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Progesterone, estradiol 17-beta and luteinizing hormone plasma concentration after aglepristone administration during follicular phase in bitches

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In human as well as in the canine species, it is suggested that the slight pre-ovulatory increase of plasma progesterone concentration (P4) might regulate together with estradiol the pre-ovulatory pituitary secretion of LH and FSH and subsequently induces the ovulatory process. Furthermore, in the human species, it is observed that progesterone receptor agonist administration during the follicular phase inhibits the ovulation\textsuperscript{1}. The progesterone receptor agonist, aglepristone and mifepristone, bind with high affinity to nuclear and cellular progesterone receptors at peripheral and central levels without any own progestin-like activity\textsuperscript{2}. Consequently, progesterone receptor agonists (and antagonists) are used, in many species, to functionally prevent progesterone binding and specific action. The aim of the present work was to evaluate, for the first time in the dog, the effects of aglepristone administration during the early follicular phase on P4, estradiol 17-beta and LH plasma concentrations. Eight healthy and fertile German shepherd bitches were used. Ovarian ultrasound and vaginal smears were performed daily from the onset of proestrus (D0) until the first day of cytological diestrous (D1). Treated bitches (n=5) received the first subcutaneous injection of aglepristone (T1, Alizine\textsuperscript{®}) at the dose of 10 mg/kg when P4 concentration was still lower than 1 ng/ml and when the vaginal cytology reached 30\% of superficial and abundance of RB cells. The next two injections were performed 24 hours (T2) and 7 days (T3) later. The control group included 3 German Shepherd bitches and received injections of saline solution (0.3 mL/kg), subcutaneously following the same protocol. At D0, 2 mL of blood were collected from each dog every 20 min for 2 h, to determine basal LH values. Later, to evaluate hormonal patterns, 2mL of blood were collected daily every 6 h from D0 to D1. The ovulation day was identified as the day when the first pre-ovulatory follicle disappeared and when P4 raised over 5ng/mL. Data were analysed by independent t-test or linear mixed models. The LH AUC was calculated by trapezoid method. All treated animals ovulated as observed at sonography but tended to prolong the period from ovulation to D1 (mean difference±SE = 5±2 days) characterized by prolonged bleedings confirmed by vaginal cytology. Plasma concentrations of 17-\beta estradiol and P4 were not affected by groups. However, differences were found in the characteristic and amplitude of the pre-ovulatory LH pulses. No pre-ovulatory LH peaks was detected in the treated group while the LH peak was clearly observed in the control one 9±1 days after the D0. The overall pre-ovulatory LH AUC was lower in treated than control group (mean difference±SE = 12±3 ng/mL x d; P < 0.01). In the control group, P4 at the initiation of the pre-ovulatory LH peak was 2.3±0.6 ng/mL. In conclusion, the administration of aglepristone during the early follicular phase, does not affect the steroid hormone patterns but does prevent the occurrence of a pre-ovulatory LH peak while ovulation is still observed as reported by Reynaud et al\textsuperscript{3}. Anti-progestin administration also affected oestrus duration possibly associated with delayed ovulation of some of the follicles. As FSH was not evaluated in this work, its role as mentioned by Concannon and Verstegen (unpublished) in ovulation in the canine species cannot be excluded and deserves further investigation. \textsuperscript{[1]} Ledger WL, Sweeting VM, Hillier H, Baird DT. Hum Reprod. 1992 Aug;7(7):945-50. Inhibition of ovulation by low-dose mifepristone (RU 486) \textsuperscript{[2]} Hoffman B, Schuler H. Receptor blockers general aspects with respect to their use in domestic animal reproduction. Anim Reprod Sci 2000;60–61:295–312. \textsuperscript{[3]} Reynaud K, Saint-Dizier M, Tahir MZ et al. Progesterone plays a critical role in canine oocyte maturation and fertilization. Biol Reprod. 2015 Oct;93(4):87.