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Progestin and Estrogen Regulation of Pulsatile LH Release and Development of Persistent Ovarian Follicles in Cattle

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Progestin and Estrogen Regulation of Pulsatile LH Release and Development of Persistent Ovarian Follicles in Cattle[1,2]

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ABSTRACT: When doses of progestin used commercially are administered to synchronize the stage of the estrous cycle among bovine females, fertility is reduced compared with that of untreated controls. The reduced fertility that results from the use of progestin-based estrus synchrony regimens is associated with the development of persistent ovarian follicles. Persistent ovarian follicles develop as a result of the greater frequency of LH pulses that occurs during the period of treatment with progestins. The greater release of LH pulses results in enhanced secretion of 17β-estradiol from persistent ovarian follicles. The greater frequency of LH release or the greater secretion of 17β-estradiol associated with development of persistent ovarian follicles probably contributes to the reduced fertility that occurs when progestins are used to synchronize stage of the estrous cycle.

Key Words: Estrus, Synchronization, Progestin, LH, Estrogen

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Introduction

Regulation of LH release from the anterior pituitary is controlled primarily by progesterone and 17β-estradiol. These two hormones function at the hypothalamus to control the frequency of release of LHRH pulses into the portal vessels that carry blood from the stalk median eminence to the anterior pituitary. Consequently, release of LH pulses from the anterior pituitary is primarily controlled by release of LHRH pulses. Luteinizing hormone is involved in regulation of ovarian follicular function (i.e., steroidogenesis) during the estrous cycle of cattle. The increased frequency of LH pulses during the follicular phase of the estrous cycle is a primary factor in developing dominant ovarian follicles to the point of ovulation.

When progestin treatment regimens are used to synchronize stage of the estrous cycle among bovine females, ovarian follicles grow to larger sizes and persist in the ovaries for longer periods of time than do ovarian follicles during a typical estrous cycle. Development of persistent ovarian follicles only occurs if the corpus luteum is not present during a portion of the period of progestin administration. A primary contributing factor to the development of persistent ovarian follicles with use of progestins is the greater release of LH pulses compared with what typically occurs during the bovine estrous cycle. When persistent ovarian follicles are present, greater concentrations of 17β-estradiol are present in circulation than when normally developing dominant follicles are present. Fertility of cows is reduced after ovulation of persistent ovarian follicles. This reduced fertility is likely the result of the more advanced stage of development of oocytes at the time of ovulation and(or) embryonal death as a result of impaired oviductal or uterine conditions during the 1st wk subsequent to the time of fertilization.

Secretory Pattern of Luteinizing Hormone During the Estrous Cycle of Bovine Females

Rahe et al. (1980) characterized changes in the pattern of circulating LH and suggested that the frequency at which LH pulses are released is modulated by the changing steroid hormone milieu that occurs during the estrous cycle of cattle. Early in the luteal phase of the estrous cycle (2 to 3 d after estrus), concentrations of progesterone in circulation are lower and LH pulses occur with greater frequency than during the mid-luteal phase (Rahe et al., 1980;

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Peters et al., 1994). Before the corpus luteum develops after ovulation, large estrogen-active follicles develop in the ovaries (Holst et al., 1972; Ireland and Roche, 1982). These follicles are the likely source of the greater circulating concentrations of 17β-estradiol present during the first few days of the estrous cycle (d 0 = estrus) as compared to concentrations during the mid-luteal phase (Cupp et al., 1995b; Rhodes et al., 1995). In some cows, concentration of 17β-estradiol present in circulation after ovulation but before development of a fully functional corpus luteum is comparable to the concentration during the follicular phase of the estrous cycle (Glencross et al., 1973; Walters and Schallenberger, 1984). The preovulatory surge of LH, however, does not occur during the luteal phase because progesterone concentrations are greater than those during the follicular phase of the estrous cycle (Short et al., 1979).

Concentrations of LH, progesterone, and 17β-estradiol during the luteal phase of the estrous cycle of bovine females were recently evaluated on each day of the luteal phase by Cupp et al. (1995b; Table 1). Mean concentrations of LH are fairly constant during the 1st wk after ovulation (Schams et al., 1977), but mean concentrations of LH are lower on d 11 to 13 (d 0 = onset of estrus) than during the early and late luteal phase (Cupp et al., 1995b). During the early luteal phase, concentrations of progesterone are lower, frequency of LH pulses is greater, and circulating concentration of 17β-estradiol is greater than during the mid-luteal phase (Cupp et al., 1995b).

During the mid-luteal phase, concentrations of progesterone are greater, frequency of LH pulses lesser, and concentrations of 17β-estradiol lower compared with the early and late luteal phase (Cupp et al., 1995b). Most interesting is the greater amplitude of LH pulses between d 8 and 10 (d 0 = onset of estrus) than during the early and late luteal phase (Table 1; Cupp et al., 1995b). The relationship of changing patterns of LH in circulation during the estrous cycle to pattern of ovarian follicular development has not been delineated.

After luteolysis there is a greater mean concentration of LH and frequency of LH pulses as a consequence of the lower circulating concentrations of progesterone than during the mid-luteal phase of the estrous cycle (Figure 1; Imakawa et al., 1986, Cupp et al., 1995a). The increased frequency of LH pulses during the follicular phase of the estrous cycle results in greater circulating concentrations of 17β-estradiol, and this is the primary ovarian steroid secreted during this phase of the estrous cycle in cattle (Cupp et al., 1995a). During the follicular phase of the estrous cycle of cattle, amplitude of LH pulses is enhanced by the greater amounts of 17β-estradiol (Stumpf et al., 1989; Cupp et al., 1995a), and the preovulatory surge of LH is induced as a result (Stumpf et al., 1991).

Steroid Hormone Regulation of Pulsatile Luteinizing Hormone Release

General. Regulation of LH release by steroids at the hypothalamic-pituitary axis has been frequently studied in ovariectomized animals. This reduces the

Table 1. Mean concentrations of LH, FSH, progesterone, and 17β-estradiol and amplitude and frequency of LH pulses during the luteal phase of the estrous cycle of cows[a]

	LH					
Day of estrous cycle	Pulse amplitude, ng/mL	Pulse frequency, pulse/12 h	Concentration, ng/mL	FSH, ng/mL	Progesterone, ng/mL	17β-Estradiol, pg/mL
4	.50^{b}	4.48^{b}	.70^{b}	1.56^{b}	3.38^{b}	7.97^{b}
5	.68^{bc}	4.88^{b}	.81^{bd}	1.86^{cd}	5.94^{c}	6.36^{bc}
6	.80^{bc}	4.11^{b}	.64^{bc}	1.53^{b}	7.49^{cd}	5.74^{c}
7	.65^{b}	2.67^{c}	.69^{b}	1.79^{c}	9.90^{e}	4.36^{cd}
8	1.28^{d}	4.00^{b}	.72^{b}	1.67^{ce}	8.82^{de}	4.79^{cd}
9	1.31^{d}	2.78^{c}	.79^{bd}	2.01^{d}	10.86^{e}	4.44^{cd}
10	1.04^{cd}	3.44^{bc}	.64^{bc}	1.66^{ce}	9.61^{e}	4.08^{cd}
11	1.09^{cd}	3.11^{bc}	.74^{bd}	1.72^{c}	12.21^{fg}	3.67^{de}
12	.66^{b}	2.89^{c}	.55^{c}	1.52^{b}	11.18^{eg}	3.72^{de}
13	.80^{bc}	2.78^{c}	.64^{bc}	1.56^{b}	13.07^{f}	2.73^{e}
14	.82^{bc}	3.89^{bc}	.60^{bc}	1.50^{b}	11.63^{fg}	3.88^{de}
15	.97^{bc}	4.56^{b}	.86de	1.63^{be}	12.15^{fg}	3.52^{de}
16	1.24^{d}	6.90^{d}	.99^{ef}	1.45^{b}	8.45^{de}	5.30^{c}
17	1.03^{cd}	4.19^{b}	.94^{e}	1.69^{ce}	10.43^{e}	5.20^{c}
18	.71^{b}	4.47^{b}	.70^{b}	1.32^{b}	7.18^{c}	5.11^{c}
19	1.10^{cd}	7.57^{d}	1.29^{f}	1.62^{be}	3.16^{b}	10.89^{f}
Pooled SEM	.2	.99	.09	.09	1.23	.80

[a]Data based on Cupp et al. (1995b).
[b,c,d,e,f,g]Values with different superscripts within a column differ ($P < .05$).

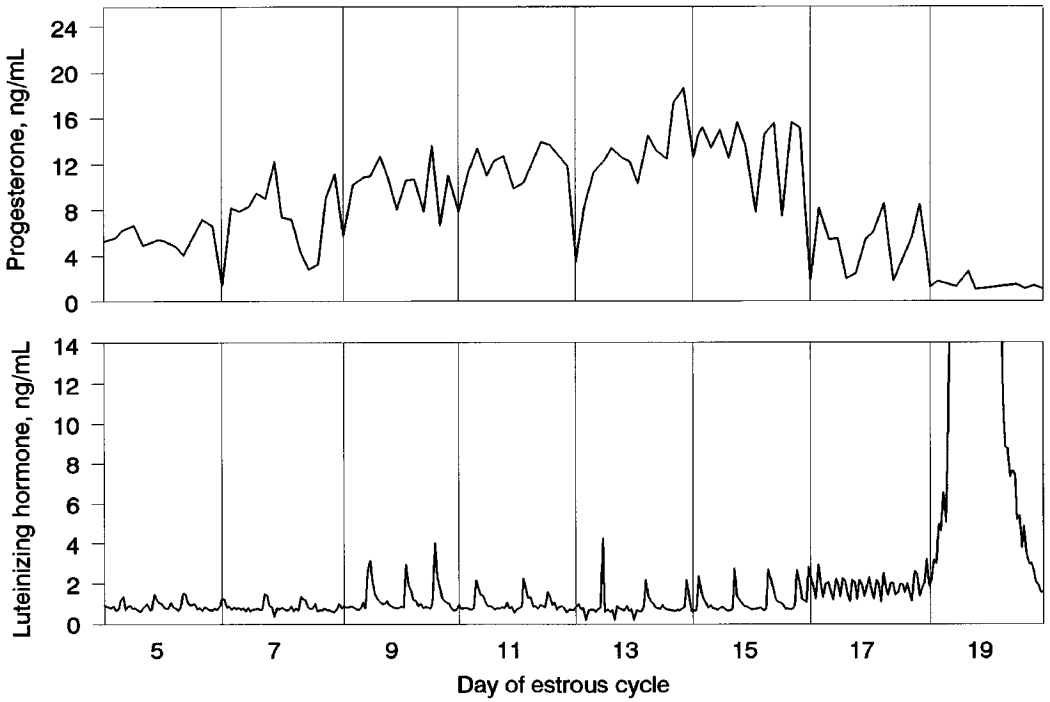

Figure 1. Patterns of progesterone and pulsatile LH release in a cow during different days of the luteal phase of the estrous cycle. Note the increase in frequency of release of LH pulses after the decrease in progesterone near the end of the estrous cycle and the surge of LH release on d 19. Adapted from Cupp et al. (1995b).

probability of results being confounded by steroids produced by the ovary. Ovariectomy of mature bovine females results in an increase in concentrations of LH in circulation and an enhanced frequency of LH pulses from the pituitary (Hobson and Hansel, 1972; Short et al., 1973; Beck et al., 1976; Schallenberger and Peterson, 1982).

Progesterone. Administration of progesterone to ovariectomized cows suppresses the release of LH (Beck et al., 1976). Progesterone and 17β-estradiol are the primary factors responsible for the lesser frequency of LH pulses during the luteal phase of the bovine estrous cycle, and the combination of these two hormones suppresses the frequency of LH pulses to a much greater extent than either of the two hormones administered separately (Table 2; Stumpf et al., 1993).

In sheep, suppressed release of LH pulses by progesterone occurs directly at the hypothalamus due to a suppressed frequency in release of LHRH pulses (Karsch et al., 1987). As a consequence of the suppressive effect of progesterone on release of LH pulses, the final stages of maturation of an ovulatory follicle are inhibited during the luteal phase of the estrous cycle.

Estradiol. In the absence of progesterone, the effects of 17β-estradiol on secretion of LH depends on circulating concentrations, method of administration, and the time when secretion of LH is examined following administration of estradiol. Bolus administration of doses of 17β-estradiol that result in supraphysiological concentrations in circulation has a biphasic effect on secretion of gonadotropins (Kesner et al., 1981; Butler et al., 1983). Secretion of gonadotropins is initially inhibited for several hours, and this is followed by a surge release of LH and FSH.

Treatment with progestins blocks the estradiol-induced gonadotropin surge in cattle (Bolt et al., 1971; Short et al., 1973; Kesner et al., 1981, 1982). Small doses of the progestins that are capable of blocking the estradiol-induced preovulatory surge of gonadotropins do not slow frequency of release of LH pulses like larger doses of the progestins.

When 17β-estradiol is administered via sequential implants to ovariectomized cattle, the sudden shifts in circulating concentrations of this hormone are avoided

Table 2. Frequency of release of LH pulses in ovariectomized cows that were treated with doses of 17β-estradiol and progesterone that resulted in luteal phase concentrations of these two hormones[a]

Treatment	LH pulse frequency, pulses/h
Estradiol	.97 ± .07[b]
Progesterone	.52 ± .08[c]
Progesterone and estradiol	.14 ± .07[d]

[a]Data based on Stumpf et al. (1993).
[b,c,d]Values with different superscripts within a column differ ($P < .01$).

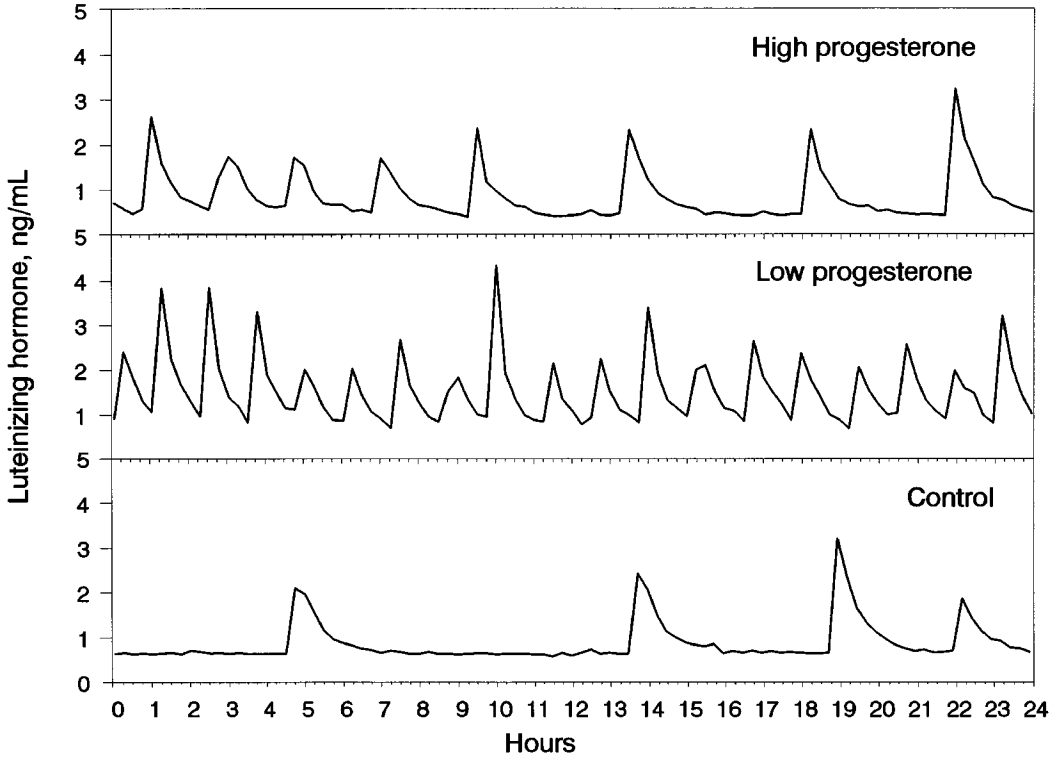

Figure 2. Patterns of LH secretion of cows treated with a high dose of progesterone (7 to 9 ng of progesterone / mL of blood plasma), a low dose of progesterone (1 to 2 ng of progesterone / mL of blood plasma) for 10 d and a control cow in the luteal phase of her estrous cycle 15 d after detection of estrus. Cows administered progesterone were treated with $PGF_{2\alpha}$ at the initiation of the 10-d treatment period. Adapted from Roberson et al. (1989).

and concentrations of 17β-estradiol are similar to those in intact control females during the follicular phase of the estrous cycle (Cupp et al., 1995a). This implant regimen results in greater mean concentrations of circulating LH of females treated with implants containing 17β-estradiol than in ovariectomized females treated with sham implants (Critser et al., 1983; Day et al., 1986; Stumpf et al., 1988; Kinder et al., 1991). Greater mean concentrations of LH are a consequence of an enhanced amplitude of LH pulses (Kinder et al., 1991). These results indicate that 17β-estradiol functions at the pituitary to increase responsiveness to LHRH and, therefore, increase LH pulse amplitude (Schoenemann et al., 1985; Stumpf et al., 1989).

Estradiol stimulates secretion of LH in cattle by enhancing the amplitude of LH pulses when concentrations of 17β-estradiol in circulation are similar to those during the follicular phase of the estrous cycle (Day et al., 1986; Kinder et al., 1991; Stumpf et al., 1988, 1989). When doses of 17β-estradiol are administered that result in concentrations similar to those present during late gestation of cattle, circulating concentrations of LH are dramatically reduced as a result of a lesser frequency of release and amplitude of LH pulses (Wolfe et al., 1992).

Modulation of Luteinizing Hormone Release by Exogenous Progesterone

Frequency of release of LH pulses from the anterior pituitary is differentially controlled depending on the dose of progesterone administered (Figure 2; Roberson et al., 1989). Cows administered doses of progesterone that resulted in circulating concentrations that are similar to those during the luteal phase (6 to 8 ng/mL of plasma) of the estrous cycle have less frequent LH pulses than cows treated with a smaller dose of progesterone that resulted in 1 to 2 ng/mL in blood plasma (Roberson et al., 1989). Cows treated with the greater dose of progesterone had a greater frequency of LH pulses than cows in the mid-luteal phase of their estrous cycle, even though circulating concentrations of progesterone were similar among cows in the two groups (Roberson et al., 1989). A similar response occurred in subsequent research of Kojima et al. (1992); indeed, progesterone from exogenous sources did not seem to suppress the release of LH from the anterior pituitary to the extent of endogenous progesterone from the corpus luteum.

Subsequent research evaluating the influence of endogenous and exogenous progesterone in modulation of LH release in cattle indicated, however, that endogenous and exogenous sources of progesterone

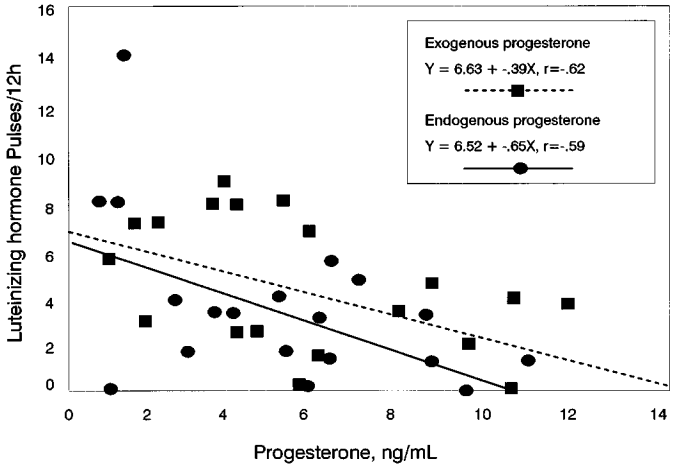

Figure 3. Regression of frequency of release of LH pulses when varying concentrations of progesterone come from endogenous (corpus luteum) or exogenous (progesterone-releasing intravaginal device) sources. Regression coefficients do not differ between the two groups. Adapted from Bergfeld et al. (1995).

have similar effects in controlling the release of LH (Figure 3; Bergfeld et al., 1995). In this study, females of one group were administered differing doses of progesterone, which resulted in a physiological range of concentrations of circulating progesterone from an exogenous source. Several doses of $PGF_{2\alpha}$ were administered to cows of another group to partially destroy the corpus luteum and, therefore, induce varying concentrations of progesterone in circulation that came from the corpus luteum (endogenous source). Pulses of LH are released less frequently when greater concentrations of progesterone are present, regardless of the endogenous or exogenous source of progesterone (Figure 3; Bergfeld et al., 1995). From this study (Bergfeld et al., 1995) and contrary to indications in our previous work (Roberson et al., 1989; Kojima et al., 1992), we conclude that progesterone from endogenous and exogenous sources has a similar suppressive action in inhibiting release of LH pulses from the anterior pituitary.

Sudden shifts in doses of progesterone (either large to small or small to large) result in rapid changes in frequency of release of LH pulses (Figure 4; Bergfeld et al., 1996). Frequency of LH release is dramatically reduced within the first 6 h after changing from a small to large dose of progesterone (Bergfeld et al., 1996). Conversely, frequency of release of LH pulses increases within the first 6 h after changing from a large to small dose of progesterone (Bergfeld et al., 1996). We anticipated that frequency of release of LH pulses would change gradually over a period of several hours after the shift in doses of progesterone; however, the hypothalamic pulse generator for LHRH is more exquisitely sensitive to circulating concentration of progesterone than we anticipated.

Regulation of Luteinizing Hormone Release by Synthetic Progestins

In cattle having estrous cycles, we evaluated the release of LH pulses after treatment with various progestins that are used to synchronize estrus (Figure 5; Kojima et al., 1992). Luteolysis was induced at initiation of the treatment period, and pattern of LH release was evaluated the day before cessation of the 10 d of treatment with the synthetic progestins. Feeding of melengestrol acetate (**MGA**; .5 mg/cow daily) or administration of a norgestomet implant (6 mg) with an injection of estradiol valerate (5 mg) and norgestomet (3 mg) in the Syncro-Mate-B regimen results in secretory patterns of LH similar to those that occur when progesterone (1.55 g) and estradiol benzoate (10 mg) are administered via progesterone-releasing intravaginal devices in doses used commercially for estrus synchrony (Kojima et al., 1992). Neither the synthetic progestins nor the natural progestin, progesterone, when administered at the doses and in combination with the estrogens as used commercially for estrus synchrony, suppresses frequency of release of LH pulses to the extent that occurs in cows during the mid-luteal phase of the estrous cycle (Kojima et al., 1992).

We subsequently evaluated whether greater doses of progestin than those used commercially for estrus synchrony would suppress frequency of release of LH pulses to the extent that occurs during the luteal phase of the bovine estrous cycle. When four norgestomet (6 mg each) implants are administered, frequency of LH pulses are similar to those of cows in their luteal phase (Figure 6; Sanchez et al., 1995). There is, however, variation in frequency of LH pulses with frequency being greater near the end of a 10-d treatment than during the initial period after administration of norgestomet even when norgestomet is administered at doses that are eight times greater than those used commercially (Figure 6).

Based on the change in pattern of pulsatile LH over the progestin-treatment in the study of Sanchez et al. (1995), we speculate that the greater frequency of LH pulses detected in our earlier studies in cows treated with progesterone compared with cows in the luteal phase of their estrous cycles is the result of serial blood samples having been collected near the end of the progestin-treatment period (Roberson et al., 1989; Kojima et al., 1992). Secretory pattern of LH was evaluated the day before cessation of treatment with progestins. If secretory pattern of LH had been evaluated earlier in the treatment period, frequency of LH pulses would likely have been less than when evaluated near the end of the treatment period.

When greater doses of MGA (1.0 and 1.5 mg/cow daily) than the dose recommended in estrus synchrony programs (.5 mg daily) are administered, frequency of LH pulses is still greater in cows

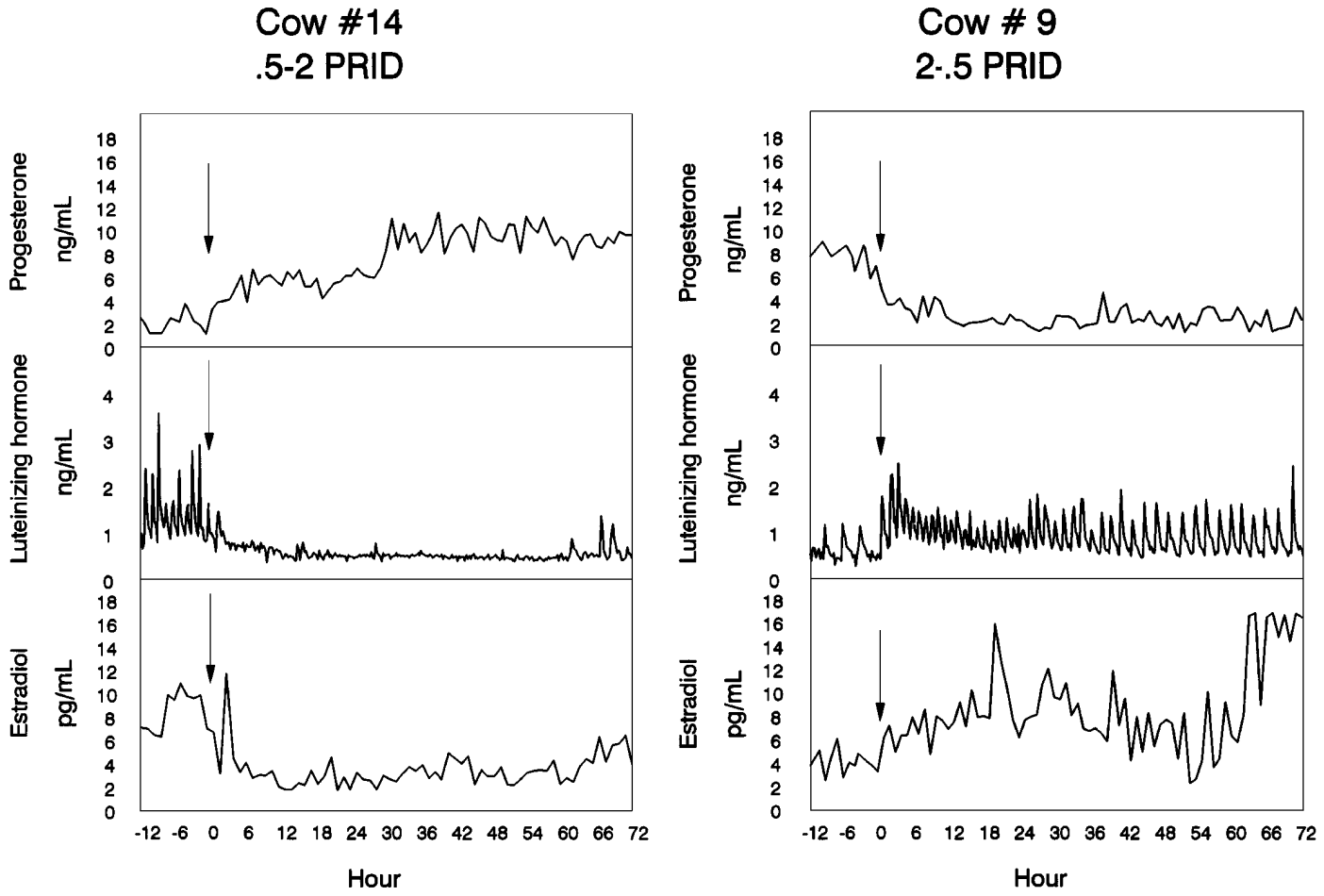

Figure 4. Pattern of LH secretion and circulating concentrations of 17β-estradiol and progesterone in two cows changed from a low to high (left panel) or high to low dose (right panel) of progesterone. Arrow indicates the time at which the dose of progesterone was changed. Cows were administered $PGF_{2\alpha}$ and exogenous progesterone 8 d before the time doses of progesterone were shifted. Adapted from Bergfeld et al. (1996).

administered the greater doses (1.0 or 1.5 mg) of MGA than in control cows in the luteal phase of their estrous cycle (Kojima et al., 1995). Unlike the variable secretory pattern of LH in which frequency of LH pulses increases as the period of treatment with the norgestomet implant progresses (Sanchez et al., 1995), MGA administered orally each day of the treatment period induces a markedly similar pattern of LH release from the beginning to the end of the treatment period (Figure 7; Kojima et al., 1995). This likely results from the relatively constant amount of MGA that entered the circulatory system each day of treatment compared with what occurs when progestins are administered via the implants or intravaginal devices.

It is important to recognize that studies evaluating the influence of exogenous progestins on frequency of LH pulses were performed with bovine females in which the corpus luteum was not present because of natural or induced luteolysis. If the corpus luteum is present when progestins are administered, frequency of release of LH pulses is similar to that in cows with a corpus luteum in which no progestin is administered (Table 3; Kojima et al., 1995).

Ovarian Follicular Development During the Estrous Cycle

Ovarian follicular development during typical estrous cycles of cattle is characterized by the presence of either two or three waves of ovarian follicular growth (Figure 8; Sirois and Fortune, 1988; Savio et al., 1988; Ginther et al., 1989; Lucy et al., 1992). Pattern of growth of ovarian follicles can be divided into phases of selection, dominance, and atresia (Ireland and Roche, 1987). A cohort of follicles starts to develop during the selection phase, but only one follicle continues to increase in size and becomes larger than all other follicles (Savio et al., 1988; Sirois and Fortune, 1988; Ginther et al., 1989). The largest follicle is described as the dominant follicle and is

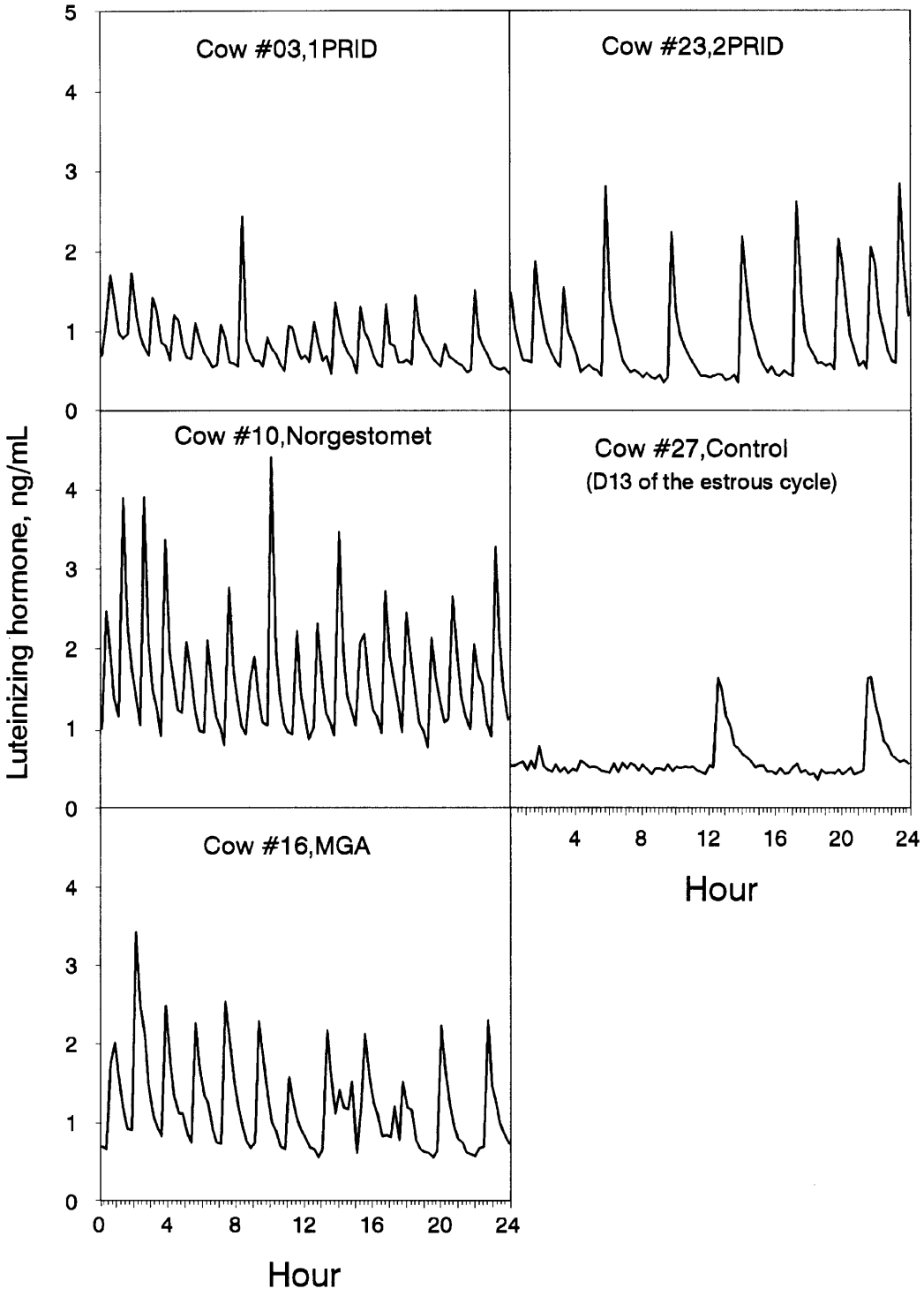

Figure 5. Pattern of LH secretion on d 9 of a 10-d treatment period in cows administered regimens of progestins (Syncro-Mate-B; norgestomet plus estradiol valerate), melengestrol acetate (MGA; .5 mg/d), or a progesterone-releasing intravaginal device (PRID; progesterone plus estradiol benzoate) used commercially for estrus synchrony. Patterns of LH secretion are also shown for a cow treated with a high dose of progesterone (7 to 9 ng/mL of blood plasma) and a control cow during the mid-luteal phase of the estrous cycle. Cows treated with hormones were administered $PGF_{2\alpha}$ at initiation of the treatment period. Adapted from Kojima et al. (1992).

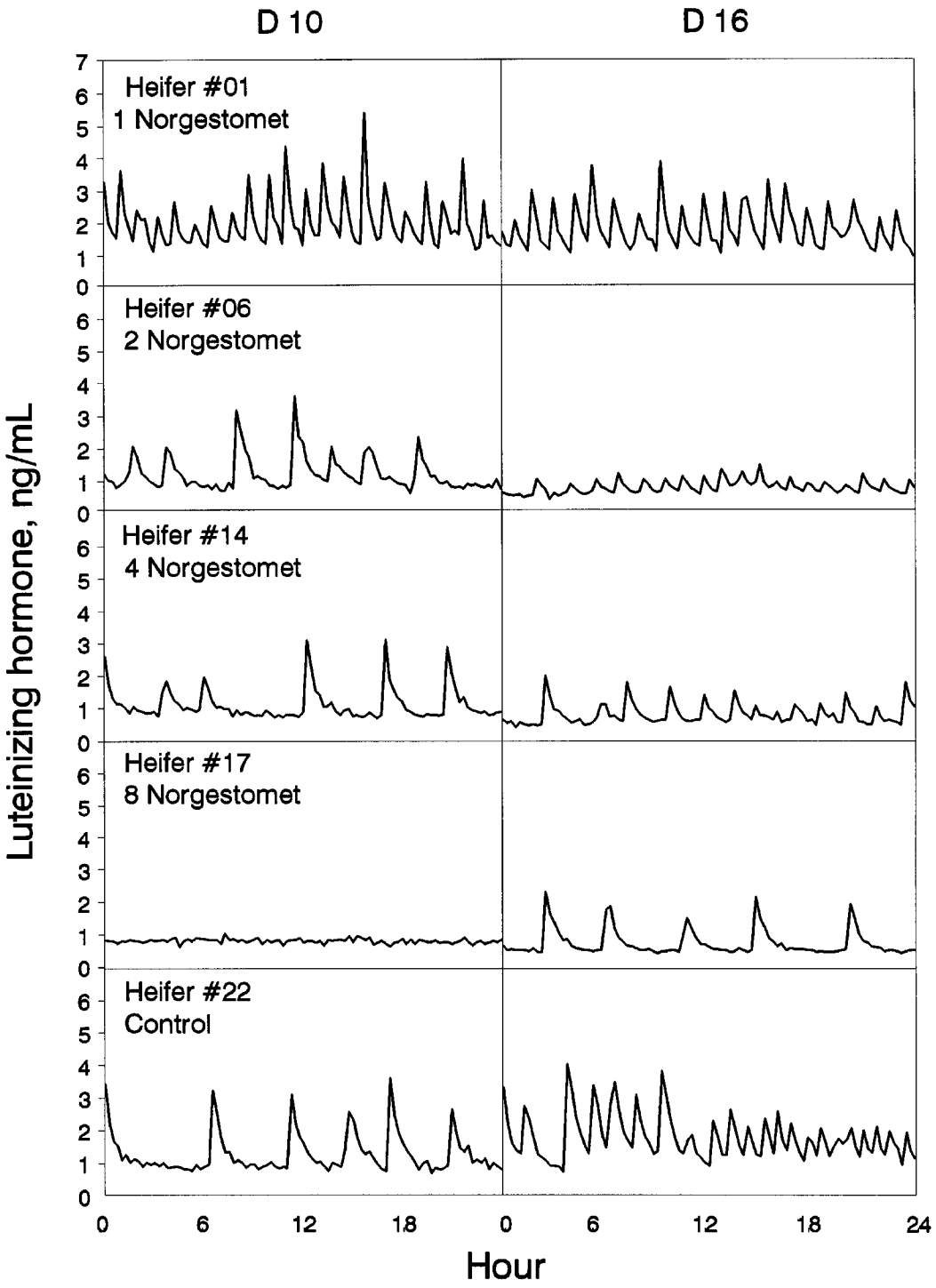

Figure 6. Patterns of LH secretion during d 10 and 16 (d 0 = estrus) of the estrous cycle of an untreated control cow and cows treated with 1, 2, 4, or 8 norgestomet implants for a period of 9 d. Treatments were initiated on d 7 of the estrous cycle. Note the change in frequency of LH pulses during the treatment period in cows treated with 2, 4, or 8 implants and that the control cow was in the follicular phase of the estrous cycle at the latter period of blood collection. Cows treated with norgestomet were treated with $PGF_{2\alpha}$ at initiation of treatment. Adapted from Sanchez et al. (1995).

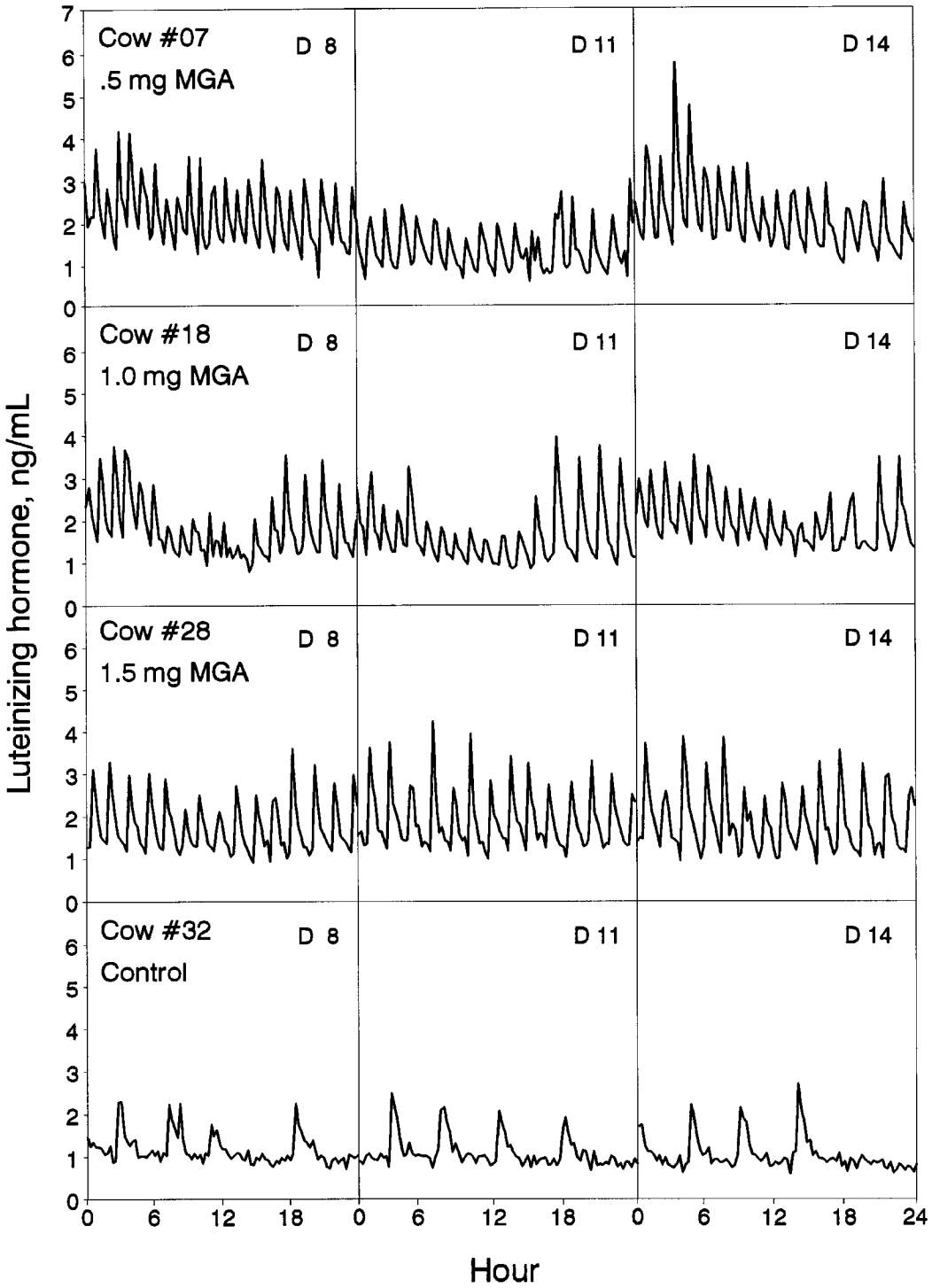

Figure 7. Patterns of LH secretion during d 8, 11, and 14 (d 0 = estrus) of a 10-d treatment period with .5, 1.0, or 1.5 mg of melengestrol acetate (MGA)/cow daily. A profile of LH for an individual control cow in the luteal phase of her estrous cycle is also shown. Treatments were initiated on d 5 of the estrous cycle. Cows treated with MGA were administered $PGF_{2\alpha}$ at initiation of the treatment period. Note the similarity in profiles of LH secretion from the early to latter portion of the treatment period. Adapted from Kojima et al. (1995).

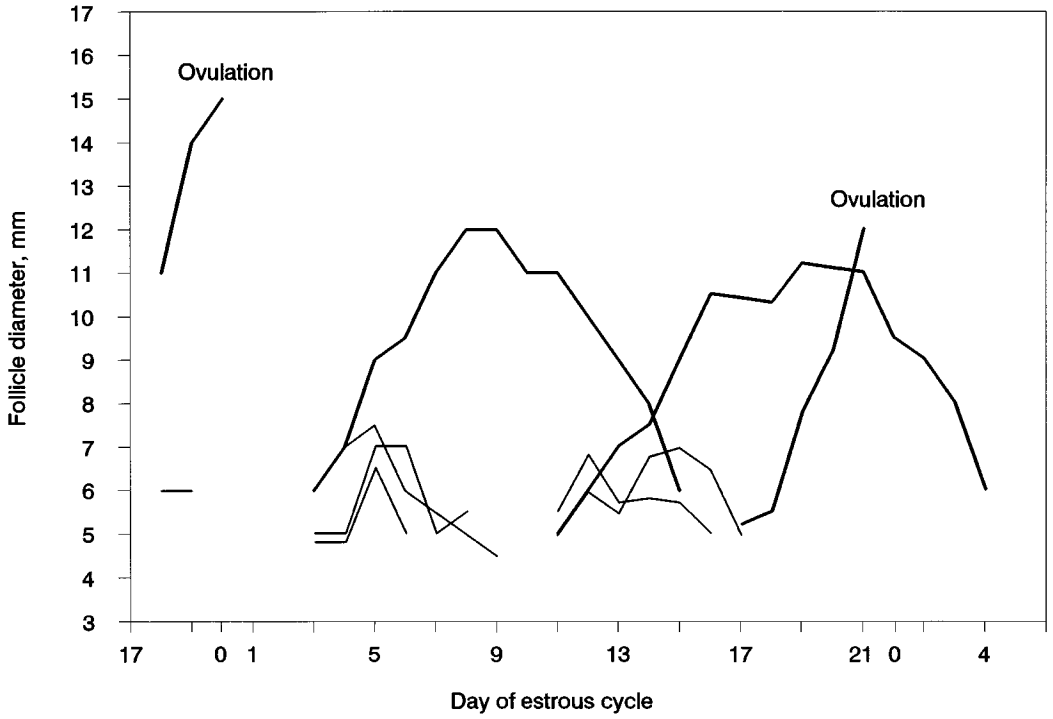

Figure 8. Pattern of ovarian follicular development in a cow during an estrous cycle (period between two single ovulations). Note the initial development of a cohort of growing follicles followed by development of a dominant follicle with three different follicular waves of the estrous cycle. Adapted from Sirois and Fortune (1988).

responsible for the greater circulating concentrations of estradiol following ovulation but preceding development of a fully functional corpus luteum and during the follicular phase of the estrous cycle (Ireland et al., 1984; Guilbault et al., 1993). During the luteal phase, dominant follicles undergo atresia and are replaced by a second or third dominant follicle (Savio et al., 1988). It has been suggested that the dominant follicle of the first follicular wave may become atretic because of the lesser frequency of LH pulses during the mid- compared with early luteal phase (Sirois and Fortune, 1990; Lucy et al., 1992; Stock and Fortune, 1993; Savio et al., 1993; Cupp et al., 1995b).

Circulating concentrations of FSH fluctuate in a pattern that is associated with waves of ovarian follicular development (Adams et al., 1992; Sunderland et al., 1994). Recently, Rhodes et al. (1995) evaluated the frequency of release of LH pulses and circulating concentrations of FSH, 17β-estradiol, and progesterone in blood from the vena cava flowing away from the ovaries at three stages of the first wave of ovarian follicular development. Hormonal characteristics were evaluated during the growth, plateau, and regression phases of the first wave dominant ovarian follicle. The growth, plateau, and regression phases are similar to the selection, dominance, and atresia

Table 3. Frequency of LH pulses during the early (day 8), middle (day 11), or late (day 14) luteal phase of an estrous cycle in cows that were administered .5, 1.0, or 1.5 mg of MGA daily while a functional corpus luteum was present[a]

		Frequency of LH pulses/24 h			
Treatment[b]	n	d 8	d 11	d 14	Overall mean
.5 mg MGA	5	5.0	4.4	3.4	4.3
1.0 mg MGA	5	3.4	3.6	3.6	3.5
1.5 mg MGA	4	7.8	5.8	7.3	6.9
Control	4	6.0	4.5	4.5	5.0
Pooled SEM		1.3	1.3	1.3	.8

[a]Data based on Kojima et al. (1995). Within a column, values did not differ among treatments ($P > .05$).
[b]The amount MGA was orally dosed daily in a gelatin capsule.

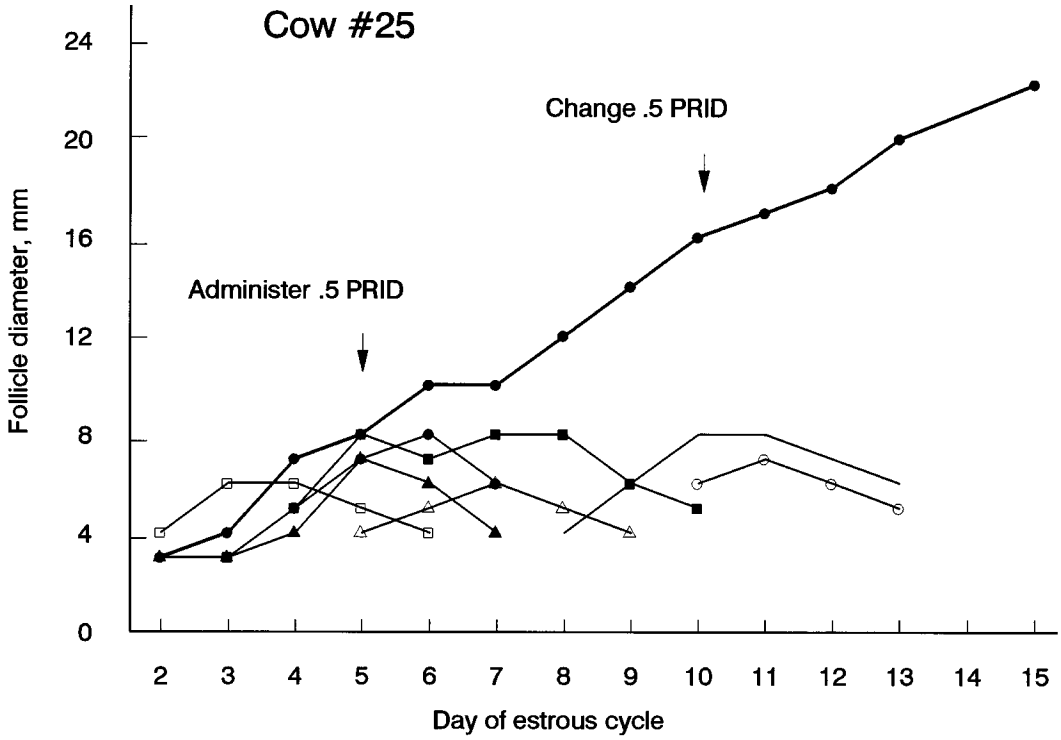

Figure 9. Pattern of ovarian follicular development in a cow treated with a low dose of progesterone (.5 PRID) from d 5 to 15 after detection of estrus. Note the continued development of the dominant follicle and the failure of this follicle to undergo atresia during the treatment period. Prostaglandin $F_{2\alpha}$ was administered at the start of the period of treatment with progesterone. Data reported by Cupp et al. (1992).

phases previously described (Ireland and Roche, 1987). Frequency of LH pulses and mean concentration of LH are greatest during the growth phase of development of the first wave dominant follicle (Rhodes et al., 1995). Mean concentration and amplitude of pulses of 17β-estradiol are also greater during the growth than during the plateau and regression phases of the first wave dominant follicle (Rhodes et al., 1995). In agreement with earlier studies (Adams et al., 1992; Sunderland et al., 1994), circulating concentrations of FSH are greater during the growth and plateau phases than during the regression phase of the first wave dominant follicle (Rhodes et al., 1995). Results from these studies indicate that dynamic changes in circulating concentrations of gonadotropins and gonadal steroids occur that are related to waves of ovarian follicular growth.

Development of Persistent Ovarian Follicles

Administration of doses of progestin that are approved for commercial use in cattle results in development of dominant ovarian follicles that grow to larger sizes and persist in the ovary for extended periods of time (Figure 9; Lucy et al., 1990; Sirois and Fortune, 1990; Rajamahendran and Taylor, 1991; Cupp et al., 1992; Savio et al., 1993; Stock and Fortune, 1993; Taylor et al., 1993; Mihm et al., 1994a). During the estrous cycle of cattle, concentrations of progesterone that are typical of those during the luteal phase are, therefore, necessary for maintenance of ovarian follicular dynamics similar to what is observed during the luteal phase (Lucy et al., 1992). Development of persistent ovarian follicles occurs as a result of treatment with doses of progestin that are used commercially to synchronize stage of estrous cycles if the corpus luteum is absent for most of the treatment period (Savio et al., 1993; Sanchez et al., 1995).

The secretory pattern of LH during treatment with the progestins is similar to that during the follicular phase of the bovine estrous cycle (Imakawa et al., 1986) and is likely the stimulus for development of persistent follicles (Cupp et al., 1992). Greater populations of LH receptors are detected on the granulosal and thecal cells of persistent ovarian follicles than on the same cell types of typical dominant follicles (Cupp et al., 1993). The greater populations of LH receptors in the persistent ovarian follicles might have resulted from the greater frequency in pulsatile release of LH in cows with persistent follicles.

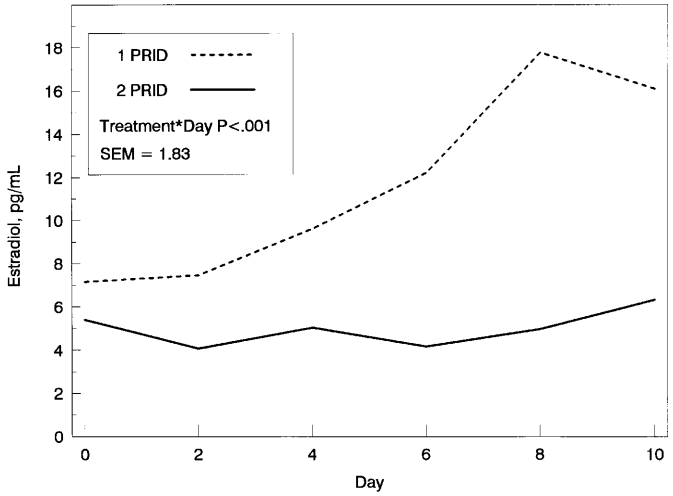

Figure 10. Concentrations of 17β-estradiol in cows treated with a low (1 PRID) or high (2 PRID) dose of progesterone for 10 d. Cows were administered $PGF_{2\alpha}$ during the treatment period to destroy the corpus luteum. Adapted from Wehrman et al. (1993).

Function of Persistent Ovarian Follicles

When cows are treated with doses of progesterone or synthetic progestins that are used commercially to synchronize stage of the estrous cycle, greater circulating concentrations of 17β-estradiol result than those present during the luteal phase of the estrous cycle (Figure 10; Roberson et al., 1989; Sirois and Fortune; 1990; Kojima et al., 1992, 1995; Sanchez et al., 1993, 1995; Savio et al., 1993; Wehrman et al., 1993). The greater amount of 17β-estradiol in cows treated with doses of progestins that are used commercially likely results from development of the persistent ovarian follicle. When greater doses of the progestin norgestomet are used than administered commercially, circulating concentrations of 17β-estradiol are maintained at concentrations similar to those during the luteal phase of the estrous cycle of cattle (Figure 11; Sanchez et al., 1995).

The greater amounts of 17β-estradiol produced by persistent ovarian follicles compared with dominant follicles that develop during typical estrous cycles likely results from the greater pulsatile release of LH (Roberson et al., 1989; Kojima et al., 1992, 1995; Savio et al., 1993; Sanchez et al., 1995). The greater frequency of LH pulses during the follicular phase has been attributed to lower circulating concentrations of progesterone (Imakawa et al., 1986). It is likely, therefore, that the greater circulating 17β-estradiol that is present when persistent ovarian follicles develop is a consequence of LH being released at a frequency similar to that during the follicular phase of the estrous cycle of cattle.

Consequences If Persistent Ovarian Follicles Ovulate

Reduced conception rates result from breeding cattle at the first estrus after withdrawal of progesterone if doses are the same as those used commercially compared with conception rates if doses of progesterone that are administered are larger during the period preceding estrus (Figure 12; Savio et al., 1993; Wehrman et al., 1993). Pregnancy rates are sequentially decreased as duration of persistence of dominant follicles increases from 4 to 8 d and are further reduced if persistence of the largest ovarian follicle exceeds 10 d (Mihm et al., 1994a).

Reduced fertility may result because of the greater concentrations of 17β-estradiol that are maintained over longer periods of time when persistent ovarian follicles develop. When increased 17β-estradiol is present for longer periods of time than typically occur during the estrous cycle of female rats, abnormal oocytes and aberrations in embryonic development result (Butcher and Pope, 1979; Page and Butcher, 1982). Exposure of oocytes contained in persistent follicles to greater concentrations of 17β-estradiol over longer periods of time than typically occur in dominant follicles may have detrimental effects on the oocyte (Ahmad et al., 1995). Furthermore, increased concentrations of 17β-estradiol for extended periods of time may affect the oviductal or uterine environment

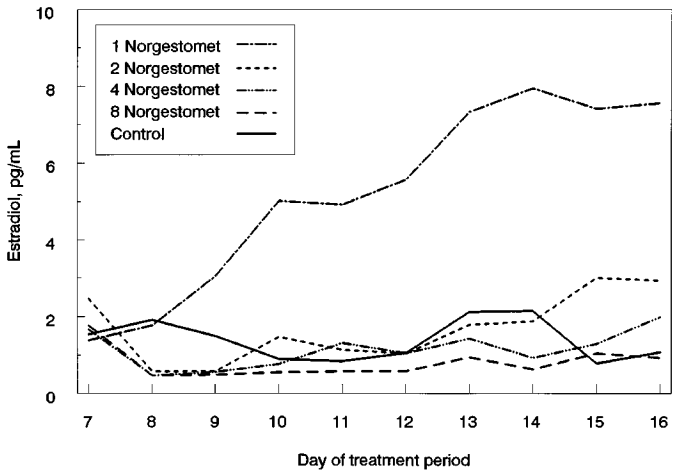

Figure 11. Concentrations of 17β-estradiol in untreated control cows in the luteal phase of their estrous cycle and cows treated with 1, 2, 4, or 8 norgestomet implants over a 9-d period. Cows were treated with norgestomet on d 7 (d 0 = estrus) of the estrous cycle and were administered $PGF_{2\alpha}$ at initiation of the period of treatment with norgestomet. Note the greater amounts of 17α-estradiol in cows treated with one implant compared with those of control cows and cows treated with 2, 4, or 8 implants. Adapted from Sanchez et al. (1995).

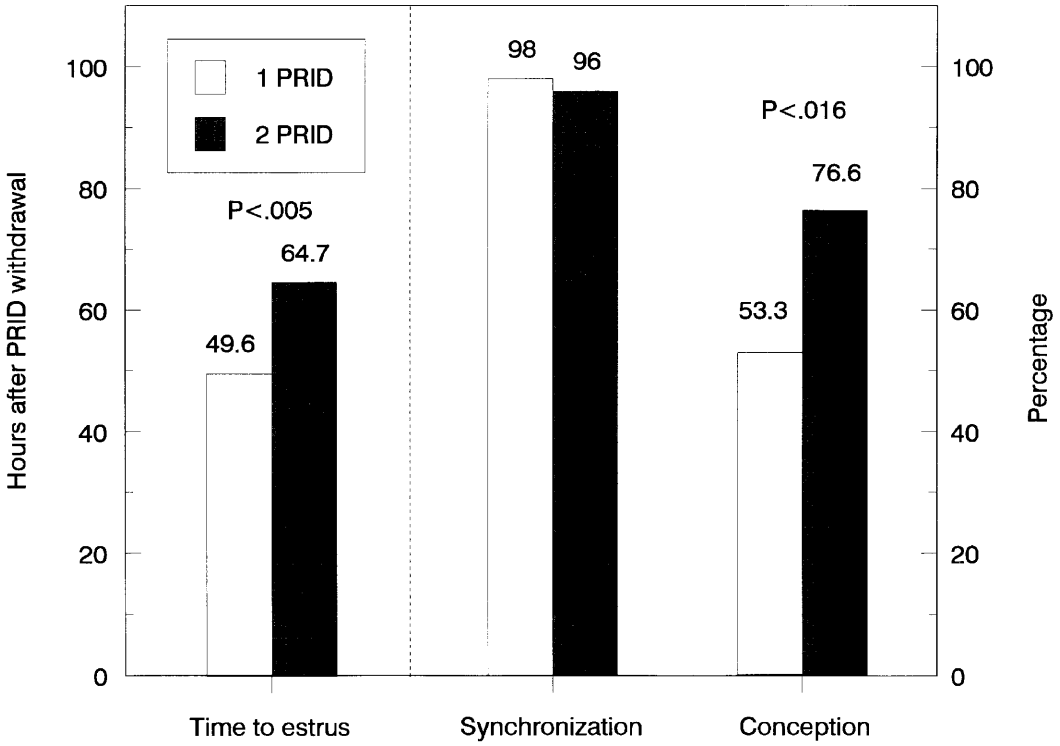

Figure 12. Pregnancy rates of cows treated with a low (1 PRID) or high (2 PRID) dose of progesterone for a 10-d period where cows were inseminated after their first estrus following withdrawal of the PRID. Note the earlier onset of estrus following PRID withdrawal in cows treated with the low dose of progesterone. This is indicative of the more advanced stage of ovarian follicular development at the time of progesterone withdrawal in this group of cows. Also note that there was no difference in percentage of cows with a synchronized estrus (estrus detected within 7 d after PRID withdrawal). Cows were treated with $PGF_{2\alpha}$ during the period of PRID treatment to destroy the corpus luteum. Adapted from Wehrman et al. (1993).

so that early embryonic development is compromised (Ahmad et al., 1995).

Recent data from our laboratory indicate that conception rate is similar in recipient cows that ovulated persistent ovarian follicles and those ovulating normal dominant follicles when frozen thawed embryos from donor cows are transferred into the recipient cows on the 7th d after detection of estrus (Wehrman et al., 1996b). Recent publications have provided valuable information elucidating why conception rates are lower if cattle are bred after withdrawal of sources of progesterone or synthetic progestins that contain doses of these hormones that are used commercially. Embryonic development (Figure 13) and quality of embryos are compromised by the 6th d after breeding cows that ovulated persistent follicles compared with cows ovulating dominant follicles that developed in a typical fashion (Ahmad et al., 1995).

We recently compared the quality of embryos from cows with a persistent ovarian follicle during the period of superstimulation of ovarian follicular development with FSH to the quality of embryos from cows with a typical dominant ovarian follicle during the period of FSH superstimulation (Wehrman et al., 1996a). An interesting finding is that cows with persistent ovarian follicles during the period of FSH superstimulation developed embryos that are of similar quality to those of control cows that did not have a persistent ovarian follicle during the period of superstimulation of follicular development with FSH. Oocytes and embryos from follicles induced to develop as a result of the superstimulatory treatment regimen in the recent study (Wehrman et al., 1996a) traversed through the same oviductal and uterine environment as oocytes ovulated from persistent ovarian follicles in the previous study (Ahmad et al., 1995). In the more recent study, all of the oocytes, with the possible exception of the ones from the persistent ovarian follicles, are derived from follicles that are newly recruited as a result of FSH treatment (Wehrman et al., 1996a). The similarity of embryo quality among cows that developed persistent follicles and those that did not indicates that the oviductal and uterine environments are not detrimental to oocyte or embryonic development.

Another possibility is that exposure of persistent ovarian follicles to a greater frequency of LH pulses over extended periods of time than what typically

occurs may result in premature development of the oocyte compared with what normally occurs in developing dominant follicles. Completion of the first meiotic division is typically induced by the preovulatory surge of gonadotropins, which occurs near the time of onset of estrus. Exposure of oocytes in persistent ovarian follicles to the greater frequency of LH pulses over a prolonged period may result in resumption of meiosis before the preovulatory surge of gonadotropins is released (Mihm et al., 1994b; Revah and Butler, 1995).

Oocytes from persistent ovarian follicles are in a more advanced stage of development than are those from normally developed dominant follicles (Mihm et al., 1994b; Revah and Butler, 1995). It is proposed that the reduced fertility resulting from ovulation of persistent dominant ovarian follicles is the result of asynchronous nuclear and cytoplasmic maturation of the oocyte (i.e., meiosis in the oocyte probably resumed before the preovulatory LH surge; Mihm et al., 1994b).

When results from studies in various laboratories are evaluated, the most likely cause for reduced fertility of cows ovulating persistent ovarian follicles is abnormal oocyte development. Fertilization rates are similar with oocytes from persistent follicles and those from normally developed dominant follicles, but early embryonal death occurs in a greater percentage of cows ovulating persistent ovarian follicles (Ahmad et al., 1995), and this might result from ovulation of an "aged" oocyte (Mihm et al., 1994b; Revah and Butler, 1995).

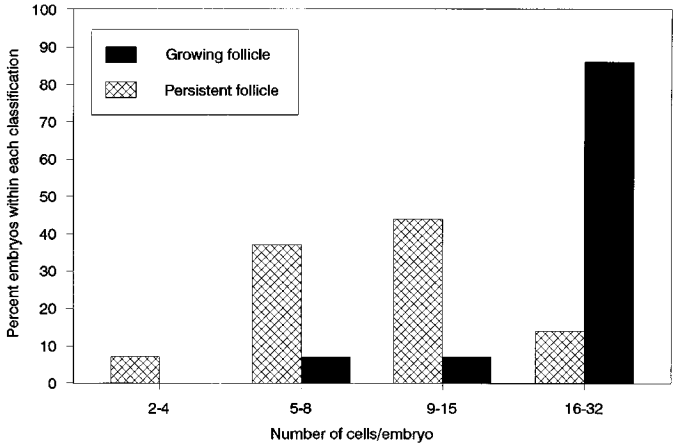

Figure 13. Number of cells in embryos collected on d 6 after mating of cows. Embryos were derived from cows ovulating persistent follicles as a result of being treated with a low dose of progesterone before ovulation. Cows in the control group ovulated dominant growing follicles that developed in the presence of a corpus luteum. Cows treated with progesterone were also administered $PGF_{2\alpha}$ to destroy the corpus luteum at the time of initiation of the progesterone treatment period. Embryos from cows ovulating persistent follicles had a quality score of 4.5 ± .3, and those ovulating normally developed growing follicles had a quality score of 2.7 ± .4 (scale 1 = excellent and 5 = very poor). Adapted from Ahmad et al. (1995).

Control of Development of Persistent Ovarian Follicles

There are two ways to control the development of ovarian follicles while using progestins to synchronize stage of estrous cycles without compromising conception rates. Administration of greater doses of progestin than typically used for estrus synchrony inhibits development of persistent ovarian follicles, and conception rates are greater than in cows in which persistent ovarian follicles develop (Savio et al., 1993; Wehrman et al., 1993).

Another way to control development of dominant ovarian follicles is to allow for development of persistent dominant follicles by administering small doses of progestin and subsequently inducing regression of persistent dominant follicles. If the progestin block on ovulation is removed shortly after the induced regression of the persistent dominant follicle, a normally developed dominant follicle ovulates before another persistent follicle can develop.

When MGA is fed to cattle, a persistent ovarian follicle develops. An injection of progesterone (200 mg) induces regression of the persistent dominant follicle (Figure 14; Anderson and Day, 1994). Conception rates are greater in cows that are administered progesterone than in cows not administered progesterone to induce regression of the persistent ovarian follicle (Anderson and Day, 1994). Injection of doses of progesterone as small as 150 mg induces atresia of persistent dominant ovarian follicles (Rajamahendran and Mannikkam, 1994). Recent data from our laboratory indicate that conception rates are similar in cows in which development of persistent ovarian follicles does not occur as a result of administration of a large dose of norgestomet and in cows in which persistent ovarian follicles develop and then are induced to regress (Peters et al., 1995).

The likely reason that administration of progesterone induces regression of the persistent ovarian follicle is that a dramatic reduction in the frequency of LH pulses occurs when the dose of progesterone is shifted from a small to relatively large dose (Figure 4; Bergfeld et al., 1996). Administration of 10 mg of 17β-estradiol also induces regression of persistent ovarian follicles (Rajamahendran and Mannikkam, 1994). This likely occurs because concentrations of 17β-estradiol in circulation of cattle that are greater than typically present during the follicular phase of the estrous cycle drastically suppress release of LH (Wolfe et al., 1992).

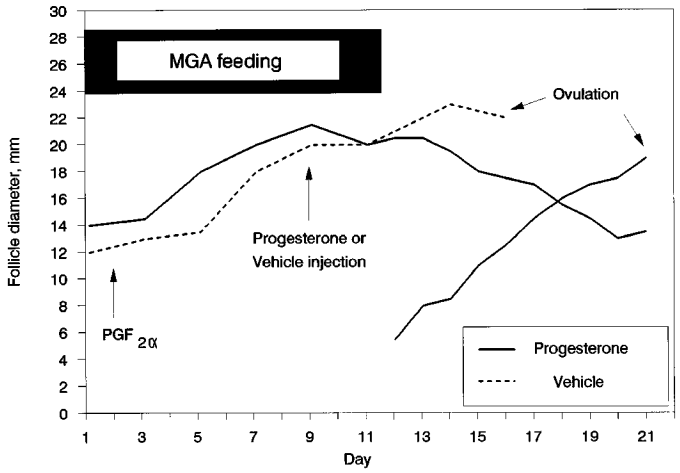

Figure 14. Diameter of ovarian follicles and time of ovulation subsequent to cessation of a MGA feeding period in cows fed .5 mg of MGA daily for 11 d and administered 200 mg of progesterone or vehicle on d 9 of the MGA treatment period. All cows were administered $PGF_{2\alpha}$ to destroy the corpus luteum at initiation of the MGA treatment period. Cows administered vehicle ovulated the persistent follicle and cows administered progesterone ovulated a newly developed dominant follicle. Pregnancy rates of cows inseminated at the synchronized estrus were 50 and 17% ($P < .05$) for cows administered progesterone and vehicle, respectively. Adapted from Anderson and Day (1994).

Implications

If a functional corpus luteum is not present during the period of progestin treatment, minimal effective doses of progestin for inhibition of estrus and ovulation are lower than needed to control development of dominant ovarian follicles. Doses of progestin that are typically used to synchronize estrus allow for development of dominant follicles that grow to larger sizes over extended periods of time and produce more 17β-estradiol than those that typically develop during the estrous cycle. Persistent ovarian follicles develop because of increased frequency of LH pulses. When breeding occurs after development of persistent ovarian follicles, fertility is reduced.

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