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Review

Mechanisms underlying reduced fertility in anovular dairy cows

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A B S T R A C T

Resumption of ovulation after parturition is a coordinated process that involves recoupling of the GH/insulin-like growth factor 1 axis in the liver, increase in follicular development and steroidogenesis, and removal of negative feedback from estradiol in the hypothalamus. Infectious diseases and metabolic disorders associated with extensive negative energy balance during early lactation disrupt this pathway and delay first ovulation postpartum. Extended periods of anovulation postpartum exert long-lasting effects on fertility in dairy cows including the lack of spontaneous estrus, reduced pregnancy per artificial insemination (P/AI), and increased risk of pregnancy loss. Concentrations of progesterone in anovular cows subjected to synchronized programs for AI are insufficient to optimize follicular maturation, oocyte competence, and subsequent fertility to AI. Ovulation of first wave follicles, which develop under low concentrations of progesterone, reduces embryo quality in the first week after fertilization and P/AI in dairy cows. Although the specific mechanisms by which anovulation and low concentrations of progesterone impair oocyte quality have not been defined, studies with persistent follicles support the involvement of premature resumption of meiosis and degradation of maternal RNA. Suboptimal concentrations of progesterone before ovulation also increase the synthesis of $PGF_{2\alpha}$ in response to oxytocin during the subsequent estrous cycle, which explains the greater incidence of short luteal phases after the first AI postpartum in anovular cows compared with estrous cyclic herd mates. It is suggested that increased spontaneous luteolysis early in the estrous cycle is one of the mechanisms that contributes to early embryonic losses in anovular cows. Anovulation also leads to major shifts in gene expression in elongated conceptuses during preimplantation stages of pregnancy. Transcripts involved with control of energy metabolism and DNA repair were downregulated, whereas genes linked to apoptosis and autophagy were upregulated in Day 15 conceptuses collected from anovular cows compared with estrous cyclic counterparts. Similar changes in conceptus transcriptome were not observed in estrous cyclic cows induced to ovulate follicles that grew under low and high concentrations of progesterone, indicating an effect of anovulation on embryonic development that is not mediated solely by progesterone concentrations before ovulation. Finally, risk factors for anovulation have direct effects on embryo development and uterine receptivity to pregnancy that complement those determined by insufficient concentrations of progesterone during follicular growth. One approach to minimize the impact of anovulation on fertility is supplementation with progesterone during recruitment, selection and final stages of development of the preovulatory follicle. It is suggested that a minimum

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of 2.0 ng/mL of progesterone is needed during growth of the preovulatory follicle to achieve P/AI similar to that of cows growing the preovulatory follicle during diestrus.

1. Introduction

Reproductive efficiency plays a key role in the economic success of dairy herds, as it influences milk production per day of calving interval and culling policies [1]. In spite of recent advances related to management of reproduction with experiments achieving pregnancy per artificial insemination (P/AI) in high-producing Holstein cows of 45% to 50% [2,3], still less than 35% of lactating dairy cows subjected to AI carry gestation to term [4,5]. The establishment and maintenance of pregnancy rely on a delicate cross talk among the maternal hypothalamic-pituitary-gonadal axis, the endometrium, and the developing embryo. As expected, physiological, metabolic, and pathological conditions that disrupt these pathways largely impair fertility. Extensive research supports the concept that anovulation is a major impediment to reproductive performance in dairy cows. The proportion of cows that remain anovular by the end of the voluntary waiting period varies among herds, genetic groups, and management schemes, ranging between 5% and 40% [6–8]. In addition to the lack of estrous behavior that precludes insemination because of lack of estrous cyclicity, anovular cows subjected to synchronization protocols consistently have reduced P/AI and increased risk of pregnancy loss compared with estrous cyclic herd mates [5,7].

Although the detrimental effect of anovulation on reproduction is conspicuous, defining the specific mechanisms contributing to the poor fertility observed in anovular dairy cows continues to challenge researchers. The hallmark of anovulatory conditions is the absence of CL and ensuing insufficient concentrations of progesterone during growth of the ovulatory follicle, which reduces embryo quality in the first week after fertilization [9,10], increases the release of $PGF_{2\alpha}$ in response to oxytocin during the subsequent estrous cycle [11,12], and decreases P/AI in lactating dairy cows [13]. On the other hand, some of the risk factors for anovulation also have direct effects on fertility responses. Delayed resumption of ovulation is associated with dystocia, extensive negative energy balance and loss of body condition postpartum, as well as the occurrence of diseases during early lactation [6–8,14]. The hormonal and metabolic milieus imposed by such circumstances have been shown to decrease the frequency of LH pulses [15,16], impair follicular development, function of follicular cells, and oocyte competence [17–19], upregulate the expression of inflammatory mediators in the endometrium [20], and impair conceptus elongation [21]. Therefore, strategies to improve reproduction in high-producing dairy cows must combine therapies to increase fertility of anovular cows that is coupled with adequate management during the transition period to promote health and expedite resumption of ovulation postpartum.

2. Insufficient concentrations of progesterone during follicular growth

Decreased fertility in anovular cows subjected to timed AI programs is largely mediated by insufficient concentrations of progesterone during growth of the ovulatory follicle. For instance, P/AI did not differ between anovular cows and estrous cyclic herdmates without a functional CL at the first injection of GnRH of the synchronization protocol [13]. As opposed to cows in diestrus at the initiation of the synchronization protocol, anovular and estrous cyclic cows without CL are induced to ovulate a first wave follicle at insemination, which develops simultaneously with the CL and under low concentrations of progesterone. The fact that the wave of the ovulatory follicle had a greater impact on P/AI (i.e., P/AI in cows ovulating the second wave follicle was greater than cows ovulating the first wave follicle) than did estrous cyclicity (i.e., P/AI in anovulatory cow was similar to that of estrous cyclic cows ovulating first wave follicle), suggests that the hormonal milieu during the final stages of follicular development and oocyte maturation is a major determinant of poor fertility in anovular cows [13]. In fact, supplementation with progesterone during growth of the ovulatory follicle improved embryo quality in cows induced to ovulate first wave follicles [10] and restored P/AI in anovular cows at the initiation of the timed AI program [3,22]. Moreover, cows that initiated the resynchronization protocol without a CL had reduced P/AI compared with cows with a CL, and supplemental progesterone was effective at reestablishing fertility in cows without a CL similar to that of cows in diestrus [22]. Such findings support a causal role of progesterone during growth of the ovulatory follicle affecting P/AI.

It remains unknown the ideal concentrations of progesterone during follicle growth to optimize fertility in anovular cows or cows that lack a CL when the preovulatory follicle is recruited for subsequent ovulation. Wiltbank et al. [23] clearly indicated the importance of high concentrations of progesterone during the preovulatory period coupled with very low concentrations during proestrus. Their group reported that not only P/AI increased, but pregnancy loss decreased (6.8 vs. 14.3%) when cows had high compared with low progesterone concentrations during the follicular wave that resulted in the ovulatory follicle [9]. Lactating dairy cows in mid diestrus have concentrations of progesterone that are highly variable and dynamic [23], but usually range from 3 to 6 ng/mL [3,11,22]. Evidence from experiments in which progesterone concentrations were manipulated pre-AI suggest that a minimum of 2.0 to 3.0 ng/mL are needed to achieve P/AI in anovular cows that resemble those of cows in diestrus [22].