adaptation to hot weather has been examined (Olson *et al.,* 2003; Berman, 2004). It is generally accepted that the dark fur shows greater absorption and reduced reflection of thermal radiation, resulting in greater heat stress for animals. However, it has been demonstrated that light fur shows greater penetration of solar radiation than dark (Cena & Monteith, 1975); Hutchinson & Brown, 1969; Da Silva *et al.,* 2012). However, the thickness, density, and length are important determinants of the heat loss from the body surface (Bennett, 1964). The *slick hair* gene transmits to the animal the characteristic of short and fine hair; it was introduced in Holstein cows and improved their heat tolerance (Olson & Lucena 2003; Dikmen *et al.,* 2008). Furthermore, cows with the slick hair phenotype have higher sweating rates, lower respiration rates and can sustain a better milk yield when calving during summer (Dikmen *et al.,* 2014).

The ability of the animal to maintain its temperature may influence the rates of pregnancy and pregnancy maintenance (Vasconcelos *et al.,* 2006) and this ability can be observed even in animals of high milk production. In a recent study, Vasconcelos and colleagues (2011), showed that Holstein cows with high milk production (> 35 kg / day) who managed to maintain rectal temperature below 39 ° C showed pregnancy rates, after embryo transfers, as good as the animals with lower milk production (<35 kg / day). This characteristic of thermotolerance has a moderate heritability in Holstein cows and is related to milk production in days, fat and protein in milk, and profit (Seath & Miller 1947; Dikmen *et al.,* 2012).

Some studies have shown the relationship between genetic polymorphisms and response to heat stress in dairy cows (Chrenek *et al.,* 2003). During stress, heat stress proteins (HSP) are activated, which are linked to heat stress factors (HSF) in the cytosol. When dissociated, HSPs are free to bind to proteins denatured by heat.

Polymorphisms in HSP promoters and quantitative changes in expression of HSP70 have been correlated to changes in thermotolerance in fish, insects and cell bloodlines, to differences of environmental adaptation in plants and animals, and disease susceptibility or resistance in humans. Substitutions, insertions or deletion of amino acids may modulate the promoter region and transcription (Deguchi & Kishimoto, 1990; Dhillon & McCallum, 1993; Shimizu *et al.,* 1996; Favatier *et al.,* 1997). A functional test in mononuclear blood cells of individuals with both HSP70-2 genotypes showed that individuals with the polymorphism had lower expression of HSP70-2 (Lyashko *et al.,* 1994). The presence of polymorphisms (C / -

and G / T) in the 5 'region of the HSP70.1 gene improves response and tolerance to heat stress in mononuclear cells of Holstein cows (Basiricò *et al.,* 2011b). A polymorphism in the 5 'region of the HSP70 gene was associated with apoptosis in lymphocytes. The expression of BCL2 and HSP70 were significantly increased in cows with polymorphism, as well as the percentage of apoptosis (Cai *et al.,* 2005).

Holstein heifers with a polymorphism within the intron 3 HSP90AB1 gene had an improvement in thermotolerance (Charoensook *et al.,* 2012). Two polymorphisms were identified in the HSF1 gene of Holstein cows and an association study showed better thermal tolerance in these animals (Li *et al.,* 2011). Holstein cows with polymorphisms in the ATP1A1 gene, which encodes for the Na, K-ATPase, responsible for maintaining the electrolyte balance of Na and K, also showed higher thermotolerance (Liu *et al.,* 2011). Mice mutants for type 1 calsequestrin gene (CASQ1), Ca2 binding protein; presented sudden death caused by exposure to high temperatures (Dainese *et al.,* 2009; Protasi *et al.,* 2011).

A recently published genome-wide association study in lactating Holstein cows performed during heat stress identified several SNP variations in candidate genes for regulation of rectal temperature. Those genes included SLC01C1, which regulates metabolic rates and controls body temperature and other genes important for maintaining cellular function during heat stress (Dikmen *et al.,* 2013).

With the discovery of these molecular markers for thermotolerance it will be possible to disseminate this phenotype without having to cede on milk production or fertility. Thermotolerant animals present better quality oocytes, better pregnancy rates, need fewer artificial inseminations per pregnancy; therefore require fewer bulls in the farm and consequently give greater profit. The investigation of this genotype is possible in young heifers or in embryos through biopsy. A polymerase chain reaction assay can be custom-made with specific SNP generating a cheap and fast way to identify the animals.

CONCLUSION

This review shows that with genome wide knowledge and the discovery of SNPs associated with thermotolerance in concert with important reproductive traits it is possible to hasten the selection of Holstein cows that have good fertility rates withal are high milk producers. These could prove useful especially for Holstein cows raised in tropical and subtropical regions.

REFERENCE

Al-Katanani, Y.M., D.W.Webb, and P.J. Hansen. 1999. Factors affecting seasonal variation in 90-day nonreturn rate to first service in lactating Holstein cows in a hot climate. *J. Dairy Sci*. 82: 2611–2616.

Al-Katanani, Y.M., R.M.Rivera, and P.J. Hansen. 2002. Seasonal variation in development of *in vitro* produced bovine embryos. *The Veterinary Record*. 150: 486–487.

Alliston, C., and L. Ulberg. 1961. Early Pregnancy Loss in Sheep at Ambient Temperatures of 70 ° and 90 ° F. as Determined by Embryo Transfer. *J. of Animal Sci*. 20: 608–613.

Badinga, L., W.W. Thatcher, T. Diaz, M. Drost, and D. Wolfenson. 1993. Effect of environmental heat stress on follicular development and steroidogenesis in lactating Holstein cows. *Theriogenology.* 39(4): 797–810.

Barros, C.M., M.F. Pegorer, J.L.M. Vasconcelos, B.G. Eberhardt, and F.M. Monteiro. 2006. Importance of sperm genotype (indicus versus taurus) for fertility and embryonic development at elevated temperatures. *Theriogenology*. 65: 210–218.

Basiricò, L., P. Morera, V. Primi, N. Lacetera, A. Nardone, and U. Bernabucci. 2011. Cellular thermotolerance is associated with heat shock protein 70.1 genetic polymorphisms in Holstein lactating cows. *Cell Stress and Chaperones*. 16(4): 441–448.

Bennett, J. 1964. Thermal insulation of cattle coats. *Proceedings of the Australian Society Animal*. 5: 160–166.

Berman, A., Y. Folman, M. Kaim, M. Mamen, Z. Herz, D. Wolfenson, Y. Graber. 1985. Upper Critical Temperatures and Forced Ventilation Effects for High-Yielding Dairy Cows in a

Subtropical Climate. *J. Dairy Sci*. 68(6): 1488–1495.

Berman, A. 2004. Tissue and External Insulation Estimates and Their Effects on Prediction of Energy Requirements and of Heat Stress. *J. Dairy Sci*. 87(5): 1400–1412.

Block, J., C.C. Chase, and P.J. Hansen. 2002. Inheritance of resistance of bovine preimplantation embryos to heat shock: Relative importance of the maternal versus paternal contribution. *Molecular Reproduction and Development*. 63: 32–37.

Bohmanova, J., I. Misztal, and S. Tsuruta. 2005. National genetic evaluation of milk yield for heat tolerance of United States Holsteins. *Interbull Bull*. 33: 160–162.

Butler, W.R., and R.D. Smith. 1989. Interrelationships between energy balance and postpartum reproductive function in dairy cattle. *J. Dairy Sci*. 72(3): 767–783.

Cai, Y., Q. Liu, G. Xing, and L. Zhou. 2005. Polymorphism of the promoter region of Hsp70 gene and its relationship with the expression of HSP70mRNA, HSF1mRNA, Bcl-2mRNA and Bax-αmRNA in lymphocytes in peripheral blood of heat shocked dairy cows. *Asian-Aust. J. Anim*. 18(5): 734–740.

Cena, K., and J.L. Monteith. 1975. Transfer processes in animal coats. I. Radiative transfer. Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character. *Royal Society (Great Britain)*. 188: 377–393.

Chapinal, N., S.J. Leblanc, M.E. Carson, K.E. Leslie, S. Godden, M. Capel, T.F. Duffield. 2012. Herd-level association of serum metabolites in the transition period with disease, milk production, and early lactation reproductive performance. *J. Dairy Sci.* 95(10): 5676–5682.

Charoensook, R., K. Gatphayak, A.R. Sharifi, C. Chaisongkram, B. Brenig, and C. Knorr. 2012. Polymorphisms in the bovine HSP90AB1 gene are associated with heat tolerance in Thai indigenous cattle. *Tropical Animal Health and Production*. 44(4): 921–928.

Chrenek, P., J. Huba, D. Vasicek, D. Peskovicová, and J. Bulla. 2003. The Relation between Genetic Polymorphism Markers and Milk Yield in Brown Swiss Cattle Imported to Slovakia. *Asian-Aust. J. Anim. Sci*. 16(10): 1397–1401.

Dainese, M., M. Quarta, A.D. Lyfenko, C. Paolini, M. Canato, C. Reggiani, F. Protasi. 2009. Anesthetic- and heat-induced sudden death in calsequestrin-1-knockout mice. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*. 23(6): 1710–1720.

Deguchi, Y., and S. Kishimoto. 1990. Enhanced expression of the heat shock protein gene in peripheral blood mononuclear cells of patients with active systemic lupus erythematosus. *Annals of the Rheumatic Diseases*. 49: 893–895.

Demetrio, D.G.B., R.M. Santos, C.G.B. Demetrio, and J.L.M. Vasconcelos. 2007. Factors affecting conception rates following artificial insemination or embryo transfer in lactating Holstein cows. *J. Dairy Sci*. 90(11): 5073–5082.

Dhillon, V., and S. McCallum. 1993. Differential heat shock protein overexpression and its clinical relevance in systemic lupus erythematosus. *Annals of the Rheumatic Disease*. 52: 436–442.

Dikmen, S., E. Alava, E. Pontes, J.M.Fear, B.Y. Dikmen, T.A. Olson, and P.J. Hansen. 2008. Differences in Thermoregulatory Ability Between Slick-Haired and Wild-Type Lactating Holstein Cows in Response to Acute Heat Stress. *J. of Dairy Sci.* 91(9): 3395–3402.

Dikmen, S., and P.J. Hansen. 2009. Is the temperature-humidity index the best indicator of heat stress in lactating dairy cows in a subtropical environment? *J. Dairy Sci*. 92: 109–116.

Dikmen, S., J.B. Cole, D.J. Null, and P.J. Hansen. 2012. Heritability of rectal temperature and genetic correlations with production and reproduction traits in dairy cattle. *J. Dairy Sci*. 95(6): 3401–3405.

Dikmen, S., J.B. Cole, D.J. Null, and P.J. Hansen. 2013. Genome-wide association mapping for identification of quantitative trait loci for rectal temperature during heat stress in Holstein cattle. *Plos One*. 8(7): e69202.

Dikmen, S., Khan, F. a, Huson, H.J., Sonstegard, T.S., Moss, J.I., Dahl, G.E., and Hansen, P.J. 2014. The Slick hair locus derived from Senepol cattle confers thermotolerance to intensively managed lactating Holstein cows. *J. Dairy Sci*. 97(9): 5508–5520.

Ealy, A.D., M. Drost, and P. Hansen. 1993. Developmental changes in embryonic resistance to adverse effects of maternal heat stress in cows. *J. Dairy Sci*. 76(10): 2899–2905.

Ealy, A.D., C.F. Aréchiga, D.R. Bray, C.A. Risco, and P.J. Hansen. 1994. Effectiveness of Short-Term Cooling and Vitamin E for Alleviation of Infertility Induced by Heat Stress in Dairy Cows. *J. Dairy Sci*. 77(12): 3601–3607.

Ealy, A., J. Howell, C. Moterroso, C.F. Arechiga, and P.J. Hansen. 1995. Developmental changes in sensitivity of bovine embryos to

heat shock and use of antioxidants as thermoprotectants. *J. of Animal Sci.* 73: 1401–1407.

Edwards, J., and P.J. Hansen. 1997. Differential responses of bovine oocytes and preimplantation embryos to heat shock. *Molecular Reproduction and Development*. 46: 138–145.

Favatier, F., L. Bornman, L. Hightower, E. Gunther, and B.C. Pollard. 1997. Variation in hsp gene expression and Hsp polymorphism: do they contribute to differential disease susceptibility and stress tolerance? *Cell Stress and Chaperones*.2(3): 141–155.

Gendelman, M., and Z. Roth. 2012a. Seasonal effect on germinal vesicle-stage bovine oocytes is further expressed by alterations in transcript levels in the developing embryos associated with reduced developmental competence. *Biology of Reproduction*. 86: 1–9.

Gendelman, M., and Z. Roth. 2012b. *In vivo* vs. *in vitro* models for studying the effects of elevated temperature on the GV-stage oocyte, subsequent developmental competence and gene expression. *Animal Reproduction Science*. 134: 125–134.

Guzeloglu, A., J.D. Ambrose, T. Kassa, T. Diaz, M.J. Thatcher, and W.W. Thatcher. 2001. Long-term follicular dynamics and biochemical characteristics of dominant follicles in dairy cows subjected to acute heat stress. *Animal Reproduction Science*. 66: 15–34.

Hansen, P.J. 2009. Effects of heat stress on mammalian reproduction. Philosophical Transactions of the Royal Society of London. *Series B, Biological Sciences*. 364: 3341–3350.

Hernandez, J.A., C.A. Risco, F.S. Lima, and J.E.P. Santos. 2012. Observed and expected combined effects of clinical mastitis and low body condition on pregnancy loss in dairy cows. *Theriogenology*. 77: 115–121.

Hernández-Cerón, J., C.C. Chase, and P.J. Hansen. 2004. Differences in heat tolerance between preimplantation embryos from Brahman, Romosinuano, and Angus breeds. *J. Dairy Sci*. 87: 53–58.

Howell, J.L., J.W. Fuquay, and A.E. Smith. 1994. Corpus Luteum Growth and Function in Lactating Holstein Cows During Spring and Summer. *J. Dairy Sci*. 77(3): 735–739.

Huang, C., S. Tsuruta, J.K. Bertrand, I. Misztal, T.J. Lawlor, and J.S. Clay. 2008. Environmental effects on conception rates of Holsteins in New York and Georgia. *J. Dairy Sci*. 91(2): 818–825.

Hutchinson, J.C., and G.D. Brown. 1969. Penetrance of cattle coats by radiation. *J. Appl. Physiol*. 26: 454–464.

Kadokawa, H., M. Sakatani, and P.J. Hansen. 2012. Perspectives on improvement of reproduction in cattle during heat stress in a future Japan. *Animal Science Journal*. 83(6): 439–445.

Krininger III, C., S.H. Stephens, and P.J. Hansen. 2002. Developmental Changes in Inhibitory Effects of Arsenic and Heat Shock on Growth of Pre-Implantation Bovine Embryos. *Molecular Reproduction and Development*. 340: 335–340.

Li, Q.L., Z.H. Ju, J.M. Huang, J.B. Li, R.L. Li, M.H. Hou, J.F. Zhong. 2011. Two novel SNPs in HSF1 gene are associated with thermal tolerance traits in Chinese Holstein cattle. *DNA and Cell Biology*. 30(4): 247–254.

Liu, Y., D. Li, H. Li, X. Zhou, and G. Wang. 2011. A novel SNP of the ATP1A1 gene is associated with heat tolerance traits in dairy cows. *Molecular Biology Reports*. 38: 83–88.

Loureiro, B., A.M. Brad, and P.J. Hansen. 2007. Heat shock and tumor necrosis factor-alpha induce apoptosis in bovine preimplantation embryos through a caspase-9-dependent mechanism. *Reproduction (Cambridge, England)*. 133(6): 1129–1137.

Lyashko, V.N., V.K. Vikulova, V.G. Chernicov, V.I. Ivanov, K.A. Ulmasov, O.G. Zatsepina, and M.B. Evgen'ev. 1994. Comparison of the heat shock response in ethnically and ecologically different human populations. *Proceedings of the National Academy of Sciences of the United States of America*. 91: 12492–12495.

Malayer, J.R., P.J. Hansen, and W.C. Buhi. 1988. Effect of day of the oestrous cycle, side of the reproductive tract and heat shock on in-vitro protein secretion by bovine endometrium. *Journal of Reproduction and Fertility*. 84(2): 567–578.

Olson, T.A., C. Lucena, C.C. Chase, and A.C. Hammond. 2003. Evidence of a major gene influencing hair length and heat tolerance in *Bos taurus* cattle. J.of Animal Sci. 81: 80–90.

Ozawa, M., M. Hirabayashi, and Y. Kanai. 2002. Developmental competence and oxidative state of mouse zygotes heat-stressed maternally or *in vitro*. *Reproduction*. 124: 683–689.

Paula-Lopes, F.F., C.C. Chase, Y.M. Al-Katanani, K.C. Erininger, R.M. Rivera, S. Tekin, P.J. Hansen. 2003. Genetic divergence in cellular resistance to heat shock in cattle: differences between breeds developed in temperate versus hot climates in responses of preimplantation embryos, reproductive tract tissues and lymphocytes to increased culture

temperatures. *Reproduction (Cambridge, England)*. 125(2): 285–294.

Protasi, F., C. Paolini, M. Canato, C. Reggiani, and M. Quarta. 2011. Lessons from calsequestrin-1 ablation *in vivo*: much more than a Ca(2+) buffer after all. *J. of Muscle Research and Cell Motility*. 32: 257–270.

Putney, D.J., M. Drost, and W.W. Thatcher. 1988. Embryonic development in superovulated dairy cattle exposed to elevated ambient temperatures between Days 1 to 7 post insemination. *Theriogenology*. 30(2): 195–209.

Roman-Ponce, H., W.W. Thatcher, D. Caton, D.H. Barron, and C.J. Wilcox. 1978. Thermal Stress Effects on Uterine Blood Flow in Dairy Cows. *J. of Animal Sci*. 46: 175–180.

Roth, Z., R. Meidan, R. Braw-Tal, and D. Wolfenson. 2000. Immediate and delayed effects of heat stress on follicular development and its association with plasma FSH and inhibin concentration in cows. *Journal of Reproduction and Fertility*. 120: 83–90.

Roth, Z., R.Meidan, A. Shaham-Albalancy, R. Braw-Tal, and D. Wolfenson. 2001. Delayed effect of heat stress on steroid production in medium-sized and preovulatory bovine follicles. *Reproduction (Cambridge, England)*. 121(5): 745–751.

Roth, Z., A. Arav, R. Braw-Tai, A. Bor, and D. Wolfenson. 2002. Effect of treatment with follicle-stimulating hormone or bovine somatotropin on the quality of oocytes aspirated in the autumn from previously heat-stressed cows. *J. Dairy Sci*. 85(6): 1398–1405.

Roth, Z. 2008. Heat stress, the follicle, and its enclosed oocyte: mechanisms and potential strategies to improve fertility in dairy cows. *Reproduction in Domestic Animals*. 43(Suppl 2): 238–244.

Sakatani, M., S.I. Kobayashi, and M. Takahashi. 2004. Effects of heat shock on *in vitro* development and intracellular oxidative state of bovine preimplantation embryos. *Molecular Reproduction and Development*. 67: 77–82.

Sartori, R., R. Sartor-Bergfelt, S.A.Mertens, J.N. Guenther, J.J. Parrish, and M.C. Wiltbank, 2002. Fertilization and early embryonic development in heifers and lactating cows in summer and lactating and dry cows in winter. *J. Dairy Sci*. 85(11): 2803–2812.

Seath, D.M., and G.D. Miller, 1947. Heat tolerance comparisons between Jersey and Holstein cows. *J. of Animal Sci*. 6: 24–34.

Shimizu, S., K. Nomura, M. Ujihara, K. Sakamoto, H. Shibata, T. Suzuki, and H. Demura. 1996. An Allel-Specific Abnormal Transcript of the Heat Shock Protein 70 Gene in Patients with Major Depression. *Biochemical and Biophysical Research Communications*. 219(3): 745–752.

Shimizu, T., I. Ohshima, M. Ozawa, S.Takahashi, A.Tajima, M.Shiota, Y. Kanai. 2005. Heat stress diminishes gonadotropin receptor expression and enhances susceptibility to apoptosis of rat granulosa cells. *Reproduction (Cambridge, England)*. 129(4): 463–472.

Silva, R. da, A. Maia, L. Costa, and J. Queiroz. 2012. Latent heat loss of dairy cows in an equatorial semi-arid environment. *International Journal of Biometeorol*. 56: 927–932.

Silva, C.F., E.S. Sartorelli, A.C.S. Castilho, R.A. Satrapa, R.Z. Puelker, E.M. Razza, C.M. Barros. 2013. Effects of heat stress on development, quality and survival of *Bos indicus* and *Bos taurus* embryos produced *in vitro*. *Theriogenology*. 79(2): 351–357.

Sugiyama, S., M. McGowan, M. Kafi, N. Phillips, and M. Young. 2003. Effects of increased ambient temperature on the development of *in vitro* derived bovine zygotes. *Theriogenology.* 60: 1039–1047.

Thatcher, W.W., A. Guzeloglu, R. Mattos, M. Binelli, T.R. Hansen., and J.K. Pru. 2001. Uterine-conceptus interactions and reproductive failure in cattle. *Theriogenology*. 56(09): 1435–1450.

Vasconcelos, J.L.M., D.G.B. Demétrio, R.M. Santos, J.R. Chiari, C. Rodrigues, and O.G. Sá Filho. 2006. Factors potentially affecting fertility of lactating dairy cow recipients. *Theriogenology*. 65: 192–200.

Vasconcelos, J.L.M., R.F. Cooke, D.T.G. Jardina, F.L. Aragon, M.B. Veras, S. Soriano, A.B.Scarpa. 2011. Associations among milk production and rectal temperature on pregnancy maintenance in lactating recipient dairy cows. *Animal Reproduction Science.* 127: 140–147.

West, J.W. 2003. Effects of heat-stress on production in dairy cattle. *J. Dairy Sci*. 86(6): 2131–2144.

Wilson, S.J., R.S.Marion, J.N. Spain, D.E. Spiers, D.H. Keisler, and M.C. Lucy. 1998. Effects of controlled heat stress on ovarian function of dairy cattle. 1. Lactating cows. *J. Dairy Sci*. 81(8): 2124–2131.

Wolfenson, D., W.W. Thatcher, L. Badinga, J.D. Savio, R. Meidan, B.J. Lew, A. Berman. 1995. Effect of heat stress on follicular development during the estrous cycle in lactating dairy cattle. *Biology of Reproduction*. 52(5): 1106–1113.

Wolfenson, D., B.J. Lew, W.W. Thatcher, Y. Graber, and R. Meidan. 1997. Seasonal and acute heat stress effects on steroid production

by dominant follicles in cows. *Animal Reproduction Science*. 47: 9–19.

Wolfenson, D., Z. Roth, and R. Meidan. 2000. Impaired reproduction in heat-stressed cattle: basic and applied aspects. *Animal Reproduction Science*. 60-61: 535–547.