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Review on mechanisms of dairy summer infertility and implications for hormonal intervention

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Abstract
In dairy cows and buffaloes, summer heat stress (HS) reduces milk yield and delays return to pregnancy leading to financial loss. Clues for effective interventions against summer infertility (SI) lie in understanding the underlying mechanisms. This article reviews current knowledge on the mechanisms of bovine SI and their implication for hormonal management. Under HS dairy animals encounter anestrous, silent cycles and repeat breeding which extend their open period. These effects are attributed mainly to HS induced disturbances in luteinizing hormone (LH) secretion, follicular dominance and estrogen secretion, ovulation and oocyte competence, luteal development and progesterone secretion, utero-placental function and embryo-fetal development. Hormonal timed artificial insemination protocols and LH support around estrous improved summer pregnancy rates by avoiding need for estrus detection, assisting follicular development and ovulation, enhancing quality oocytes and stimulating luteal function. Progesterone supplementation to enhance embryonic development did not produce significant improvement in summer pregnancy rates. There is need for evaluating integrated approaches combining hormones, metabolic modifier and cyto-protective agents.
Keywords: Bovines, Heat stress, Hormones, Infertility.

Introduction

Cows and buffaloes under summer heat stress (HS) face depressed reproductive activity. Summer infertility (SI) is characterized by anestrous, poor estrus expression and reduced fertility on breeding (Nardone *et al*., 2010). SI is more important in tropical and sub-tropical areas, and in high yielding animals (Hansen, 2004). With current trends of rising global temperature, negative impact of SI on dairy production is expected to increase.

Current evidence indicates that HS and associated physiological changes hold immediate and delayed negative effects on: gonadotrophins secretion, follicular dynamics, ovulation, corpus luteum (CL) development, steroidogenesis, oocyte developmental competence, embryonic survival, utero-placental function, lactation and post-natal development (Wolfenson *et al*., 1997; Bilby *et al*., 2008; Hansen, 2009).

Knowledge that major SI mechanisms involve endocrine disturbance led to the development of hormone based interventions. Along with proper husbandry, hormonal supplementation and synchronization protocols demonstrate promise in enabling quick return to pregnancy (Hansen, 2012). Integration with supportive and protective interventions to address other physiological disturbances and cell injury could further improve response to hormonal SI management strategies.

This review aimed to summarize the current knowledge on the mechanisms of bovine SI and examine their implication for successful hormonal intervention strategies.

Bovine Heat Stress

The bovine Thermoneutral Zone (TNZ) is between 16ºC to 25ºC. Within this range, animals maintain a physiological body temperature of 38.4ºC to 39.1ºC (Yousef, 1985). Ambient temperatures above 20ºC to 25ºC enhance heat gain beyond that lost from the body inducing a state of HS with elevated internal body temperature (Yousef, 1985; Kennedy, 1999; Vale, 2007; Sunil Kumar *et al*., 2011).

Animals try to restore thermal balance through mechanisms which reduce heat production - gain (reduced food intake, metabolism and activity; shade seeking; etc) and/or enhance heat loss (increasing water intake; bathing in ponds or mud; increased sweating respiration and salivation; redistributing blood flow towards peripheral integuments; etc). Cellular response to HS involves increased production of heat shock proteins (HSP) like HSP-70 and antioxidants to limit protein damage (Basiricò *et al*., 2011). Physiological adjustments in HS pose negative consequences on energy availability, water and ionic

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balance, milk production and fertility (Kennedy, 1999; Sunil Kumar *et al*., 2011).

Reproductive Impact of Summer Heat Stress

The major impact of HS on reproduction involves delaying a return to gestation due to decreased submission rate and low conception / pregnancy rates (Nardone *et al*., 2010). In heat stressed cows, duration and intensity of estrus decreases and incidence of anoestrous and silent ovulation increases (Hansen and Aréchiga, 1999; Lucy, 2002).

Cold season conception rates of 40% to 60% declines to 10% or 20% during hot summer months (Cavestany *et al*., 1985). HS during gestation can compromise fetal development, lactation and neonatal development as well as postpartum ovarian activity (Bilby *et al*., 2008). Buffaloes are more prone to HS and assume a seasonal calving avoiding summer breeding (Vale, 2007; Singh *et al*., 2013).

Mechanisms of Summer Infertility

Summer heat stress disrupts reproduction in two general ways i.e. physiological adjustments such as redistribution of blood flow and energy deficits compromise reproductive activity indirectly and elevated internal body temperature directly disrupts endocrine mechanisms and cellular physiology (ovarian cells, germ cells, embryo or other) (Wolfenson *et al*., 2000). Following sections attempt to summarize impacts of HS at various stages of the reproductive process, examine relationships between such effects and outline implications on key fertility indicators.

Effect on gonadotropin secretion

Both tonic and surge luteinizing hormone (LH) levels were depressed by HS in cows with low circulating estradiol concentrations (Gilad *et al*., 1993). Poor LH surge interferes with maturation and ovulation of dominant follicles whereas low tonic LH levels hinder lutenization (luteal development) (Wolfenson *et al*., 2000) and inhibit follicular growth and turnover in cyclic cows (Sirard, 2001).

Gonadotropin releasing hormone (GnRH) induced follicle stimulating hormone (FSH) secretion was similarly depressed during HS. However, tonic FSH secretion in HS is elevated due probably to reduced inhibition of negative feedback from small follicles (Wolfenson *et al*., 1993; Khodaei-Motlagh *et al*., 2011). FSH change related fertility effects are considered less relevant (Wolfenson *et al*., 1993; Edwards and Hansen, 1996). Increased circulating prolactin level was reported during HS which could lead to acyclicity and infertility (Alamer, 2011; Singh *et al*., 2013).

Effect on ovarian activity

HS reduced follicular dominance by inducing multiple large (> 10 mm) follicles as well as prolonged dominance of ovulatory follicles (Hansen, 2009). Normal follicular selection and dominance could be disturbed by high tonic FSH availability. LH and negative energy balance (NEB) during HS can prevent maturation and ovulation of dominant follicles. Multiple dominant follicles can increase the rates of double ovulation and twin conceptions (Hansen, 2009). Prolonged follicular dominance disrupts normal oocyte maturation (Eg. premature meiosis) and reduces developmental competence (Mihm *et al*., 1994).

Follicular estradiol secretion is depressed under HS primarily due to reduced theca cell androstenedione production associated with low 17a-hydroxylase expression. Reduced granulosa cells aromatase activity and viability also contribute to poor estradiol secretion (Badinga *et al*., 1993; Wolfenson *et al*., 2000; Khodaei-Motlagh *et al*., 2011). Low estrogen secretion disrupts expression of estrus, gonadotropin surge, ovulation, transport of gametes and fertilization (Wolfeson *et al*., 2000).

In case dominant follicle/s ovulate, subsequent plasma progesterone concentrations are reduced during HS (Khodaei-Motlagh *et al*., 2011). This could be attributed to small size of ovulatory follicle/s and low tonic LH stimulation of luteinization and steroidogenesis. Moreover, *in vitro* studies have indicated that HS compromised the viability of small luteal cells which represent a major source of progesterone (Wolfeson *et al*., 2000). Low progesterone secretion limits endometrial function and embryo development (Wolfeson *et al*., 2000; Khodaei-Motlagh *et al*., 2011).

Effect on oocyte competence

Summer HS reduces oocyte developmental competence by affecting growth and maturation (Ju, 2005; Hansen, 2009). This could reflect a direct effect on the oocyte or an indirect consequence to supportive follicular cell changes. Direct effects on oocytes include: increased oxidative damage and apoptotic cell death (Paula-Lopes and Hansen, 2002), irreversible changes on cytoskeleton and meiotic spindle which interferes with cell division (Hansen, 2002; Ju, 2005), reduced mRNA and protein reserves for early embryonic development and altered membrane integrity which affects signal transduction and protein transport (Zeron *et al*., 2001; Hansen, 2002).

On the other hand, tangible differences in important gene transcript levels (progesterone and prostaglandin receptors, transcription factors Egr-1 and DNA binding protein, etc) were detected between follicles with competent vs. incompetent oocytes (Robert *et al*., 2001). Moreover, prolonged follicular dominance leads to premature meiosis and aged oocytes having poor developmental prospect (Hansen, 2002).

Reduced oocyte competence results in poor fertility rate after service. Stress capable of inducing oocyte

lesions in early stages of follicular growth could impair fertility even long after its removal meaning that depressed summer fertility persists even to autumn months (Wolfenson *et al*., 2000; Hansen, 2002; Ju, 2005).

Effect on embryo and fetus

HS is a recognized cause of embryonic mortality. Embryonic loss in HS may result from poor oocyte quality. Moreover, peri-implantation embryos in early cleavage are highly sensitive to direct deleterious effects of HS (Ealy *et al*., 1993; Bilby *et al*., 2008; Hansen, 2009). HS causes embryonic death by interfering with protein synthesis (Edwards and Hansen, 1996), causing widespread apoptosis (Paula-Lopes and Hansen, 2002) and oxidative cell damage (Wolfenson *et al*., 2000; Hansen, 2009) and reducing interferon-tau production for signaling pregnancy recognition (Wolfensen *et al*., 1993; Bilby *et al*., 2008).

Exposure of post-implantation embryos (early organogenesis) and fetus to HS leads to various teratologies (Wolfenson *et al*., 2000; Hansen, 2009).

Genotype, stage of development and presence of cytoprotective molecules in female reproductive tract determine embryonic response to elevated temperature (Hansen, 2007). Embryonic susceptibility to HS declines in late cleavage (8 cells to morula stages). This was attributed to developmentally regulated protective mechanisms like: increasing expression of heat shock proteins (recently questioned by Sakatani *et al*. (2012)), declining oxidant production, increasing cytoplasmic antioxidant (glutathione) concentration and improving capacity for regulated apoptosis (Hansen, 2002; Paula-Lopes and Hansen, 2002; Ju, 2005; Hansen, 2009). The principle gave basis for successful application of embryo transfer advanced stage embryos to avoid pregnancy losses in summer (Hansen, 2012).

Effect on uterus and placenta

Rise in internal body temperature causes re-distribution of blood flow away from uterus which hampers supply of nutrients and hormones to the conceptus. Endometrial PGF-2α secretion tends to increase in HS thereby threatening pregnancy maintenance (Vale, 2007; Bilby *et al*., 2008). Placental weight and hormone secretion are reduced whereas vascular resistance is increased during HS. These effects further reduce perfusion of nutrients to the fetus and impair lactation (Hansen, 2009). Retarded fetal development due to inadequate nutrition can manifest as physiological and performance problems long after birth (Wolfenson *et al*., 2000; Hansen, 2009).

Hormonal Intervention to Summer Infertility

Considering the role of endocrine disturbances in delaying service and hampering conception, hormonal intervention presents a logical response for management of SI (Khodaei-Motlagh *et al*., 2011). Multiple principles and protocols have been tried.

- Timed artificial insemination (TAI) protocols like OvSynch (GnRH – PGF-2α - GnRH) help to circumvent estrus detection, resolve anestrous and silent cycle constraints, facilitate LH support to follicular and oocyte development. Such protocols helped to increase pregnancy rates and reduce open periods in HS. Replacing GnRH with human Chorionic Gonadotropin (hCG) (Hansen and Aréchiga, 1999) and simultaneous supplementation with cryoprotective agents (such as bovine somatotropin and antioxidants) further improved response to TAI strategies (Aréchiga *et al*., 1998; Hansen, 2007). Dirandeh (2014) recently reported better outcome in heat stressed cows when ovsynch was initiated 6 days after estrus detected post the 30th day postpartum. The approach enhanced response to first GnRH, an important determinant of both synchronization and fertility on ovsynch TAI.
- Administration of GnRH during early estrus coinciding with endogenous LH surge enhances LH surge and improves synchrony between estrus-LH surge-ovulation-insemination. Timely ovulation, competent oocytes and enhanced luteal progesterone secretion during first 30 days of gestation improves fertilization and embryo survival. Better summer pregnancy rates of 18% to 29 % were reported using this approach (Wolfenson *et al*., 2000).
- Progesterone supplementation at critical stages of embryonic development was another alternative for improving summer pregnancy rates. Induction of accessory corpora lutea after breeding (by ovulatory doses of hCG or GnRH) and long term application of progesterone supplements by controlled intravaginal drug releasing (CIDR) device to inseminated animals represent the main strategies evaluated. Despite their theoretical soundness, these strategies have thus far failed to unequivocally prove beneficial for improving summer pregnancy rates (Wolfenson *et al*., 2000).

Conclusion

SI hinders profitable milk production and the problem is escalating with raising global temperatures. Mechanisms underlying SI involve disturbances in development and viability of follicular, luteal, germ, conceptus, endometrial and placental cells. These disturbances are driven by endocrine and energy deficits, physical, oxidative and apoptotic cell injuries and reduced protein synthesis and function. Developments on hormonal interventions assist to alleviate or circumvent certain aspects of SI. Further molecular insights on mechanisms underlying SI can lead to more novel management approaches. Lasting solution to SI requires creating more adaptable dairy herds and/or improving the production environment.

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