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Dosage of the Synthetic Progestin, Norgestomet, Influences Luteinizing Hormone Pulse Frequency and Endogenous Secretion of 17β-Estradiol in Heifers[1]

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ABSTRACT

The objective of this study was to determine whether there were doses at which the synthetic progestin, norgestomet, could mimic midluteal phase concentrations of progesterone in regulating the secretion of LH and 17β-estradiol in bovine females. Heifers were randomly assigned to one of five groups to receive: 1) one (1Norg, n = 5), 2) two (2Norg, n = 5), 3) four (4Norg, n = 5), or 4) eight (8Norg, n = 5) norgestomet implants or to serve as untreated control heifers (control, n = 5). On Day 7 (Day 0 = behavioral estrus), implants containing norgestomet were inserted, and they remained in place for 10 days. All heifers implanted with norgestomet were treated with 25 mg prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) on Days 7 and 8 to lyse the CL. Controls were treated with 25 mg $PGF_{2\alpha}$ at the time norgestomet implants were removed from heifers of the other treatment groups. Blood samples were collected every 15 min for 24 h on Days 10 and 16 to determine the frequency of LH pulses. Beginning 24 h after removal of implants, samples of blood were collected at 4-h intervals for 96 h to determine the time of the preovulatory surge of LH. Daily blood samples were collected from Day 2 to Day 48 to determine concentrations of progesterone, and samples collected between Days 2 and 17 were used to determine concentrations of 17β-estradiol. Ultrasonography was performed daily from Day 2 until Day 23 to evaluate ovarian follicular development. Mean concentrations of LH (Days 10 and 16), frequency of LH pulses (Days 10 and 16), and mean concentrations of 17β-estradiol during the treatment period were greater ($p < 0.05$) in heifers from the 1Norg group than in heifers from the other groups. The interval to the preovulatory surge of LH after treatment withdrawal was longer ($p < 0.05$) in heifers from the 8Norg group than in heifers from the 1Norg, 2Norg, and 4Norg groups. Rate of ovarian follicular growth during the treatment period was greater ($p < 0.05$) in heifers from the 1Norg group (1.68 ± 0.14 mm/d) than in controls, but heifers among the other groups did not differ from controls. Size of the largest follicle on the day before ovulation was greater ($p < 0.05$) in heifers treated with 1Norg (18.6 ± 1.2 mm) than in controls (14.8 ± 0.66 mm). In summary, one of the doses (4Norg) of norgestomet used in the present study did mimic midluteal phase concentrations of progesterone with respect to modulation of frequency of LH pulses, rate of ovarian follicular growth, secretion of 17β-estradiol, time to the preovulatory surge of LH after removal of progestin, and size of the ovulatory follicle.

INTRODUCTION

Treatment with norgestomet in the presence of the CL has been shown to result in greater pregnancy rates than in cows and heifers treated with a norgestomet implant (6 mg) in the absence of the CL [1]. This indicated that norgestomet at the dose used to synchronize estrus does not function like endogenous progesterone from the CL in preparing the reproductive system of bovine females for pregnancy. Treatment with norgestomet at doses (6 mg) that are used to synchronize estrus in the Syncro-Mate-B regimen also resulted in increased secretion of 17β-estradiol compared to that in control cows with CL [2].

Treatment of cows with one norgestomet implant induced development of persistent follicles, and treatment with a second norgestomet implant resulted in regression of these persistent follicles [3]. It is likely that development of persistent ovarian follicles in the absence of the CL resulted from the greater frequency in release of LH pulses in these animals as compared to females with a functional CL [2].

Increasing the dose of the injectable norgestomet (6 mg) in the Syncro-Mate-B regimen that was administered during metestrus resulted in greater pregnancy rates than in cows that received lower doses of injectable norgestomet [4]. It has been reported [3, 5] that greater doses of exogenous progesterone during synchronization of estrus decreased endogenous 17β-estradiol and increased conception rate as compared to the values in cows treated with lower doses of progesterone. Circulating concentrations of progesterone indicative of luteal phase deficiency (2–3 ng/ml) resulted in increased concentrations of 17β-estradiol and in prolonged elevated concentrations of 17β-estradiol compared to those in heifers treated with greater concentrations of progesterone [6].

Luteal phase deficiency has been associated with lowered fertility in cattle [7]. Previous studies in our laboratory [2, 6] indicated that when cows were treated with doses of progesterone that result in circulating concentrations mimicking those of luteal phase deficiency, secretion of LH pulses was increased and ovarian follicular development was enhanced as indicated by increased concentrations of 17β-estradiol in peripheral circulation. Treatment with greater doses of progesterone reduced secretion of LH [6] and circulating 17β-estradiol [2, 6].

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Our working hypothesis in the present study was that there are doses of the synthetic progestin, norgestomet, that mimic midluteal phase concentrations of progesterone in regulating secretion of LH and ovarian follicular development in heifers.

MATERIALS AND METHODS

Animals and Experimental Design

Twenty-five beef heifers of composite breeding (1/4 Hereford, 1/4 Angus, 1/4 Pinzgauer, 1/4 Red Poll) were used in this study (20 months of age, 337 ± 5 kg; mean ± SEM). Stage of the estrous cycle was synchronized via two treatments with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 25 mg; Lutalyse Sterile Solution; Upjohn Co., Kalamazoo, MI) 11 days apart. Heifers were randomly assigned to one of five groups to receive: 1) one (1Norg, n = 5); 2) two (2Norg, n = 5); 3) four (4Norg, n = 5), or 4) eight (8Norg, n = 5) norgestomet implants or to serve as untreated control heifers (n = 5).

On Day 7 of the estrous cycle (Day 0 = behavioral estrus; Day 7 = Day 0 of treatment period), the norgestomet (6 mg/implant; Sanofi Animal Health, Inc., Overland Park, KS) implants were inserted in the ear to remain in place for 10 days. All heifers implanted with norgestomet were also administered 25 mg of $PGF_{2\alpha}$ on Days 7 and 8 to induce regression of CL. On Days 10 and 16, catheters were inserted in the jugular vein of all heifers, and blood samples were collected every 15 min for 24 h. These samples were used to determine frequency of LH pulses in the different treatment groups. On Day 17, norgestomet implants were removed and control heifers were treated with $PGF_{2\alpha}$. Starting 24 h after either removal of the implants or treatment with $PGF_{2\alpha}$ (controls), blood samples were collected at 4-h intervals for 96 h. These samples were used to determine timing of the preovulatory surge of LH during the follicular phase following cessation of treatment.

Blood samples collected at 15-min intervals on Days 10 and 16 were allowed to clot at room temperature and were then stored at 4°C for 24 h. Serum was obtained after centrifugation at 1500 × *g* for 15 min. Serum was collected and stored at −20°C until assayed for LH.

From all heifers, daily samples (10 ml) were collected in tubes treated with 50 μl of 30% EDTA (Fisher Scientific, Fair Lawn, NJ) from Day 2 of the estrous cycle until Day 48 to determine concentrations of progesterone during treatment and during the subsequent estrous cycle. To minimize degradation of progesterone, the samples were placed on ice immediately and the plasma was obtained by centrifugation at 1500 × *g* for 15 min within 1 h of collection. Plasma samples collected from Days 7–17 were also assayed for 17β-estradiol. Plasma samples were stored at −20°C until assays were performed.

Concentrations of LH [8, 9] were determined by RIA. Intra- and interassay coefficients of variation for the LH assays were 4.6% and 12.8%, respectively. Concentrations of progesterone [6] and 17β-estradiol [2] were determined by RIA. Intraassay coefficients of variation for progesterone and 17β-estradiol were 5.3 and 3.6%, respectively; interassay coefficients of variation for progesterone and 17β-estradiol were 11.5 and 13.1%, respectively.

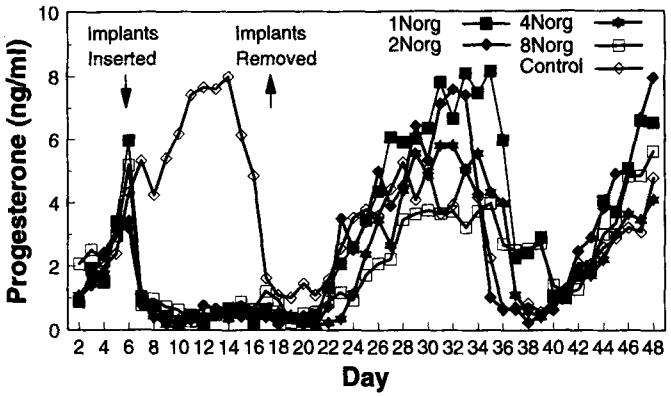

FIG. 1. Mean daily concentrations of progesterone during the estrous cycle in which treatments were imposed, during the estrous cycle that ensued after cessation of treatment, and during the initial portion of the subsequent estrous cycle.

Ovarian Follicle Evaluations

To characterize changes in size of ovarian follicles, real-time linear ultrasonography was conducted daily from Day 2 until Day 23. Ultrasonographic scanning was conducted through use of an Equisonic LS300 Real-Time Linear Scanner with a 7.5-MHz intrarectal transducer (Tokyo Keiki LS-300A; Products Group International, Boulder, CO). This allowed for measurement of ovarian follicles as small as 3 mm in diameter and for evaluation of the changes in growth of individual follicles. Appropriate images of each ovary were recorded daily and follicles were measured by means of a built-in caliper system; two pictures from the sonograph of each ovary were taken using a Sony High Contrast printer. Rate of growth ([maximum size minus 5 mm]/number of days) and maximum size of the dominant follicle were measured [10].

Data Reduction and Statistical Analyses

Mean concentrations (ng/ml) of LH, frequency of LH pulses (pulses/24 h), and amplitude of LH pulses (ng/ml) were determined by the use of algorithms (Pulsar software modified for the IBM-PC by J.F. Gitzen and V.D. Ramirez, Univ. of Illinois, Urbana, IL). The G values used were: G(1) = 4.25; G(2) = 3.25; G(3) = 3.00; G(4) = 2.80, and G(5) = 2.70. The length of the luteal phase during the estrous cycle subsequent to treatment was determined by calculating the number of days when progesterone was above 1 ng/ml of plasma during the cycle.

Pulsatile secretion of LH on Days 10 and 16 and the interval to the preovulatory surge of LH were examined by

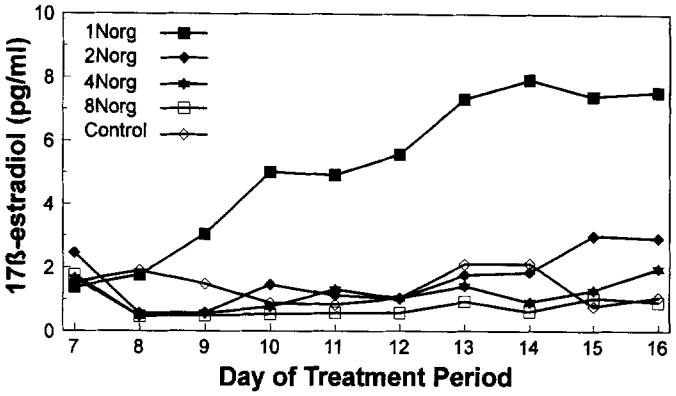

FIG. 2. Mean daily concentrations of 17β-estradiol during the period of treatment with various doses of norgestomet.

analysis of variance using the general linear models procedure of SAS [11]. Concentrations of progesterone and 17β-estradiol were analyzed by a mixed model procedure for repeated measurements over time [11, 12]. Differences between means were determined by Fisher's least significance difference test [11, 13].

RESULTS

Concentrations of progesterone during the treatment period were greater ($p < 0.05$) in control heifers (6.28 ± 0.42 ng/ml; mean ± SEM) than in those from the 1Norg, 2Norg, 4Norg, and 8Norg groups (0.50 ± 0.08, 0.46 ± 0.07, 0.50 ± 0.08, and 0.64 ± 0.07 ng/ml, respectively; Fig. 1). Mean concentrations of 17β-estradiol during the treatment period were greater ($p < 0.05$) in heifers from the 1Norg group (5.19 ± 0.77 pg/ml) as compared to the other groups (1.68 ± 0.28, 1.14 ± 0.15, 0.79 ± 0.13, and 1.38 ± 0.17 pg/ml for 2Norg, 4Norg, 8Norg, and control groups, respectively; Fig. 2).

On Day 10 (Day 3 of treatment), mean concentrations of LH were greater ($p < 0.05$) in heifers from the 1Norg group than in the other groups (Table 1). Frequency of LH pulses was greater ($p < 0.05$) in heifers from the 1Norg group and frequency of LH pulses was suppressed ($p < 0.05$) in

TABLE 1. Mean concentrations of LH and frequency and amplitude of LH pulses on Days 10 post estrus (Day 3 of treatment with norgestomet).

Group[1]	Mean concentration (ng/ml)	Pulse frequency (pulses/24 h)	Pulse amplitude (ng/ml)
1Norg	1.99 ± 0.18[a]	17.4 ± 1.2[a]	1.7 ± 0.28
2Norg	1.32 ± 0.10[b]	8.4 ± 1.6[b]	2.2 ± 0.40
4Norg	1.09 ± 0.13[bc]	5.2 ± 1.8[bc]	2.3 ± 0.71
8Norg	0.82 ± 0.03[c]	0.4 ± 0.4[c]	2.7**
Control	1.23 ± 0.22[bc]	8.8 ± 2.7[b]	2.1 ± 0.38

[abc]Means with different letters within columns differ ($p < 0.05$)
**Only one heifer in this group exhibited LH pulses.
[1]One, two, four, or eight norgestomet implants inserted on Day 7 and removed on Day 17 of the estrous cycle except for control group.

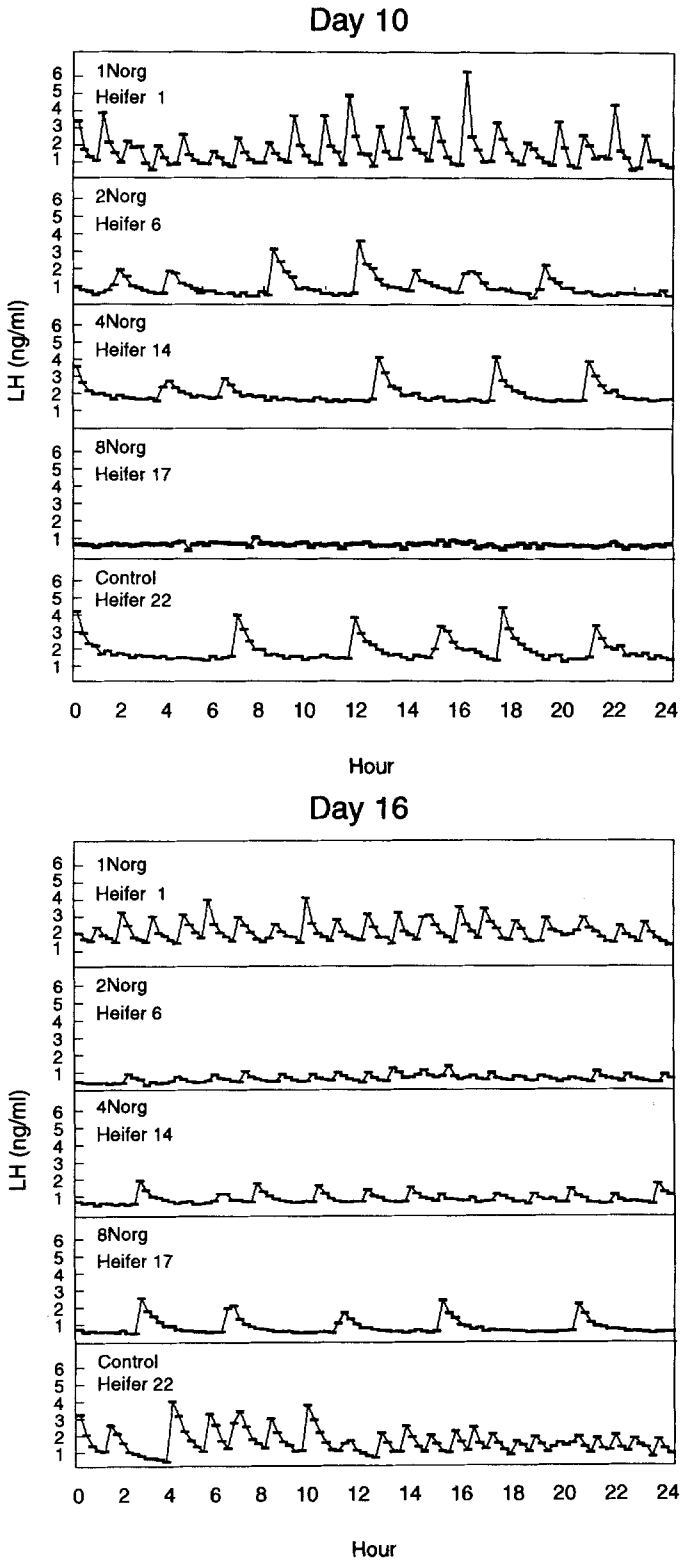

FIG. 3. Frequency of LH pulses from representative heifers treated with various doses of norgestomet on Day 10 (Day 10 = Day 3 of treatment period) and on Day 16 (Day 16 = Day 9 of treatment period).

TABLE 2. Mean concentrations of LH and frequency and amplitude of LH pulses on Days 16 post estrus (Days 9 of treatment with norgestomet).

Group[1]	Mean concentration (ng/ml)	Pulse frequency (pulses/24 h)	Pulse amplitude (ng/ml)
1Norg	1.97 ± 0.24[a]	19.6 ± 0.6[a]	1.63 ± 0.42[a]
2Norg	0.54 ± 0.05[c]	14.0 ± 1.7[b]	0.75 ± 0.10[b]
4Norg	0.68 ± 0.10[c]	8.0 ± 4.6[c]	1.27 ± 0.11[a]
8Norg	0.83 ± 0.12[c]	5.2 ± 2.7[c]	1.97 ± 0.30[a]
Control	1.53 ± 0.11[b]	14.4 ± 1.9[b]	1.96 ± 0.31[a]

[abc]Means with different letters within columns differ ($p < 0.05$)
[1]One, two, four, or eight norgestomet implants inserted on Day 7 and removed on Day 17 of the estrous cycle except for control group.

heifers of the 8Norg group as compared to heifers from the 1Norg, 2Norg, and control groups. Frequency of LH pulses did not differ in heifers of the 2Norg, 4Norg, and control groups. Amplitude of LH pulses did not differ ($p > 0.05$) among heifers from the 1Norg, 2Norg, 4Norg, and control groups; however, only one heifer in the 8Norg group had any pulses of LH, and this heifer had two pulses (Table 1). Data for representative heifers of each group are depicted for individual heifers in Figure 3.

On Day 16 (Day 9 of treatment), mean concentrations of LH and frequency of LH pulses were greater ($p < 0.05$) in heifers treated with 1Norg compared to controls and compared to heifers from the other groups treated with norgestomet (Table 2). Frequency of LH pulses was greater in heifers from the 1Norg group than in those of any other group. Frequency of LH pulses did not differ ($p > 0.10$) among the 2Norg and control groups and was lowest ($p < 0.05$) in heifers from the 4Norg and 8Norg groups (Table 2). Amplitude of LH pulses was lowest ($p < 0.05$) in heifers from the 2Norg group but did not differ ($p > 0.10$) among heifers from the other four groups (Table 2).

The interval to the preovulatory surge of LH was longer in heifers from the 8Norg group (92.0 ± 10.7 h) than in those from any other treatment group (Table 3). Rate of growth of the dominant ovarian follicle was greater ($p < 0.05$) in heifers from the 1Norg group than in those from the other groups, but did not differ among heifers in the other four groups (Table 4). Mean size of the ovarian follicle the day before ovulation was greater ($p < 0.05$) in heifers from the 1Norg group than that of 4Norg and control heifers (Table 4). Duration of the luteal phase during the estrous cycle subsequent to the period of treatment did not differ ($p > 0.10$) among heifers from the five groups.

TABLE 3. Time to preovulatory surge of LH (hours after implant removal or treatment with $PGF_{2\alpha}$ in controls) and luteal phase length of the subsequent estrous cycle.

Group[1]	LH surge (hours)	Luteal phase length (days)
1Norg	50.8 ± 15.4[b]	14.4 ± 1.53[a]
2Norg	46.4 ± 3.2[b]	12.0 ± 0.84[ab]
4Norg	65.0 ± 3.0[b]	11.8 ± 1.06[ab]
8Norg	92.0 ± 10.7[a]	9.2 ± 2.55[b]
Control	66.0 ± 13.1[ab]	13.0 ± 0.55[ab]

[abc]Means with different letters within column differ ($p < 0.05$)
[1]One, two, four, or eight norgestomet implants inserted on Day 7 and removed on Day 17 of the estrous cycle except for control group.

TABLE 4. Rate of ovarian follicle growth and size of dominant follicle the day before ovulation.

Group[1]	Rate of growth (mm/d)	Size of dominant follicle (mm)
1Norg	1.68 ± 0.04[a]	18.6 ± 1.2[a]
2Norg	1.20 ± 0.04[b]	17.0 ± 1.0[ab]
4Norg	1.07 ± 0.05[b]	15.2 ± 0.6[b]
8Norg	1.00 ± 0.12[b]	16.7 ± 0.8[ab]
Control	1.12 ± 0.06[b]	14.8 ± 0.7[b]

[abc]Means with different letters within column differ ($p < 0.05$)
[1]One, two, four, or eight norgestomet implants inserted on Day 7 and removed on Day 17 of the estrous cycle except for control group.

DISCUSSION

Frequency of LH pulses on Day 10 (Day 3 of treatment) in heifers from the 2Norg, 4Norg, and control groups agree with those previously reported [14] for cows during the midluteal phase of the estrous cycle. Data for frequency of LH pulses of heifers from the 1Norg group agree with data for cows treated with the Syncro-Mate-B regimen for synchronization of estrus [2] and for heifers receiving doses of progesterone that resulted in circulating concentrations of 1 to 2 ng/ml of progesterone in plasma [6]. Profiles of LH secretion in heifers of the 1Norg group are similar to those detected during the follicular phase of the estrous cycle of bovine females [15]. Therefore, the dose (6 mg) of norgestomet used commercially to synchronize estrus does not mimic concentrations of progesterone during the midluteal phase of the estrous cycle in modulating the frequency of LH pulses. In heifers from the 8Norg group, there was a greater suppression of release of LH pulses than in controls. Only one heifer treated with 8Norg exhibited LH pulses on Day 10, and this animal had only two pulses/24 h.

Frequency of release of LH pulses on Day 16 (Day 9 of treatment) was greater than on Day 10 (Day 3 of treatment). This is in agreement with previous work showing that frequency of LH pulses fluctuated depending upon the relative concentration of gonadal steroids in circulation [14]. Onset of luteolysis had started in most controls, explaining the increased frequency of LH pulses due to decreased circulating progesterone on Day 16 in these heifers. Heifers in all the groups treated with norgestomet had an increased frequency of LH pulses as the duration of treatment with norgestomet progressed. This might indicate that the rate of norgestomet release from the implants was reduced to levels that did not inhibit pulsatile secretion of LH to the same degree as earlier in the treatment period. It is likely that this decreased release of norgestomet resulted from depletion of norgestomet from the implants.

Timing of the preovulatory surge of LH occurred about 50 h after cessation of treatment in heifers receiving 1Norg

or 2Norg; it occurred 65–66 h after cessation of treatment in heifers from the 4Norg group or after treatment with $PGF_{2\alpha}$ in controls. Preovulatory surges occurred about 92 h after cessation of treatment in heifers given 8Norg. This indicates that ovarian follicular development might have been inhibited to a greater degree in heifers treated with 8Norg than in those of the other groups. Treatment with the greater doses of norgestomet suppressed secretion of 17β-estradiol below the concentrations present at initiation of treatment. It is likely that this was due to the lowered frequency of LH pulses, particularly in heifers treated with 8Norg. It has been reported [16] that a negative correlation exists between relative size of the preovulatory follicle after the decline of progesterone and the interval from the decline in progesterone to the preovulatory LH surge. Alternatively, treatment with 8Norg might have resulted in more residual norgestomet for longer periods after treatment withdrawal in this group than in the others. This might have led to the longer period from norgestomet withdrawal to onset of the preovulatory surge of gonadotropins in heifers of this group.

Mean circulating concentration of 17β-estradiol did not differ among treatment groups at the beginning of the treatment. Lower concentrations of 17β-estradiol were maintained in control heifers and heifers treated with 2Norg, 4Norg, and 8Norg than in heifers from the 1Norg group throughout the treatment period. By Day 9, greater concentrations of 17β-estradiol were present in the circulation of heifers receiving 1Norg, and these concentrations remained above those of heifers in the other groups for the remainder of the treatment period. There appeared to be increased circulating concentrations of 17β-estradiol at the end of the treatment period in heifers given 2Norg. In addition, treatment with 4Norg or 8Norg appeared to suppress circulating concentrations of 17β-estradiol during the earlier portion of the treatment period.

According to previous reports, cows treated with norgestomet have elevated circulating concentrations of 17β-estradiol that are associated with increased size of the largest follicle [17]. In the present experiment, rate of growth and size of the dominant ovarian follicle were greatest in heifers treated with 1Norg, and this resulted in the greater 17β-estradiol concentrations in these heifers.

Recent research has indicated that slight increases in LH pulse frequency promoted prolonged ovarian follicular growth and dominance associated with increased concentrations of 17β-estradiol plasma [18]. This suggests that the demise of nonovulatory dominant follicles during the typical estrous cycle occurs through feedback effects of luteal progesterone on secretion of LH.

Previous research from our laboratory [1] indicated that there were increased concentrations of 17β-estradiol over extended periods of time in cows and heifers treated with norgestomet in the absence of a CL as compared to cows and heifers treated with norgestomet in the presence of a CL. In addition, cows with low circulating concentrations of progesterone have elevated concentrations of 17β-estradiol, and prolonged exposure to elevated concentrations of 17β-estradiol may alter the cascade of endocrine and physiological events required to establish or maintain pregnancy in cattle [5]. A corresponding decrease in pregnancy rate occurred in animals treated with norgestomet in the absence of the CL compared to those with the CL present [1]. This suggested that the greater concentrations of 17β-estradiol may be altering the oocyte, rendering it defective or incapable of being fertilized [19], or that the increase in 17β-estradiol over extended periods of time may adversely affect the uterine or oviductal environment to make it hostile for the developing embryo [20].

In summary, there is variation in the pattern of release of LH that is related to the dose of norgestomet, and this in turn affects circulating concentrations of 17β-estradiol as well as duration in time to onset of behavioral estrus and ovulation after implant removal. The rate of growth and size of dominant ovarian ovulatory follicles also vary depending on the dose of norgestomet; however, there was no difference in the duration of the luteal phase among heifers of the different groups during the estrous cycle subsequent to treatment. There are doses at which the synthetic progestin norgestomet can be used to mimic the function of CL in modulating secretion of LH and 17β-estradiol. Doses of norgestomet that modulate the secretion of LH and 17β-estradiol in a manner similar to progesterone from the midluteal phase CL may vary depending on the size of bovine females. For example, the numbers of norgestomet implants that were effective in mimicking CL function in heifers in the present study may not be effective in mature cows. Implants designed to release norgestomet at concentrations that mimic luteal function in the modulation of LH and 17β-estradiol may result in greater pregnancy rates if used in programs of estrous cycle control in bovine females.

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