J. Dairy Sci. 98:1–16
http://dx.doi.org/10.3168/jds.2014-8954

Meta-analysis of progesterone supplementation during timed artificial insemination programs in dairy cows

R. S. Bisinotto,* I. J. Lean,† W. W. Thatcher,* and J. E. P. Santos*[1]
*Department of Animal Sciences, D.H. Barron Reproductive and Perinatal Biology Research Program, University of Florida, Gainesville 32611
†SBScibus, PO Box 660, Camden 2570, New South Wales, Australia

ABSTRACT

A systematic review of the literature was performed with the objective to evaluate the effects of progesterone supplementation using a single intravaginal insert during timed artificial insemination (AI) programs on fertility in lactating dairy cows. A total of 25 randomized controlled studies including 8,285 supplemented cows and 8,398 untreated controls were included in the meta-analysis. Information regarding the presence of corpus luteum (CL) at the initiation of the synchronization protocol was available for 6,883 supplemented cows and 6,879 untreated controls in 21 experiments. Studies were classified based on service number (first AI vs. resynchronized AI), use of presynchronization (yes vs. no), and insemination of cows in estrus during the synchronization protocol (inseminated in estrus and timed AI vs. timed AI only). Reproductive outcomes of interest were pregnancy per AI (P/AI) measured on d 32 (27 to 42) and 60 (41 to 71) after AI, and pregnancy loss between d 32 and 60 of gestation. Random effects meta-analyses were conducted and treatment effect was summarized into a pooled risk ratio with the Knapp-Hartung modification (RR_{K+H}). The effect of moderator variables was assessed using meta-regression analyses. Progesterone supplementation increased the risk of pregnancy on d 32 [RR_{K+H} = 1.08; 95% confidence interval (CI) = 1.02–1.14] and 60 after AI (RR_{K+H} = 1.10; 95% CI = 1.03–1.17). The benefit of progesterone supplementation was observed mainly in cows lacking a CL at the initiation of the timed AI program (d 60: RR_{K+H} = 1.18; 95% CI = 1.07–1.30) rather than those with CL (d 60: RR_{K+H} = 1.06; 95% CI = 0.99–1.12). Progesterone supplementation benefited P/AI in studies in which all cows were inseminated at timed AI (d 60: RR_{K+H} = 1.20; 95% CI = 1.10–1.29), but not in studies in which cows could be inseminated in estrus during the timed AI program (d 60: RR_{K+H} = 1.04; 95% CI = 0.92–1.16). Progesterone supplementation tended to reduce the risk of pregnancy loss (RR_{K+H} = 0.84; 95% CI = 0.67–1.00). Service number and presynchronization did not influence the effect of progesterone supplementation on fertility. In summary, progesterone supplementation using a single intravaginal insert during the timed AI program increased P/AI mostly in cows without CL and reduced the risk of pregnancy loss in lactating dairy cows. Insemination of cows in estrus during the synchronization protocol eliminated the benefit of supplemental progesterone on P/AI.
Key words: controlled internal drug release (CIDR), corpus luteum, progesterone, reproduction

INTRODUCTION

Mounting evidence indicates that insufficient concentrations of progesterone during the development of the ovulatory follicle is a major impediment for fertility in high-producing dairy cows subjected to timed AI programs (Bisinotto et al., 2014; Wiltbank et al., 2014). Approximately 30% of the cows lack a corpus luteum (**CL**) at the initiation of the synchronization protocol (Fricke et al., 2003; Stevenson et al., 2008; Bisinotto et al., 2010a), which encompasses anovular and estrous cyclic cows. This cohort, when subjected to timed AI protocols, ovulates first-wave follicles that develop under low concentrations of progesterone and result in reduced pregnancy per AI (**P/AI**) compared with herdmates whose follicles grow during diestrus (Bisinotto et al., 2010a; Denicol et al., 2012).

Lactating dairy cows have lower concentrations of progesterone in plasma during diestrus compared with nonlactating heifers (Sartori et al., 2004) because of the extensive catabolism by the splanchnic tissues resulting from increased feed intake (Sangsritavong et al., 2002; Wiltbank et al., 2014). Reduced progesterone concentrations has been linked to increased growth rate of the ovulatory follicle (Cerri et al., 2011b), impaired embryo quality (Rivera et al., 2011), and reduced P/AI in lactating cows (Fonseca et al., 1983; Meisterling and Dailey, 1987). The reduced concentrations of progesterone in lactating cows compared with dairy heifers has been suggested as one of the reasons for

Received October 9, 2014.
Accepted December 11, 2014.
[1]Corresponding author: jepsantos@ufl.edu

the reduced fertility with onset of lactation (Sartori et al., 2002, 2004). Lactating cows classified as having low progesterone concentrations in the week preceding spontaneous estrus had less P/AI than herdmates with high concentrations of progesterone during the same period (Folman et al., 1973; Fonseca et al., 1983; Meisterling and Dailey, 1987). Finally, dairy cows selected for high fertility, based on estimated breeding values, had greater progesterone concentrations during diestrus compared with contemporaneous herdmates selected against fertility traits (Moore et al., 2014). Although in many of the aforementioned studies the experimental designs did not allow for the establishment of causality, these results point out that high concentration of progesterone during follicle development is important for fertility in dairy cows. However, supplementing progesterone using a single intravaginal insert has not enhanced fertility in a consistent manner (Rabiee et al., 2004). Improved P/AI has been reported in some (Stevenson et al., 2006; Bisinotto et al., 2010b; Colazo et al., 2013), but not all studies (Galvão et al., 2004; Lima et al., 2009; Bilby et al., 2013; Chebel et al., 2013). Identifying the sources of this heterogeneity is critical not only for understanding the mechanisms by which progesterone before AI affects fertility, but also for the development of supplementation strategies that improve reproductive performance and optimize the use of hormones in dairy cows.

A single intravaginal insert increases progesterone concentrations in plasma of lactating dairy cows by approximately 0.8 ng/mL (Cerri et al., 2009a; Lima et al., 2009), which is less than typically observed in cows in diestrus. In fact, a narrative review of the literature using studies only with high-producing dairy cows suggested that response to a progesterone insert during the timed AI protocol did not improve P/AI of anovular cows (Bisinotto and Santos, 2011), but did improve that of cows in diestrus. Those authors suggested that a single insert delivers sufficient progesterone to improve fertility in estrous cyclic cows by incrementing plasma concentrations during the development of the ovulatory follicle (Bisinotto and Santos, 2011), which has been observed by others (Bartolome et al., 2009; Bisinotto et al., 2010b).

Progesterone supplementation during timed AI protocols improves synchrony of ovulation by minimizing the risk of ovulation before the day of scheduled AI. Presynchronization protocols also improve synchrony of ovulation by increasing the proportion of cows in early diestrus when the timed AI protocol initiates (Moreira et al., 2001). Thus, it is possible that response to progesterone supplementation might be influenced by presynchronizing the estrous cycle before timed AI. Finally, the benefit of progesterone supplementation can be diminished by insemination of cows in estrus during the timed AI program. Five to 7% of the cows enrolled in timed AI programs are observed in estrus between the first GnRH and the $PGF_{2\alpha}$ injection (Chebel et al., 2013; Bisinotto et al., 2015). These cows that show early estrus are unlikely to become pregnant at timed AI. Progesterone supplementation prevents the occurrence of spontaneous estrus, thereby benefiting P/AI when cows are inseminated at a fixed time (Stevenson et al., 2006). Conversely, delaying ovulation with supplemental progesterone prolongs the period of follicular dominance, which might reduce fertility in herds that inseminate cows in estrus during the timed AI program (Bleach et al., 2004; Cerri et al., 2009b).

Individual studies often encompass a limited number of herds with similar management practices. Therefore, this meta-analysis was designed to evaluate the effects of progesterone supplementation during the timed AI program across different managerial and physiological conditions. The main hypothesis of the present study was that supplementation with progesterone using a single intravaginal insert increases P/AI and decreases pregnancy loss in lactating dairy cows. Moreover, it was anticipated that the benefits of supplemental progesterone would be observed mainly in cows with CL at the initiation of the timed AI program, those not subjected to presynchronization, and in studies in which detection of estrus was not performed.

MATERIALS AND METHODS

Literature Search

The literature search was conducted in PubMed (http://www.ncbi.nlm.nih.gov/pubmed), ScienceDirect (http://www.sciencedirect.com), and Google Scholar (http://scholar.google.com) using the keywords dairy cow and progesterone. A total of 1,539, 7,611, and 25,200 results were obtained in each engine, respectively. Additional studies were obtained directly from researchers in the field of reproductive biology. Results from the online search and personal communications were assessed individually for the initial screening to be considered for the meta-analysis.

Inclusion and Exclusion Criteria

We considered only randomized controlled studies using a single intravaginal insert during the timed AI program that measured pregnancy outcomes in lactating dairy cows. Hence, studies in which progesterone supplementation occurred before the initiation of the timed AI program as a presynchronization strategy or after insemination were not included. Studies were