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Route of Prostaglandin $F_{2\alpha}$ Injection and Luteolysis in Mares[1] (38519)

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The uterus plays a key role in regression of the corpus luteum (CL) in several species including swine, cattle, sheep and horses (1, 2). In swine, cattle and sheep, uterine-induced luteolysis involves a local utero-ovarian pathway; whereas, in horses, uterine-induced luteolysis occurs primarily via a systemic pathway (3). Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), a postulated uterine luteolysin, is a useful tool for comparative studies on uteroovarian pathways. On a body weight basis, mares are considerably more sensitive than ewes to luteolytic effects of $PGF_{2\alpha}$ administered systemically (intramuscular (im) or subcutaneous (sc)); the minimum dose of a single systemic injection of $PGF_{2\alpha}$, which significantly shortened the interval from treatment to estrus, was approximately 24 times higher in ewes (4) than in pony mares (5). In ewes, luteolysis was more pronounced when $PGF_{2\alpha}$ was given by an intrauterine (iu) route than when injected systemically (4). In mares, critical comparisons of the luteolytic effect of local vs systemic administration of $PGF_{2\alpha}$ apparently have not been done.

The present experiment was conducted to compare luteolytic effects of a single injection of various doses of $PGF_{2\alpha}$ when given locally (iu or intraluteal (il)) vs systemically (im) in pony mares.

Materials and Methods. Twenty-seven pony mares were used during July and August, 1973. The mares were of unknown breeding, three to 16 yr of age and ranged in weight from 115 to 280 kg. Prior to treatment, all mares were teased daily for the occurrence of estrus and the ovaries of those mares showing signs of estrus were palpated daily, per rectum, to determine day of ovulation. On the day of ovulation (day 0), mares were assigned by randomization to nine groups (three mares/group) in a 3 × 3 factorial experiment. The factors were dose of $PGF_{2\alpha}$ (0, 0.25 or 1.25 mg) and route of administration (im, iu or il).

A $PGF_{2\alpha}$ stock solution was prepared by dissolving $PGF_{2\alpha}$-tham salt in a Tris–HCl vehicle (pH = 8.0) as described (6). All $PGF_{2\alpha}$ dosage levels used herein are on a free acid basis (1.34 mg $PGF_{2\alpha}$-tham salt is equivalent to 1.00 mg $PGF_{2\alpha}$ free acid). The dosage levels of $PGF_{2\alpha}$ were based on results from a previous experiment in which $PGF_{2\alpha}$ was injected im or sc; the interval from treatment to estrus and ovulation and the interovulatory interval were shortened significantly for mares given 1.25 mg but not for mares given 0.25 mg (5).

On the afternoon of day 7, a blood sample was collected (0 hr), mares were anesthetized as described (7) and a midventral laparotomy was performed to expose the uterus and ovaries. Feed and water were withheld for 1 day prior to surgery. The side of the CL was noted, the uterus and ovaries were handled and the assigned treatment was given. Intramuscular injections were given in a volume of 3 ml. Intrauterine injections were given in a volume of 1 ml into the lumen of the uterine horn ipsilateral to the CL (no mares had CL in both ovaries) using a syringe and 20 gauge needle. Intraluteal injections were given in a volume of 0.5 ml directly into the CL using a syringe and 23 gauge needle. Mares in the 0 mg dose group (controls) were given the appropriate volume of vehicle only.

In addition to the pretreatment blood collection (0 hr), all mares were bled at 1, 6, 12, 24, 48 and 72 hr posttreatment. Blood

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was collected by jugular venipuncture in 20 ml heparinized vacutainers. The samples were cooled, centrifuged and the plasma was divided into 5 ml aliquots for freezer storage. Plasma samples were randomized into five assays and analyzed for progesterone concentration by radioimmunoassay. The protocol and validation of the assay for progesterone in equine plasma have been described (8). Each assay included all samples collected for each mare assigned to that assay. Progesterone data were examined by a $7 \times 3 \times 3$ factorial analysis of variance for a nested classification and Duncan's new multiple-range test was used to make comparisons among means.

Beginning the day after treatment, mares were teased daily for the occurrence of estrus and ovaries were palpated to determine day of ovulation. Mares having follicles <30 mm were palpated at least every 3 days; mares having follicles ≥ 30 mm were palpated every day until ovulation occurred. Teasing and palpation end points were: interval from treatment to estrus, length of the posttreatment estrus, interval from treatment to ovulation and interovulatory interval (number of days from the pretreatment ovulation to the posttreatment ovulation). Data for these three end points were examined by a 3×3 factorial analysis of variance and Waller–Duncan's multiple-range test.

Results. Progesterone. There was a significant main effect of route of $PGF_{2\alpha}$ administration (im, iu and il), dose of $PGF_{2\alpha}$ (0, 0.25 and 1.25 mg) and time of bleeding (0, 1, 6, 12, 24, 48 and 72 hr posttreatment) on progesterone concentration. There were no significant route $\times$ dose $\times$ time, route $\times$ dose or route $\times$ time interactions; however, there was a significant dose $\times$ time interaction.

Results of comparisons of mean progesterone values among the three routes for each dose at each time of blood collection are shown in Table I (c, d superscripts). In mares given 0 mg (controls), progesterone values did not differ significantly among the three routes at 1 or 72 hr posttreatment; however, progesterone concentration at 6, 12, 24 and 48 hr posttreatment for mares injected il was less ($P < 0.05$) than that for mares injected im or iu. In mares given either 0.25 mg or 1.25 mg, progesterone concentrations were not significantly different among the three routes at any of the times studied except at 0 hr (prior to treatment, 0.25 mg group) and at 6 hr posttreatment (0.25 mg and 1.25 mg groups). In mares given 0.25 mg, progesterone concentration at the pretreatment collection (0 hr) was greater ($P < 0.05$) for mares injected im than for mares injected il; the value at 6 hr posttreatment was less ($P < 0.05$) for mares injected il than for mares injected im or iu. In mares given 1.25 mg, progesterone concentration at 6 hr posttreatment was less ($P < 0.05$) for mares injected im than for mares injected iu.

Results of comparisons of mean progesterone values among the three doses for each route at each time are shown in Table I (a, b superscripts). In mares injected im or iu, progesterone values were not significantly different between mares given 0.25 mg and mares given 1.25 mg $PGF_{2\alpha}$ at any of the posttreatment hours studied. In mares injected im, progesterone values were greater ($P < 0.05$) at 1 hr and less ($P < 0.05$) at 6 hr posttreatment for mares given 1.25 mg than for controls and values at 12, 24, 48 and 72 hr posttreatment were less ($P < 0.05$) both for mares given 0.25 mg and for mares given 1.25 mg than for controls. In mares injected iu, the progesterone values at 1 and 6 hr posttreatment were not significantly different among the three doses; the value at 12 hr posttreatment was less ($P < 0.05$) for mares given 0.25 mg than for controls; and values at 24, 48 and 72 hr posttreatment were less ($P < 0.05$) both for mares given 0.25 mg and for mares given 1.25 mg than for controls. In mares injected il, progesterone values at 1, 12, 24 or 48 hr posttreatment were not different among the three doses; the concentration at 6 hr was less ($P < 0.05$) for mares given 0.25 mg than for mares given 1.25 mg; and the value at 72 hr posttreatment was less both for mares given 0.25 mg and mares given 1.25 mg than for controls.

To study the effect of $PGF_{2\alpha}$ on progesterone concentration within each route of administration over the seven times of blood collection, data for the 0.25 mg and 1.25

TABLE I. EFFECT OF INTRAMUSCULAR (IM), INTRAUTERINE (IU), OR INTRALUTEAL (IL) INJECTION OF $PGF_{2\alpha}$ ON PROGESTERONE LEVELS IN THE JUGULAR VEIN.

Time from treatment to blood sample collection (hr)	Route	Dose $PGF_{2\alpha}$[a] (mg)					
		0 (controls)		0.25		1.25	
		Progesterone (ng/ml)		Progesterone (ng/ml)		Progesterone (ng/ml)	
		Mean[b]	SE	Mean[b]	SE	Mean[b]	SE
0 (pretreatment)	im	10.1^{A}	±5.4	21.0$^{c\ B}$	±2.5	12.1^{A}	±2.5
	iu	14.4	±1.7	16.8$^{c,\ d}$	±4.7	13.0	±2.5
	il	12.4	±2.4	13.8^{d}	±2.6	9.2	±4.0
1	im	8.4^{A}	±2.9	11.4^{AB}	±1.9	15.5^{B}	±2.9
	iu	12.9	±1.3	12.2	±3.9	13.1	±1.9
	il	9.6	±1.8	6.1	±0.4	11.1	±4.5
6	im	19.0$^{c\ A}$	±1.6	14.1$^{c\ AB}$	±2.6	9.7$^{c\ B}$	±0.4
	iu	17.5^{c}	±0.8	16.8^{c}	±5.2	19.1^{d}	±1.9
	il	9.9$^{d\ AB}$	±2.0	7.2$^{d\ B}$	±1.0	14.1$^{c,\ d\ A}$	±4.4
12	im	16.1$^{c\ A}$	±6.3	7.4^{B}	±2.3	10.4^{B}	±0.8
	iu	16.3$^{c\ A}$	±1.9	9.6^{B}	±1.3	11.3^{AB}	±5.5
	il	9.5^{d}	±2.4	7.1	±0.5	11.7	±5.3
24	im	16.8$^{c\ A}$	±3.4	3.6^{B}	±0.5	3.7^{B}	±1.4
	iu	13.0$^{c\ A}$	±2.2	5.9^{B}	±1.2	2.3^{B}	±0.5
	il	6.9^{d}	±3.0	2.1	±0.5	2.1	±0.2
48	im	16.3$^{c\ A}$	±2.5	4.2^{B}	±1.1	1.8^{B}	±0.2
	iu	11.3$^{c\ A}$	±3.3	2.7^{B}	±0.9	1.0^{B}	±0.3
	il	3.3^{d}	±1.1	0.9	±0.2	1.2	±0.2
72	im	14.7^{A}	±2.0	4.7^{B}	±0.9	1.3^{B}	±0.1
	iu	10.3^{A}	±2.9	1.5^{B}	±0.3	0.8^{B}	±0.2
	il	10.3^{A}	±0.5	1.4^{B}	±0.5	0.8^{B}	±0.1

[a] $PGF_{2\alpha}$ given as a single injection on day 7 postovulation. All doses are amount of $PGF_{2\alpha}$ and not $PGF_{2\alpha}$-tham salt.

[b] Mean of three blood samples for each subgroup (time/route × dose combination) except one sample was lost for 0 hr, im, 0.25 mg; 1 hr, il, 0.25 mg; 6 hr, im, 1.25 mg.

[c, d] Means within a column within each time which have one or more common superscript letters are not significantly different.

[A, B] Means within a row which have one or more common superscript letters are not significantly different.

mg groups were combined for each route and examined by analysis of variance and Duncans new multiple-range test (Fig. 1). In mares injected im, progesterone concentration was less ($P < 0.05$) than the pretreatment concentration at 12 hr posttreatment and values at 24, 48 and 72 hr were less ($P < 0.05$) than those for all previous times of blood collection. In mares injected iu or il, the first significant reduction in progesterone concentration, compared to the pretreatment sample, occurred at 24 hr posttreatment; in the iu group, a significant increase in progesterone concentration occurred between 1 and 6 hr followed by a significant decrease at 12 hr posttreatment.

Occurrence of estrus and ovulation. A large (>70 mm) anovulatory follicle developed during the first posttreatment estrus in one mare injected il with 0.25 mg $PGF_{2\alpha}$ and in one mare injected il with 1.25 mg $PGF_{2\alpha}$. These follicles appeared to regress (based

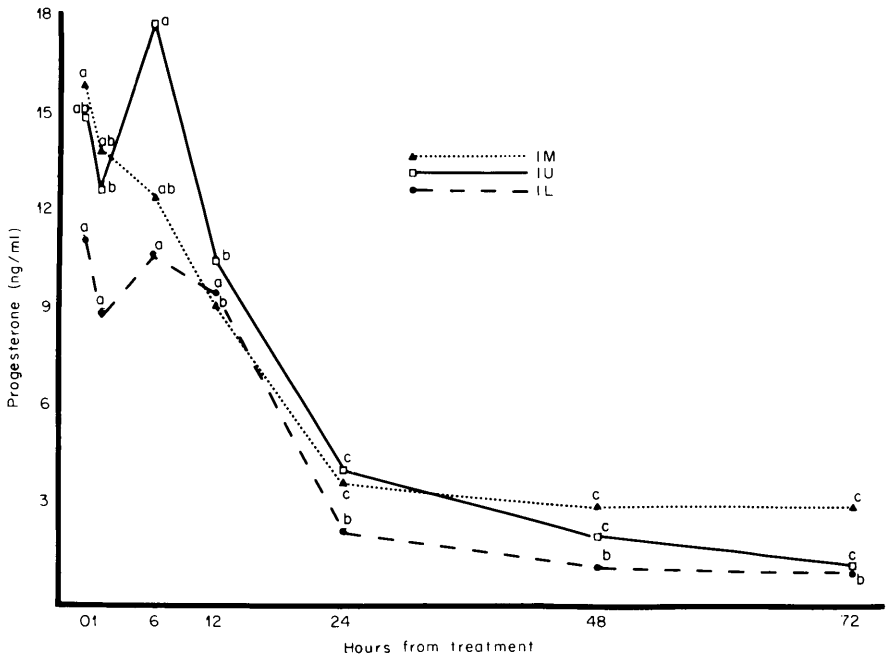

FIG. 1. Mean progesterone concentration in jugular venous blood following intramuscular (im), intrauterine (iu) or intraluteal (il) injection of $PGF_{2\alpha}$ (0.25 mg and 1.25 mg groups combined). Means within a route (im, iu or il) with one or more common superscripts are not significantly different.

on rectal palpation) and ovulation apparently did not occur in the two mares until the next estrus (approximately 40 days after $PGF_{2\alpha}$ injection). Data for these two mares were not included in statistical analyses involving length of posttreatment estrus, interval from treatment to ovulation and interovulatory interval.

There was no significant effect of dose of $PGF_{2\alpha}$ on length of the posttreatment estrus, but there was a significant effect of dose on interval from treatment to estrus, interval from treatment to ovulation and interovulatory interval. There was no significant effect of route of administration or route × dose interaction for the four end points. Therefore, data were combined over the three routes of administration at each dose level of $PGF_{2\alpha}$ and analyzed by analysis of variance and Waller–Duncan's multiple-range test to study the effect of dose. Injection of either 0.25 mg or 1.25 mg $PGF_{2\alpha}$ significantly shortened the interval from treatment to estrus (Table II). Although injection of 0.25 mg $PGF_{2\alpha}$ tended to shorten (approached significance) the interval from treatment to ovulation and interovulatory interval, these two end points were shortened ($P < 0.05$) only in mares given 1.25 mg $PGF_{2\alpha}$.

Discussion. In the present study, the precipitous decrease in progesterone concentration in mares given $PGF_{2\alpha}$ and the length of the interval from $PGF_{2\alpha}$ treatment to estrus were similar to those reported in other studies with $PGF_{2\alpha}$ in mares (9, 10). Recently it was reported that estrus in mares given $PGF_{2\alpha}$ was significantly longer than estrus in the same mares during the previous cycle (9). However, an earlier experiment in this laboratory (11) and the present experiment failed to find any significant effect of $PGF_{2\alpha}$ on length of posttreatment estrus. On the average, the length of the interval from $PGF_{2\alpha}$ treatment to ovulation in the present study and in previous studies in this laboratory (5, 11) was approximately 11 days which appears to be longer than the 7- to 8-day interval reported in the aforementioned study (9).

The significant dose × time interaction for progesterone apparently involved a decrease in progesterone concentration over time in mares given 0.25 mg or 1.25 mg

TABLE II. EFFECT OF INTRAMUSCULAR (IM), INTRAUTERINE (IU) OR INTRALUTEAL (IL) INJECTION OF $PGF_{2\alpha}$ ON INTERVAL TO ESTRUS, INTERVAL TO OVULATION AND INTEROVULATORY INTERVAL IN MARES.

End point	Route	Dose $PGF_{2\alpha}$ (mg)					
		0 (controls)		0.25		1.25	
		Mean	SE	Mean	SE	Mean	SE
Interval from treatment to estrus (days)	im	12.3	±2.7	6.7	±2.3	5.5	±1.5
	iu	16.0	±2.5	7.7	±2.3	4.0	±1.2
	il	11.7	±1.3	3.3	±0.3	2.7	±0.3
	combined data[a]	13.3[c]	±1.3	5.9[d]	±1.2	3.9[d]	±0.6
Length of estrus (days)	im	7.0	±1.5	8.0	±1.0	5.3	±0.7
	iu	5.7	±0.9	6.3	±1.8	5.5	±0.5
	il	6.5	±1.5	9.0	±0.6	9.0	±1.2
	combined data	6.4[c]	±0.7	7.8[c]	±0.7	6.8[c]	±0.8
Interval from treatment to ovulation (days)	im	17.0	±0.6	15.0	±1.5	11.0	±1.2
	iu	19.0	±3.5	12.7	±1.2	10.0	±3.2
	il[b]	18.7	±0.3	14.0	±0	13.0	±2.0
	combined data[a]	18.2[c]	±1.1	13.9[c, d]	±0.7	11.1[d]	±1.2
Interovulatory interval (days)	im	24.0	±0.6	22.0	±1.5	18.0	±1.2
	iu	26.0	±3.5	19.7	±1.2	17.0	±3.2
	il[b]	25.7	±0.3	21.0	±0	20.0	±2.0
	combined data[a]	25.2[c]	±1.1	20.9[c, d]	±0.7	18.1[d]	±1.2

[a] There was a significant effect of dose of $PGF_{2\alpha}$. There was no significant effect of route (im, iu or il) or a route × dose interaction, therefore, data were combined over the three routes at each dose level.

[b] Two mares for il, 0.25 mg and il, 1·25 mg; three mares for all other subgroups (route × dose combination).

[c, d] For each end point, any two means which have one or more common superscript letters are not significantly different.

$PGF_{2\alpha}$ and a relatively static progesterone concentration in controls. The comparatively high progesterone concentration at the pretreatment blood collection (0 hr, Table I) for mares in the il, 0.25 mg group was apparently due to chance since no treatment had been given. Regardless of route of administration, injection of 0.25 mg appeared to be as effective (not significantly different) as injection of 1.25 mg in reducing progesterone concentration at 24, 48 and 72 hr posttreatment and in shortening the interval from treatment to estrus (Table II). It is noteworthy, however, that for all three routes of administration progesterone values at 72 hr posttreatment for mares given 1.25 mg were approximately half the values for mares given 0.25 mg. This may be related to the finding that the interval from treatment to ovulation and interovulatory interval were significantly shortened only in mares given 1.25 mg $PGF_{2\alpha}$. Similarly, in a previous study in mares (5), of the doses given (0, 0.25, 0.75 or 1.25 mg $PGF_{2\alpha}$), 1.25 mg was the minimum effective systemic (im or sc) dose which significantly shortened the interval from treatment to ovulation and the interovulatory interval.

The significant decrease in progesterone concentration which occurred at 6, 12, 24 and 48 hr posttreatment in il injected controls (Table I), appeared to be temporary since progesterone values at 72 hr were not different among the three routes and the end points involving estrus and ovulation did not appear to be affected in controls injected il. However, the reason for this decrease in progesterone was not apparent and the observation should be confirmed.

In cows that were pregnant or in diestrus, administration of $PGF_{2\alpha}$ into the jugular vein, into the uterine artery or iu caused an initial increase in progesterone followed by luteolysis 1 day later (12). Similarly, studies

in monkeys (13), pseudopregnant–hysterectomized hamsters (14) and in sheep (15) have reported an initial increase in progesterone concentration following administration of low (usually nonluteolytic) doses of $PGF_{2\alpha}$. In the present experiment, progesterone concentration, averaged over the 0.25 mg and 1.25 mg dose levels (Fig. 1), increased significantly between 1 and 6 hr posttreatment in mares injected iu but not in mares injected im or il. In mares injected iu, the initial increase in progesterone concentration at 6 hr apparently was not related to dose of $PGF_{2\alpha}$ since progesterone values at 6 hr were not different among mares given 0, 0.25 or 1.25 mg $PGF_{2\alpha}$ (Table I). Therefore, this observation should be considered preliminary and needs corroboration.

Presumably, a more rapid decrease in progesterone concentration would occur when $PGF_{2\alpha}$ was injected il than when injected im or iu. In mares given 0.25 mg $PGF_{2\alpha}$, progesterone tended to be less (approached significance) at 1 hr and was significantly less at 6 hr posttreatment for mares injected il than for mares injected im or iu (Table I). It should be noted, however, that in mares given vehicle only (controls), progesterone values at 6, 12, 24 and 48 hr posttreatment were less ($P < 0.05$) for controls injected il than for controls injected im or iu; in mares given 1.25 mg, progesterone values for mares injected il were not significantly different from values for mares injected im or iu at any of the times studied. In addition, progesterone values at 1, 6 and 12 hr posttreatment for mares injected il with 1.25 mg were approximately two times the values for mares injected il with 0.25 mg or with vehicle, suggesting an apparent stimulatory effect on progesterone. The possibility is recognized, however, that a rapid clearance of $PGF_{2\alpha}$ into the systemic circulation following il injection would result in a systemic action of $PGF_{2\alpha}$, circumventing a local effect on the CL. Thus, although the data are somewhat beclouded, il injection of $PGF_{2\alpha}$ did not appear to result in a more rapid rate of luteolysis. Furthermore, compared to pretreatment progesterone values, $PGF_{2\alpha}$ (0.25 mg and 1.25 mg groups combined) administration significantly decreased progesterone concentration by 12 hr posttreatment in mares injected im and by 24 hr in mares injected iu or il (Fig. 1). There were no significant differences in progesterone values among the three routes from 12 to 72 hr posttreatment. This was reflected by the failure to find a significant main effect or route of administration on intervals from treatment to estrus and ovulation or on interovulatory interval (Table II). Previously, it was found that treatment of mares with antiserum against an equine pituitary fraction during diestrus caused a significant decrease in CL weight (16, 17). Perhaps in mares, $PGF_{2\alpha}$-induced luteolysis involves, at least in part, a central effect on the hypothalamus and/or pituitary. A similar hypothesis has been suggested for the mechanism of $PGF_{2\alpha}$-induced luteolysis in rats (18, 19).

In sheep, hysterectomy, insertion of an IUD, surgical anastomosis of uterine veins or ovarian arteries and other techniques, have clearly demonstrated that in this species the uterus exerts its luteolytic effect through a local pathway between a uterine horn and adjacent ovary (2). In mares, although complete hysterectomy prolonged the life of the CL, maintenance of CL occurred in two of five ipsilaterally hysterectomized mares and in three of five contralaterally hysterectomized mares, failing to indicate a unilateral or local uterine luteolytic effect (7). Comparative differences in the vascular anatomy of the uterus and ovaries in sheep and horses are compatible with the presence or absence of a local pathway between a uterine horn and adjacent ovary (3, 20). In sheep, the ovarian artery was in close apposition to the wall of the uteroovarian vein and the contact area between vein and artery was increased by the tortuous path of the artery over the surface of the vein. In horses, the ovarian artery did not contact the uteroovarian vein; the artery was in contact with the uterine branch of the uteroovarian vein, in a limited area as it passed obliquely across the vein. Thus, the vascular anatomy of uterus and ovaries in sheep would afford a greater potential than that in horses for local transfer of a luteolysin between uterus and ovaries. These comparative differences in uteroovarian vascular anatomy are consistent with the

observation in ewes (4) that the luteolytic efficacy of $PGF_{2\alpha}$ is greater when injected locally (iu) than when injected systemically (im) and with the present data which indicate a failure to improve the luteolytic efficacy of $PGF_{2\alpha}$ in mares by local (iu) injection over systemic (im) injection. In a previous study in mares (9) it was reported that luteolysis after sc injection of 15 mg $PGF_{2\alpha}$ was not different from that following 10 mg $PGF_{2\alpha}$ iu. It is the present authors' opinion that the experimental design and high doses used did not permit a critical test of route differences.

The present data also confirm the comparative sensitivity of the mare to luteolytic effects of a single systemic injection of $PGF_{2\alpha}$ (5); <6 μg/kg was luteolytic in mares as compared to a minimum systemic dose of 144 μg/kg in ewes (4).

Summary. Nine groups of pony mares (3/group) were used in a 3 × 3 factorial experiment. The factors were dose of $PGF_{2\alpha}$ (0, 0.25 or 1.25 mg) and route of administration (im, iu or il). Mares were laparotomized and treated on day 7 postovulation. Jugular blood was collected for progesterone RIA at 0 (pretreatment) and 1, 6, 12, 24, 48 and 72 hr posttreatment.

In mares given either 0.25 mg or 1.25 mg $PGF_{2\alpha}$, progesterone concentrations were not significantly different among the three routes at any of the posttreatment times studied except at 6 hr posttreatment. In mares given 0.25 mg, progesterone concentration at 6 hr was less ($P < 0.05$) for mares injected il than for mares injected im or iu. In mares given 1.25 mg, the concentration at 6 hr was less ($P < 0.05$) for mares injected im than for mares injected iu. Compared to pretreatment progesterone values, $PGF_{2\alpha}$ (0.25 mg and 1.25 mg groups combined) administration significantly decreased progesterone concentration by 12 hr posttreatment in mares injected im and by 24 hr in mares injected iu or il. In the iu group, a significant increase in progesterone concentration occurred between 1 and 6 hr followed by a significant decrease at 12 hr posttreatment.

There were no significant differences among the three routes for intervals from treatment to estrus or ovulation, length of posttreatment estrus or length of interovulatory interval. Injection of either 0.25 mg or 1.25 mg $PGF_{2\alpha}$ significantly shortened the interval from treatment to estrus. Although 0.25 mg tended to shorten the interval from treatment to ovulation and interovulatory interval, these two end points were significantly shortened only in mares given 1.25 mg $PGF_{2\alpha}$.

Results indicated that local administration (iu or il) did not improve the luteolytic efficacy of $PGF_{2\alpha}$ over systemic administration (im).

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