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Comparing the effects of heat stress and mastitis on ovarian function in lactating cows: basic and applied aspects

Z. Roth*, D. Wolfenson

Department of Animal Sciences, Faculty of Agriculture, Food and Environment, The Hebrew University, Rehovot 76100, Israel

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ABSTRACT

Reduced reproductive performance of lactating cows is strongly associated with environmental and pathogenic stressors. This review summarizes the most recent knowledge on the effects of acute or chronic heat stress (HS) and acute or chronic intramammary infection (IMI) on ovarian function. It also offers various approaches for improving the fertility of cows under chronic HS or IMI. Comparing the 2 stressors reveals a few similarities in the mode of alteration in the hypothalamus–pituitary–ovarian axis, in particular, in the follicle and its enclosed oocyte. Both HS and IMI cause a reduction in the preovulatory LH surge, with a pronounced effect in cows with IMI, and consequently, ovulation is being delayed or inhibited. Both stresses induce changes in follicular growth dynamics, reduce follicular steroidogenesis, and disrupt follicular dominance. Unlike their effects on follicular function, the effects of mastitis and HS on corpus luteum (CL) function are debatable. Under chronic summer thermal stress, several, but not all, studies show reduced progesterone secretion by the CL. Subclinical mastitis does not affect CL function, whereas the effect of clinical mastitis is controversial; some show a reduction in progesterone, whereas others do not. Both stresses have been found to impair cytoplasmic and nuclear maturation of oocytes, associated with reduced embryonic development. These findings have provided insights into the mechanism by which HS and IMI compromise fertility, which enable developing new strategies to mitigate these effects. For instance, treatment with GnRH and $PGF_{2\alpha}$ to induce follicular turnover successfully improved conception rate in subpopulations of HS cows during the summer, in particular, primiparous cows and cows with high BCS. The "Ovsynch" program, also based on the use of GnRH and $PGF_{2\alpha}$, has been shown to improve conception rate of subclinical mastitic cows, most likely due to better synchronization of timing of ovulation with that of AI. Supplementing progesterone after AI improves conception rate of HS cows, particularly those with postpartum uterine disease and low BCS. It should be noted that similarities between the 2 stressors do not necessarily suggest a shared mechanism. Although not clear enough, an additive deleterious effects of HS and IMI on reproduction is suggested.

1. Background

It is well accepted that intensive selection for increased milk yield is associated with a decline in reproductive performance of dairy cows [1]. In addition, accumulating evidence indicates that reproductive competence of lactating cows is drastically affected by climate and health [2–4]. Taken together, improving fertility has become a major goal of the dairy industry because it will significantly increase the sustainability and efficiency of dairy farms. Therefore, an understanding of the mechanism that underlies the reduction in fertility is required to develop new approaches to cope with the problem. Although the effects of acute stress (ie, short-term heat stress [HS] and acute clinical mastitis) on reproduction have been intensively studied, the

* Corresponding author. Tel.: 972-8-9489103; fax: 972-8-9489552.
E-mail address: z.roth@mail.huji.ac.il (Z. Roth).

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long-term effects (ie, seasonal HS and subclinical-chronic mastitis) on fertility are much more important. The current review discusses and compares 2 main stressors, HS and mastitis, known to be involved in reduced fertility.

1.1. Effects of environmental thermal stress on fertility

Reduced reproductive performance of high producing cows during the summer is mainly associated with intensive genetic selection for high milk production, and increased feed intake and metabolic rate, which place a great load on thermoregulation. In light of global warming, it seems that the reduced fertility of lactating cows during the summer will worsen in the coming years. The most common strategy to alleviate the effect of HS is to provide shade and evaporative cooling, based on combining sprinkling and ventilation in both the holding pen and the feeding area [2,4]. However, although intensive cooling mostly prevents the decline in milk production, this approach barely improves conception rate and fertility remains relatively low during the summer [4]. Nevertheless, efficient cooling management is a prerequisite for other additional strategies to improve reproductive responses under HS. Importantly, the disruptive effect of HS on fertility is not limited to the hot months; a carryover effect of the hot summer to the cool autumn has also been documented.

1.2. Impact of health status on reproduction

Stresses associated with various diseases disrupt reproduction and lower fertility of dairy cows. Mastitis, postpartum uterine disease, and lameness are widespread diseases in commercial dairy herds in developed countries. Postpartum uterine disease is diagnosed in about 40% of cows in North America and Europe [3]. In England, lameness has been found in about 23% of cows [5]. Mastitis is a major disease of dairy cattle, found in about 20% to 40% of lactating cows [6], which causes great economic losses to the dairy industry [7].

Clinical mastitis is an acute short-term event caused by gram-negative (G−) bacteria, such as *Escherichia coli*, or gram-positive (G+) bacteria, such as *Staphylococcus aureus* or *Streptococcus uberis*. In severe cases, it is characterized by local mammary gland features of inflammation that are commonly accompanied by systemic signs such as fever. In most cases, the clinical event of mastitis is characterized by a sharp rise in somatic cell count (SCC) in the milk, in a pathogen-specific pattern [8]. For instance, after *E coli* inoculation, the SCC peaks after 2 d and the preinfection value is approached within 3 to 4 wk [9]. On the other hand, after inoculation with *S aureus,* SCC remains high for >7 wk [10]. In addition, intramammary infection (IMI) during a clinical event of mastitis triggers a suite of acute-phase responses that include increased secretion of inflammatory proteins, cytokines, prostaglandins, and more, which can be detected in the milk and plasma [11,12]. These factors have been suggested to be involved in the mechanism by which IMI disrupts reproduction, as discussed in section 3.2.

Subclinical mastitis is more common and widespread than clinical mastitis. It is considered a long-term chronic disease, characterized by moderate SCC elevation, almost without detectable signs of local or systemic inflammation. Although subclinical mastitis can be caused by both G+ and G− bacteria, it is mainly induced by G+ bacteria such as *S aureus* and coagulase-negative staphylococci and streptococci.

Although the long-term effects of subclinical mastitis decrease fertility, its negative impact on reproduction has been less documented. In the current review, a SCC cut-off of 150,000 cell/mL milk was set to distinguish between uninfected and subclinical mastitic cows. This cut-off is based on a meta-analysis of several studies showing that cows infected with coagulase-negative staphylococci, which are frequently isolated from infected udder [13], have a mean SCC of 155,000 cell/mL [14]. It should be noted, however, that the SCC cut-off value varies among studies, as reviewed earlier [15]. We categorize mastitis as acute short-term clinical or chronic, long-term subclinical. Such a distinction between clinical and subclinical mastitis is common in several studies dealing with mastitis effects on reproduction and fertility [6,11,16–18]. In particular, we focus on the impact of clinical and subclinical mastitis on ovarian responses.

1.3. Potential interactions between mastitis and HS

Heat stress and mastitis, 2 major stressors in the dairy cows, are both associated with reduced production and reproduction. Studies have indicated a higher occurrence of mastitis during periods of hot weather [19–21]. Accordingly, an increase in milk SCC, a marker for the intensity of the mammary inflammatory response, has been reported during the summer [22], suggesting a seasonal effect on mastitis. Moreover, given that both stressors deleteriously affect reproduction in dairy cows, additive effects cannot be ruled out. Data from the Israeli Herd Book (2014) indicate that the first-insemination conception rate for uninfected cows is 43.8% during the winter and 32.9% in the summer, further dropping to 26.3% in subclinical mastitic cows during the summer.

The current review summarizes the most recent knowledge on thermal stress and mastitis effects on fertility in dairy cows, with a focus on their effects on ovarian functions. Although the 2 stressors (HS and mastitis) differ in nature, some similarities in their mode of alteration are evident. In addition, it seems that mastitis and HS have an additive negative effect on fertility. This knowledge is important for developing new strategies to alleviate the effects of HS and mastitis on fertility.

2. Experimental model to study the effects of stress on cow fertility

Studying the effects of HS and mastitis on reproduction is an enormous challenge. Various models have explored clinical, hormonal, cellular, and molecular modifications. None of these models is perfect, but together their findings extend our knowledge and might explain in part the mechanism underlying the reduced fertility caused by these stressors.