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ABSTRACT

Cows exhibiting estrus near fixed-time artificial insemination (AI) had greater pregnancy success than cows not showing estrus. The objective of this study was to determine the relationship between follicle size and peak estradiol concentration between cows that did or did not exhibit estrus during a fixed-time AI protocol. Ovulation was synchronized in beef cows by applying the CO-Synch protocol [GnRH (100 μg) on day-9, prostaglandin $F_{2\alpha}$ ($PGF2\alpha$; 25 mg) on day-2, and a second injection of GnRH 48 h after $PGF_{2\alpha}$ (day 0)] to both suckled (experiment 1) and nonsuckled (experiment 2) cows. Follicle size (day 0) and ovulation (day 2) was determined by ultrasonography. Blood samples were collected every 3 or 4 h beginning at the time of $PGF_{2\alpha}$ injection (0 h). Estrus was detected by visual observation with the aid of estrus-detection patches, and cows that ovulated were classified as exhibited estrus ($n = 46$) or did not exhibit estrus ($n = 63$). In both suckled and nonsuckled cows, there was a positive relationship between all cows ($P < 0.05$) and among those that exhibited estrus ($P < 0.05$) between follicle size and peak estradiol concentration, but no linear relationship ($P > 0.50$) between follicle size and peak estradiol concentration was observed among cows not exhibiting estrus. Cows that exhibited estrus had greater ($P < 0.01$) peak estradiol concentrations than cows that did not exhibit estrus. Suckled cows exhibiting standing estrus had greater ($P < 0.001$) preovulatory concentrations of estradiol beginning 6 h (replicate 1) or 4 h (replicate 2) after the injection of $PGF_{2\alpha}$ on day-2 compared with cows not exhibiting standing estrus. Nonsuckled cows exhibiting standing estrus had greater ($P < 0.001$) preovulatory concentrations of estradiol beginning at the injection of $PGF_{2\alpha}$ on day-2 compared with cows not exhibiting standing estrus. Furthermore, cows that exhibited estrus had an increased ($P < 0.01$) rate in the rise in concentrations of estradiol following the $PGF_{2\alpha}$ to peak estradiol than cows not exhibiting estrus. In summary, follicle diameter had a positive relationship with peak concentrations of estradiol, but only among cows that exhibited standing estrus, and estradiol increased earlier in cows that exhibited estrus compared with cows that did not.

Names are necessary to report factually on available data; however, neither South Dakota State University nor the USDA guarantees nor warrants the standard of the product, and use of names by South Dakota State University or the USDA implies no approval of the product to the exclusion of others that may also be suitable.

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1. Introduction

Successful pregnancy requires synchrony between embryo development and the uterus [1], and ovarian estradiol plays an important role in establishing the timing of uterine receptivity [2]. More specifically, estradiol plays a direct role in regulating oviductal secreted glycoproteins [3] and in the regulation of the biological clock in the uterus [4]. Concentrations of estradiol peak approximately 36 h before ovulation [5] and increased preovulatory concentrations of estradiol resulted in increased fertilization success, improved embryo quality and viability [6,7], and a >60% improvement in pregnancy success [8]. Preovulatory concentrations of estradiol also have been reported to influence sperm transport [9], embryo survival [10], and the uterine environment [11–13].

Initiation of estrus in cattle occurs following a rise in circulating concentrations of estradiol [14]. Expression of P450 aromatase was usually only detected in the follicle that became dominant (≥8 mm in diameter) during the follicular wave, and expression of P450scc and P450 17α *messenger RNA* increased in the selected follicle as it continued to develop [15]. Increased concentrations of estradiol also were found in the follicular fluid of the future dominant follicle and continued to increase as the follicle continued to develop [16]. Large dominant follicles, however, can be induced to ovulate in response to GnRH-induced luteinizing hormone (LH) release that do not produce large amounts of estradiol, as measured by circulating concentrations of estradiol. Therefore, the objective of this study was to determine differences in preovulatory concentrations of estradiol in cows with different sized ovulatory follicles that did or did not exhibit standing estrus.

2. Materials and methods

2.1. Experiment 1

2.1.1. Experimental design

All procedures were approved by the South Dakota State University Institutional Animal Care and Use Committee. Postpartum (20–40 d) multiparous (aged 3–13 yr) crossbred Angus beef cows at the South Dakota State University Beef Breeding Unit were synchronized with the CO-Synch protocol in two replicates (n = 80 and 24). Cows were injected with GnRH (100 μg as 2 mL of OvaCyst intramuscular (i.m.); Teva Animal Health, St Joseph, MO) on day-9 and $PGF_{2\alpha}$ (25 mg as 5 mL of ProstaMate i.m.; Teva Animal Health) on day-2. Forty-eight hours after $PGF_{2\alpha}$ (day 0) cows received GnRH (OvaCyst; 100 μg i.m.). Cows in each replicate were maintained as a single group, and calves were allowed to suckle without restriction throughout the experiment. Cows were removed from the study if they failed to ovulate after the second injection of GnRH (n = 15). Cows that failed to ovulate had ovulatory sized follicles (11.9 ± 0.33 mm), but none of them exhibited standing estrus. Due to the possible stress associated with the frequent blood collection cows were not inseminated as part of this study.

2.1.2. Ultrasonography and estrus detection

Ovaries of all cows were examined on days-2, 0, and 2 by transrectal ultrasonography to characterize follicular development and ovulation using an Aloka 500V ultrasound with a 7.5 MHz linear probe (Aloka, Wallingford, CT). All follicles ≥8 mm in diameter were recorded. Follicle diameter was determined at the time of the second GnRH injection by averaging follicular diameter at the widest point and at a right angle to the first measurement using the internal calipers on the Aloka 500V. Ovulation was defined as the disappearance of a previously recorded large follicle from an ovary on day 2. Standing estrus was detected by visual observation every 3 h beginning on day-2 through day 2 with the aid of Estrotect (Western Point, Inc, Apple Valley, MN) estrus-detection patches. Cows that had greater than half of the patch coating removed were classified as exhibited standing estrus. In both replicates, cows that ovulated to the second GnRH injection were classified as having exhibited estrus (n = 42) or no estrus (n = 52).

2.1.3. Blood sampling

Blood samples were collected by venipuncture of the tail vein into 10 mL Vacutainer tubes (Fisher Scientific, Pittsburgh, PA) for determination of serum concentrations of estradiol. In replicate 1, blood samples were collected every 3 h from the $PGF_{2\alpha}$ injection until 84 h after the $PGF_{2\alpha}$ injection. In replicate 2, blood samples were collected every 4 h from the $PGF_{2\alpha}$ injection until 80 h after the $PGF_{2\alpha}$ injection. Blood was allowed to coagulate at room temperature for 1 h, stored at 4°C for 24 h, and centrifuged at 1,200*g* for 30 min. Serum was harvested and stored at −20°C until analysis was performed by radioimmunoassay (RIA).

2.2. Experiment 2

2.2.1. Experimental design

All procedures were approved by the South Dakota State University Institutional Animal Care and Use Committee. Postpartum multiparous (aged 3–13 yr) crossbred cows with calves weaned >30 d at the South Dakota State University Beef Breeding Unit were synchronized with the CO-Synch protocol (n = 22). Cows were injected with GnRH (100 μg as 2 mL of Cystorelin i.m.; Merial, Athens, GA) on day-9 and $PGF_{2\alpha}$ (25 mg as 5 mL of Lutalyse i.m.; Pfizer Animal Health, Madison, NJ) on day-2. Forty-eight hours after $PGF_{2\alpha}$ (day 0) cows received GnRH (Cysterelin 100 μg i.m.). Cows were maintained as a single group. Cows were removed from the study if they failed to ovulate after the second injection of GnRH (n = 2). Cows that failed to ovulate had ovulatory-sized follicles (>10 mm), but neither of them exhibited standing estrus. Because of the possible stress associated with the frequent blood collection, cows were not inseminated as part of this study.

2.2.2. Ultrasonography and estrus detection

Ovaries of all cows were examined by transrectal ultrasonography to characterize follicular development using an Aloka 500V ultrasound with a 7.5-MHz linear probe (Aloka) as described in experiment 1. Occurrence of estrus was determined at 60 h after the $PGF_{2\alpha}$ injection by coloration of Estrotect patches. Cows that had greater than half

of the patch coating removed were classified as exhibited standing estrus. Cows that ovulated to the second GnRH injection were classified as having exhibited estrus ($n = 6$) or no estrus ($n = 14$).

2.2.3. Blood sampling

Blood samples were collected by venipuncture of the tail vein into 10 mL Vacutainer tubes (Fisher Scientific, Pittsburgh, PA) for determination of serum concentrations of estradiol. Blood samples were collected at the time of the $PGF_{2\alpha}$ injection and every 3 h beginning 12 h after the $PGF_{2\alpha}$ injection until 60 h after the $PGF_{2\alpha}$ injection. Blood samples were not collected at hours 3, 6, or 9 after the $PGF_{2\alpha}$ injection due to conditions not related to the study. Blood was allowed to coagulate at room temperature for 1 h, stored at 4°C for 24 h, and centrifuged at 1,200*g* for 30 min. Serum was harvested and stored at −20°C until analysis was performed by RIA.

2.3. Radioimmunoassays

Circulating concentrations of estradiol-17β were analyzed in all samples by RIA using methodology described by Perry and Perry [12]. Intra- and interassay coefficients of variation for estradiol-17β assays were 4.0% and 15.4%: 6.1% and 9.0% for replicates 1 and 2 of experiment 1 and 5.2% and 13.0% for experiment 2. Assay sensitivity was 0.4 pg/mL.

2.4. Statistical analyses

Peak concentrations of estradiol were defined as the greatest concentration of estradiol measured after the $PGF_{2\alpha}$ injection on day-2. Concentrations of estradiol at the time of the second GnRH injection were the concentrations on day 0 at the time GnRH was administered regardless of whether estrus had been expressed or not. Rate of increase in concentrations of estradiol were determined by subtracting concentration of estradiol at the time of $PGF_{2\alpha}$ injection on day-2 from the peak concentration and dividing by the number of hours between the two samples.

Analysis of variance (PROC GLM; SAS Inst. Inc, Cary, NC) was used to determine the effect of follicle diameter (experiments 1 and 2), replicate (experiment 1), and any follicle diameter by replicate interaction (experiment 1). When no effect ($P > 0.05$) of replicate or follicle diameter by replicate interaction was detected, an analysis of covariance model was fitted using PROC GLM procedure of SAS to investigate the regression relationship between follicle diameter and estradiol concentration with replicate as a covariate. The slope of the regression of estradiol on follicle diameter was found to be similar for replicates if the interaction of diameter by replicate in the analysis of covariance model was insignificant [17].

Occurrence (yes vs no) of estrus on circulating concentrations of estradiol was determined by analysis of variance for repeated measures in SAS (Proc Mixed, [18]) for each replicate in experiment 1 and for experiment 2. Different covariance structures were modeled in the initial analysis. The indicated best fit covariance structure was autoregressive, which was used for the final analysis. The model included the independent variables of estrus, time, and the estrus by time interaction. Occurrence of estrus on circulating concentrations of estradiol was tested by the cow within estrus occurrence error term, and effects of time and estrus by time were tested by using the residual error term.

Rate of increase of estradiol from the $PGF_{2\alpha}$ injection to peak concentrations (highest detected concentration) was analyzed using PROC GLM. The model included the main effects of estrus (experiments 1 and 2) and replicate (experiment 1 only) and their interaction (experiment 1 only). Mean separation was performed using least significant differences (means ± standard error of the mean, [19]), and significance was determined at $P < 0.05$ and tendency was determined at $0.05 < P < 0.10$.

3. Results

3.1. Experiment 1

Standing estrus within 24 h of the second GnRH injection was detected in 42% of cows treated with the CO-Synch protocol (48% and 33% for replicates 1 and 2) and occurred at 45.4 ± 1.4 h and 45.2 ± 5.0 h after the injection of $PGF_{2\alpha}$ in replicates 1 and 2, respectively. There was no effect of replicate on the relationship between follicle diameter and peak estradiol concentrations detected in all cows, in cows exhibiting estrus, or in cows not exhibiting estrus ($P = 0.70$, 0.85, and 0.62, respectively). Furthermore, there was no follicle diameter by replicate effect on the relationship between follicle diameter and peak estradiol concentrations detected in all cows, in cows exhibiting estrus, or in cows not exhibiting estrus ($P = 0.95$, 0.54, and 0.67, respectively). In contrast, among all cows ($P = 0.04$) and those exhibiting estrus ($P < 0.01$), a significant positive relationship was detected between follicle diameter and peak estradiol concentrations. However, there was no relationship ($P = 0.77$) between follicle diameter and peak estradiol concentration in cows not exhibiting estrus. There was no difference ($P = 0.43$) in follicle diameter between cows that did and did not exhibit estrus (13.2 ± 0.28 and 12.9 ± 0.23 mm, respectively); however, cows that exhibited estrus had greater ($P < 0.01$) peak estradiol concentrations (12.8 ± 0.61 pg/mL) than cows not exhibiting estrus (8.1 ± 0.55 pg/mL).

For concentration of estradiol at the time of the second GnRH injection, there was no effect of replicate detected in all cows, in cows exhibiting estrus, or in cows not exhibiting estrus ($P = 0.14$, 0.32, and 0.14, respectively). Furthermore, there was no follicle diameter by replicate effect detected in all cows, in cows exhibiting estrus, or in cows not exhibiting estrus ($P = 0.25$, 0.58, and 0.16, respectively). No relationship was detected between follicle diameter and estradiol concentration at the second GnRH injection in all cows ($P = 0.34$), in cows exhibiting estrus ($P = 0.28$), or in those that did not exhibit estrus ($P = 0.66$). In contrast, cows exhibiting estrus (9.7 ± 0.61 pg/mL) had greater ($P < 0.01$) concentrations of estradiol at the second GnRH injection than cows that did not exhibit estrus (6.2 ± 0.51 pg/mL). However, half of the cows that exhibited estrus ($n = 21$) had a peak concentration of estradiol before the second injection of GnRH.

In both replicates, an interaction was detected between time and expression of estrus ($P < 0.001$) on preovulatory concentrations of estradiol. Cows exhibiting estrus had greater ($P < 0.001$) preovulatory concentrations of estradiol beginning 6 and 4 h (replicates 1 and 2, respectively) after the injection of $PGF_{2\alpha}$ on day-2 than those cows not exhibiting estrus (Fig. 1). Occurrence of estrus ($P = 0.04$) but neither replicate ($P = 0.10$) nor estrus by replicate interaction ($P = 0.21$) was detected to affect the rate in the increase in the concentration of estradiol. Cows that exhibited estrus had an increased ($P < 0.01$) rate in the increase of concentrations of estradiol after the $PGF_{2\alpha}$ injection on day-2 to peak estradiol compared with cows that did not exhibit estrus (0.24 ± 0.05 pg/h and 0.11 ± 0.04 pg/h, respectively).

3.2. Experiment 2

Standing estrus was detected in 30% of the cows, but interval to initiation of estrus was not determined. In all cows ($P < 0.01$) and those exhibiting estrus ($P = 0.02$), a significant positive relationship was detected between follicle diameter and peak estradiol concentration, but there was no relationship ($P = 0.52$) between follicle diameter and peak estradiol concentration in cows not exhibiting estrus. Cows exhibiting estrus had larger ($P < 0.01$) follicles (14.8 ± 0.66 mm) and greater ($P < 0.01$) peak estradiol concentrations (9.9 ± 1.0 pg/mL) than cows not exhibiting estrus (11.8 ± 0.43 mm and 6.2 ± 0.67 pg/mL). No relationship was detected between follicle diameter and estradiol concentrations at the second GnRH injection in all cows ($P = 0.53$), in cows exhibiting estrus ($P = 0.79$), or in those that did not exhibit estrus ($P = 0.16$). Furthermore, there was no difference ($P = 0.96$) in concentrations of estradiol at the second GnRH injection between cows exhibiting estrus (4.6 ± 1.1 pg/mL) and cows that did not exhibit estrus (4.7 ± 0.71 pg/mL). However, 4 of the 6 cows that exhibited estrus had exhibited estrus and had a peak concentration of estradiol before the second injection of GnRH.

Cows exhibiting estrus had elevated concentrations of estradiol at the time of $PGF_{2\alpha}$ and at 12 h after the injection

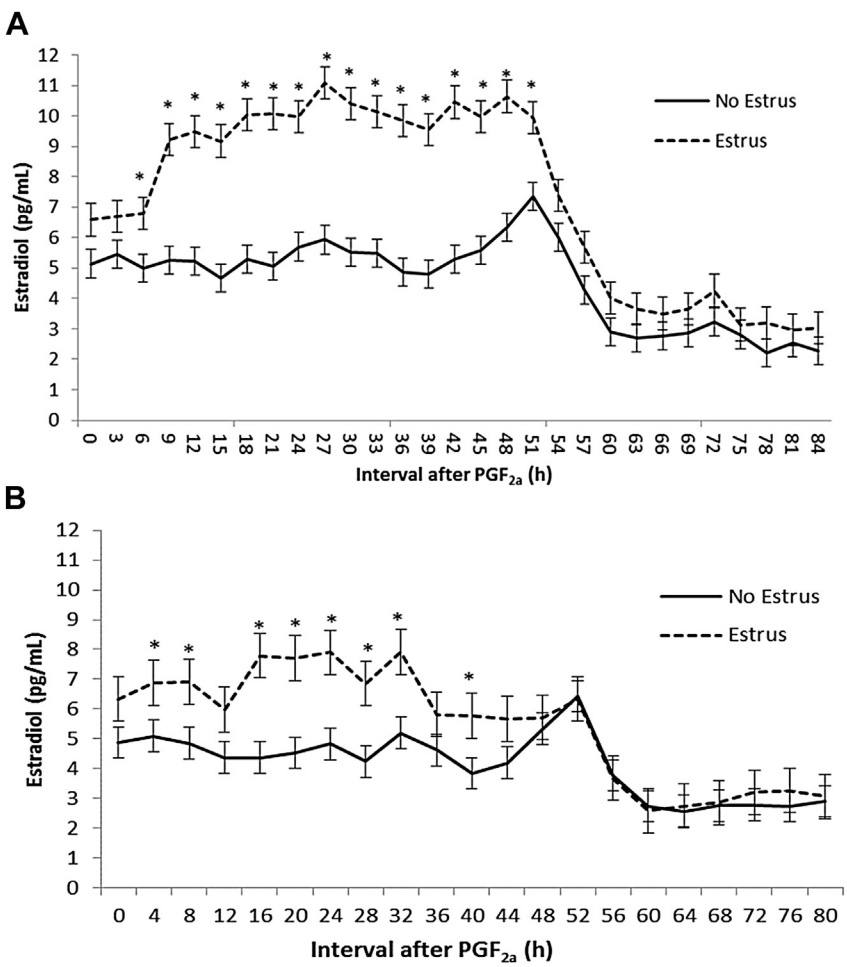

Fig. 1. Differences in circulating concentrations of estradiol following the injection of $PGF_{2\alpha}$ between cows that exhibited estrus and those that did not exhibit estrus in replicates 1 (A) and 2 (B) in experiment 1 (* $P < 0.05$). Interval from the injection of $PGF_{2\alpha}$ on day-2 to the onset of estrus was 45.4 ± 1.4 h and 45.2 ± 5.0 h for replicates 1, and 2, respectively.

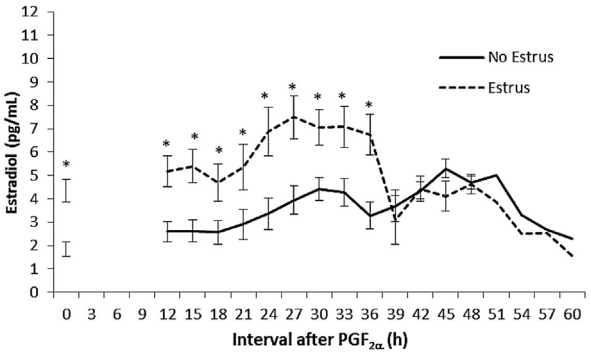

Fig. 2. Differences in circulating concentrations of estradiol following the injection of $PGF_{2\alpha}$ between cows that exhibited estrus and those that did not exhibit estrus in experiment 2 (* $P < 0.05$).

of $PGF_{2\alpha}$ on day-2 compared with cows that did not exhibit standing estrus (Fig. 2). Occurrence of estrus ($P = 0.12$) did not impact the rate in the increase in concentration of estradiol. Cows that exhibited estrus had an increased rate of increase in concentrations of estradiol after the $PGF_{2\alpha}$ injection on day-2 to peak estradiol compared with cows that did not exhibit estrus (0.33 ± 0.13 pg/h and 0.08 ± 0.09 pg/h, respectively).

4. Discussion

Role of the preovulatory concentration of estradiol in the initiation of estrus has been well documented [14], and in cattle, concentrations of estradiol peak approximately 36 h before ovulation [5]. In the present study, 42% of cows were detected in estrus (48% and 33% for replicates 1 and 2 of experiment 1, respectively, and 30% for experiment 2), and in both suckled and nonsuckled cows, cows detected in standing estrus had elevated concentrations of estradiol at or by 6 h after the $PGF_{2\alpha}$ injection compared with cows that did not exhibit standing estrus.

In the present study, when all cows were included, a significant correlation between the preovulatory follicle diameter and peak concentrations of estradiol was detected, regardless of suckling status. This relationship is similar to a report [7] of a significant correlation between follicle diameter at second GnRH and concentrations of estradiol at second GnRH in cows not exhibiting standing estrus. One difference between these studies is that all cows in the present study, regardless of estrus occurrence were included in this analysis. In addition, the present study also examined peak concentrations of estradiol compared with a set time point (second GnRH injection) in the previously discussed studies. When only cows that exhibited estrus were evaluated a significant positive correlation also was detected between follicle diameter and peak concentrations of estradiol. Previous researchers have reported a strong correlation between diameter of the dominant follicle and intrafollicular estradiol concentrations during the preovulatory period [20,21]. In contrast, in both suckled and nonsuckled cows, among cows that did not exhibit estrus, there was no correlation between follicle diameter and peak concentrations of estradiol. In the study by Jinks et al [7], follicle diameter was not always predictive of serum concentrations of estradiol, and 39% of cows with small follicles (<12.5 mm) were classified as having elevated concentrations of estradiol (≥8.4 pg/mL) at the time of the second GnRH injection. Furthermore, in the present study, over half of the animals that exhibited estrus had exhibited estrus and had a peak concentration of estradiol before the second injection of GnRH. Therefore, concentrations of estradiol were decreased at the time of the second GnRH injection and may have affected the ability to detect the previously reported positive correlation.

It is not known why some dominant follicles are capable of producing enough estradiol to initiate standing estrus, whereas others of similar diameter are not. Because threshold concentrations of estradiol are required to initiate estrus, a relationship likely exists between dose and duration of estradiol. Ewes infused at a high or medium rate initiated an LH surge sooner and at a greater concentration of estradiol than ewes infused at a low rate [22]. In the present study, the rate at which estradiol increased following the $PGF_{2\alpha}$ injection on day-2 was greater in cows that exhibited estrus than those cows that did not exhibit standing estrus. It is not known when or if these cows would have exhibited estrus because GnRH was administered at 48 h after $PGF_{2\alpha}$ and all cows did have a follicle of preovulatory diameter that ovulated in response to the injection of GnRH on day 0. The injection of GnRH abrogated estradiol production because once the LH surge occurs aromatase activity is inhibited within the follicle [23].

Increased estradiol production by preovulatory follicles depends on the enhanced ability of the theca interna cells to produce androstendione and the enhanced ability of granulosa cells to convert androstendione to estradiol [24]. Estradiol production also can be increased by the production of pregnenolone by granulosa cells, which can be converted to androstendione by the theca interna cells, which can then be converted to estradiol by the granulosa cells [25]. Furthermore, estradiol is reported to induce follicle-stimulating hormone/LH receptor expression in granulosa cells [26] and increase the stimulatory action of follicle-stimulating hormone on aromatase activity [27].

Estradiol production is further increased by an increase in LH pulse frequency [28]. Pituitary gonadotropes produce and secrete LH, and the response of gonadotropes to GnRH is directly correlated with the number of GnRH receptors on the cell surface [29]. Expression of the GnRH receptor can be regulated by estradiol, progesterone, and GnRH itself [30–32]. Increased sensitivity of gonadotropes to GnRH and increased expression of GnRH receptors occurs before an increase in concentrations of estradiol [33]. Therefore, the decrease in progesterone before proestrus may be important to initiate an increase in LH release that results in an increase in estradiol production. As progesterone decreases to basal concentrations at luteolysis, GnRH pulse frequency increased [34] and that increase in GnRH stimulated greater expression of GnRH receptors [35]. Therefore, ability of some dominant follicles to produce sufficient concentrations of estradiol to induce estrus may result from increased pituitary sensitivity to GnRH following a decrease in progesterone [34].

In summary, pregnancy success has been reported to be influenced by both preovulatory follicle diameter and

increased preovulatory concentrations of estradiol. In the present study, cows exhibiting estrus had greater preovulatory concentrations of estradiol than cows not exhibiting estrus. In addition, cows that exhibited estrus had greater preovulatory concentrations of estradiol at or by 6 h after the injection of $PGF_{2\alpha}$ on day-2 than cows not exhibiting estrus. Furthermore, cows that exhibited estrus also had an increased rate in the rise in concentrations of estradiol following the $PGF_{2\alpha}$ injection on day-2 compared with cows that did not exhibit estrus. When ovulatory follicle diameter was evaluated, a positive correlation was detected between follicle diameter and peak estradiol concentrations in cows that exhibited estrus, but no such relationship was observed between ovulatory follicle diameter and peak concentrations of estradiol in cows not exhibiting estrus. Therefore, decreased pregnancy rates in cows induced to ovulate and not detected in estrus may result from insufficient production of estradiol during the preovulatory period.

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