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How effective are exogenous progestins in mimicking the function of the corpus luteum of female cattle?

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ABSTRACT

An intensive evaluation of the hormones that are primarily involved in regulating reproductive function in cows treated with progestins was undertaken and comparisons were made to cows with a functional corpus luteum. Cows with a functional corpus luteum were found to have reduced circulating luteinizing hormone (LH) and oestradiol than cows treated with a single progesterone releasing intravaginal device (PRID), norgestomet (progestin used in Syncro-Mate-B synchrony) or melengestrol acetate (progestin used for oestrous synchrony in the USA). If greater doses of progesterone than that released from a single PRID are used, concentrations of LH and oestradiol are like those of control cows in the midluteal phase of their oestrous cycle. In addition, conception rates are significantly improved when greater doses of progesterone are used compared to that of cows in which oestrus is synchronised with a single PRID. We propose that one reason for reduced conception with oestrous synchrony programmes presently in use is the failure of the progestins to effectively mimic the function of the corpus luteum.

Keywords: progestin, oestrous synchrony, lutenizing hormone, oestradiol, corpus luteum.

INTRODUCTION

Progestins such as the naturally occurring hormone, progesterone, and the synthetic progestins, norgestomet and melengestrol acetate (MGA), have been used to synchronise the oestrous cycles of cows in many countries. The rationale behind their use is to mimic function of the corpus luteum. Upon removal of the progestin, all cows should come on oestrus in a relatively short period of time.

All of the progestins currently used are effective at synchronising time of oestrus. However, in many cases conception at the synchronised oestrus is quite low compared to what normally occurs with artificial insemination where oestrous synchrony programmes are not employed.

There has been very little attention given to determining why conception is compromised when progestins are used for oestrous synchrony. We have recently done an intensive evaluation of the hormones that are primarily involved in regulating reproductive function of cows treated with progestins and compared this to cows with a normally functioning corpus luteum. All of the research discussed in this paper was performed with a composite breed of cattle (1/4 Hereford, 1/4 Angus, 1/4 Red Poll, 1/4 Pinzgauer). The rationale for our initial study was that the corpus luteum is the endocrine gland that prepares the cow for pregnancy in the naturally occurring oestrous cycle and that the progestins used to sychronize oestrus have to substitute for the corpus luteum when oestrous synchrony procedures are used. Control cows with a functional corpus luteum were found to have lower circulating luteinizing hormone (LH) and lower oestradiol than cows treated with a single progesterone releasing intravaginal device (PRID), norgestomet (progestin used in Syncro-Mate-B synchrony, SMB) or MGA (progestin used for oestrous synchrony in USA). The level of progesterone in circulation of cows treated with the single PRID (1PRID) was lower than that of control cows. If two PRID's (2PRID) were used, circulating concentrations of progesterone and oestradiol were similar to that of control cows.

Based on the above findings we decided to determine if cows from the 2PRID group, which had similar levels of progesterone as cows in the mid-luteal phase of their oestrous cycle would also have enhanced conception at artificial insemination as compared to cows from the 1PRID group. We also compared conception rates in cows and heifers that had a functional corpus luteum present during treatment with norgestomet to that of cows and heifers treated with norgestomet, but that had their corpus luteum destroyed by injection of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) at the time treatment was initiated. It was found that cows and/or heifers from the 2PRID group and those with functional corpora lutea that received norgestomet had greater rates of conception than those from the 1PRID group and those treated with norgestomet that did not have a corpus luteum.

At this point we concluded that the reduced conception that results when current oestrous synchrony procedures that employ progestins are used occurs because the progestins fail to control LH secretion and the development of ovarian follicles in a manner similar to the corpus luteum in the normal oestrous cycle.

Do Progesterone and Progestins as used in oestrous synchrony programmes mimic the corpus luteum in regulation of LH and oestradiol secretion?

We compared LH and oestradiol secretion in cows treated with one PRID, two PRID's, norgestomet (as used in the Syncro-Mate-B®, SMB program) or MGA to that of cows with a corpus luteum. Treatments were administered for nine days (Day 0 = initiation of treatment). All cows from 1PRID,

2PRID, SMB, and MGA groups were injected with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) on days 2 and 5 of the treatment period to regress the corpus luteum. Cows in the 1PRID and SMB groups were also administered exogenous oestrogens according to the respective oestrous synchronisation protocols for these products. Cows in the Control group were on Day 5 of their oestrous cycle at the time treatments were initiated. Daily blood samples were collected from Day 0 to 35 to determine concentrations of progesterone. On Day 8, blood samples were collected at 15-min intervals for 24 hours to determine patterns of LH secretion. On day 9, all treatments ceased and cows in the Control group received an injection of $PGF_{2\alpha}$. Blood samples were collected at 1-hour intervals after cessation of treatments to determine time of the preovulatory surge of LH.

During the treatment period, mean concentrations of progesterone in the 2PRID and Control groups were greater than in cows from the other groups (Table 1). Mean concentrations of oestradiol in cows from the SMB group were greater compared to cows from the other groups during the treatment period (Table 2). In addition, concentrations of oestradiol in cows from the 1PRID group were greater than in cows from the 2PRID and Control groups (Table 2).

TABLE 1: Mean concentrations of progesterone in circulation and duration of the luteal phase of the oestrous cycle following treatment.

Treatment	Treatment Period Mean Progesterone (ng/ml)	Subsequent Oestrous Cycle[a] Mean Progesterone (ng/ml)	Subsequent Oestrous Cycle[a] Luteal Phase[b] (days)
1 PRID	3.9[c]	4.3[c]	16.3
SMB	1.4[d]	2.7[c]	15.3
MGA	2.4[d]	3.4[c]	16.4
2PRID	10.1[e]	7.3[d]	18.7
Control	9.0[e]	7.6[d]	18.7
Pooled SEM	2.7	2.0	2.9

[a]Oestrous cycle following removal of treatments.
[b]Interval between first rise in progesterone above 1 ng/ml and decline in progesterone below 1 ng/ml of plasma.
[c,d,e]Numbers with differing superscripts within column differ ($p < 0.05$).

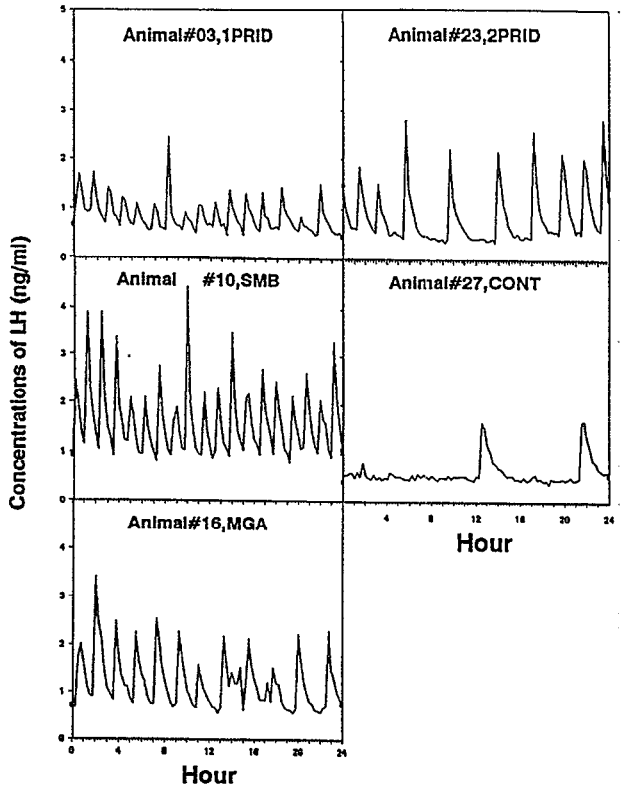
TABLE 2: Mean concentrations of plasma oestradiol at the time of cessation of treatments.

Treatment	Mean Concentrations of Oestradiol Day 9 (pg/ml)[a]
1PRID	7.7[c,d]
SMB	17.8[b]
MGA	12.2[b,c]
2PRID	4.3[d]
Control	3.2[d]
Pooled SEM	4.5

[a]At the time of treatment cessation on day 9.
[b,c,d]Numbers with different superscripts within column differ ($p < 0.05$).

Secretion of LH from the pituitary gland into circulation occurs in a pulsatile manner. The patterns of this pulsatile secretion of LH are depicted in Figure 1 for a single cow from each treatment group over the 24-hour period of blood collection. Obviously, the pattern of secretion differs when the patterns of cows from the Control group are compared to that of cows from the treatment groups.

FIGURE 1: Secretory profile of LH from individual representative animals from each treatment group during the 24-hour blood collection on Day 8 of treatment. Samples were collected at 15-minute intervals over the 24-hour period.



On Day 8 of treatment, frequency of LH pulses in cows treated with SMB was greater and mean concentrations of LH were lower in cows from the Control group as compared to that of cows from the other groups (Table 3).

TABLE 3: Mean concentrations of progesterone and frequency of LH pulses.

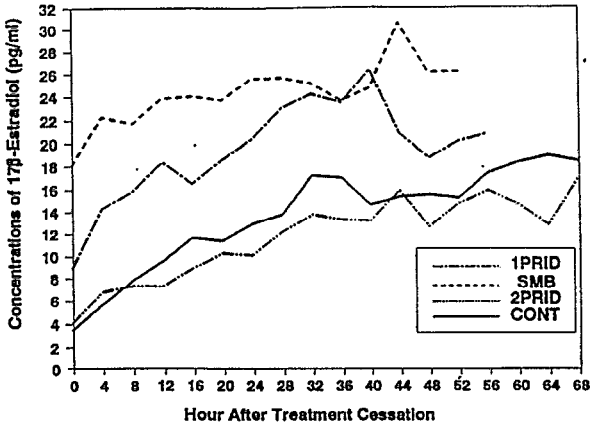
Treatment	Mean Progesterone (ng/ml)	LH Frequency (ng/ml)
1PRID	1.9[a]	11.8[b]
SMB	0.3[a]	18.8[a]
MGA	1.7[a]	13.4[b]
2PRID	8.5[b]	9.5[b]
Control	10.2[c]	2.5[c]
Pooled SEM	1.4	3.0

[a,b,c]Numbers with differing superscripts within column differ ($p < 0.05$).

Initiation of the preovulatory surge of LH occurred 20 hours earlier in cows from the SMB group and tended to be earlier in cows from the 1PRID group than cows in the 2PRID and Control groups. The earlier initiation of the preovulatory LH surge in the 1PRID and SMB groups probably resulted

from the altered pattern of oestradiol secretion after cessation of treatments (Figure 2). Concentrations of progesterone during the oestrous cycle subsequent to treatment were greater in cows from the 2PRID and Control groups than in cows from the other groups (Table 1).

FIGURE 2: Mean concentrations of oestradiol after cessation of the 9-day treatment. Only one animal treated with MGA had a preovulatory surge of LH during the period of blood collection after cessation of treatment, therefore, this group is not represented in the figure.



In summary, the low levels of progesterone and synthetic progestins (norgestomet and MGA) administered in the regimens used to synchronise oestrus alter the pattern of pulsatile secretion of LH and apparent ovarian activity. The latter is indicated by the increased secretion of oestradiol during the later part of the treatment period and subsequent follicular phase. The reason oestradiol secretion is greater is because follicles are thought to persist for longer periods due to the increased frequency of LH pulses. In cows with a functional corpus luteum, LH support is not sufficient to maintain follicle growth and waves of follicle growth and atresia occur as a result. The observations from our research suggest that abnormal development of ovarian follicles by the alteration in secretion pattern of LH could lead to production of an abnormal oocyte that would be less fertile, and ovulation of an abnormal follicle that may lead to altered function of the subsequent corpus luteum.

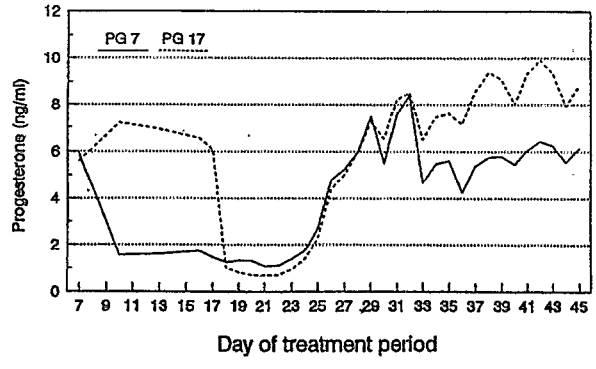
How do conception rates to artificial insemination compare in cows treated with lower doses to those treated with higher doses of exogenous progesterone?

Cows (n = 100) were treated with the 1PRID or 2PRID regimen to synchronise oestrus. Cows in both groups were given $PGF_{2\alpha}$ on days 3 and 5 of the treatment period, thus the only progesterone involved in preparing cows for pregnancy was from the exogenous source. Following PRID removal all cows in oestrus during the next 7 days were artificially inseminated 12 hours after detection of oestrus. Cows from the 2PRID group had significantly greater concentrations of progesterone throughout the 10-day treatment period. In cows from the 1PRID group, oestradiol increased 2.4 fold with peak concentrations being achieved two days before cessation of treatment. Following PRID removal cows from the 1PRID group exhibited oestrus earlier and had reduced conception rates (53 vs 77%) compared to cows from the 2PRID group. In conclusion, prolonged exposure to elevated concentrations of oestradiol may alter the cascade of events required to establish pregnancy and results in reduced conception rates in beef cows.

Does the synthetic progestin, norgestomet, when used in doses that are currently used for oestrous synchrony prepare the cow for pregnancy like the progesterone from the corpus luteum?

Sixty six heifers (1 herd) and 125 cows (two herds) were randomly assigned to two treatment groups. All animals were fed MGA for 10 days to synchronise stage of the oestrous cycle. Seven days after oestrus all animals that had exhibited oestrus within a 2-day period after cessation of feeding MGA were implanted with norgestomet. Cows and heifers from one group received an injection of $PGF_{2\alpha}$ on Day 7 (Day 0 = day of oestrus; PG7, norgestomet without a corpus luteum) and those in the other group received an injection of $PGF_{2\alpha}$ on Day 17 (PG17, norgestomet with corpus luteum). All heifers and cows that exhibited behaviourial oestrus over a 7-day period after cessation of norgestomet treatment were artificially inseminated 12 hours after detection of oestrus. Blood samples were collected from cows of one replicate each day from time of initiation of norgestomet treatment up to Day 45. Samples were used to assay for progesterone and oestradiol. Percentages of animals exhibiting behaviourial oestrus over the 7-day period following cessation of norgestomet treatment in the three groups of animals were 95, 91 (cows) and 97 (heifers). Average time from cessation of norgestomet treatment to initiation of behaviourial oestrus was longer in animals from the PG17 group [70, 52 (cows) and 51 hours (heifers)] compared to those from the PG7 group [62, 48 (cows) and 32 hours (heifers)]. Percentage of females that had calves as a result of artificial insemination was greater in the PG17 (74%) than the PG7 (38%) group.

FIGURE 3: Mean concentrations of progesterone (P_4) in daily plasma samples in PG 7 (norgestomet without corpus luteum) and PG 17 (norgestomet with corpus luteum) groups. Differences in progestrone before day 17 resulted due to treatment. Differences in progestrone after day 33 occurred due to differences in conception rate between the two groups thus corpus luteum regression resulted in a greater percentage of cows from the PG 7 group.



Concentrations of progesterone were greater in cows from the PG17 group during the treatment period since these animals had corpora lutea (Figure 3). Concentrations of oestradiol were not different between the two groups at initiation of treatment on Day 7 but were greater in cows from the PG7 than those from the PG17 group for the remainder of the treatment period. In conclusion, norgestomet when administered at doses that are presently used for oestrous synchrony is not as effective in preparing bovine females for pregnancy as endogenous progesterone produced by the corpus luteum.

SUMMARY

When the synthetic progestins and progesterone are used at doses that are recommended in oestrous synchrony programmes they do not regulate pulsatile secretion of LH like the corpus luteum. The increased frequency of LH pulses stimulates greater development of ovarian follicles than normally occurs during the oestrous cycle. This results in increased oestradiol secretion from the ovary over an extended period of time. Prolonged exposure to elevated oestradiol or subnormal levels of progesterone may result in abnormal oocyte maturation, gamete and/or embryo transport or inadequate preparation of the uterus for maintenance of pregnancy. If oestrous synchrony programmes that result in higher fertility are to be developed, it will be necessary to have treatment regimens that control endocrine and physiological processes in a manner similar to that imposed by progesterone from the corpus luteum.

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