

*Review*

# Effects of heat stress changes in steroid hormone concentrations in peripheral blood of Cattle

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In dairy cows inseminated during the hot months of the year, there is a decrease in fertility. Different factors contribute to this situation; the most important are a consequence of increased temperature and humidity that result in a decreased expression of overt estrus and a reduction in appetite and dry matter intake. Heat stress reduces the degree of dominance of the selected follicle and this can be seen as reduced steroidogenic capacity of its theca and granulosa cells and a fall in blood estradiol concentrations. Plasma progesterone levels can be increased or decreased depending on whether the heat stress is acute or chronic, and on the metabolic state of the animal. These endocrine changes reduce follicular activity and alter the ovulatory mechanism, leading to a decrease in oocyte and embryo quality. The uterine environment is also modified, reducing the likelihood of embryo implantation. Systems activated by heat stress can influence reproduction at the hypothalamus, pituitary gland or gonads. However, the major impact is thought to be within the brain or at the pituitary gland. Measurement of plasma concentrations of the gonadotrophins provides a good indication of the effects at these higher levels, since the pulsatile secretion of luteinizing hormone (LH) is a reflection of the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. Both the secretion and actions of GnRH are influenced by the feedback actions of gonadal sex steroids and inhibin. Recent studies suggest that the use of gonadotropins to induce follicular development and ovulation can decrease the severity of seasonal postpartum infertility in dairy cows.

**Key words:** Reproductive hormones, dairy cow and heat stress.

## INTRODUCTION

The most comfortable and productive environmental temperature range for dairy cows is between -4 to 8°C (Khodaei Motlagh et al., 2010 and McDowell, 1972). This is the thermal comfort zone. Summer heat stress is a

major factor contributing to low fertility in lactating dairy cows. Conception rates drop from about 40 to 60% in cooler seasons to 10 to 20% in warm seasons (Cavestany et al., 1985). The substantial rise in average milk yields in recent years has aggravated the low summer fertility syndrome, because of the concurrent rise in metabolic heat production. Every dairy cow has a natural body heat balance which is optimal for normal physiological processes and productive functions. A normal body heat balance exists only when the net heat gain equals the net heat loss.

Stimuli that challenge homeostasis like heat are commonly called stressors. Heat stress can be defined

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**Abbreviations:** FSH, Follicle stimulating hormone; LH, luteinizing hormone; GnRH, gonadotropin-releasing hormone; ACTH, adrenocorticotrophic hormone; CRF, corticotrophin-releasing factor; AVP, arginine vasopressin; CIDR, controlled intra-vaginal delivery device.

as the sum of forces external to a homeothermic animal that acts to displace body temperature from the resting state (Yousef, 1984). Such a stress can disrupt the physiology and productive performance of an animal. The increase in body temperature caused by heat stress has direct, adverse consequences on reproductive hormones (Hansen and Arechiga, 1999). Hence, heat stress is a major contributing factor to the low fertility of dairy cows inseminated in the late summer month (Ingraham et al., 1974, Ray et al., 1992; Thompson et al., 1996; Al-Katanani et al., 1999; Khodaei et al., 2006). Effects of heat stress on reproductive hormones and other physiological functions are a direct consequence of the increase in body temperature caused by heat stress or of the physiological changes cows undergo to reduce the magnitude of hyperthermia (De Renesis and Scaramuzzi, 2003; Khodaei et al 2003). High ambient temperature has affected adversely normal reproduction in cattle (Plasse et al., 1970), swine (Edwards et al., 1968) and sheep (Thwaites, 1968), the syndrome being short estrus, abnormal estrus cycle, increased proportion of abnormal ova shed, decreased fertilization rate, and increased embryonic and fetal mortality early in gestation (Stott, 1972). These physiological manifestations as influenced by environmental heat have been associated with altered endocrine functions (Stott and Wierama, 1971). A number of experimental conditions have been used to evaluate hormonal secretion during heat stress including short-term and long-term temperature modification using environmental chambers, seasonal comparisons of hormonal profiles and the use of microclimatic modification during periods of heat stress. Differences in experimental conditions have presumably contributed to the disparity of results that are found in the literature concerning hormonal secretions during heat stress. Some of the variation in hormonal responses to heat stress probably reflects the fact that ovarian steroid concentrations are dependent not only on rate of secretion from ovarian tissue but also on rate of vascular perfusion of the ovary, on possible adrenal release (at least for progesterone), on metabolism in the liver and other organs, and on the degree of hemodilution or hemoconcentration (Wise et al., 1988). The extent to which heat stress affects these other physiological characteristics could lead to variable changes in steroid hormone concentrations in peripheral blood. For example, heat stress can cause either dilution, concentration, or no effect on blood plasma volume (Richards, 1985; McGuire et al., 1989; Johnson et al., 1991; Elvinger et al., 1992), and the nature of effect of heat stress on blood volume will affect steroid hormone concentrations in blood. Hyperthermia has been shown to decrease ovarian blood flow (Lublin and Wolfenson, 1996) and to inhibit angiogenesis (Fajardo et al., 1988). Blood flow and vascular density determine the follicular perfusion rate, which directly influences the rates of nutrient uptake and hormonal release by the follicle. The relationships among heat stress, vascularity and steroidogenic capacity require

further investigation. Although, heat stress impacts on the reproductive axis at the hypothalamus (to affect gonadotropin-releasing hormone (GnRH) secretion) and the pituitary gland (to affect gonadotrophins secretion), with direct effects on the gonads being of less importance.

## **EFFECTS OF HEAT STRESS ON REPRODUCTIVE HORMONES**

### **Estradiol and progesteron**

Secretion of the hormones regulating reproductive tract function such as estradiol-17 and progesterone may be altered by heat stress. The effect of heat stress on plasma progesterone concentration is controversial. Wilson et al. (1998) found that heat stress had no effect on the plasma progesterone concentrations but that luteolysis was delayed. Several other studies have reported increased (Trout et al., 1998; Abilay et al., 1975; Vaught et al., 1977), decreased (Rosenberg et al., 1977, Younas et al., 1993; Howell et al., 1994; Jonsson et al., 1997; Ronchi et al., 2001) or unchanged (Roth et al., 2000; Guzeloglu et al., 2001) blood concentrations of this hormone during summer heat stress in dairy cows. These differences probably arise because of uncontrolled changes in other factors that affect blood progesterone concentrations. For example, the type of heat stress (that is, acute or chronic) and differences in dry matter intake will independently affect blood progesterone concentrations, thus confusing the situation. The cells of the corpus luteum differentiate from the cells of the follicle therefore, if heat stress decreases blood progesterone then the decrease could arise from the effects of heat stress on the follicle which ultimately carries over to the corpus luteum (Roth et al., 2001). Plasma progesterone concentrations are determined by the differences between the rate of luteal production and the rate of hepatic metabolism. Both are affected by changes in dry matter intake. If the concentration of plasma progesterone is reduced by heat stress this would have consequences for fertility. Low plasma progesterone concentrations during the luteal phase of the pre-conception estrous cycle can compromise follicular development leading to abnormal oocyte maturation and early embryonic death (Ahmad et al., 1995). During the conception cycle, low progesterone concentrations can also lead to the failure of implantation (Mann et al., 1999; Lamming and Royal 2001). In the conception cycle, the effect of progesterone is most probably related to the need for synchronous development of the embryo and delayed or advanced development of the corpus luteum will lead to higher rates of implantation failure (Lamming and Royal 2001). In fact, it has been reported that the pattern of the post-ovulatory rise in progesterone is related to fertility (Darwash et al., 1999). However, the use of exogenous progesterone post-insemination to supplement endogenous progesterone has mixed effects on pregnancy rate, with one paper

reporting an improvement (Robinson et al., 1989) and another reporting no benefit (Breuel et al., 1990) of this treatment.

It has been shown that early atresia of bovine follicles is characterized by a decrease in androgen production by thecal cells (McNatty et al., 1984). Early atresia in medium sized follicles because of heat stress could also be associated with low oestradiol production by granulosa cells and increased progesterone concentrations in the follicular fluid of heat-stressed cows (Roth et al., 2000).

Plasma estradiol concentrations are reduced by heat stress in dairy cows (Wolfenson et al., 1997; Wolfenson et al., 1995; Wilson et al., 1998) an effect that is consistent with decreased concentrations of luteinizing hormone (LH) and reduced dominance of the selected follicle, although, this effect has not always been observed (Rosenberg et al., 1982). Also recent experiments suggest that heat stress can cause an increase in peripheral concentrations of estradiol-17 between day 1 and 4 of the estrous cycle (Wolfenson et al., 1995) and a reduction from day 4 through 8 (Wolfenson et al., 1995) and 11 through 21 of the cycle (Wilson et al., 1998). These results must be compared with earlier reports of no effect of heat stress (Roman-Ponce et al., 1981; Wise et al., 1988ab). Decrease of estradiol concentration in the follicular fluid is more likely to occur after exposure to long-term, chronic (summer) heat stress than to acute heat stress.

The mechanisms by which heat stress alters the concentrations of circulating reproductive hormones are not known. Some effects of heat stress may involve adrenocorticotrophic hormone (ACTH). Heat stress can cause increased cortisol secretion (Roman-Ponce et al., 1981; Wise et al., 1988a; Elvinger et al., 1992), and ACTH has been reported to block estradiol-induced sexual behavior (Hein and Allrich, 1992). Increased corticosteroid secretion has been suggested (Roman-Ponce et al., 1977) because this can inhibit GnRH and thus LH secretion (Gilad et al., 1993). In a detailed study, heat stress inhibited the secretion of gonadotropins to a greater degree in cows with low plasma concentrations of estradiol compared to those with high concentrations (Gilad et al., 1993). This study suggests that high concentrations of estradiol can counteract the effect of heat stress, or alternatively, that the neuroendocrine mechanism controlling gonadotropin secretion is more sensitive to heat stress when concentrations of plasma estradiol are low. It has been suggested that heat stress could also act directly on the ovary to decrease its sensitivity to gonadotropin stimulation (Wolfenson et al., 1997). Also the somatic cells within the follicles (theca and granulosa cells) can be damaged by heat stress. In terms of steroid production, the thecal cells and granulosa cells were found to be susceptible to heat stress (Roth et al., 2001).

Regardless of the precise mechanism, any alteration in the secretory activity of the follicle and perhaps the corpus luteum caused by heat stress would be important

factors in summer infertility.

### **Follicle stimulating hormone (FSH), luteinizing hormone (LH) and Inhibin**

Since the main factors regulating ovarian activity are gonadotrophin-releasing hormone from the hypothalamus and the gonadotrophins, LH and FSH, from the anterior pituitary gland, some authors have studied the effect of heat stress on the secretion of these hormones. The effects of heat stress on LH concentrations in peripheral blood are inconsistent. Some studies report unchanged concentrations (Gwazdauskas et al., 1981; Howel et al., 1994; Nobel et al., 1997; Pennington et al., 1985; Gauthier, 1986) while others report increased concentrations (Roman-Ponce et al., 1981) and still others report decreased concentrations (Modon and Johnson, 1973; Wise et al., 1988; Gilad et al., 1993; Lee, 1993) following heat stress. With regard to the pattern of LH secretion in heat stressed cows, decrease in LH pulse amplitude (Gilad et al., 1993) and LH pulse frequency (Wise et al., 1988) have been reported. The effect of heat stress on the preovulatory surge of LH is similarly controversial; a reduction of the endogenous LH surge by heat stress was reported in heifers (Modon and Johnson, 1973) but not in cows (Gwazdauskas et al., 1981; Gauthier, 1986; Rosenberg et al., 1982). The reasons for these discrepancies are unclear. It has been suggested that these differences are related to preovulatory estradiol levels because the amplitude of tonic LH pulses and GnRH-induced preovulatory plasma LH surges are decreased in cows with low plasma concentrations of estradiol but not in cows with high plasma concentrations of estradiol (Gilad et al., 1993). Because most studies report that LH levels are decreased by heat stress, we are drawn to conclude that in summer, the dominant follicle develops in a low LH environment and these results in reduced estradiol secretion from the dominant follicle leading to poor expression of estrus, and hence, reduced fertility. Plasma inhibin concentrations in summer are lower in heat stressed cows (Wolfenson et al., 1993) and in cyclic buffaloes in India (Palta et al., 1997), perhaps reflecting reduced folliculogenesis since a significant proportion of plasma inhibin comes from small and medium size follicles.

The small amount of published information available on the effect of heat stress on blood concentrations of FSH and inhibin in cattle suggests that FSH is increased by heat stress and this may be due to decreased plasma inhibin production by compromised follicles. However, a reduced FSH response in heat stressed compared to control cows was observed after administration of a GnRH analogue (Gilad et al., 1993). Further research is required before a conclusion can be reached. However, FSH, if increased, appears insufficient to overcome the effect of low LH concentrations and therefore a reduced

availability of androgen precursors for estradiol synthesis (Roth et al., 2000).

### **Gonadotrophins and corticosteroids**

Usually, in long-term a stressor like heat stress activates the hypothalamo-pituitary-adrenal axis and the sympathoadrenal system (Tibrook et al., 2000). Stimulation of the hypothalamo-pituitary-adrenal axis is characterized by activation of corticotrophin-releasing factor (CRF) and arginine vasopressin (AVP) neurones in the paraventricular nucleus, and secretion of these neuropeptides into the hypophysial portal system to stimulate the corticotrophs of the anterior pituitary gland (Tibrook et al., 2000). The corticotrophs produce a variety of peptides derived from pro-opiomelanocortin, including ACTH, endorphin and melanocyte-stimulating hormone, all of which are released in response to heat stress (Engler et al., 1989). In terms of the response to heat stress, the physiological significance of the release of  $\beta$ -endorphin and melanocyte-stimulating hormone is not clear, but ACTH acts on the cortex of the adrenal glands to stimulate the synthesis and secretion of glucocorticoids like cortisol. Higher concentration of this catabolic hormone may have been produced by heat stressed cows to maintain milk production (Abilay et al., 1975). It is tempting to speculate that the higher concentrations of cortisol in the heat stressed cows influences LH release, because cortisol has been implicated as an inhibitor of anterior pituitary release of LH in the bovine species (Gangwar et al., 1965). Various studies have shown that administration of natural or synthetic glucocorticoids can inhibit the secretion of the gonadotrophins in sheep (Juniewicz et al., 1987), pigs (Turner et al., 1999a, b) and especially in dairy cattle (Thibier and Rolland, 1976). Nevertheless, increased secretion of glucocorticoids is not always associated with decreased secretion of the gonadotrophins, particularly in cases of acute stress. Suppression of reproduction is more likely under conditions of chronic stress and may involve action at the hypothalamus or pituitary. Furthermore, there may be species differences in the extent to which glucocorticoids inhibit the secretion of LH and FSH (Tibrook et al., 2000). When heat stress is prolonged, it is likely that the secretion of the gonadotrophins will be suppressed and reproduction will be inhibited. However, for acute stress or repeated acute stress, it is unclear whether, or how, reproduction will be affected. It is apparent from various studies that glucocorticoids can inhibit gonadotrophin secretion in some circumstances.

### **Prostaglandin**

It has been shown that heat stress can increase secretion from endometrium and in some cases early activation of luteolysis mechanism, leading to failure in implantation.

For instance heat shocks of 42 and 43°C increased output of prostaglandins by cultured endometrium collected at day 17 of the estrous cycle (Putney et al., 1988b; Malayer and Hansen 1990). Furthermore, heat stress on day 17 of pregnancy increased uterine production of in response to oxytocin (Wolfenson et al., 1993).

### **Androstenedion**

Culture of thecal cells at 40.5°C reduced androstenedione production from cultured thecal cells but generally had no effect on estradiol-17 production from cultured granulosa cells (Wolfenson et al., 1997). The mechanism by which heat stress induces a decrease in androstenedione production in thecal cells is not clear. Recent analyses of mRNA content for LH receptor in thecal cells obtained from preovulatory follicles did not provide any evidence for alterations of mRNA content related to previous heat exposure (Roth et al., 2000). However, the significant decrease of LH-stimulated androstenedione production by thecal cells may indicate that heat exposure induces impairment of LH receptor function. Heat stress from day 3 to 5 of the estrous cycle increased androstenedione and reduced estradiol-17 concentrations in follicular fluid of the dominant follicle collected at day 7 (Wolfenson et al., 1997).

## **USE OF EXOGENOUS HORMONES**

An alternative approach to improving summer fertility is the use of reproductive hormones to stimulate fertility. While not necessarily addressing the fundamental causes of summer infertility, this approach offers the opportunity to overcome its effects on fertility.

In heat stressed cows, the administration of GnRH induces follicular development and a healthy preovulatory follicle (Guzeloglu et al., 2001). In summer, the administration of GnRH to lactating dairy cows at estrus increased the conception rate from 18 to 29% (Ullah et al., 1996). However, luteal support from a single administration of human chorionic gonadotropin (hCG) (3000 iu) on day 5 or 6 after insemination did not improve summer fertility (Schmitt et al., 1996). Similar results have been reported following exogenous administration of progesterone with the CIDR intravaginal delivery device (Wolfenson et al., 1994). In recent years the effect of timed artificial insemination (that is, without estrus detection) on fertility in summer has been examined (Wolfenson et al., 1994; De la Sota et al., 1998). The results of these studies suggest that these techniques can help overcome the effects of heat stress and reduce summer infertility.

The use of fixed time insemination (TAI) has the distinct advantage of not requiring the detection of estrus and effective synchronization methods for fixed time insemination have been developed. They are based on

administration of GnRH or hCG to induce ovulation, followed by a luteolytic dose of 6 to 7 days later and a second treatment with GnRH or hCG 24 to 60 h after the luteolytic treatment to induce a fertile ovulation (Schmitt et al., 1996; Pursley et al., 1995; Schmitt et al., 1996). In the summer, these programs did not increase the number of cows pregnant to the fixed time insemination but they did increase the number of cows pregnant by 120 days postpartum and reduced the number of days open (De Rensis et al., 2002; Almier et al., 2002; Wolfenson et al., 2000; Arechiga et al., 1998; De la Sota et al., 1998; Cartmill et al., 1999). These results suggest that the principal benefit of these treatments is to induce cyclicity and the development of normal corpora lutea leading to good fertility. These approaches lead to an increase in the number of pregnant cows simply by increasing the number of cows that are inseminated at estrus, and although, they limit the effects of summer heat stress on fertility, they do not address the underlying pathology.

Injecting cows with GnRH causes a predictable release of LH and a significant increase in serum progesterone. In one study, Ullah et al. (1996) indicated that if cows were injected with 100 ug of GnRH when estrus was first detected, followed by insemination (AI) ten or twelve hours later, the pregnancy rate from the first AI was 28.6% for all treated cows. This can be compared to 17.7% in the control cows. The same ovulation synchronization protocol has also been used by Lee (1999) in Taiwan. The pregnancy rate of lactating cows in summer, when cows were first serviced postpartum using Ovsynch, was 25.0%. This can be compared to the 15% pregnancy rate when cows were first serviced when estrus was detected. The results suggest that timed AI using the Ovsynch protocol in mid-lactation is an effective and economic way of managing the reproduction of lactating cows in a subtropical environment.

## CONCLUSION

There is a widely observed decrease in the fertility of postpartum dairy cows inseminated in the summer compared to cows inseminated in winter. The precise mechanism of this effect has not been conclusively identified. However, the plasma levels of LH and estradiol are decreased in heat stressed cows and this is one of the factors contributing to low fertility during the hot months of the year. With regard to FSH, there is also general agreement that its secretion in summer is increased probably due to decreased inhibin secretion from small follicles. Research into the effects of heat stress on plasma progesterone report an inconsistent picture and the role of progesterone in summer infertility is not very clear. There are many possible reasons for the lack of agreement among the published reports. These include: the type of stress, (chronic versus acute), genetic factors associated with milk yield (high milk versus low/normal milk), and environmental and management

factors.

As discussed above heat stress may affect the secretion of the gonadotrophins through mechanisms that modify the synthesis or the secretion of GnRH, the responsiveness of the gonadotrophs to the actions of GnRH or the feedback actions of gonadal hormones. Prolonged or chronic heat stress results in suppressed gonadotrophins secretion and inhibition of reproduction but, when the duration of the stress response is transient or acute, the effects are less clear. Variable effects of acute stress have been found in dairy cattle, with reports of no effect, stimulatory and inhibitory effects on reproductive hormones secretion. To reduce the adverse effects of heat stress on reproductive hormones during heat stress, it has been suggested to use exogenous hormones like GnRH, progesterone and hCG.

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