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Feedback effects of estradiol and progesterone on ovulation and fertility of dairy cows after gonadotropin-releasing hormone-induced release of luteinizing hormone¹

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ABSTRACT

An experiment was conducted with the objective to determine the effects of estradiol, progesterone, presence of a corpus luteum (CL), and size of a dominant follicle on the characteristics and patterns of GnRH-induced LH release and subsequent ovulation during a timed artificial insemination (TAI) program, or a combination of these. In 70 lactating dairy cows, a total of 163 blood collection periods resulting in a GnRH-induced LH release were analyzed. Concentrations of LH were measured in hourly samples (0 through 6 h after GnRH) during each of the blood collection periods, whereas concentrations of progesterone and estradiol were measured in the sample before GnRH treatment (0 h). Measures of LH included time to LH peak concentration during the 6-h blood collection period, the 2 largest concentrations of LH, mean, and variance of the 6 LH concentrations under each LH curve. Individual and combination effects of CL presence and a dominant follicle $\leq$ or >13.5 mm, in addition to individual and combination effects of progesterone: low (<0.45 ng/mL; $n = 83$), medium (0.53 to 2.41 ng/mL; $n = 25$), and high (2.66 to 10.7 ng/mL; $n = 55$), and estradiol: low (<4.0 pg/mL; $n = 89$) and high (≥ 4.0 pg/mL; $n = 74$) were independent variables in models to determine their influence on characteristics of LH and ovulation. Injections of GnRH induced LH release during 6 h after each of 163 injections. Measures of GnRH-induced LH concentration were inhibited at greater concentrations of progesterone and in the presence of a CL. In contrast, GnRH-induced LH concentrations were increased when estradiol was ≥ 4.0 pg/mL, but relatively unaffected by the size of the dominant follicle. Furthermore, resulting incidences of ovulation were decreased at

greater progesterone concentrations and presence of a CL, and increased at greater estradiol concentrations and presence of follicles >13.5 mm. In cows with or without a CL, the presence of a follicle >13.5 mm did not increase mean LH concentration or incidence of ovulation. We conclude that when progesterone concentration exceeded 0.5 ng/mL at the time of GnRH treatment, subsequent LH concentrations and ovulation were suppressed. At that same concentration of progesterone or when concentrations of estradiol were ≥ 4 pg/mL, TAI pregnancy outcomes were improved in the face of similar incidences of ovulation suggesting greater progesterone or lesser estradiol at the time of AI may inhibit pregnancy establishment by other mechanisms.

Key words: estradiol, gonadotropin-releasing hormone-induced luteinizing hormone release, ovulation, progesterone

INTRODUCTION

Controlling follicular development and corpus luteum (CL) function are essential components of timed AI (TAI) programs. Superior ovulatory responses to GnRH to start and end the traditional Ovsynch TAI program [GnRH-7 d-PGF_{2α}-48 to 72 h-GnRH-TAI 72 h after PGF_{2α}] facilitate acceptable pregnancy per AI (P/AI; Pursley et al., 1997; Stevenson et al., 2012; Bisinotto et al., 2015). Few studies have reported concentrations of LH after GnRH in lactating dairy cows (Lucy and Stevenson, 1986; Souza et al., 2009) and none associated with the sequence of GnRH treatments in a TAI program. A recent study of 24 cows evaluated the effect of progesterone concentration on GnRH-induced LH release in a TAI setting (Giordano et al., 2012), but insufficient numbers of observations prevented any conclusions regarding the effects of GnRH-induced LH release on ovulation success in the face of the authors' defined low and high progesterone concentrations. Furthermore, the effects of estradiol on LH release in that study were not examined in its relationship to facilitating LH release and subsequent ovulation. The

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relationship of LH release to GnRH, subsequent ovulation, and concentrations of estradiol and progesterone of milked cows subjected to TAI programs has not been documented.

The importance of further understanding of these relationships is critical to enhancing the success of TAI programs. In the absence of any presynchronization treatment, synchronization of follicle growth by inducing ovulation in response to the first GnRH treatment of the TAI program occurs in only 45 to 50% of dairy cows (Pursley et al., 1995; Moreira et al., 2000). In addition, approximately 50 to 66% of dairy cows (Pursley et al., 1995; Vasconcelos et al., 1999) in various stages of the estrous cycle ovulate in response to GnRH. Ovulation (Stevenson et al., 2008) and GnRH-induced LH release are suppressed in the presence of a CL and at larger concentrations of progesterone in dairy cattle (Giordano et al., 2012; Pulley et al., 2015).

A second limitation to success of TAI programs is the inability of a single dose of PGF_{2α} to induce complete CL regression. To achieve high P/AI, concentrations of progesterone on the day of TAI must be relatively low (<0.4 ng/mL) in lactating dairy cows (Santos et al., 2010; Wiltbank et al., 2014). Administering PGF_{2α} as a single dose on d 7 or as 2 doses on d 5 and 6 after GnRH usually results in only 70 to 84% of cows with progesterone <0.3 ng/mL on the day of the TAI (Santos et al., 2010), and likely influences the characteristics of GnRH-induced LH release when progesterone concentrations are at or near baseline at the final GnRH treatment and subsequent P/AI.

A third limitation is the inability to synchronize ovulation between 24 and 32 h after the final GnRH treatment (Pursley et al., 1995). Synchronized ovulation averages 85% in dairy cows (Santos et al., 2010), and this percentage seems to decrease when cows are exposed to heat stress because of the supposed deleterious effects of hyperthermia on ovulation (López-Gatiús et al., 2005). Of the 3 identified limitations, 2 are related to the success of ovulation, which is dependent on GnRH-induced LH release and its in vivo pre-GnRH steroid milieu.

Progesterone and estradiol regulate LH secretion from the anterior pituitary in ruminants (Goodman and Karsch, 1980; Schoenemann et al., 1985; Nett et al., 2002). Steroids modulate LH release through indirect mechanisms that regulate hypothalamic GnRH secretion or directly on the pituitary by enhancing or suppressing pituitary response to GnRH (Schoenemann et al., 1985; Baratta et al., 1994; Rispoli and Nett, 2005). Increase in estradiol secretion by the preovulatory follicle during the preovulatory period increases the sensitivity of the anterior pituitary to GnRH by upregulating GnRH receptor mRNA in gonadotrophs

(Schoenemann et al., 1985). In addition, estradiol enhances hypothalamic GnRH secretion, eventually leading to the preovulatory GnRH surge, which subsequently initiates the LH surge. In contrast, in the presence of a functional CL, progesterone seems to block the stimulatory effects of estradiol at the hypothalamus (Schoenemann et al., 1985; Girmus and Wise, 1992) and possibly at the anterior pituitary (Baratta et al., 1994; Rispoli and Nett, 2005).

Because ovulation is solely dependent on spontaneous or exogenous GnRH-induced LH release, which is a key component of successful TAI programs, we hypothesized that concentrations of estradiol and progesterone likely facilitate or inhibit GnRH-induced LH release, respectively. Therefore, the objective of the present investigation was to determine the effects of the presence of a CL, dominant follicle, and acute effects of varying concentrations of progesterone and estradiol on GnRH-induced LH release and ovulatory responses in lactating cows subjected to a TAI program before first AI.

MATERIALS AND METHODS

The data for the present study came from our recently published (Pulley et al., 2015) report that was designed to determine the incidence of spontaneous and predictable GnRH-induced LH surges and subsequent ovulation in lactating dairy cows enrolled in a TAI program preceded by the presynchronization of estrous cycles. Ancillary measures of progesterone, estradiol, and ovarian structures also were made to confirm our previous findings in response to the same 2 treatments (Stevenson et al., 2012) as well as improved P/AI in a previous large 4-herd study (Stevenson and Pulley, 2012). The purpose of the present investigation was to examine in more detail the relationships of estradiol and progesterone to GnRH-induced LH release and subsequent ovulation.

Cows, Housing, and Diets

The previous study from which these data were derived was approved by the Kansas State University Institutional Animal Care and Use Committee. Seventy lactating Holstein cows were enrolled at calving from September 2011 through March 2012 at the Kansas State University Dairy Teaching and Research Center. First-lactation cows ($n = 45$) averaged 42.4 ± 0.5 kg of ECM per day (61.3 ± 0.8 DIM) and 25 multiple-lactation cows averaged 51.5 ± 1.3 kg per day (60.7 ± 1.1 DIM). Cows were considered to be healthy and housed individually in a tie-stall barn equipped with individual feed boxes, automatic water basins, and stall mats covered with wood shavings. Cows were moved to

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