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CHANGES IN PLASMA PROGESTERONE AND ŒSTRADIOL DURING NATURAL PROSTAGLANDIN $F_{2\alpha}$-INDUCED PARTURITION IN THE RABBIT.

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ABSTRACT : The influence of administration of natural prostaglandin $F_{2\alpha}$ (PgF) on plasma progesterone (P_4) and estradiol-17β (E_2) levels during the last days of pregnancy (days 29-32) was studied in 13 doe rabbits of the California x New Zealand White breed. Animals were allocated to receive either a single intramuscular injection of 800 or 1200µg of natural PgF on day 29 of pregnancy at 10 h (treated groups) or no injection (control group). All does treated with PgF kindled within 60 h after injection, whereas the variation in birth time in control group was greater (79.2 ± 8.9 h). No influence of the prostaglandin treatment on mean plasma estradiol (5.2 pg/ml) and both litter size and born dead (7.2 ± 0.7 and 0.4 ± 0.6, respectively) was observed. A significant fall in progesterone concentration was detected in treated animals at 20 h on day 29 compared with control group (3.17 ± 0.22 and 3.47 ± 0.32 *vs.* 6.7 ± 1.4 ng/ml; $P<0.05$). Our results suggest that the induction of parturition with natural PgF has similar effects on plasma P_4 levels and in synchronization of parturitions to synthetic analogues, although the dose administered is greater.

RESUME : Variation de la progestérone et de l'œstradiol plasmatique durant la mise-bas provoquée par la prostaglandine naturelle $F_{2\alpha}$, chez la lapine.
L'influence de l'administration de prostaglandine naturelle $F_{2\alpha}$ (PgF) sur le taux de progestérone (P_4) et d'estradiol-17b (E2) plasmatique durant les derniers jours de la gestation (29-32 jours) a été étudié sur 13 lapines de race Californien x NZW. Les animaux ont été répartis en trois lots, deux recevant une seule injection intramusculaire de 800 ou 1200 µg de PgF naturelle, à 10 heures, au 29ème jour de gestation, l'autre ne recevant aucune injection (lot contrôle). Toutes les lapines traitées avec PgF ont mis bas environ 60 heures après l'injection, tandis que pour celles du groupe contrôle le moment de la mise bas a été plus variable : 79,2 ± 8,9 heures. Le traitement par la prostaglandine n'a pas eu d'influence sur le taux moyen d'œstradiol plasmatique (5,2 pg/ml) ni sur la taille de la portée ou le nombre de mort-nés (7,2 ± 0,7 et 0,4 ± 0,6, respectivement). Une chute significative de la concentration en progestérone, par rapport au groupe contrôle, a été observée chez les animaux traités à 20 heures au 29ème jour (3,17 ±0,22 et 3,47 ± 0,32 vs 6,7 ± 1,4 ng/ml, $P<0,05$). Nos résultats suggèrent que l'induction de la mise bas avec PgF naturelle a des effets sur les taux de P_4 plasmatique et sur la synchronisation des mises-bas similaires à ceux de la même molécule synthétique, bien que la dose administrée soit supérieure.

INTRODUCTION

The length of rabbit's pregnancy range from 30 to 32 days. Earlier studies in rabbits showed that a decrease in levels of progesterone (P_4) around parturition is the key regulatory step preceding the onset of labour (CSAPO, 1976). Precise control of the time of birth is a valuable aid to animal management. Prostaglandin $F_{2\alpha}$ (PgF) has been shown to posses luteolytic properties in the rabbit (ABEL *et al.* 1973; UBILLA *et al.* 1988; REBOLLAR *et al.* 1992), and to induce a fall in progesterone concentrations when is administered on the last days of pregnancy (UBILLA *et al.* 1988). The precocious fall in progesterone levels during the last days of pregnancy after treatment with PgF can also influences an improvement of follicular growth (UBILLA *et al.*, 1988) and, therefore, an earlier fall in the inhibitory effect of progesterone on gonadotropin release (BATTAGLINI *et al.*, 1984).

The aim of this study was to determine the possible effects of parturition induction with a natural prostaglandin administered on day 29 of pregnancy at 10 h, on grouping of parturitions, litter size and born dead, on plasma progesterone and estradiol-17β concentrations.

MATERIALS AND METHODS

Thirteen multiparous pregnant does of the California x NZW breed, housed in individual cages with controlled light/dark cycles (16h/8h) and fed *ad libitum* using a commercial pelleted diet (Purina), were used in this study. Two groups of 4 does each were randomly allocated to PgF treatment and another group of 5 does was not injected (control group). Parturition was induced in the two first groups by the administration of an injection of 800µg or 1200µg (i.m.) of natural PgF (Inducel PG, Lab. Ovejero, Spain) at 10h on day 29 of pregnancy. Doses were chosen because previous experiments (ALVARIÑO *et al.*, 1995) suggest that the threshold dose for the induction of parturition with a natural prostaglandin is equal or higher to 700µg administered i.m. on day 29 of pregnancy at 16h.

In order to study plasma P_4 and E_2 level variations from day 29 to day 32 post-partum, seven blood samples were obtained at 12 h intervals, from the marginal ear vein, using sterile heparinized tubes. Plasma obtained after centrifugation was stored at - 20° C until analyzed.

Plasma E_2 concentrations were measured by an enzyme immuno assay (EIA) (SILVAN *et al.* 1993). The sensitivity of the assay was 0.1pg per well. The intra- and inter-assay coefficient of variation (CV) was less than 6 % and 7 %, respectively. Plasma P_4 concentrations were also measured by an enzyme immuno assay (EIA) (MUNRO and STABENDFELD 1984). The sensitivity of assay was 1 pg per well. The intra- and inter-assay CV was less than 7 % and 8 %, respectively.

To determine the moment of parturition, all animals were observed starting from the moment of injection on day 29, at 12 h intervals, until parturition occurred. Litter size at birth and number of born dead per litter were determined after parturition.

Table 1 : Prolificacy (litter size LS and born dead BD ± s.e.m.) and cumulative proportion of parturitions occurred on days 30, 31, 32 and 33 of pregnancy at 8:00 h (m) and 20:00 h (a) respectively, in rabbit does treated with 0, 800 and 1200µg of natural $PgF_{2\alpha}$ on day 29 of pregnancy at 10.00 h. Values with different superscripts within each column are significantly different (P<0.05).

	PROLIFICACY		CUMULATIVE PROPORTION OF PARTURITIONS					
$PgF_{2\alpha}$	LS ± sem	BD ± sem	30a	31m	31a	32m	33m	33a
0	7.4 ± 1.5	0.4 ± 0.3	0	1/5	1/5[a]	2/5	3/5	5/5
800	7.0 ± 0.3	0.5 ± 0.3	0	3/4	4/4[b]	4/4	4/4	4/4
1200	7.0 ± 0.4	0.5 ± 1.6	0	3/4	4/4[b]	4/4	4/4	4/4

Statistical analysis of the effect of the treatment on the plasma P_4 and E_2 levels and on the prolificacy was made with the General Linear Model (GLM) procedure and the means were compared using the Duncan test (SAS/STAT 1985).

RESULTS

The results are shown in table 1 and figures 1 and 2. Both litter size and born dead at birth were not affected by treatment.

Doses of 800µg and 1200µg of natural PgF significantly reduced the injection-parturition interval when compared with the control group (P<0.05). On day 31 at 20 h, 100 % of kindlings of does treated with PgF had occurred whereas it had occurred in only 20 % of the control group. The post injection mean gestation length in control group was 79.2 ± 8.9 h and 51h ± 3 h in treated group.

No significant differences in mean plasma P_4 and E_2 concentrations on day 29 before treatment were detected among groups. A significant fall in mean P_4 levels on day 29 at 20 h compared with results 12 hours before was found in two treated groups (9.5 ± 2.1 and 11.12 ± 1.6 *vs.* 3.17 ± 0.22 and 3.47 ± 0.32 ng/ml ; P<0.05), whereas a gradual decline of concentrations of P_4 was observed in control group (8.52 ± 1.19 *vs.* 6.7 ± 1.48 ng/ml). In this group, low level of P_4 was observed on day 30 at 20 h (2.62 ± 0.5 ng/ml; P<0.003)compared with previous days. On the other hand, plasma E_2 levels were similar in three groups studied and the variation in this steroid was not affected by treatment.

DISCUSSION

Prolificacy in this study was in agreement with previous results in animals submitted to similar conditions (UBILLA and REBOLLAR, 1995). Litter size at birth was not affected by treatment with natural prostaglandin which could be explained by the frequent observation of nests in the experimental groups, not usual in a rabbit farm. This agrees with results obtained by PARTRIDGE *et al.* (1986) and UBILLA and RODRIGUEZ (1989 a)

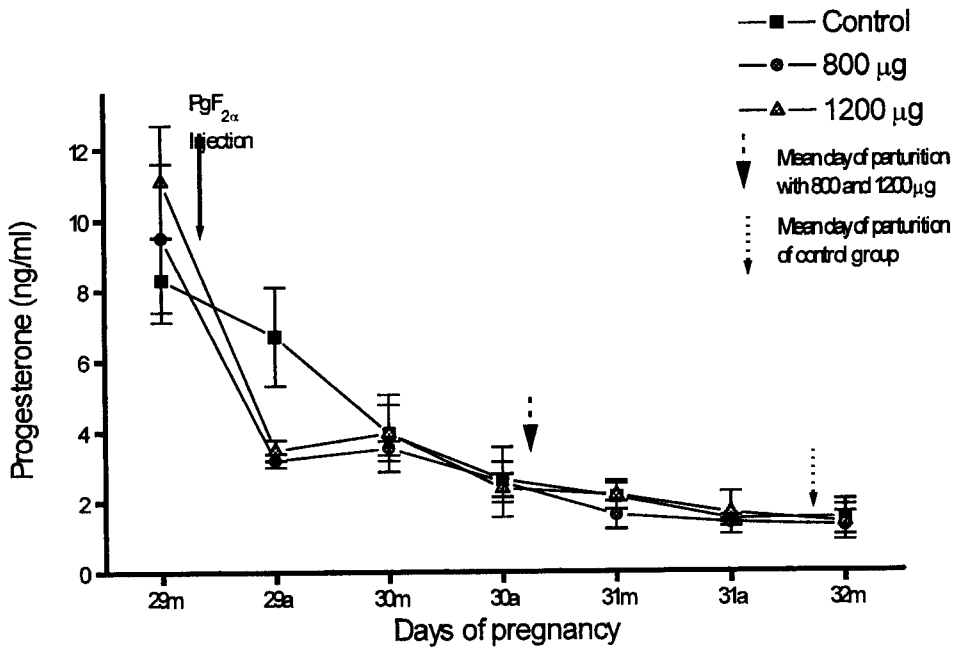

Figure 1. Plasma progesterone mean levels during days 29, 30, 31 and 32 of pregnancy at 8:00 h. (m) and 20:00 h. (a) respectively, in rabbit does treated with 0, 800 and 1200µg of Prostaglandin $F_{2\alpha}$ on day 29 of pregnancy at 10:00 h.

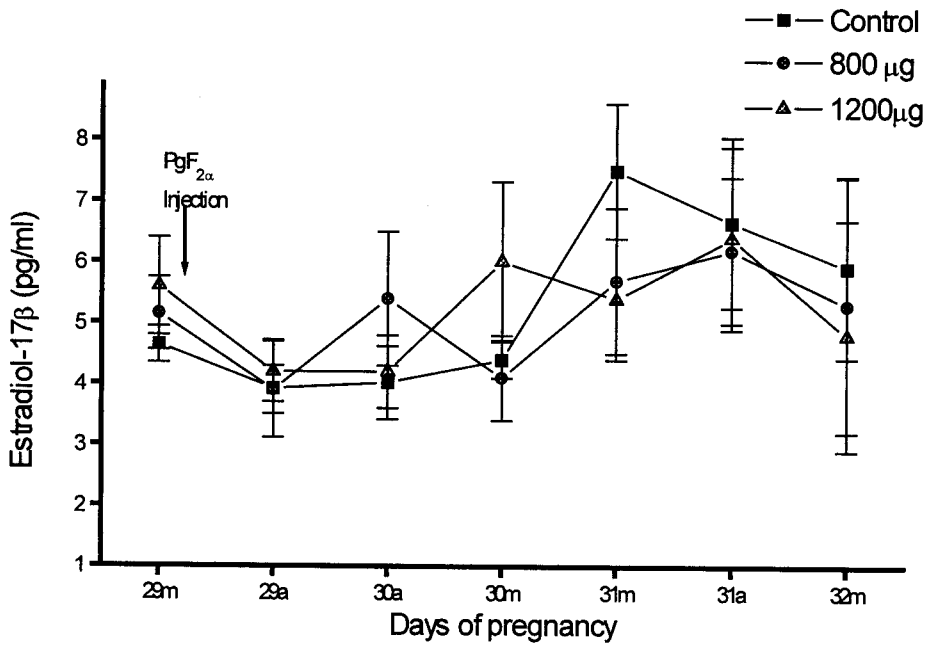

Figure 2 : Plasma estradiol 17-β mean levels during days 29, 30, 31 and 32 of pregnancy at 8:00 h. (m) and 20:00 h. (a) respectively, in rabbit does treated with 0, 800 and 1200µg of prostaglandin $F_{2\alpha}$ on day 29 of pregnancy at 10:00 h.

employing synthetics analogues of PgF, although these authors also observed that individual weight of kits and neonatal mortality were reduced significantly.

Although using a low number of animals, a significant decrease of gestation length in does treated with natural prostaglandin *vs* control group was observed. The two doses of natural PgF routinely administered on day 29 of pregnancy at 10 h, reduces the injection-parturition interval, permitting a grouping of parturitions on day 31. This effect agrees with the data of UBILLA and RODRIGUEZ (1989 a) and ALVARIÑO *et al.* (1995).

Mean plasma P_4 and E_2 concentrations found in all animals are in agreement with those reported in doe rabbits in the same period (MUNSEL *et al.* 1982, GADSBY 1989).

Several studies indicate that prostaglandins terminate pregnancy by virtue of their luteolytic property by inhibiting the production of progesterone in the rabbits does (ABEL *et al.* 1973; UBILLA *et al.* 1988). PgF has been shown to act on both the cholesterol ester synthetase and sterol esterase, which would decrease the availability of cholesterol for the conversion to steroids (BERHMAN *et al.* 1971).

The decrease in plasma P_4 levels from day 29 of pregnancy at 20:00 h. in treated animals could be explained by the luteolytic action of PgF administered eight hours earlier. This fall in plasma P_4 levels in control animals is gradual and similar with those previously observed during the last stage of pregnancy in untreated rabbits (GADSBY, 1989).

The action of PgF in plasma P_4 levels could be related with the shortening of gestation length in treated animals because the PgF administered could induce an earlier regression of corpora lutea in these animals. Luteal regression induced by exogenous administration of PgF has been demonstrated by many authors (LAU *et al.* 1976; UBILLA *et al.*,1988). An additional effect of synchronization is observed. In fact, in the control animals, the progesterone decline is only 12 hours delayed on respect to treated animals, but nevertheless the parturition span over more then 48 hours, compared to 24 hours in PgF treated animals. Probably that means that other factors than PgF are controlling the exact time in which delivery occurs.

KEYES *et al.* (1994) showed that the progesterone secretion in the rabbit corpus luteum does not require LH as a luteotrophic factor. Therefore, the role of oestrogen is to maintain the viability of corpus luteum during pregnancy. In this study, plasma E_2 levels fluctuate during the 3 days before parturitions. However, no significant differences between the 3 groups were observed. This is in agreement with the observations reported by LAU *et al.* (1976).

In conclusion, our results suggest that the induction of parturition on day 29 of pregnancy at 10 h with 800µg or 1200µg of a natural PgF, has similar effects on plasma P_4 levels and in synchronization of parturition of pregnant rabbits to synthetics analogues of PgF. This decrease in dispersion of parturition time and the high proportion of does kindling on day 31 *post-coïtum* permits a greater control of the parturition process. Although the dose of natural PgF administered is 8 and 184 times greater than the dose of synthetic PgF employed by UBILLA and RODRIGUEZ (1989 a, b) and PARTRIDGE *et al.* (1986), respectively, no side effects were observed on the reproductive parameters following this trial.

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