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Effects of flunixin meglumine on pregnancy establishment in beef cattle[1]

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ABSTRACT: The objective of this research was to determine effects of a single injection of the PG synthesis inhibitor flunixin meglumine (FM; 1.1 mg/kg of BW, intramuscularly) approximately 13 d (range 10 to 15 d) after AI on pregnancy establishment. Three experiments were conducted using estrus-synchronized heifers and cows. Technicians and AI sires were equally represented across treatments within locations and experiments. Bulls were introduced on the day of FM treatment. Pregnancy to AI was diagnosed 28 to 50 d after AI using ultrasonography. In Exp. 1, beef heifers (n = 1,221) were divided within 5 locations to receive FM or no further treatment (control). At insemination, heifers were divided into 2 similar pastures or pens, and approximately 13 d later, 1 group of heifers within each location was processed through an animal handling facility to administer FM treatment. There was no location × treatment interaction ($P = 0.62$) on AI pregnancy rates, so data were pooled. Pregnancy rates to AI were reduced ($P = 0.02$) among heifers receiving the FM treatment procedure (66%) compared with control heifers (72%). In Exp. 2, suckled beef cows (n = 719) were assigned within 2 locations to receive FM or no further treatment (control) approximately 13 d after AI. At insemination, control and FM cows were divided into separate pastures, and only FM cows were handled after AI for the FM treatment procedure. There was no location × treatment interaction ($P = 0.75$), so data were pooled. Pregnancy rates to AI did not differ ($P = 0.80$) between FM (57%) and control cows (59%). In Exp 3, beef heifers (n = 247) and suckled beef cows (n = 335) from 1 location received no injection (control) or injection of FM approximately 13 d after AI when all cows and heifers were processed through a working facility. Pregnancy rates to AI were not different ($P = 0.37$) between FM (45%) and control (42%) cows or between FM (56%) and control (55%) heifers. We conclude FM administration at 1.1 mg/kg of BW approximately 13 d after AI did not improve pregnancy establishment in beef cows and heifers and that the effects of handling heifers at this time may decrease pregnancy establishment.

Key words: cattle, flunixin meglumine, pregnancy establishment

INTRODUCTION

Fertilization occurs in 90 to 100% of beef cows that are bred by natural service or AI (Maurer and Chenault, 1983; Sreenan and Diskin, 1983). However, conception rates to a single service are generally less than 70%, indicating that embryonic loss occurs in 20 to 30% of cows. This loss has been characterized (Hanly, 1961; Maurer and Chenault, 1983) but is difficult to measure because ultrasound visualization of a fetal heartbeat is not discernable until approximately 27 d after breeding. The majority of early embryonic loss occurs because the embryo fails to produce sufficient interferon tau (**IFN-τ**) to initiate maternal recognition of pregnancy approximately 14 d after breeding (Bazer et al., 1991; Roberts, 1991; Thatcher et al., 1994). Without sufficient IFN-τ, the uterus produces $PGF_{2\alpha}$, causing cor-

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pora lutea regression and loss of progesterone secretion (Roberts et al., 1992, 1996; Thatcher et al., 2001).

Flunixin meglumine (**FM**) is a potent nonsteroidal, anti-inflammatory agent that inhibits cyclooxygenase, preventing conversion of arachadonic acid to $PGF_{2\alpha}$ (Anderson et al., 1990; Odensvik, 1995). Intramuscular treatment with FM decreased serum $PGF_{2\alpha}$ metabolite (**PGFM**) concentrations in nonlactating cows for at least 12 h (Guilbault et al., 1987). Cows that received FM 14 d after AI had 10% greater AI pregnancy rates and 21% less serum PGFM than controls (Merrill et al., 2007). In that study, AI pregnancy rates of transported and nontransported cows were 59 and 64%, respectively, whereas AI pregnancy rates of transported + FM and nontransported + FM cows were 70 and 73%, respectively. We hypothesized that the pregnancy rates of transported cows were not different than nontransported cows (Merrill et al., 2007) because all cows were gathered and handled to administer FM or collect blood. The objective of this study was to determine effects of a single injection of FM approximately 14 d after AI on pregnancy establishment in the absence of handling stress.

MATERIALS AND METHODS

This research was conducted in accordance with procedures approved by the Fort Keogh Animal Care and Use Committee.

Animals and Treatments

In Exp. 1, 1,221 predominantly Angus heifers [BW: 365 ± 1.54 kg; BCS: 5.23 ± 0.03 (scale: 1 to 9; Whitman, 1975)] were divided within 5 locations to receive FM or no further treatment (control). Estrus was synchronized in heifers with 0.5 mg·animal^{-1}·d^{-1} melengestrol acetate (**MGA**) for 14 d and $PGF_{2\alpha}$ (500 µg of cloprostenol sodium) 19 d after the last oral treatment with MGA. Heifers were artificially inseminated approximately 12 h after observation of estrus, and heifers that were not detected in estrus were not used for this experiment. Heifers at each location were stratified by AI date and assigned within strata into 2 similar pastures or pens (with the same diet) at AI. Approximately 13 d (range 10 to 15 d) after AI, 1 group of heifers within each location was processed through an animal handling facility to administer a single intramuscular (**i.m.**) injection of FM (1.1 mg/kg of BW). Immediately after the FM treatment procedure, these heifers were placed into the same pasture as control heifers, and bulls were introduced for the remainder of the breeding season. Pregnancy to AI was diagnosed approximately 35 d after AI using transrectal ultrasonography with a 5-MHz probe.

In Exp. 2, Angus-cross cows (n = 705) at 2 locations were stratified by calving date and assigned within strata to receive FM or control treatment as described in

Exp. 1. Estrus was synchronized with the Select Synch (100 µg of GnRH on d −7 and 25 mg of $PGF_{2\alpha}$ on d 0; location 1, n = 256) or Select Synch + CIDR protocol [addition of a controlled internal drug releasing device (**CIDR**; Pfizer, New York, NY); location 2, n = 449]. Cows were artificially inseminated approximately 12 h after observation of estrus. Cows not detected in estrus by 72 h (location 1) or 80 h (location 2) after $PGF_{2\alpha}$ received timed AI with GnRH (100 µg, i.m.). At insemination, control and FM cows were divided into separate, but similar, pastures, and only FM cows were gathered and processed through a handling facility at the time of FM injection approximately 13 d (range 11 to 13.5 d) after AI. Immediately after this FM treatment procedure, these cows were placed into the same pasture as control cows, and bulls were introduced for the remainder of the breeding season. Pregnancy to AI was diagnosed approximately 47 d after AI using transrectal ultrasonography with a 5-MHz probe.

In Exp. 3, heifers (n = 247) and cows (n = 335) from 1 location were stratified by age (heifers) and calving date (cows) and assigned within strata to receive no injection (control) or an injection of FM when processed through an animal handling facility approximately 13 d later. The genetic composition of cows and about one-half of the heifers in this experiment was CGC Composite (1/2 Red Angus, 1/4 Charolais, 1/4 Tarentaise), whereas the remaining heifers were predominantly Angus. Estrus was synchronized among heifers using the Select Synch + CIDR protocol as described previously. Heifers were artificially inseminated approximately 12 h after observation in estrus, and those heifers not observed in estrus by 72 h after $PGF_{2\alpha}$ received GnRH (100 µg, i.m.) + timed AI. Estrus was synchronized among cows using the CO-Synch + CIDR protocol (100 µg of GnRH on d −9, 25 mg of $PGF_{2\alpha}$ on d −2, and 100 µg of GnRH and timed AI on d 0). Cows that were observed in estrus before 36 h after $PGF_{2\alpha}$ were artificially inseminated approximately 12 h after first observed estrus. Cows not detected in estrus received GnRH (100 µg, i.m.) + timed AI at 48 h after $PGF_{2\alpha}$. At 13 d after timed AI, all cows and heifers were handled through a working facility, but only one-half of each age group received the FM treatment. Bulls were introduced into breeding pastures after treatment on d 13 after timed AI. Initial pregnancy diagnosis was performed 29 d and confirmed 75 d (heifers) or 99 d (cows) after timed AI using transrectal ultrasonography with a 5-MHz probe.

Statistical Analyses

Factors affecting pregnancy rates in each experiment were evaluated using logistic regression (SAS Inst. Inc., Cary, NC). The initial model included fixed effects of treatment and location (Exp. 1 and 2), interval from AI to day of FM (one-half day increments) as a continuous variable, and the interactions of treatment × time interval and treatment × location. Because the interval
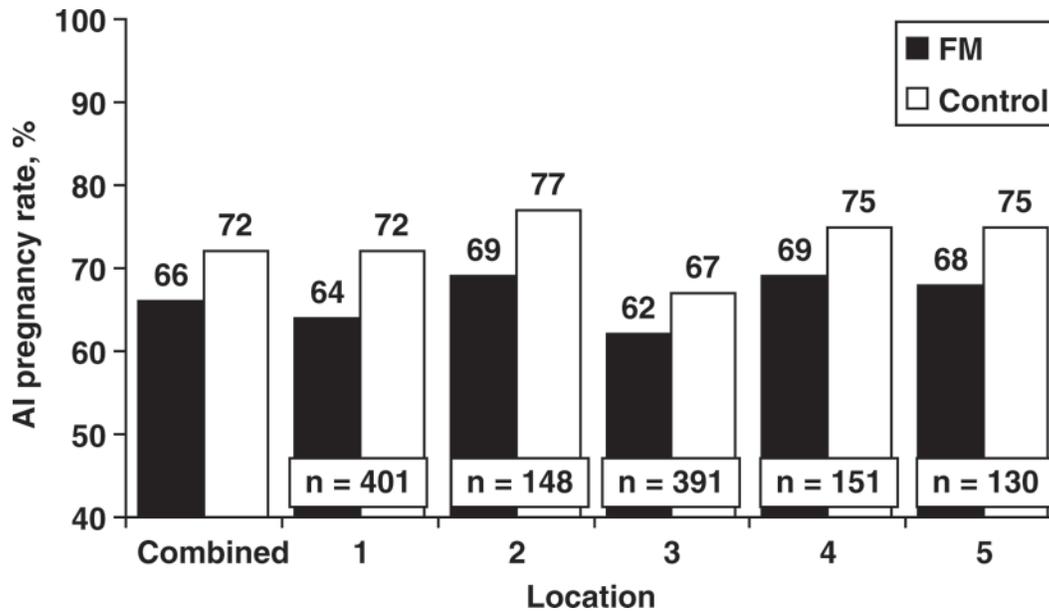
Figure 1. Pregnancy rate to AI for heifers from 5 locations (denoted on x-axis) in Exp. 1 that received flunixin meglumine (FM) or no further treatment (control) approximately 13 d after AI ($P = 0.02$, treatment). Only FM heifers were gathered from pasture and processed for treatment administration.

from AI to day of treatment varied based on interval to estrus after synchronization, we evaluated the effect of interval from AI to FM on pregnancy rate (treatment × interval interaction). If interval from $PGF_{2\alpha}$ to AI had an effect on pregnancy rate, then interval from AI to FM is only separable if differences exist between control and FM heifers (Exp. 1) and cows (Exp. 2). Factors not affecting pregnancy rate ($P > 0.2$) were sequentially removed from the model using a step-down approach. Inseminators and AI sires were nested within locations, but each was approximately equally represented across treatments within location.

RESULTS

In Exp. 1, there was no location × FM treatment procedure interaction ($P = 0.62$) on pregnancy rates to AI, so data were pooled. Pregnancy rates to AI were reduced ($P = 0.02$) among heifers that were processed through a chute and administered FM (66%) compared with control heifers (72%) that remained at pasture (Figure 1). This response between heifers receiving the FM treatment procedure or control treatment was consistent across locations (Figure 1). As the interval from $PGF_{2\alpha}$ to AI increased, pregnancy rate also increased ($P = 0.0003$) in FM and control heifers (Figure 2). The AI pregnancy rate was not affected ($P = 0.32$) by any treatment-interval interaction.

In Exp. 2, there was no location × treatment interaction ($P = 0.75$) on pregnancy rates to AI, so data were pooled. Pregnancy rates to AI did not differ ($P = 0.80$) between FM treatment procedure (57%) and control cows (58%; Figure 3) and was not affected by interval from $PGF_{2\alpha}$ to AI ($P = 0.48$) or treatment × interval interaction ($P = 0.17$). Pregnancy rates were greater (P

< 0.0001) for cows at location 2 (66%) than location 1 (44%; Figure 3).

In Exp. 3, pregnancy rates to AI were greater ($P = 0.04$) for heifers than cows, but did not differ ($P = 0.37$) between FM-injected (50%) and control (48%) females (Figure 4). There was no interaction ($P = 0.81$) of cow age × treatment on pregnancy rate to AI (Figure 4). There was no interval × treatment interaction ($P = 0.55$) on AI pregnancy rate.

DISCUSSION

Flunixin meglumine is a potent nonsteroidal, anti-inflammatory agent that inhibits cyclooxygenase, thereby preventing conversion of arachadonic acid to $PGF_{2\alpha}$ (Anderson et al., 1990; Odensvik, 1995). Intramuscular treatment with FM has decreased plasma PGFM concentrations in nonlactating cows for at least 12 h (Guilbault et al., 1987). This mode of action and previous reports of increased pregnancy rates when FM was administered to cattle after AI (Merrill et al., 2007) or at the time of embryo transfer (Purcell et al., 2005; Scenna et al., 2005) led to the expectation of favorable responses to FM treatment. In the study by Merrill et al. (2007), FM was administered approximately 14 d after AI with or without transportation stress and was presumably acting in an antiluteolytic manner to suppress $PGF_{2\alpha}$ synthesis and perhaps allow additional time for maternal recognition of pregnancy to occur. Administration of FM at the time of embryo transfer is expected to suppress $PGF_{2\alpha}$ synthesis and secretion in response to uterine manipulation (Wann and Randel, 1990) that might have embryo toxic effects (Buford et al., 1996; Seals et al., 1998; Scenna et al., 2004). However, $PGF_{2\alpha}$ does not appear to be embryo toxic after d 8
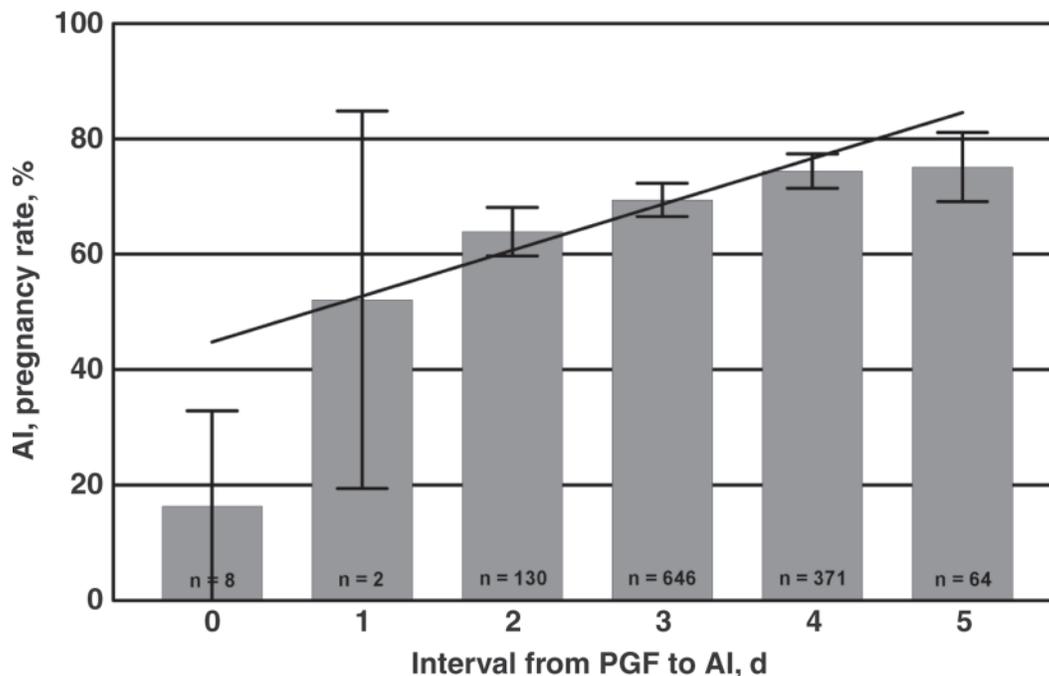
Figure 2. Least squares means (±SE) and regression line of AI pregnancy rate for all beef heifers (treated and control) in Exp. 1 by interval from $PGF_{2\alpha}$ to AI ($P = 0.0003$). There was no treatment × interval interaction ($P = 0.32$) on AI pregnancy rate.

after fertilization (Seals et al., 1998). Controls in those studies were also worked through a chute, in contrast to Exp. 1 and 2 in which control heifers or cows were not handled and exposed to stress after AI. In the present study, AI pregnancy rates in heifers were decreased, relative to control heifers that were not handled, when they were processed through a chute and administered FM (Exp. 1), and no response was observed to similar paradigms in cows (Exp. 2). We are unaware of an explanation why FM administration to heifers would have different physiological effects than administration to cows. Our contrasting results between Exp. 1 and Exp. 2 lead us to speculate that heifers may have been more sensitive than cows to the effects of handling or unknown negative effects of FM injection, or that the dosage of FM used was effective toward alleviating effects of handling in cows but not in heifers.

The design of Exp. 3 differed from that of Exp. 1 and Exp. 2 in that all heifers and cows were gathered and processed through a cattle handling facility in Exp. 3, whereas only treated females were processed in Exp. 1 and Exp. 2 (because they belonged to commercial producers). We speculate that the lack of response to treatments in Exp. 2 and Exp. 3 may result from prior habituation to processing as observed by Waynert et al. (1999). The cows used in Exp. 2 had been worked through a chute for routine husbandry. The heifers used in Exp. 3 were handled through working facilities at least 12 times at Fort Keogh as part of routine data collection before the imposition of treatments for this study. Taken together, a logical conclusion of these experiments is that processing relatively naive heifers through a chute may have caused sufficient stress to re-

duce pregnancy rate in the FM-treated-processed heifers of Exp. 1.

Others have reported that stress from transportation at critical times after breeding can impair establishment of pregnancy (Harrington et al., 1995). Merrill et al. (2007) reported that cortisol concentration in serum collected from heifers before transportation was greater than that of cows, potentially reflecting greater stress of the heifers from handling. Subsequent transportation for 2.5 to 3 h resulted in an approximate 2-fold increase in cortisol concentration among cows, but very
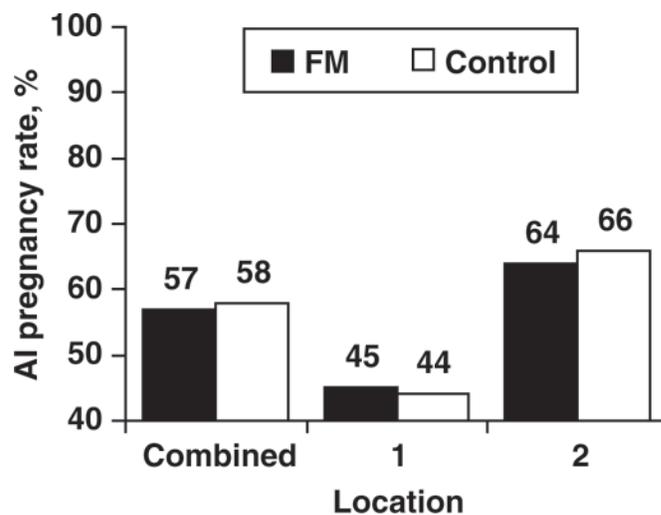

Figure 3. Pregnancy rate to AI for beef cows in Exp. 2 that received flunixin meglumine (FM) or no further treatment (control) approximately 13 d after AI ($P = 0.80$, treatment). Only FM cows were gathered from pasture and processed for treatment administration.

little change in cortisol concentration among the heifers. Merrill et al. (2007) also reported that these FM-treated heifers and cows had greater pregnancy rates than untreated cohorts, irrespective of whether or not they were transported. An alternative interpretation of the results of Merrill et al. (2007), consistent with the results from the present studies, is that all heifers and cows were subject to sufficient stress from handling before transport to reduce pregnancy rates and that treatment with FM mitigated (or partially mitigated) effects of the stress. Thus, FM administration may decrease embryonic loss among cows and heifers subject to unavoidable stress (in situations where producers must handle cattle after AI) by suppressing $PGF_{2\alpha}$ concentrations in the bloodstream. It is also possible that heifers are more sensitive to $PGF_{2\alpha}$ than cows. Others have demonstrated a similar occurrence in pigs in which the induced corpora lutea in prepubertal gilts was more susceptible to $PGF_{2\alpha}$ luteolysis than a spontaneously formed corpora lutea in the mature gilt (Puglisi et al., 1979). At the dosage evaluated in the present studies, a single administration of FM did not improve pregnancy establishment above that of nonstressed females. The dosage of FM chosen for the current study was based on the dosage used in previous studies in cattle (Guilbault et al., 1987; Merrill et al., 2007).

Several other laboratories have used postbreeding strategies in an attempt to increase pregnancy rates in cattle. Postbreeding strategies have included daily progesterone administration to repeat breeder dairy cows (Wiltbank et al., 1956); exogenous progesterone delivery via a progesterone-releasing intravaginal devices or CIDR to dairy cows (Robinson et al., 1989; Macmillian et al., 1991; Stevenson et al., 2007), beef cows (Larson et al., 2009), or heifers (Van Cleeff et al., 1991); use of GnRH, GnRH agonists, or hCG to stimulate endogenous progesterone secretion in cows (Macmillian et al., 1986; Santos et al., 2001; Stevenson et al., 2007) or heifers (Funston et al., 2005); and daily or single injections of recombinant IFN-τ in heifers (Barros et al., 1992). Effects of the above strategies on pregnancy rates compared with contemporary control females were variable (including herd × treatment effects; Funston et al., 2005; Stevenson et al., 2007) with some studies demonstrating increased pregnancy rates (Macmillian et al., 1986, 1991; Robinson et al., 1989; Santos et al., 2001), some decreased (Barros et al., 1992), and some having no effect (Wiltbank et al., 1956; Macmillian et al., 1991; Van Cleeff et al., 1991; Larson et al., 2009). None of the postbreeding strategies resulted in increased pregnancy rates in heifers (Van Cleeff et al., 1991; Barros et al., 1992; Funston et al., 2005). Even administration of recombinant IFN-τ, which required repeated handling of heifers, resulted in decreased pregnancy rates (Barros et al., 1992). These data are consistent with the results reported here that perhaps the handling of heifers after breeding has a negative effect on pregnancy establishment. Prostaglandin synthesis inhibitors, such as FM (Merrill et al., 2007) or ibuprofen lysinate (Elli et al.,
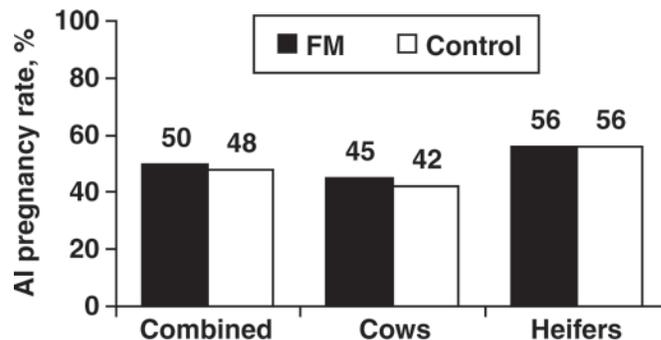

Figure 4. Pregnancy rate to AI for beef heifers and cows in Exp. 3 that received flunixin meglumine (FM) or no treatment (control) approximately 13 d after AI ($P = 0.37$, treatment). Both FM and control females were gathered from pasture and processed for treatment administration, but only FM females received an injection.

2001), are the only postbreeding treatments administered during the early to mid-luteal phase that have increased pregnancy establishment in heifers. It is possible that the reason heifers in Exp. 3 did not have increased pregnancy rates in response to FM in the current study is because these heifers may have become acclimated to gathering and handling. The heifers in Exp. 3 were handled through working facilities at least 12 times at Fort Keogh as part of routine data collection before FM or control treatment.

Although not an objective of this study, an interesting finding is the difference in pregnancy rate for heifers based on interval from $PGF_{2\alpha}$ to AI (or equivalently from AI to treatment) when synchronized with the MGA/$PGF_{2\alpha}$ protocol (Exp. 1). These data were analyzed to determine if day of FM treatment after AI affected pregnancy rates, but because the interval from $PGF_{2\alpha}$ to treatment was constant, the 2 effects were not separable. This increase in AI pregnancy rates was consistent in FM and control heifers and may suggest that rapid ovulatory follicle growth in the absence of progesterone (prolonged proestrus) results in greater fertility. The heifers that were in estrus later during the synchronization period likely had undergone follicular turnover just before $PGF_{2\alpha}$ administration and, thus, would have experienced follicular growth in the absence of progesterone. The follicles that ovulated from these heifers would therefore have been exposed to increased LH pulse frequency (Bergfeld et al., 1995) during a longer period of follicular dominance that may have stimulated theca and granulosa cells of the dominant follicle, resulting in ovulation of a larger follicle (Carvalho et al., 2008) and increased progesterone secretion by the early corpus luteum. Ovulation of larger follicles among heifers has resulted in greater pregnancy rates (Perry et al., 2007). Unlike Bridges et al. (2008), who reported improved pregnancy rates for cows induced to ovulate with GnRH after a prolonged proestrus, all of the heifers used in this study were observed in estrus approximately 12 h before AI. Pulse frequency of LH, ovulatory follicle size, and subsequent progesterone concentrations were not measured in the present study,

so the exact mechanism(s) by which a prolonged interval from PGF to estrus or a decreased interval from estrus to FM improved fertility are unknown.

During maternal recognition of pregnancy, the embryo must produce sufficient IFN-τ to prevent $PGF_{2\alpha}$ release by the uterus to establish pregnancy. Subjecting cattle to stressors, such as handling stress, may be sufficient in some females to interfere with embryonic inhibition of $PGF_{2\alpha}$ release that signals maternal recognition of pregnancy. Experiments reported here provide evidence that handling stress may interfere with this process more in heifers than cows. A single injection of FM (1.1 mg/kg of BW, i.m.) was inadequate to overcome the effects of handling stress in heifers.

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