ABSTRACTS

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GnRH agonist implants results in oestrus induction and oestrus suppression

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Over the last 10-15 years, long-acting GnRH agonists have become widely available. In the field of small animal reproduction, most recent studies have focused on the use of two compounds developed under the form of subcutaneous implants: azagly-nafarelin and deslorelin. Only the latter has been commercially available for the use in male dogs, first in Australia and New Zealand, and in several countries of the European Union since 2008. Although officially marketed for male dogs, this compound has been also studied in bitches, and more recently in queens. Some published papers or recent presentations at congresses – still unpublished - have focused on the use of GnRH agonists implants in females.

OESTRUS INDUCTION IN BITCHES. The rate of oestrus induction after the administration of a SC GnRH agonist implant in anoestrous bitches is high and oestrus occurs very quickly after implantation. All the bitches in a study using a 2.1 mg implant came into heat at the latest 6 days after the start of the treatment, with oestrus generally appearing in the 3 to 5 days following implantation. In a recent study on 32 bitches of different breeds, Fontaine and Fontbonne (1) obtained similar results with 4.7 mg deslorelin implants, with all bitches coming into heat 4.2 ± 1.4 days post-implantation. Walter et al. (2) detected a bloody vaginal discharge on average 4.8 days after implantation of 11/11 implanted Beagle bitches with a similar 4.7 mg deslorelin implant. Prooestrus appears to be significantly shorter than in the case of naturally coming heats, with ovulation occurring at 11.8 ± 2.1 days after implantation. However, not all induced bitches ovulated. In the study by Fontaine and Fontbonne (1), ovulation was reported in 87.5% of bitches when implanted in late anoestrus (200-590 days following their previous oestrus), while it occurred only in 62.5% of bitches implanted in early anoestrus (80-160 days following their previous oestrus). In the study from Walter et al. (2), all implanted bitches ovulated, although the stage of anoestrus of these bitches was not specified. It is still cautionable if the removal of the implant is absolutely necessary to avoid subsequent hypoluteidism caused by gonadotrophic insufficiency. Some unpublished personal observations showed that some bitches were able to deliver successfully although the implant had not been removed. To avoid this phenomenon, implants are usually placed in an area where they could be removed easily, beneath the vulvar mucosa, in the umbilical area, or on the medial side of the leg. Time of implant removal varies also depending on the authors, at the beginning of clinical heats, around the time of the LH peak or around the time of ovulation. Luteal failure was suspected in 5 bitches in the study of Fontaine and Fontbonne, 3 of them were pregnant, 2 were successfully supplemented with micronized progesterone and gave birth normally while the third one was not supplemented and gave birth prematurely 58 days after ovulation. The fertility results differed among studies and treated groups, and varied between 25 to 69.6 %. Some factors are suspected to play a role in these differences such as the stage of the cycle of implanted bitches or the time of implant removal.

OESTRUS PREVENTION IN ADULT BITCHES. Cycle stage and age are seen to affect the response to the primary stimulating effect of GnRH agonists. Adult bitches seem to respond to implantation by a frequent induced oestrus. It may occur whatever the stage of the anoestrus (early, mid or late) but sometimes also in dioestrus with high level of progesterone. The medical prevention of this preliminary induced oestrus is not standardized yet. Whereas Wright et al. (3) noted that megestrol acetate was able to prevent the induced oestrus, Corrada et al (4) observed oestrus in 3 bitches between 26 to 51 days after implantation. The treatment with progestagens simply time-shifted the induced oestrus. However, when starting the treatment 4 days before implantation, the same team obtained oestrus in only 10% of the bitches. Sung et al. (2006) attempted the same experiment by starting the treatment 7 days before implantation, but 4 of the 5 treated bitches expressed oestrus. In a recent study, we implanted adult bitches and concomitantly treated them with the aromatase inhibitor anastrozole 0.1mg/kg (Group 1, n=3, Arimidex®, Astrazeneca, France) or the anti-oestrogen clomifén acetate 5mg/kg (Group 2, n=8, Clomid®, Sanofi-Aventis, France) during 15 days per os. In Group 1, 2 bitches presented bloody discharge and keratinization of the vaginal epithelium after 5 and 6 days post-implantation. Ovulation was confirmed in these 2 bitches. In Group 2, no bloody discharge was observed in 6/8 bitches but keratinized cells were observed in vaginal smears of all bitches. Ovulation occurred in 5/8 bitches between 16 and 18 days post-implantation. As a result, these compounds cannot be considered as valuable alternatives to prevent the induced oestrus occurring in anoestrous bitches. Therefore up to now, the prevention of induced oestrus after implantation of GnRH agonists in adult bitches still has to be further studied. Some eventual side effects may be noticed by authors. In an unpublished study in bitches implanted with a 4.7 mg SC implant in our laboratory (oral presentation at the EVSSAR 2010 congress in Louvain La Neuve, Belgium), 7/57 bitches presented prolonged heats (including 2 cases of ovarian cysts), 5/57 had an induced lactation, 3/57 presented some...
behavioral changes and 8/57 miscellaneous problems (cystitis, vomiting, allergic reactions). Most of the time, the removal of the implant improved the state of the bitch within 15 days, however, ovario-hysterectomy was necessary in some cases. Recently, a case of induced ovarian cysts followed by a subsequent pyometra following implantation was published (5). The stage of the cycle at which the treatment is started would appear to have an impact on the duration of oestrus suppression after implantation. According to our observations (work still under investigation), adult bitches implanted once only with a 4.7 mg deslorelin implant came in heat 10.2 ± 5.1 months after implantation (2.1 to 23.3 months). Return to fertility after implantation is still unclear, although 6/9 bitches became pregnant at the following oestrus post-implantation (6). Unpublished observation still under investigation in our laboratory tend to show that there is a good fertility after returning to oestrus, and that bitches are able to give birth naturally, with no sign of hypoluteoidism during pregnancy. 3/5 bitches were pregnant post-implantation and produced 2, 6 and 10 puppies (unpublished data).

OESTRUS PREVENTION IN PREPUBERTAL BITCHES: Very few studies have been conducted about the postponement of puberty using GnRH agonists implants in bitches. Using azagly-nafarelin sub-cutaneous (SC) implants in bitches aged 4.88 ± 0.32 months, and removing the implant one year after implantation, the age of puberty in these bitches was 25.5 ± 5 months. Using a 4.7 mg deslorelin SC implant in 4 months old bitches, Trigg et al. (6) did not observe any signs of oestrus for the following 36 weeks, but the exact date and clinical and hormonal features of the first oestrus after implantation were not mentioned. Interstingly, in the same study the use of deslorelin implants in bitches aged 7 months or more systematically induced oestrus.

To our knowledge, no study has been published so far evaluating the SC 9.4 mg deslorelin implant to postpone puberty in bitches.

OESTRUS PREVENTION AND SUPPRESSION IN QUEENS. Few clinical information has been published concerning the use of GnRH agonists implants in the queen. Although signs of oestrous behaviour were reported after implantation, most of the time no vaginal smears or routine additional informations were performed to evidence the oestrus in study queens. Most studies assaying oestrogens in faeces seemed to demonstrate an increase in the week following implantation, but with no correlated clinical data. In queens implanted in interoestrus, an initial increase in oestradiol was first observed, followed by a decline while progesterone concentrations were rising, indicating ovulation induction (Goericke-Pesch unpublished – oral presentation at the 2011 EVSSAR congress in Milano, Italy). Concerning the prevention of oestrous signs using a 4.7 mg deslorelin implant, Goericke-Pesch observed a duration of 11.1 ± 2.3 days. Although unpublished data seems to demonstrate that some of previously implanted queens are able to reproduce later, to our knowledge no publication has been produced so far to demonstrate it.

REFERENCES:
(5) Arlt SP, Spankowski S, Heuwieser W. Follicular cysts and prolonged oestrus in a female dog after administration of a deslorelin implant.