Proceedings of the 8th International Symposium on Canine and Feline Reproduction

ISCFR

June 22-25, 2016

Paris, France

In a joint meeting with the XIX EVSSAR Congress

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Expression of GnRH receptor in canine corpus luteum, and luteal function following deslorelin-induced puberty delay

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Long-term administration of gonadotropin-releasing hormone (GnRH) agonists, following an initial positive feedback on gonadotropin release, results in suppression of LH and FSH levels and diminishing of gonadal steroidogenic activity, thereby preventing reproductive functions. Although GnRH agonists are generally considered safe and totally reversible1, limited data are available concerning the efficacy of long-term release GnRH agonists to delay puberty and subsequent reproductive performance in bitches.2 Despite recent progress in understanding canine luteal physiology during pregnancy and in non-pregnant cycles,3 the mechanisms involved in suppression and resumption of ovarian activity and, subsequently, luteal function after short-/long-term inhibition of gonadal function remain poorly understood. Therefore, here, the effects were investigated of prepubertal application of a GnRH agonist deslorelin (Suprelorin; Virbac, France) on the luteal phase following the first estrus. After the suppression period, estrus cycles were monitored every other day by vaginal cytology, serum progesterone (P4) and estrogen (E2) concentration. Mature corpora lutea (CL) were collected during the mid-luteal phase (days 35-45) from deslorelin-treated and control bitches (n=4 per group). Expression of the following factors was determined by semi-quantitative real-time PCR: estrogen receptor-alpha and beta (ERα, ERβ), progesterone (P4) receptor (PGR), prolactin receptor (PRLR), PGE2-synthase (PTGES) and its receptors (EP2, EP4), vascular endothelial growth factor A (VEGFA) and its receptors (VEGFR1 and -2), steroid acute regulatory (STAR) protein, Cyclooxygenase 2 (Cox2) and 3β-hydroxysteroid dehydrogenase (3β-HSD). Additionally, the expression of kisspeptin 1 (Kiss1) and its receptor was evaluated. In order to assess the basic capability of canine CL to respond directly to GnRH, the expression of its receptor (GnRHR) was assessed in luteal samples collected throughout the luteal life span in non-pregnant dogs (days 5, 15, 25, 35, 45 and 65 after ovulation, n=3-5 per group), as well as in deslorelin-treated dogs. Although generally low, luteal GnRHR expression was time-dependent and was elevated during the early luteal phase, followed by a significant decrease towards late luteal regression. In both deslorelin-treated and control dogs, its expression was either low or frequently below the detection limit. The expression of EP2, VEGFA and VEGFR1 was higher (P<0.05) in the treated group compared to control, which could be a part of a possible positive feedback mechanism after suppression of reproductive activity. Interestingly, despite large individual variations, 3β-HSD was more highly expressed in the treated group. This, along with unaffected STAR expression, was apparently not mirrored in increased luteal functionality, as similar P4 levels were detected in both groups. Whereas EP4 was lower in treated animals, the expression of other factors did not differ significantly (P>0.05). In conclusion, the results from our study indicate that long-term delay of puberty with GnRH analogue-deslorelin does not have negative carry-over-effects on subsequent reproductive activity and ovarian functionality in bitches. [1] Kaya D, Schäfer-Somi S, Kurt B, et al. Clinical use of deslorelin implants for the long-term contraception in prepubertal bitches: Effects on epiphyseal closure, body development, and time to puberty. Theriogenology 2015:83:1147-1153. [2] Marino G, Rizzo S, Quartuccio M, et al. Deslorelin implants in pre-pubertal female dogs: short- and long-term effects on the genital tract. Reprod Dom Anim 2014;49(2):297-301. [3] Kowalewski, MP. Endocrine and molecular control of luteal and placental function in dogs: A Review. Reprod Dom Anim 2012;47(6):19–24.