

犬の黄体機能,着床および妊娠維持におよぼすPGF2 α - analogue投与の影響

誌名	Japanese journal of veterinary science
ISSN	00215295
著者	筒井, 敏彦 河上, 栄一 織間, 博光
巻/号	51巻3号
掲載ページ	p. 496-504
発行年月	1989年6月

Effects of Prostaglandin F_{2α}-Analogue Administration on Luteal Function, Implantation of Embryos and Maintenance of Pregnancy in Bitches

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(Received 18 February 1988/Accepted 14 January 1989)

ABSTRACT. The present experiment was carried out to clarify the effect of administration of the prostaglandin F_{2α} (PGF_{2α})-analogue on the luteal function and the maintenance of pregnancy in bitches. Fifty-one bitches received a single inoculation of PGF_{2α}-analogue by intramuscular injection. The effect of this agent was observed by monitoring progesterone (P) levels and the state of the uterus by laparotomy, the occurrence of abortion, and the state of parturition. As a result, when bitches were administered with 100 – 400 μg at the beginning of the luteal phase, the decrease in the P level was temporary. In bitches inoculated with 100 – 800 μg of PGF_{2α}-analogue at the functional luteal stage, the P level began to decrease as early as on the following day after injection. In those treated with 100 – 200 μg of PGF_{2α}-analogue at 10 – 15 days of pregnancy, pregnancy was maintained in 3 of 5 bitches that had received the treatment at day 10, while in the remaining two, all embryos died after implantation. In those that had received the same treatment at day 15, only 2 of 7 maintained pregnancy. Pregnancy was interrupted in eight bitches treated with doses of 100 – 200 μg at days 25 – 45. In four bitches treated with doses of 100 – 200 μg at day 55, premature birth was induced after 30 – 44 hr. In conclusion, regression of the corpus luteum, abortion, and premature birth were induced in bitches treated with 100 – 200 μg at each stage, except the beginning of the luteal phase and of the pregnancy.—**KEY WORDS:** bitch, luteal function, PGF_{2α}-analogue, pregnancy.

Jpn. J. Vet. Sci. 51(3): 496 – 504, 1989

Application of prostaglandin (PG) F_{2α} in the field of reproduction of bitches has been discussed in some previous papers. These papers deal with the effect of administration of PGF_{2α} on the luteal function [1, 2, 4, 8, 9, 17] and the maintenance of pregnancy [1, 4, 8, 17], and the use of PGF_{2α} for the treatment of pyometra in bitches [5, 7, 11, 12]. In those previous experiments, the authors administered PGF_{2α} at various stages of pregnancy and found that premature birth could be induced in bitches which had been administered with 5 – 10 mg per head of PGF_{2α} in the late stage of pregnancy. They pointed out that at doses less than 30 mg per head, administration of PGF_{2α} in the middle stages of pregnancy failed to cause a marked decrease in progesterone

(P) level in the peripheral plasma, abortion, and deaths of some of the fetuses in a litter [17]. Therefore, application of PGF_{2α} to the induction of miscarriage in bitches was thought to be difficult.

Recently, Vickery and McRae [18], Vickery *et al.* [19], Jackson *et al.* [3], and Shille *et al.* [10] each administered approximately 200 μg per head of a PGF_{2α} analogue (PGF_{2α}-A) to bitches in various stages of pregnancy. They reported that abortion was induced in bitches which had been administered in the middle stages of pregnancy. We consider that this agent could be effective in treating reproductive problems of bitches for example for abortifacient in the case of mismating, or, induction of premature birth.

Our experiment was carried out with the PGF_{2α}-A analogue (PGF_{2α}-1052) developed by the Ono Pharmaceutical Co., Ltd. to clarify the effect of this agent on the function of the corpus luteum (CL), implantation of embryos, and maintenance of pregnancy.

MATERIALS AND METHODS

Animals: A total of 49 bitches were used for 51 trials. They consisted of 30 beagles of 2 – 5 years old, which were afterwards used for 32 trials, and 19 mongrels of 2 – 3 years old weighing 8 – 15 kg and used for 19 trials. The beagles were originated from a colony maintained by serial breeding in the author's department. In addition, 8 male dogs were used for mating.

In this experiment, ovulation was assumed to occur in the bitches on day 3 of the estrous period, as the authors had previously reported [13]. As also reported by the authors [16], the first day of the estrous period was determined from the results of the copulation test performed twice a day in the morning and in the evening, beginning on the day when vulval bleeding was observed in each bitch.

Mating was conducted only once on the assumed day of ovulation, which was regarded as day 0 of pregnancy in numbering the days of pregnancy.

Effect of administration with PGF_{2α}-1052: The PGF_{2α}-A used for the experiment, PGF_{2α}-1052, contained 800 μg of 16-(3-chlorophenoxy)-ω-tetranor-trans-Δ²-PGF_{2α} methyl ester in 2 ml α-cyclodextrin solution per ampule and was supplied as a sample from the Ono Pharmaceutical Co., Ltd. Each bitch was inoculated with 100 – 800 μg of PGF_{2α}-1052 by a single intramuscular injection. The dose of administration was determined following to the results of previous studies cited above [3, 10, 18, 19].

All the bitches were held under observa-

tion for the side effects of PGF_{2α}-1052, especially salivation, lachrymation, vomiting, and diarrhea, for 1 – 2 hr after injection.

Experiment I: Effect of PGF_{2α}-1052 on luteal function.

Of 24 bitches which had not been allowed to mate during the estrous period, six bitches were administered with 100 – 800 μg of PGF_{2α}-1052; half of them at day 5, and the remainder at 10 days after ovulation. Another 15 bitches were also administered with the same amount 25 days after ovulation in the functional stage of the CL. They were examined for the effect of PGF_{2α}-1052 by measuring P levels in the peripheral plasma. The remaining three bitches served as controls, and examined for rises and falls of P levels.

Experiment II: Effect of PGF_{2α}-1052 on implantation of embryos and maintenance of pregnancy.

Of 27 bitches, twelve, eight, and four were administered with 100 or 200 μg per head of PGF_{2α}-1052 on days 10 – 15 before implantation of embryos, on days 25 – 45 in the middle stages, and on day 55 in the late stage, respectively. They were examined for the effect of PGF_{2α}-1052 by monitoring P levels and observing morphological changes at the sites of implantation of embryos in the uterus, the occurrence of abortion, and the state of parturition. The remaining three bitches served as controls for experiment II and were examined for changes in P levels over the normal gestation period. Implantation took place 21 days after ovulation in bitches [14]. Fifteen bitches which were used for the experiment after day 25 were diagnosed for pregnancy by abdominal palpation or ultrasonography to confirm the diagnosis.

After injected with PGF_{2α}-1052, the bitches were examined three times a day (at 7:00, 13:00, and 19:00) for leakage of mucus from the vulva and states of parturition.

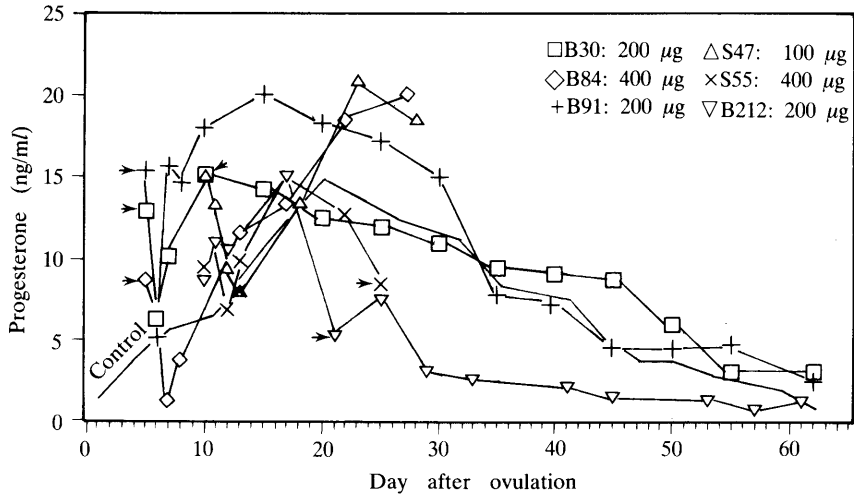


Fig. 1. Progesterone levels in peripheral plasma in bitches administered with 100, 200 or 400 μg of $\text{PGF}_{2\alpha}$ -1052 5 or 10 days after ovulation. \downarrow : administration

Detailed observation was made on the four bitches administered with $\text{PGF}_{2\alpha}$ -1052 on day 55 to determine the interval between the administration and parturition of the first puppy.

Laparotomy was performed under general anesthesia on bitches which had been treated presurgically with a combination of acepromazine and atropine sulfate. Ketamine hydrochloride and diazepam were administered intramuscularly to the bitches to induce anesthesia which was maintained by gas anesthesia (1% halothane and oxygen).

In 15 bitches which had been administered between days 10 and 25 of pregnancy, laparotomy was conducted after 9–24 days to examine the number of embryos implanted in uterus and the size, hardness, color, and other states of the site of implantation. The results were compared with those reported in the authors' previous paper, dealing with the size and condition of the uterus in each stage of normal pregnancy [15]. The embryo or fetus the implantation area of which was much smaller than that observed in the control on the same day of pregnancy and was malacic, was regarded

as dead. In this case it was confirmed by ultrasound that the fetus was not alive, and that no pregnancy was continued after operation. Nine bitches administered between days 30 and 55, laparotomy was performed after abortion or premature birth, in order to count the number of CL in both ovaries and that of attachment sites to the placenta in uterus.

Progesterone assay: Blood samples were collected from the anterior brachiocephalic vein just before $\text{PGF}_{2\alpha}$ -1052 administration and at intervals of 1–5 days after the injection.

P was measured by an enzyme immunoassay method developed by the authors [6]. The intra-assay coefficient of variation for samples with high, intermediate, and low levels was 4.9, 6.2, and 10.5%, respectively, and the inter-assay coefficients of variation for the same pools 8.7, 10.9, and 14.5%, respectively. The sensitivity of this immunoassay method was 0.25 pg/well.

RESULTS

Of the bitches treated with 100–800 μg dose of $\text{PGF}_{2\alpha}$ -1052, salivation, vomiting,

Table 1. Effects of PGF_{2α}-1052 administration on implantation of embryos

PGF _{2α} -1052 admin.		Bitch No.	Findings on laparotomy					No. of pups
Day of pregnancy	Dose (μg)		Day of pregnancy	No. of CL	No. of implantations	No. of dead embryos		
10	100	S44	25	L	6	3	0	6
				R	2	3	0	
	200	S60	31	L	2	2	1	1
				R	4	0	0	
		S63	27	L	3	0	0	0
				R	2	1	1	
B182	29	L	2	2	2	0		
		R	5	1	1			
B190	29	L	4	4	1	7		
		R	4	4	0			
15	100	S78	39	L	1	2	2	0
				R	5	3	3	
	200	S40	34	L	4	3	3	0
				R	1	2	2	
		S46	27	L	3	1	1	0
				R	2	2	2	
		B160	29	L	7	2	1	3
				R	0	2	0	
		S219	29	L	6	0	0	0
				R	2	1	1	
S235	29	L	4	3	3	1		
		R	3	4	3			
S238	29	L	4	2	2	0		
		R	3	2	2			

and diarrhea were seen in 35 bitches after about 5 min at doses ranging 200 – 800 μg. Mild salivation was seen in ten bitches treated with 100 μg of dose although vomiting was found in only three. The severity of these side effects was in proportion to the dose, but almost all the side effects disappeared completely within an hour.

Experiment I: P levels of individual bitches treated with 100 – 400 μg of PGF_{2α}-1052 on day 5 or 10 are shown in Fig. 1. The mean P levels of the three controls are also indicated. Five of the 6 bitches showed a temporary decrease in P level followed by an increase, and then showing a pattern similar that in the control group. But in the

remaining one (B212), P level decreased much faster.

P levels on the day of injection in bitches treated with 100 – 800 μg dose on day 25 was 11.5 – 22.3 ng/ml, with a mean of 17.7 ng/ml. On the following day it showed 4.5 ng/ml in 2 bitches treated with 100 μg, 2.8 ng/ml in 5 with 200 μg, 1.7 ng/ml in 5 with 400 μg, and 2.1 ng/ml in 3 with 800 μg, each showing a sudden decrease. The majority showed a drop below 1.0 ng/ml after 2 – 5 days, keeping that level thereafter.

Experiment II: (1) The effect of PGF_{2α}-1052 on the implantation of embryos is exhibited in Table 1 and Figs. 2 and 3. A bitch treated with a dose of 100 μg on day 10

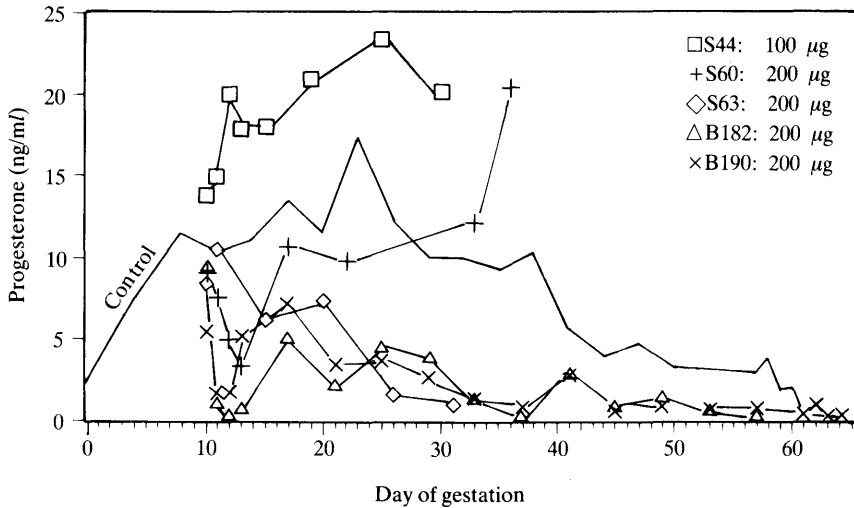


Fig. 2. Progesterone levels in peripheral plasma in bitches administered with 100 or 200 µg of PGF_{2α}-1052 10 days of gestation.

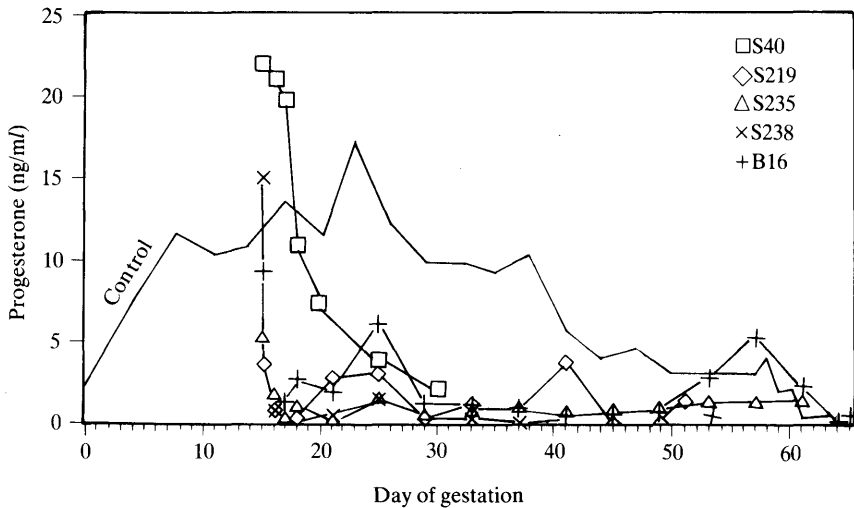


Fig. 3. Progesterone levels in peripheral plasma in bitches administered with 100 µg of PGF_{2α}-1052 15 days of gestation.

gave normal birth to six puppies on day 61. P levels did not decrease even after administration, showing essentially the same pattern of rise and fall as in the controls. In 2 of the 4 bitches treated with a dose of 200 µg, pregnancy was not maintained, and, although the sites of implantation was confirmed by laparotomy, the embryos had died at early stages after implantation. The P

levels in these bitches decreased rapidly, then rising a little and decreasing again to a level below 1.0 ng/ml after 20 days. The 2 bitches which maintained pregnancy gave birth to one and 7 puppies, respectively. The P levels in these bitches also decreased rapidly, but in one animal it increased, essentially showing the same pattern of rise and fall as in the controls, while in the

Table 2. Effects of PGF_{2α}-1052 administration on maintenance of pregnancy

PGF _{2α} -1052 admin.		Bitch No.	Findings on laparotomy				Interval from admin. to premature birth (day or hr)	No. of aborted fetuses or pups
Day of pregnancy	Dose (μg)		Day of pregnancy	L	R	No. of CL		
25	100	S81	34	L R	6 4	6 4	No overt sign	0
	200	B135	46	L R	4 0	2 2	6 day	Degeneration
		B176	41	L R	6 0	3 2	4 day	Degeneration
30	200	S62	33	L R	3 4	2 3	3 day	5
		B126	52	L R	0 8	4 4	4 day	8
		B141	51	L R	9 0	2 1	4 day	3
35	100	S50	39	L R	4 3	3 3	4 day	6
45	100	S83	49	L R	3 4	2 3	4 day	5
55	100	S77	56	L R	4 2	3 3	33 hr	6 ^{a)}
		S80	57	L R	2 2	2 2	44 hr	4 ^{a)}
	200	S19	57	L R	5 1	2 1	44 hr	3 ^{a)}
		S25	57	L R	5 5	5 5	30 hr	10 ^{a)}

a) premature birth.

others it showed a pattern of rise and fall similar to that seen in the 2 bitches which failed to maintain pregnancy.

Implantation was confirmed by laparotomy in all 7 bitches treated with 100 or 200 μg on day 15. Embryos died at early stages after implantation in 5 of these bitches. Of these 5 animals, P levels was monitored in 3 bitches. An immediate decrease was observed in 2 of them (S219, S238), and a

slow decrease in 1 (S40), though all fell below 1.0 ng/ml after 15 days. The remaining 2 bitches gave birth to 3 (number of implantations 4), and 1 (number of implantations 7) puppies, respectively. The P levels in these bitches were almost the same as in the animals in which all fetuses had died, and maintained pregnancy at a much lower level compared to the controls.

(2) The effect of PGF_{2α}-1052 on the

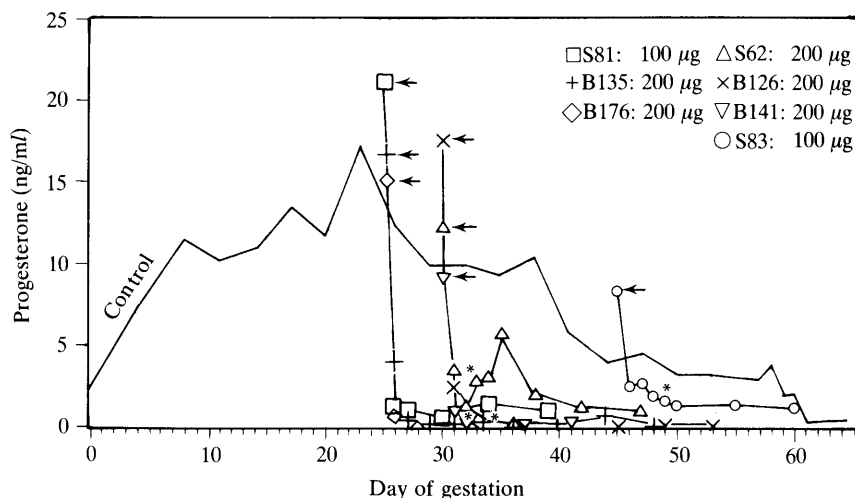


Fig. 4. Progesterone levels in peripheral plasma in bitches administered with 100 or 200 μg of $\text{PGF}_{2\alpha}$ -1052 25, 30, 45 days of gestation.

↓: administration

*: abortion

maintenance of pregnancy is shown in Table 2. Eight bitches were administered with 100–200 μg on days 25–45 in the middle stage. Laparotomy performed on them revealed that all the embryos were dead in 3 bitches treated with 100–200 μg of $\text{PGF}_{2\alpha}$ -1052 on day 25. Of these bitches, neither expulsion of embryos nor leakage of the soaked placenta from the vulva was observed; only a small amount of mucus was seen in two. Abortion was noticed in the five bitches 3 or 4 days after administration of $\text{PGF}_{2\alpha}$ -1052 which had been done on days 30–45. P levels decreased remarkably on the next day of administration, as shown in Fig. 4.

In the four bitches treated with 100–200 μg of $\text{PGF}_{2\alpha}$ -1052 on day 55 in the late stage, premature birth took place after 30–44 hr, average 38 hr. P measured in 3 of these bitches showed no distinct decrease.

DISCUSSION

In the present experiment, bitches treated with 100–400 μg of $\text{PGF}_{2\alpha}$ -1052 at the

beginning of the luteal phase showed a temporary decrease in P levels followed by an increase, causing no regression of the CL. Of bitches treated with 100–200 μg in the early stages of pregnancy, pregnancy in 3 out of 5 was not interrupted that received injection on day 10, as well as in 2 out of 7 injected on day 15. In brief, even when $\text{PGF}_{2\alpha}$ -1052 was administered at the beginning of the luteal phase, it failed to induce regression of the cycle CL and pregnant CL.

$\text{PGF}_{2\alpha}$ -1052 ranging from 100 to 800 μg was administered at 25 days after ovulation in the functional stage of CL. The difference in P levels for the various doses resulted in the 100 μg dose to increase only a little higher than the rest on the next day of administration, showing no difference thereafter. Interruption of pregnancy in all the twelve bitches treated with 100 or 200 μg of $\text{PGF}_{2\alpha}$ -1052 was caused when administration took place on or after day 25 of pregnancy. Vickery and McRae [18] administered this agent to two bitches on day 9 and to four bitches on days 20–22 of pregnancy. As a result, pregnancy was

interrupted in two of the latter four bitches, but maintained in the other bitches.

Jackson *et al.* [3] administered PGF_{2α}-A to four bitches on days 4 – 7 and 18 bitches on day 14 of pregnancy. Consequently, pregnancy had been maintained in all the bitches, but not in twelve in the latter. Vickery and McRae [18], Jackson *et al.* [3], and Shille *et al.* [10] administered PGF_{2α}-A to bitches in the middle stage of pregnancy and succeeded in causing abortion in all bitches.

In the present experiment, the dose of PGF_{2α}-A administered to pregnant bitches was equal to or half, of that used by the above-mentioned study, and the bitches were essentially of the same size as those used by authors of those papers. Therefore, it was considered that the analogue used in the present experiment might possess a stronger effect of regression on the CL in bitches than that used by the above-named researchers.

In the present experiment, 5 out of 12 bitches administered PGF_{2α}-1052 on day 10 and 15 of pregnancy gave normal birth, and sites of implantation were clearly confirmed by laparotomy in the remaining 7. Implantation in bitches is known to take place 21 days after ovulation. Therefore it is a matter of great interest that, in spite of a decrease in P levels, precursory proliferation of pregnancy in the endometritis and development of the embryo continued to occur until implantation after injection of PGF_{2α}-1052 in these bitches.

The relationship between P levels and abortion was studied by Concannon and Hansel [1] and Jackson *et al.* [3] who reported that abortion was induced in bitches 36 – 48 hr after P levels was reduced to 2.5 ng/ml or lower.

In five bitches administered PGF_{2α}-1052 on days 30 – 45 pregnancy, abortion took place after 3 – 4 days. Daily changes of the P levels in 4 of these bitches were:

12.3→3.6→1.4→2.9 (abortion)→3.1 ng/ml (S62), 17.5→2.5→0.3→0.3→0.4 (abortion)→0.4 ng/ml (B126), 9.0→0.8→0.1→0.2→0 (abortion)→0 ng/ml (B141), in 3 bitches injected on day 30, and 8.3→2.4→2.8→1.8→1.3 (abortion)→1.3 ng/ml (S83) in the remaining one that received injection on day 45. These results, though obtained from a limited number of experimental animals, support the interpretation proposed the previous researchers mentioned above.

In bitches with PGF_{2α}-1052 administration on days 10 and 15 of pregnancy, it is quite interesting to note that in 3 (B190, B160, S235) abortion did not occur and pregnancy was maintained until whelping, in spite of an early decrease of the P levels to under 1.0 ng/ml.

In the present experiment, premature birth took place in four bitches with PGF_{2α}-1052 administration on day 55 of pregnancy, 30 – 44 hr later. This result suggests that there might be a large difference in the mechanism of occurrence between abortion, which is thought to be induced by a marked decrease in P levels at the middle stages of pregnancy, and premature birth, which takes place in the late stage of pregnancy.

It was clarified that PGF_{2α}-1052 used in the present experiment had a strong effect to cause regression of the functional CL in the bitch. Therefore, it is considered that this agent can be effective as a tool for treatment of reproductive problems of bitches, in cases such as feticide in case of mismating, treatment of pyometra, and induction of premature birth. In application of PGF_{2α}-1052 for these purposes, a single intramuscular injection of 100 – 200 μg would be sufficient for bitches weighing 8 – 15 kg as proved in the present experiment. However, further studies should be made to determine an optimum dose for bitches the body weights of which are outside this range.

ACKNOWLEDGEMENTS. The authors thank the Ono Pharmaceutical Co., Ltd. for supply of the prostaglandin $F_{2\alpha}$ analogue (ONO-1052) used in this experiment. Supported by the Science Research Promotion Fund of the Japanese Private School Promotion Foundation.

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要 約

犬の黄体機能、着床および妊娠維持におよぼす $PGF_{2\alpha}$ -analogue 投与の影響：筒井敏彦・河上栄一・織間博光¹⁾・山内亮・大久保隆行・George H. Stabenfeldt²⁾ (日本獣医畜産大学・獣医臨床繁殖学教室, ¹⁾獣医放射線学教室, ²⁾Dept. of Reproduction, University of California, Davis) — 犬の黄体機能および妊娠維持におよぼす $PGF_{2\alpha}$ -analogue ($PGF_{2\alpha}$ -1052) 投与の影響について検討した。実験犬51頭を用い、 $PGF_{2\alpha}$ -1052を1頭当り、黄体期に100-800 μ g, 妊娠期に100-200 μ gを各々筋肉内1回投与し、その影響を末梢血中 progesterone (P) 濃度、開腹手術による子宮の所見および流産の有無によって観察した。その結果、黄体期の初期では、投与直後に一時的にPが低下したのみであったが、黄体開花期では、投与量に関係なく、Pは低値を推移した。また、交配後10-15日では、12頭中5頭が妊娠を継続したが、残りは着床直後に胚が死滅した。妊娠25-45日では、投与後3-4日で流産、妊娠55日では投与30-44時間後に早産が認められた。以上のように、犬では、黄体期および妊娠25日以降に $PGF_{2\alpha}$ -1052を100-200 μ g投与で、黄体退行、流産、早産を誘起することが認められた。