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CONTROL OF OVULATION, FERTILITY AND ENDOCRINE RESPONSE AFTER PROSTAGLANDIN $F_{2\alpha}$ IN CATTLE

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SUMMARY

Luteolysis was induced by intrauterine (5 mg) or intramuscular (15, 30 or 60 mg) $PGF_{2\alpha}$ treatment of cows in diestrus. After intrauterine $PGF_{2\alpha}$, progesterone fell 50 p. 100 within 12 hours, estradiol more than doubled within 24 hours, LH peaked at 17 hours, estrus began at 72 hours and ovulation occurred at 95 hours post-injection. The sequence of reproductive and endocrine changes which occurred after $PGF_{2\alpha}$ resembled that which normally occurred during the 3 days before estrus in cattle, and estrous cycles were normal after an estrus induced by $PGF_{2\alpha}$. Inseminations at predetermined intervals after treatment with $PGF_{2\alpha}$ without regard to estrus detection resulted in fertility equivalent to that of control heifers and cows. Blood prolactin, growth hormone and glucocorticoids increased several-fold within 5-15 min after im or iv injection of $PGF_{2\alpha}$, but whether $PGF_{2\alpha}$ normally participates in release of these hormones has not been established.

INTRODUCTION

Our research on the luteolytic effect of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) in cattle was motivated by the observation that $PGF_{2\alpha}$ induced luteolysis in rats (PHARISS and WYNGARDEN, 1969). Initially our principal objective was to quantify the luteolytic effect of $PGF_{2\alpha}$ in cattle, and to describe the sequence of reproductive events which followed lyteolysis after $PGF_{2\alpha}$. Later we performed preliminary trials on fertility after $PGF_{2\alpha}$ and described some acute hormonal changes which occurred after $PGF_{2\alpha}$ administration. This report is a summary of our research on $PGF_{2\alpha}$ in cattle.

LUTEOLYSIS AFTER INTRAUTERINE $PGF_{2\alpha}$ IN COWS

In the first experiment, we injected $PGF_{2\alpha}$ into the uterus to maximize chances of detecting an effect, since the uterine luteolytic factor acts locally in cattle (ANDERSON *et al.*, 1969). In each of six cows, 5 mg $PGF_{2\alpha}$ (Tham salt) was injected through

TABLE 1

Corpus luteum diameter and blood progesterone and estradiol after intrauterine $PGF_{2\alpha}$ (5 mg) in cows (1)

Interval after $PGF_{2\alpha}$ (hr)	Corpus luteum diameter (cm)	Blood serum	
		Progesterone (ng/ml)	Estradiol (pg/ml)
0	2.5	3.6	5.0
12	—	1.7	6.1
24	1.6	1.2	11.3
48	0.9	1.0	12.7
72	UP (2)	0.8	15.5

(1) Values are averages of 23 observations on cows given $PGF_{2\alpha}$ on day 7, 11, or 15 of the estrous cycle.
(2) Unpalpable.

TABLE 2

Intervals to peak LH, onset estrus and ovulation after intrauterine $PGF_{2\alpha}$ in cows (1)

$PGF_{2\alpha}$ treatment		Interval (hr) from $PGF_{2\alpha}$ to			Duration of cycle after $PGF_{2\alpha}$ (days)
Uterine Horn	Day of cycle	Peak LH	Onset estrus	Ovulation	
Ipsilateral (1)	7	69 ± 7	71 ± 7	86 ± 11	21.5 ± .4
	11	68 ± 15	68 ± 15	94 ± 13	20.8 ± .3
	15	72 ± 6	70 ± 7	97 ± 5	20.6 ± .7
Contralateral	11	77 ± 7	76 ± 10	100 ± 13	—
	AVG	71 ± 4	72 ± 5	95 ± 5	21.0 ± .3

(1) Values are averages of five or six cows. Data from Louis *et al.* (1974 *a*).

the cervix into the uterine horn ipsilateral to the corpus luteum on day 7, 11 or 15 of the estrous cycle or into the contralateral uterine horn on day 11. The responses to $PGF_{2\alpha}$ were not affected by day of treatment or site of deposition of $PGF_{2\alpha}$. Therefore, the following data are averages of all four intrauterine treatments. Corpora lutea diameter averaged 2.5 cm at $PGF_{2\alpha}$ treatment, declined to 1.6 cm at 24 hours and they were unpalpable by 72 hours (table 1). Blood serum progesterone averaged 3.6 ng/ml at $PGF_{2\alpha}$ treatment ; in parrallel with the decline in corpus luteum size, progesterone declined to 1.7 ng/ml at 12 hours and to 0.8 ng/ml at 72 hours. Blood serum estradiol increased 3-fold to a peak (table 1) which occurred near the onset of estrus after $PGF_{2\alpha}$ administration. A surge of luteinizing hormone was centered on 71 hours, estrus began at 72 hours and ovulation occurred at 95 hours after intrauterine $PGF_{2\alpha}$ administration (table 2). The relative synchrony of onset of estrus and of ovulation regardless of stage of diestrus (table 2) suggested that acceptable fertility might result from inseminations at predetermined intervals after $PGF_{2\alpha}$. Average interval from onset of estrus to ovulation after $PGF_{2\alpha}$ treatment was 24 hours, similar to 29 hours in untreated heifers (SWANSON *et al.*, 1972).

The sequence of endocrine and reproductive changes after $PGF_{2\alpha}$ resembled those which occurred during 3 days before another estrus when the same cows were not given $PGF_{2\alpha}$; it also resembled similar observations in untreated cows (WETTEMANN *et al.*, 1972). Furthermore, duration of estrous cycles was normal (table 2) after the estrus induced by $PGF_{2\alpha}$.

In overview, intrauterine $PGF_{2\alpha}$ treatment initiated a sequence of events which we could not distinguish from those which normally preceed estrus and ovulation, and $PGF_{2\alpha}$ had no residual influences on subsequent cycles. A more detailed description of this experiment was published (LOUIS *et al.*, 1974 *a*).

LUTEOLYSIS AFTER SYSTEMIC $PGF_{2\alpha}$ IN HEIFERS

Although it caused luteolysis, intrauterine administration of $PGF_{2\alpha}$ during diestrus may be difficult under practical farm conditions. Therefore, we conducted an experiment to evaluate systemic administration of $PGF_{2\alpha}$ (LOUIS *et al.*, 1973). Thirty milligrams $PGF_{2\alpha}$ (Tham salt) was injected im into five heifers or deposited in the fornix of the vagina in six heifers during diestrus. In another six heifers, 30 mg $PGF_{2\alpha}$ was given im at 3 days after estrus as a negative control, because ROWSON *et al.* (1972) reported that intrauterine $PGF_{2\alpha}$ did not cause luteolysis before the fifth day after estrus in cattle.

After 30 mg $PGF_{2\alpha}$ im during diestrus, blood progesterone fell to less than 1 ng/ml within 24 to 48 hours (fig. 1) and estrus began at 74 ± 3 hours after $PGF_{2\alpha}$, similar to our observations after intrauterine $PGF_{2\alpha}$ in cows. Luteolysis and the estrual events precipitated by intravaginal $PGF_{2\alpha}$ were delayed by about 24-36 hours, and considerably more variable than those after im $PGF_{2\alpha}$. In contrast to $PGF_{2\alpha}$ during diestrus, intramuscular administration of 30 mg $PGF_{2\alpha}$ on day 3 after estrus had no effect on corpus luteum function ; blood serum progesterone for 5 days after $PGF_{2\alpha}$ (fig. 1) was similar to that of untreated cattle from day 3 to 8 of cycle (WETTE-

MANN *et al.*, 1972), and the interestrual interval was not altered significantly by $PGF_{2\alpha}$ given on day 3.

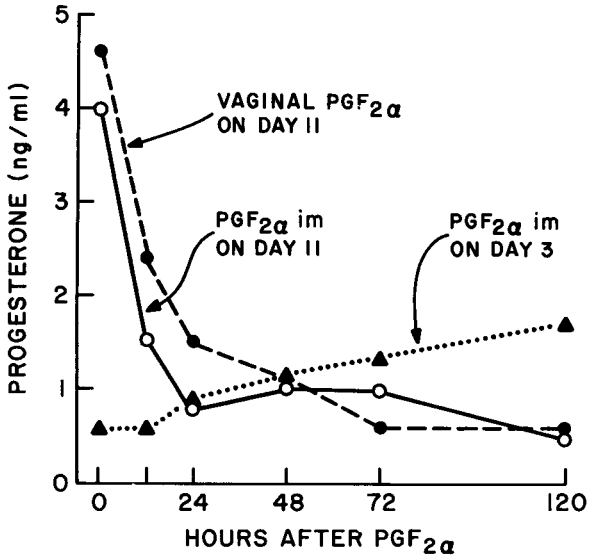

FIG. 1. — *Blood serum progesterone after intravaginal or intramuscular* $PGF_{2\alpha}$ (30 mg) *on day 3 or day 11 of the estrous cycle in heifers* (n = 5 or 6)
Data from LOUIS *et al.*, 1973

Another experiment was conducted to test whether two consecutive injections (ROWSON *et al.*, 1972) or injections of a larger quantity of $PGF_{2\alpha}$ might reduce the interval to estrus and ovulation. Heifers in diestrus were given (im) : 1) 30 mg $PGF_{2\alpha}$ (Tham salt) ; 2) two 15 mg injections of $PGF_{2\alpha}$ at 6-hours intervals or ; 3) 60 mg $PGF_{2\alpha}$, with six heifers in each treatment. The intervals from $PGF_{2\alpha}$ to onset of estrus, to the peak of the surge of LH and to ovulation were smaller after 60 mg $PGF_{2\alpha}$ than after 30 mg or 2 × 15 mg $PGF_{2\alpha}$ (table 3), but these differences only approached statistical significance. Changes in blood progesterone and estradiol did not differ among the three $PGF_{2\alpha}$ treatments.

We concluded that : 1) im administration of $PGF_{2\alpha}$ precipitated luteolysis, estrus and ovulation similar to those after intrauterine administration of $PGF_{2\alpha}$ during diestrus and ; 2) a single im injection of 30 mg $PGF_{2\alpha}$ was sufficient to induce complete luteolysis. However, the trend toward reduced intervals to estrus and ovulation after the 60 mg dose of $PGF_{2\alpha}$ suggested that $PGF_{2\alpha}$ may have actions which affected the interval to ovulation aside from those attributable to luteolysis. More details of this experiment were published (STELLFLUG *et al.*, 1973 ; HAFS *et al.*, 1974).

FERTILITY OF CATTLE AFTER $PGF_{2\alpha}$

The relative synchrony of ovulation after intrauterine or intra-muscular administration of $PGF_{2\alpha}$ (tables 2 and 3) suggested that artificial inseminations at predetermined intervals after $PGF_{2\alpha}$ may result in acceptable fertility. To test this

notion, LAUDERDALE *et al.* (1974) injected $PGF_{2\alpha}$ into cattle with palpable corpora lutea and inseminated them either when the cattle showed signs of estrus or at predetermined intervals (72 and 90 hours) after injection of $PGF_{2\alpha}$; the fertility of the $PGF_{2\alpha}$-treated cattle was equivalent to that of untreated controls (total of 277 animals). Furthermore, the fertility of cattle inseminated at predetermined intervals was equivalent to that in cattle inseminated at the estrus after $PGF_{2\alpha}$ treatment.

TABLE 3

Intervals from i.m. $PGF_{2\alpha}$ to estrus, peak LH and ovulation in cows

$PGF_{2\alpha}$ (mg)	Interval (hr) from $PGF_{2\alpha}$ to		
	Onset estrus	Peak LH	Ovulation
30	56 ± 2 (1)	65 ± 5	90 ± 5
2 × 15	66 ± 7	67 ± 6	92 ± 8
60	54 ± 4	61 ± 5	79 ± 5

(1) Values are means ± for six heifers.

Since palpation of the ovaries is impractical in many commercial herds, we designed a trial to determine the onset of estrus and fertility of 80 heifers and 99 suckled cows given $PGF_{2\alpha}$ twice at 12-day intervals (HAFS *et al.*, 1975). The first injection was intended to ensure that all animals would be in diestrus at the second injection. All $PGF_{2\alpha}$-treated animals were inseminated at 72 and 88 hours after the second injection of $PGF_{2\alpha}$. After the second injection, 88 p. 100 of the heifers and 68 p. 100 of the cows began estrus between 2 and 5 days, with the majority beginning estrus 48 to 84 hours after $PGF_{2\alpha}$ (table 4). Two heifers and ten cows

TABLE 4

Intervals from second injection (1) of $PGF_{2\alpha}$ to onset of estrus in heifers and suckled cows

Number of animals	Heifers	Cows
Total	59	66
Not observed in estrus	2	10
Beginning estrus on day 1-2	0	0
3	25	32
4	15	9
5	6	2
6	6	2
7-11	5	11

(1) Two im injections of $PGF_{2\alpha}$ were given 12 days apart.

were not observed in estrus during a 10-day period after the second injection, of $PGF_{2\alpha}$. Blood progesterone data indicated that the ten cows which were not observed in estrus were in post-partum anestrus, although they averaged 61 days post-partum.

Among $PGF_{2\alpha}$-treated animals, 54 p. 100 of the heifers and 41 p. 100 of the cows calved as a result of the inseminations at 72 and 88 hours after treatment (table 5). Comparable values for untreated control heifers ($n = 20$) and cows ($n = 33$) were 46 p. 100 and 42 p. 100, respectively. Thus, fertility of cattle which were inseminated at predetermined intervalls after $PGF_{2\alpha}$ was equivalent to that of controls.

TABLE 5

Fertility of heifers and cows inseminated at 72 and 88 hours after a second injection (1) *of* $PGF_{2\alpha}$

		No oestrus observed	Days onset oestrus after $PGF_{2\alpha}$	
			3-5	6-10
		(no fertile/no inseminated)		
Heifers	Non-return (2)	0/2 (0 %)	29/46 (63 %)	4/11 (36 %)
	Calved (3)	0/2 (0 %)	28/46 (61 %)	4/11 (36 %)
Cows	Non-return (2)	2/10 (20 %)	31/43 (72 %)	1/13 (8 %)
	Calved (3)	1/10 (10 %)	26/43 (60 %)	0/13 (0 %)

(1) Second injection given 12 days after the first.
(2) Non-returns represent heifers not returning to estrus within 30-70 days and cows within 60-85 days after insemination.
(3) Heifers calved 278 $\pm$ 10 days and cows calved 283 $\pm$ 10 days after insemination.

STEROID AND TROPIC CHANGES AFTER $PGF_{2\alpha}$

McCRACKEN *et al.* (1970) reported that $PGF_{2\alpha}$ infused into the ovarian artery of sheep in diestrus caused a transient increase in utero-ovarian venous progesterone followed by a decline to values typical of sheep in estrus. Also LIGGINS *et al.* (1972) reported that infusion of $PGF_{2\alpha}$ into the ewe caused an increase in blood estrogen. Therefore, we speculated that the mechanism of $PGF_{2\alpha}$-induced luteolysis in the cow may involve a brief increase in progesterone synthesis before the rapid decline, or that $PGF_{2\alpha}$ may effect luteolysis through a follicular action resulting in a transient rise in blood estrogen. Consequently, rapid changes in plasma progesterone and estradiol were determined (HAFS *et al.*, 1974) in the same samples of plasma used to study luteolysis after 15, 30 or 60 mg $PGF_{2\alpha}$ (table 3).

Declines in blood progesterone after the three $PGF_{2\alpha}$ treatments did not differ significantly, and the second 15 mg injection of $PGF_{2\alpha}$ did not affect the rate of

decline in progesterone (fig. 2). These data indicated blood progesterone may have begum to decline within 10 min after im injection of $PGF_{2\alpha}$ and we found no evidence for an increase before the rapid decline in progesterone after $PGF_{2\alpha}$.

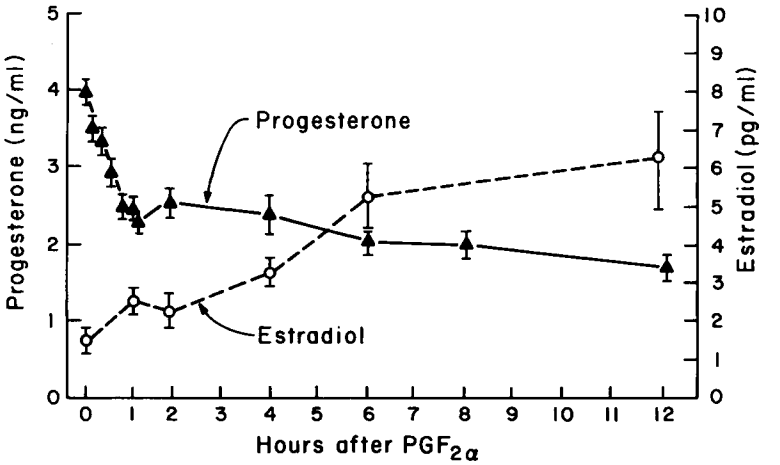

FIG. 2. — *Blood serum progesterone and estradiol after i. m. $PGF_{2\alpha}$* (15, 30 or 60 mg) *in diestrous heifers* ($n = 16$)
Data from HAFS *et al.*, 1974

Blood estradiol averaged less than 2 pg/ml prior to $PGF_{2\alpha}$ injection in these same heifers (fig. 2). Then estradiol increased continuously to 6.2 pg/ml at 12 hours and the rate of increase did not differ significantly among the three $PGF_{2\alpha}$ treatments. Although we anticipated a transient rise in estradiol, blood estradiol continued to increase in these heifers to peak values near the onset of estrus as in the first trial (table 1).

Since the E prostaglandins released growth hormone (GH) in sheep (HERTELENDY *et al.*, 1972) and in women (HENZL *et al.*, 1973), we determined prolactin, GH, glucocorticoid and LH (LOUIS *et al.*, 1974 *b*) in the same blood samples used to study luteolysis after 30 or 60 mg $PGF_{2\alpha}$ (table 3, fig. 2).

Prolactin increased over 5-fold within 10 min and peaked about 30 min after im $PGF_{2\alpha}$ (fig. 3) ; it remained elevated for at least 2 hours before returning to pre-injection values at 4-6 hours. The responses of prolactin did not differ significantly within the first 6 hours after 15, 30 or 60 mg of $PGF_{2\alpha}$ (im), and there was a similar increase of prolactin after the second 15 mg injection given 6 hours after the first. After a 5 mg intravenous injection of $PGF_{2\alpha}$, prolactin jumped 7-fold to 160 ng/ml at 15 min and then declined gradually toward basal values (23 ng/ml) at 2 hours. Within 15 min after initiation of a 30 min infusion (0.5 mg/min) of $PGF_{2\alpha}$, blood prolactin rose to 237 ng/ml and remained high until 20 mn after the infusion before declining toward basal values at 2 hours.

At 30 min after injection of im 15, 30 or 60 mg $PGF_{2\alpha}$, growth hormone (GH) increased 3-, 7-, or 26-fold respectively (fig. 4). Then blood GH declined to basal values (4 ng/ml) by 4 to 5 hours after $PGF_{2\alpha}$. GH peaked (45 ng/ml) at 30 min after a 5 mg iv injection of $PGF_{2\alpha}$, and then declined to basal values at 45 min. Infusion

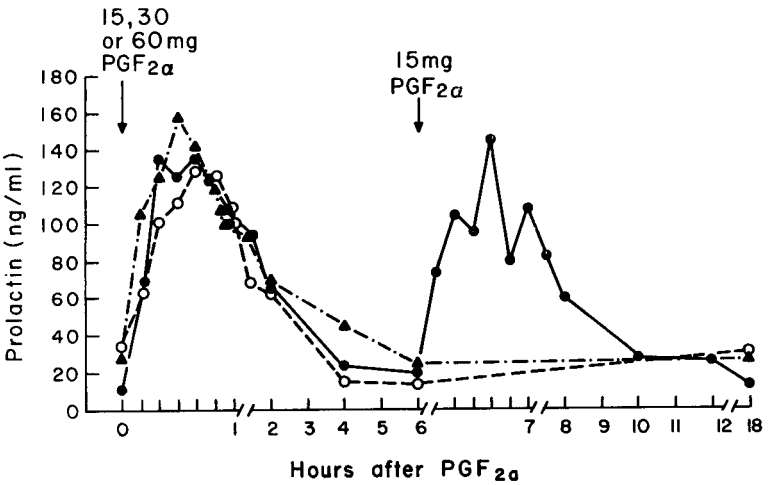

FIG. 3. — *Blood plasma prolactin after i. m.* $PGF_{2\alpha}$ (15, 30 or 60 mg) *in diestrous heifers* (n = 4 or 6)
Data from LOUIS *et al.*, 1974 *b*
●———● 15 mg $PGF_{2\alpha}$
○— — —○ 60 mg $PGF_{2\alpha}$
▲— · —▲ 30 mg $PGF_{2\alpha}$

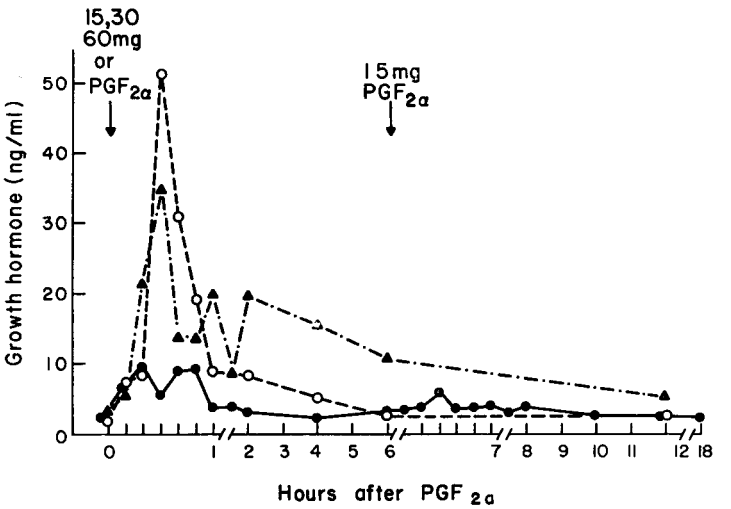

FIG. 4. — *Blood plasma growth hormone after i.m.* $PGF_{2\alpha}$ (15, 30 or 60 mg) *in diestrous heifers* (n = 4 or 6)
Data from LOUIS *et al.*, 1974 *b*
Legend see fig. 3

iv of $PGF_{2\alpha}$ resulted in a peak of GH (76 ng/ml) which occurred at 20 min after conclusion of the infusion.

Blood glucocorticoid increased up to 6-fold after im $PGF_{2\alpha}$ (fig. 5) ; it returned to pre-injection values (11 ng/ml) by 4 hours and the peak of glucocorticoid at 30 min after $PGF_{2\alpha}$ was linearly related to the log of the dose of $PGF_{2\alpha}$. When $PGF_{2\alpha}$ was given as a 5 mg iv injection, blood glucocorticoid peaked (7-fold increase) within 15 min and iv infusion of $PGF_{2\alpha}$ caused an even greater increase in blood glucocorticoid values.

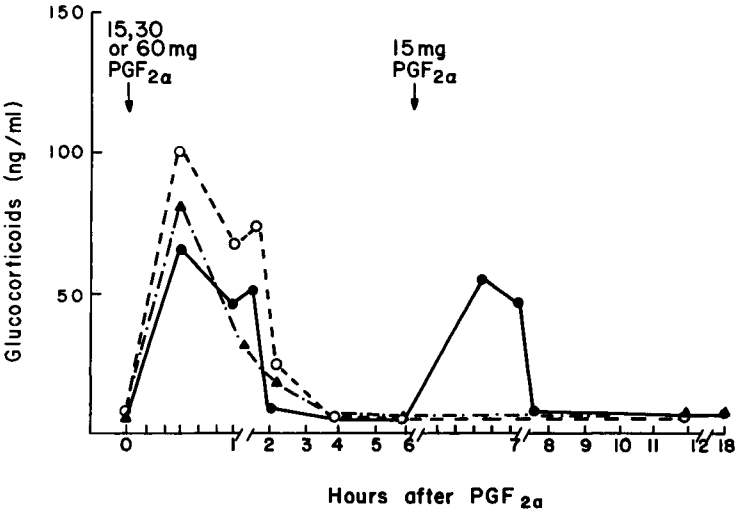

FIG. 5. — *Blood plasma glucocorticoid after i.m. $PGF_{2\alpha}$* (15, 30 or 60 mg) *in diestrous heifers* (n = 4 or 6)
Data from LOUIS *et al.*, 1974 *b*
Legend see fig. 3

In a recent review, HAFS (1975) concluded that E and F prostaglandins can cause release of prolactin, GH and ACTH in several species. Prostaglandins apparently release prolactin and ACTH by action on the hypothalamus, but GH release may be caused by action on the pituitary.

CONCLUSIONS

Luteolysis was induced by intrauterine (5 mg) or intramuscular (15, 30 or 60 mg) $PGF_{2\alpha}$ treatment of cattle in diestrus. After $PGF_{2\alpha}$ treatment, blood progesterone fell significantly within 10 mn and estradiol increased possibly within 6 hours. Blood progesterone decreased continuously at least for 48 hours and blood estradiol increased continously until onset of estrus. The sequence of reproductive changes which occurred after $PGF_{2\alpha}$ resembled that which normally occurred during the 3 days before estrus in cattle, and estrous cycles were normal after an estrus

induced by $PGF_{2\alpha}$. Ovulation occurred at 90 to 95 hours after $PGF_{2\alpha}$, although it may have been hastened by high doses of $PGF_{2\alpha}$. After two injections of $PGF_{2\alpha}$ 12 days apart, inseminations performed at predetermined intervals after the second injection resulted in fertility as high as that in untreated control heifers and suckled cows. Thus, detection of estrus may be unneccessary for high fertility after $PGF_{2\alpha}$ treatment. The physiological and practical significance of our finding that $PGF_{2\alpha}$ treatment is followed within 30 min by large increases in blood GH, prolactin and glucocorticoid remains to be determined.

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RÉSUMÉ

CONTRÔLE DE L'OVULATION, FERTILITÉ ET RÉPONSES ENDOCRINIENNES APRÈS TRAITEMENT A L'AIDE DE $PGF_{2\alpha}$ CHEZ LES BOVINS

La lutéolyse a été provoquée en administrant à des vaches en dioestrus des injections intra-utérines (5 mg) ou intramusculaires (15, 30 ou 60 mg) de $PGF_{2\alpha}$. Le niveau de progestérone a été réduit de 50 p. 100 en 12 heures ; celui d'œstradiol a plus que doublé en 24 heures et LH a atteint son maximum en 71 heures. L'œstrus a commencé 72 heures après, l'ovulation s'est produite 95 heures après l'injection. Les changements liés à la reproduction et aux niveaux endocriniens constatés après l'administration de $PFG_{2\alpha}$ sont semblables à ceux normalement observés durant les 3 jours qui précèdent l'œstrus chez les bovins ; les cycles œstriens ont été normaux après l'œstrus provoqué par l'administration de $PGF_{2\alpha}$. La fertilité des animaux inséminés après le traitement de $PGF_{2\alpha}$ indique que l'insémination à des intervalles prédéterminés sans détection de l'œstrus a donné une fertilité équivalente à celle des génisses et des vaches non injectées. Les niveaux de prolactine dans le plasma sanguin aussi bien que ceux de l'hormone de croissance et des glucocorticoïdes ont été augmentés de plusieurs fois en 5 à 15 minutes après l'injection intramusculaire ou intraveineuse de 5 mg de $PGF_{2\alpha}$ ou après une succession d'infusions de 0,5 mg/mn durant 30 minutes.

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