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Clinical application of deslorelin implants in dogs and cats

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Abstract

Deslorelin implants are licensed for fertility suppression in male dogs, ferrets, tom cats and prepubertal bitches. Off-label application of deslorelin implants as a treatment option for a great variety of clinical conditions have been researched thoroughly, although further research must be done in certain areas, due to small sample sizes. This paper aims to collect the current and relevant research performed for the off-label usage of deslorelin in clinical practices, involving dogs and cats of both sexes. The findings in this paper includes successful usage for conditions which are associated with behavior, abnormal cell growth, dermatology, and urinary incontinence. Overall, the conclusion of this paper is that deslorelin is a well-suited treatment option for the conditions mentioned, especially due to its availability, price, and low invasiveness.

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Abbreviations

GnRH: Gonadotropin-releasing hormone

GnRH-R: Gonadotropin-releasing hormone receptor

LH: Luteinizing hormone

FSH: Follicle stimulating hormone

BPH: Benign Prostatic Hyperplasia

MPA: medroxyprogesterone acetate

MA: megestrol acetate

CL: corpus luteum

OE: ovariectomy

OHE: ovariohysterectomy

PPA: phenylpropanolamine

s.c: subcutaneous

DHT: dihydrotestosterone

p.o: per os

CBC: complete blood count

FNA: fine needle aspiration

P4: progesterone

E2: estradiol

1. Introduction

The use of medical contraception has been developing over several decades for humans. There has been several products developed for companion animals over the years as well, but many of them have had various adverse effects which has limited their usage [42].

Surgical castration was previously the main method for achieving infertility in male dogs. Surgical castration has been a controversial topic among owners and veterinary professionals debating the benefits and risks of such a procedure. This topic has also caused debate due to the ethical reasons behind it. In some countries, such as Norway, surgical castration is not allowed unless the veterinary professional deems it to be a good medical reasoning behind the decision [12]. For some patients' surgical castration is not an option at all, for example due to potential risk of complication in connection with the anesthesia of the procedure. [19, 25]. Achieving infertility in dogs is crucial to help with population control. In 2019 the worldwide population of dogs were estimated to be approximately 700 million. 75% of these dogs were classifies as "free-roaming". Proper population control can help reduce the number of animals in shelters, decrease the risk of infectious diseases and promote better animal welfare [64, 65]. Development of a safe and effective drug for reproductive control in veterinary medicine has been subjected various difficulties, such as ease of use, long-term release, biocompatibility and cost [69].

In 2007 a subcutaneous slow release Deslorelin acetate implant was approved by the European Medicine Agency for suppression of fertility for male dogs and ferrets. This approval altered the commercialization of veterinary contraceptive products. This product is marketed under the name Suprelorin ® and is produced by Virbac. The subcutaneous implant comes in 4.7 mg and 9.4 mg strength [14]. As recently as 14th of July 2022, Virbac received an extension of the marketing for Suprelorin ® 4.7 mg s.c implant in the European Union, which states that the product can now be used for reproduction control in male cats (above 3 months of age) and in prepubescent bitches.

2. Objectives/Questions

This paper will summarize the EU approved label for use of deslorelin and the present knowledge of GnRH analogues in dogs. The main effects, duration of effects and side-effects will be discussed. It will also aim to investigate the various research done for the off-label application of deslorelin implants in both dogs and cats of both sexes. Mainly this paper will

focus on the alteration of the reproductive function in the species which the product is not marketed for, but other conditions such as neoplasms, behavior and dermatological conditions will also be explored.

3. Literature review

3.1. The physiology of Gonadotropic releasing hormone

Gonadotropic releasing hormone is synthesized by neurons in the hypothalamus in a pulsatile way and will be transported via the hypophyseal portal system to the anterior pituitary gland, where it will control the release of LH and FSH. FSH and LH will then modulate sex steroid production in the gonads, such as oestrogen and progesterone in the bitch and testosterone in the male dog. Spermatogenesis will also be regulated by LH and FSH in the male dog. The secretion of GnRH is activated during puberty [13, 31]. GnRH is decapeptide (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly·NH2) and is present in the hypothalamic-pituitary-gonadal axis in both humans and animals. GnRH will be coupled to GnRH receptors located in the anterior pituitary gland. This receptor is a G-coupled receptor. Overall, the production of GnRH happens in neurons in the hypothalamus and causes a chain reaction of sex hormone production in the gonads. The main function of the hormone is to regulate the onset of puberty, sexual development and ovulation in females [63]. This mechanism is regulated by both positive and negative feedback mechanisms, such as the gonadal hormone production and influenced by other external factors, such as light, social cues and food supply.

3.2. GnRH analogues

GnRH analogues are synthetic drugs that mimic the physiological appearance of GnRH which is normally found in animals. GnRH analogues are available both as agonists and antagonists. Development and improvement of these drugs are especially dependent of the improvements made in peptide chemistry, especially the peptide synthesis. Based on this, agonists with high affinity to GnRH receptors and slow degradation and/or elimination, have been developed [51]. The development of GnRH agonists is based on the substitution of L-isomers with D-isomers. Receptor binding and activation is due to the NH2- and COOH-terminal domains.

The route of administration is a factor that is especially important for GnRH analogues. Since the agonists are susceptible to degradation in the gastrointestinal system via peptidase enzymes, which makes these products unsuitable for oral administration. Intranasal administration is also deemed ineffective, since the bioavailability is only 4-21% compared to subcutaneous or intravenous injections [51].

Native GnRH: pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly.
Deslorelin acetate: H-Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-NHEt.CH_3CO_2H.
Azagly-nafarelin: H-Pyr-His-Trp-Ser-Tyr-D-2Nal-Leu-Arg-Pro-$NHNHCONH_2$.

Figure 1: Structural differences for Native GnRH, Deslorelin acetate and Azagly-nafarelin [11].

Two GnRH agonists have been researched for the purpose of controlled release formulations. These two agonists are the deslorelin and azagly-nafarelin. Azagly-nafarelin was approved as a solid implant but was not commercialized [11]. This paper will focus on the use of deslorelin acetate.

3.3. Mechanism of action of GnRH-agonist releasing implants

Deslorelin presents with a peptic sequence which is related to native GnRH. There are modifications to three of the amino acids, which are located at position 1, 6 and 9. In addition to this, the amino acid in position 10 is deleted. These modifications lead to a reduced sensitivity to proteolysis and increases the biological activity. Due to these alterations deslorelin has been found to display a potency which is 10 to 100 times higher than native GnRH in a GnRH ligand binding test and in an in vitro culture of rat pituitary cells [11, 51]. The main goal for this type of implant is to release the GnRH-agonist content over a prolonged period. A pharmacokinetic study, published as an abstract, described the plasma concentration of deslorelin after treatment. The plasma concentration peaked at 14 days after administration on a 4.7 mg implant, before gradually decreasing and reaching undetectable levels at 80 days post-implantation [48]. When the pituitary cells receive constant exposure to GnRH it will lead to pituitary desensitization and due to this, LH concentrations will reach undetectable values. Since the LH concentration will be dramatically decreased, it is no longer able to support the testosterone and sperm production in the male dog and therefore will be causing infertility [11].

3.4. Efficacy and duration of effect of deslorelin

The effect of deslorelin implants, meaning the suppression of LH and testosterone, have been documented in several studies along the years. The studies include the original formulations (3, 6 and 12 mg) [34, 36] as well as the formulations available today (4.7 and 9.4 mg) [59, 69]. For measuring the efficacy and duration of effect, parameters such as testosterone concentration, testis and prostatic size, sperm volume, sperm motility and abnormal sperm percentage were used (figure 2). This research can indicate a close coincidence between the time when testosterone concentration reaches undetectable values and semen showing alterations making it incompatible for fertilization of the bitch [11].

Implant	**Deslorelin releasing implant (DRI)**	
References	**Trigg et al. (14)[a]; *N* = 56 Romagnoli et al. (21)[b]; *N* = 6**	
End point and metric	**Time to first reduction (d)**	**Time to full reduction (d)**
LH concentrations	ND	ND
Testosterone concentrations	Day 23–32[a]	Day 6–43[a] Day 64–75[a]
Testis size	ND	ND
Prostatic size	ND	ND
Erection allowing sperm collection	Day 22[b]	Day 30–35[b]
Sperm volume	Day 37–47[b]	Day 64–75[b]
Total sperm number in the ejaculate	Day 37–47[b]	Day 64–75[b]
Sperm motility	Day 23–32[b]	Day 64–75[b]
% of Abnormal sperm	ND[a]	Increased to 70% by Day 35[a]

Figure 2: Changes in endpoints after treatment with deslorelin implant.

Duration is expressed in days. ND, not documented [11].

The most common deslorelin implant available for commercial use, Suprelorin ®, is approved to alter the normal testicular function and block fertility in male dogs for either 6 months (4.7 mg) or 12 months (9.4 mg). A study shows that 9/10 male dogs had a testosterone level below the assays limit of quantification (0.1 ng/ml) for at least 180 days for the 4.7 mg implant, and at least 400 days for the 9.4 mg implant [69]. The same study shows that there might be a correlation between the body weight of the dogs and the duration of fertility suppression, since small dogs (<10 kg) showed a longer period of testosterone suppression [69]. There was a great variability in the duration of effect among the dogs in this study (figure 3).

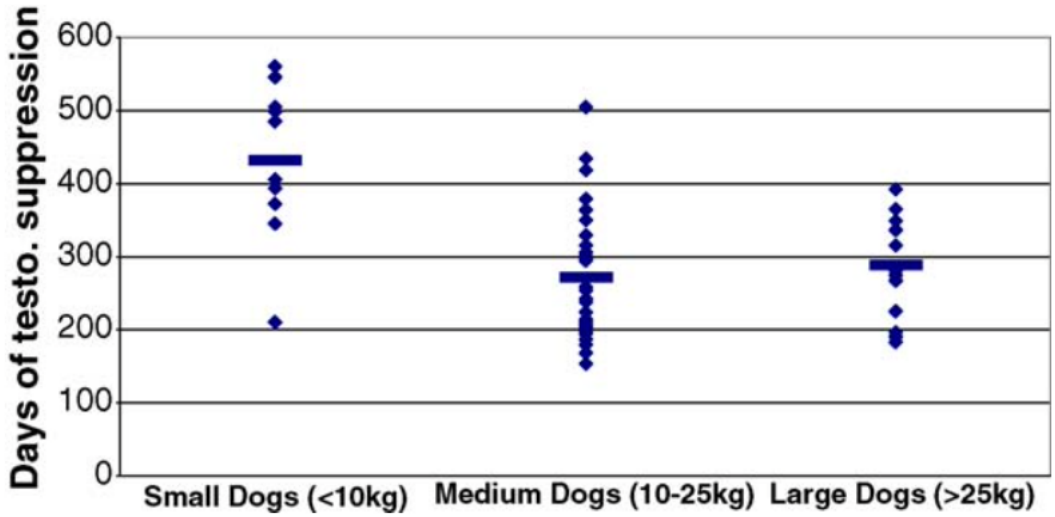

Figure 3: Duration of testosterone suppression in male dogs implanted with deslorelin [69].

The use of deslorelin can be a temporary solution for suppression of testicular function and fertility. Some indications can be temporary suppression of testicular function to evaluate if the patient is a candidate for surgical castration or to "buy time" to decide if the male dog should be used for breeding [11]. Studies has demonstrated that normal testicular function and semen quality will return to normal values after the release of GnRH agonist has discontinued from the implant, but the time period for resuming fertility may be variable [11, 69]. Deslorelin implants, such as Suprelorin ®, are fully degraded at the end of the releasing period. To be able to further suppress the fertility, it is recommended by the producer, to re-implant the male dog at intervals of 6 or 12 month, depending on the strength of the implant used. Studies have concluded that re-implantation of dogs using the 4.7 mg implant is safe and will further cause fertility suppression [69].

3.5. Side effects and safety using deslorelin implants

Studies performed for deslorelin implants show few adverse reactions. The most common adverse effect is a moderate swelling at the implantation site, which can be present for approximately 14 days [14]. In the first day's post-implantation, there can be a short period when exposure to the GnRH agonist has a stimulatory effect on the pituitary-gonadal axis. This phenomenon is called a "flare-up phase". During this period there will be a marked elevation in the serum testosterone concentration. One study involving six dogs, which were treated with 4.7 mg implant, showed an increase in serum testosterone concentration from 1-5 days post-implantation[11, 54]. One study using the 4.7 mg implant states that owners

reported an increase of sexual behavior, lasting the first week post-implantation, in 8 of the 24 dogs involved in the study. This number was decreased to 3 dogs when three weeks had elapsed [8]. According to the product information provided by Virbac, rare side effects (1-10 animals of 10 000 treated) such as hair coat disorders (hair loss, alopecia or hair modification), urinary incontinence and general down-regulation signs (decreased testicular size, reduced activity and weight gain) have been reported [14].

4. Methods

For this paper literature searches were performed using mainly Google Scholar and PubMed online platforms. The search terms used for this paper included the following words with an "OR" or "AND" combination where it was deemed suitable. Search words included the following: medical contraception; nonsurgical; deslorelin; Suprelorin; GnRH; gonadotropin releasing hormone; GnRH agonist; dog; canine; female; bitch; male; feline; queen; toms; adverse effects; side effects; off-label; oestrus; behavior; dermatology; puberty; stray; population control; incontinence; prepubertal; application; and clinical use. References from books are also included in this paper, as well as review articles were deemed relevant.

The aim for the studies selected was for them to have control groups, or that the animals were acting as their own control, and a wide selection of animals, ideally divided into various groups, but in some instances, this was not possible such as when only one subject is being studied in a case study. There should also be a thorough follow up and control of the animals, at least for 6 months or 1 year. The studies performed should also follow the ethical and animal welfare norms relevant to the country where the research took place. For the various research papers found for this systematic literature review searches done on the online platforms mentioned earlier in this section, were set to show the most recent papers for the particular topic firstly. As a base for which topics shall be included in this paper, the Journal of Society for Theriogenology and American College of Theriogenology has been used.

This paper tries to summarize the most clinically relevant uses for deslorelin implants when used off-label in both dogs and cats of both sexes. To add relevance to each topic, there should be more than one paper referring to the same result on the subject matter, as well as a thorough examination as to why the researchers concluded with it being beneficial or not.

5. Results

This section will summarize the various literature found for the off-label use of deslorelin s.c implants in both dogs and cats. The sections are divided into species and into the sex of the animals. All though Suprelorin ® received an extension of the marketing which includes use for reproductive control in tom cats and use in prepubertal bitches, these topics will still be included in this section, to give a thorough overview of the clinical usage of deslorelin implants.

5.1. Off-label use of deslorelin implants in the male dog

5.1.1. Postponement of puberty

Puberty is defined as the process of physical changes where the animal becomes an adult capable of sexual reproduction. Onset of puberty may vary according to breeds and body weight [32]. The stray dog population is a significant problem in larger cities. These stray dogs can again produce several offspring if they continue to roam streets while still being able to reproduce. Both dogs and cats can breed on their first oestrus. For population control, early-age neutering is a common procedure used for population control. In some cases, the surgical castration may not be possible [64]. Regarding postponement of puberty in male dogs, only a few studies have been performed so far, and both have fairly low patient numbers. The comparability of them is not easy, and for the use of deslorelin implants only two studies are found so far. Both are cohort studies which includes a control group.

One article state that there can be problems associated with early neutering, such as musculoskeletal and urinary tract problems, along with anaesthetic concerns [33]. Another paper states that there was no difference detected in physical development and behavioral problems in regards to early-age implantation and traditional gonadectomy [29, 64]. The study in this article consisted of a total of 11 dogs (6 male beagles and 5 mixed breeds) which was divided into two treatment groups, along with one control group. Each group of those who were treated were either implanted with the 4.7 mg or the 9.4 mg implant at 4 months of age. The dogs were examined from the age of 8 months and until they were 36 months old. During the examination the semen quality, testicular size, growth, height and non-sexual behavior was recorded (figure 4) [64]. The results from this study indicated that the control group had normal testicular development, sperm quality and male behavior from 12-15 months old. In group 1, which was implanted with the 4.7 mg deslorelin, showed male sexual behavior, along with normal sperm characteristics, from the age of 34 months old. Group 2

which were implanted with 9.4 mg deslorelin showed slight male behavior, small/soft testes and had no collectable semen when 30-36 months old. There was no difference in growth, size, height or non-sexual behavior for the treated group or the control group [64]

		Age (month)								
		8	12	15	18	24	30	32	34	36
Dog	Deslorelin implant	Sperm collection and quality								
Ba-1	4.7 mg	–	–	–	–	–	–	–	–	n/o
Bb-1	4.7 mg	–	–	–	–	–	–	–	N	n/o
M-1	4.7 mg	–	–	–	–	–	–	–	N	n/o
M-2	4.7 mg	–	–	–	–	–	–	–	–	–
Ba-2	9.4 mg	–	–	–	–	–	–	–	–	–
Bb-2	9.4 mg	–	–	–	–	–	–	–	–	–
M-3	9.4 mg	–	–	–	–	–	–	–	–	–
M-4	9.4 mg	–	–	–	–	–	–	–	–	–
Ba-3	Placebo	N	N	N	N	N	N	N	N	n/o
Bb-3	Placebo	–	N	N	N	N	N	n/o	n/o	n/o
M-5	Placebo	N	N	N	N	n/o	n/o	n/o	n/o	n/o

N: collectable with normal sperm quality; –: fail to collect sperm; n/o: no observation, dog had been neutered.

Figure 4: Table showing sperm collection and quality among the treated groups and the control group. [64]

The second study found for this topic involves a total of 24 puppies, both male and female, from 5 different litters. All of them are crossbreeds and their progenitors weighed <15 kg. 12 dogs were selected for the treatment group which consisted of two 9.4 mg (18.8 mg in total) implants at each shoulder blade, while the remaining 12 were assigned to the placebo group. The implantation was done within the first 24 hours after birth and no flare-up was observed. Follow-up examinations were performed weekly, and the puppies were also observed for 1 hour twice a day, to detect sexual behavior. For the males, puberty was defined as the time where typical sexual behavior was exhibited, and spermatozoa was present at semen collection. The results for puberty postponement in males ranged from 70.75 to 106.25 weeks, with the average being around 17 months. The implantation did not impact wither height or body weight of any dog involved in this study. Long-term effects for puberty delay, including joint health, tumor development and social behavior should need further investigations [62].

5.1.2. Treatment of behavioral problems

Surgical castration has been a commonly used method to alleviate behavioral problems in dogs, especially if the behavior is related to testosterone production [27]. Behavior related to testosterone includes sexual behavior such as mounting or mating, hypersexuality,

roaming, urine and some aspects of intraspecies aggression [22]. Due to the known "flare-up" phase post-implantation, testosterone dependent behavior may be exaggerated for a short period of time usually lasting a few days after implantation. When the second phase, the down regulation, occurs the behavior should be significantly improved or non-existing – if the behavior is dependent on testosterone [22]. Thorough distinction between behavior linked to testosterone and behavior disorders should be made [17]. Some owners are reluctant to let their pet undergo either surgical castration or chemical castration, especially if the dog is a working dog. A common saying is that the reduction of testosterone will decrease the performance of the animal, all though this statement is not well researched [20]. One study, which compared surgical castration and chemical castration, consisting of 42 dogs, where surgical castration (n=18) and chemical castration (n=24) were used to collect data for studying behavior and pituitary-testicular axis. The dogs were evaluated by a modified behavior test and questionnaires, GnRH stimulation test were also performed, and measuring LH and testosterone concentrations in plasma [9]. The results from this study observed no significant difference between surgical castration and chemical castration in relation to behavior. Approximately 50% of owners from dogs in both groups reported a decrease in aggressive behavior towards other male dogs. Both groups experienced an increase in play behavior, while the sexual behavior was reduced in both groups as well. Decreased sexual behavior towards oestrus bitches had a more significant decrease in the surgically castrated group, compared to the chemical castrated [9].

One study investigated the impact of surgical castration regarding the working ability of military dogs in Switzerland. From 2014 to 2016, 49 dogs were enrolled in the Swiss military, with ages ranging from 18 to 55 months old (mean: 27.07). Out of these 49 dogs, 42 of them has a full data set. 19 of them were implanted with Suprelorin implants, based on random selection. Trainers and judges of the test were unaware of this procedure [20]. To evaluate the dogs, a standard behavioral test performed 10 weeks post-implantation, were used. This test was established by the Swiss military previously. An external judge was responsible for the rating of the dogs. The test included sections for obedience (walk on/off leash, reaction to gunshot, recall, down/stay for 5 minutes), protection (attack toward human, fighting attacker, recall), social (walking in crowd, cars, bicycles, trains) and building (search, barking, successful finding) [20]. The results obtained by this standardized military test did not show any significant differences between the chemically castrated dogs and the intact dogs, in regards to their working ability [20].

5.1.3. Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is occurring due to long-term exposure to the active metabolite of testosterone, DHT. Testosterone is produced by the Leydig cells located in the testicles and is converted into DHT by type II 5α-reductase. With age, testosterone may also be converted to oestrogen in a larger amount. This is possible due to an enzyme called aromatase. Increased oestrogen increases the expression of nuclear receptors for DHT, which in turn increases makes the prostate more sensitive to androgens [7, 49]. DHT is active at the cellular level in the prostate gland. As a result of increased number and size of the cell, the prostate gland will become enlarged. The enlargement also leads to alter the pressure in the ducts of the prostate, which can lead to formation of cysts [13]. BPH is one of the most commonly diagnosed prostatic disorders in intact males and it is suggested that >50% will have signs of BPH by 5 years of age, and 95% of dogs >9 years of age show gross and/or microscopic alterations related to BPH. Clinical signs of BPH includes sanguineous or serosanguineous discharge from the penis, pollakiuria, stranguria, hematuria, constipation and ribbon-like feces [13]. Clinical signs are more commonly found if there is progressive enlargement of the gland.

Treatment for BPH depends on the age and breeding status of the dog. If the dog is old and not used for breeding surgical castration is the treatment of choice, as it can reduce the size of the prostate gland to 25-30% of its initial size [13, 32]. Regarding medical treatment of BPH, osaterone-acetate (Ypozane ®, Virbac), a steroidal antiandrogen, is licensed as a p.o treatment. This product should be given once daily for a total of 7 days and shall be able to reduce the size of the prostate gland with 41-46% within 14 days [71]. Overall, the goal of any treatment is to resolve the clinical signs, reduce discomfort and provide the dog with a pain-free quality of life [54]. One study compared the effectiveness of osaterone-acetate and deslorelin for the treatment of BPH. Deslorelin leads to a significant decrease in the production of androgens [49], and will decrease the size of the prostate gland which is comparable to surgical castration. This study involved 45 intact male dogs aged >5 years of various breeds. They were divided into two control (G1, G2) and two treated (G3, G4) groups. G1 consisted of healthy dogs, G2 were diagnosed with BPH but received no treatment, G3 were treated with deslorelin (4.7 mg) and G4 were treated with osaterone

acetate. The dogs included into this study after undergoing thorough physical examination, rectal palpation, CBC, serum biological and hormonal analysis, ultrasound guided FNA of the prostate gland to confirm the diagnosis, the latter only valid for group 2, 3 and 4. The dogs were examined regularly from the start until 36 weeks after treatment, following the same criteria listed above, except for the FNA procedure [49]. In this study, both group G3 and G4 showed reduction in clinical signs and size of the prostate gland. Dogs treated with deslorelin had a slower reduction in size compared to those treated with osaterone-acetate, but the reduction of clinical signs and size lasted longer in the group treated with deslorelin (figure 5) [49].

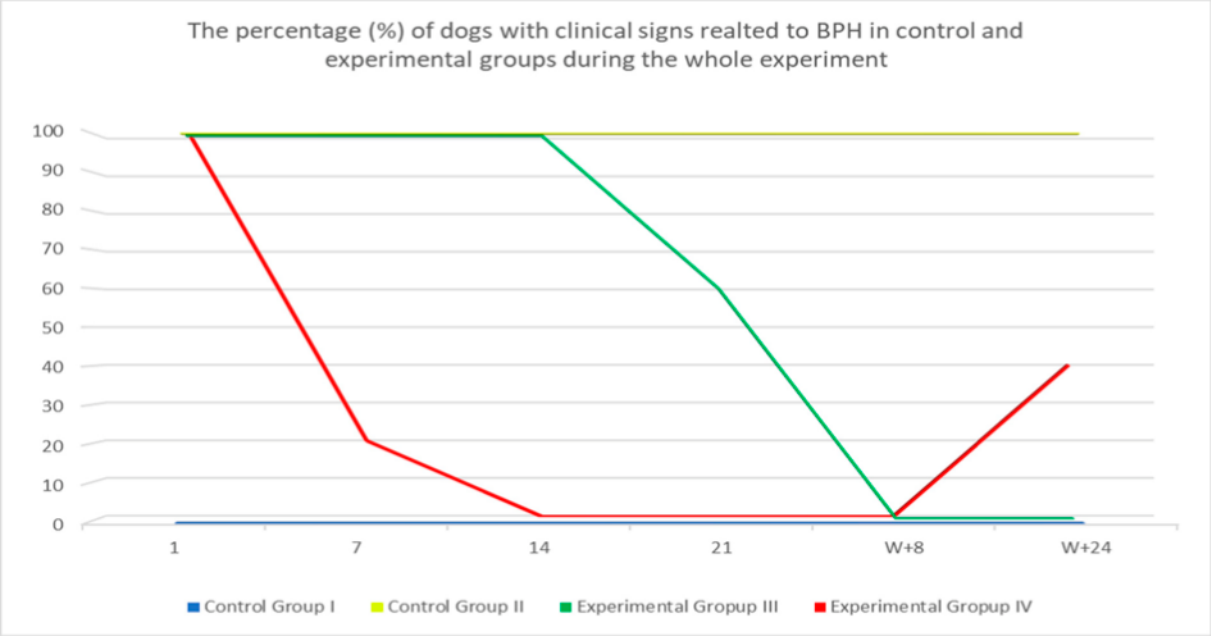

Figure 5: "The percentage (%) of investigated dogs with clinical signs related to BPH Control Group 1, 2 and Treated Groups 3,4 during the whole observation period" [49]

The side effects noted were mild, mainly weight gain and the "flare-up" effect in the group treated with deslorelin. This study suggested that both products may be used in combination in some cases, to get the faster results from osaterone-acetate and the longevity of deslorelin [49].

Another study aimed to investigate the prostatic blood flow in dogs diagnosed with BPH and treated with deslorelin implants, along with the general volume changes and sperm quality of the ejaculate. This study provided valuable knowledge in the use of B mode and Doppler imaging techniques for the diagnosis and evaluation of dogs already diagnosed with BPH [54]. This study involved 6 German Shepherd dogs which has confirmed BPH and received deslorelin implants (4.7 mg) s.c. The age of the dogs ranged from 4-8 years. They underwent

physical examinations, blood sampling, semen collection and B-mode and Doppler ultrasound scanning of the prostate gland. The result in this study concluded that the use of deslorelin implants provided a great reduction in the prostatic volume, which were detected by ultrasound scanning. This study also observed a decrease in sperm concentration, motility and an increase in abnormal sperm cells, which is consistent with the previous claims and licensing of the product [14]. The study also show a positive correlation between the reduction in serum testosterone and the prostatic volume (figure 6), aligning with previous studies done on this subject [35].

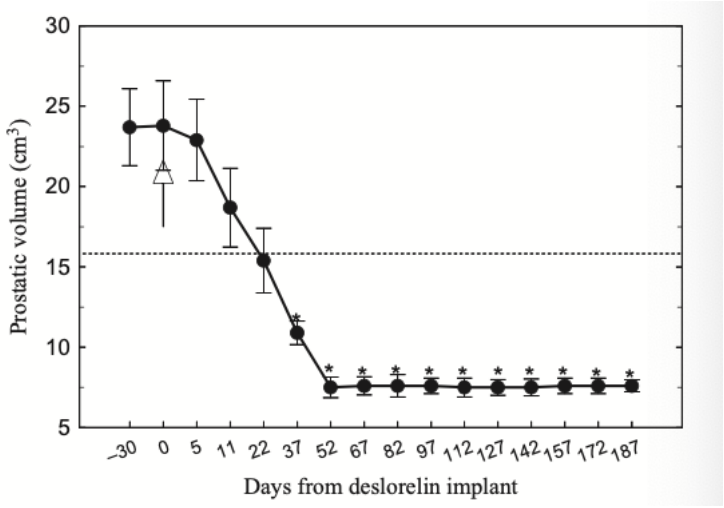

Figure 6: "Mean prostatic volume in dogs with benign prostatic hyperplasia following treatment with Deslorelin implants. Prostatic volume (cm3) evaluated according to Atalan et al. (1999) using prostatic dimensions obtained by B-mode ultrasound." [35].

5.1.4. Perianal adenomas

The perianal glands are non-secretory modified sebaceous glands occurring normally around the anus of dogs. Tumors derived from these sebaceous glands are one of the most common skin tumors in dogs. Benign circumanal adenomas are the most common, and malignant adenocarcinomas are less frequent and represent 3-17% of all perianal tumors [10]. Male dogs >8 years of age have higher chances of being diseased with hepatoid gland adenoma or perianal gland adenoma. There is some breed predisposition, and this involves breeds such as Cocker spaniel, Samoyed, Siberian Husky, English bulldog, and Beagles, even though this can also affect crossbreeds. The benign adenomas are usually well circumscribed, although they might ulcerate and become infected. This tumor is usually diagnosed based on physical examination, cytology, and histopathological examination. It is strongly suggested that the adenoma type of tumors are linked to sex steroid hormones [46], while there is no clearly demonstrated link between perianal adenocarcinomas and sex steroid hormones [41].

The most common treatment for benign adenoma is surgical castration, which usually leads to a full or partial regression of these types of tumors [73]. Based on this knowledge, a clinical trial for use of s.c deslorelin implants as a treatment option for perianal adenomas have been carried out. Since deslorelin, after the initial "flare-up" phase, will suppress the LH and FSH production on a pituitary level, which in turn will also decrease the level of testosterone – and its effect have been compared to surgical castration. This trial found that deslorelin were able to induce complete remission in at least 50% of dogs and provided a partial response to treatment for an additional 29% of dogs [46].

Based on this information, deslorelin implants can be considered as a new option for treatment of perianal gland adenomas, and especially in individuals where surgical castration may not be an option for various reasons.

5.1.5. Dermatological problems

Hair cycle arrest (alopecia X) is defined as a non-inflammatory alopecic condition in dogs with an unknown pathogenesis. The lesions are usually symmetrical, non-pruritic alopecia on the neck, perineum, caudal thigh, and trunk. This condition is usually seen in "plush-coated" or Nordic-breed dogs [47]. In intact males, surgical neutering is often the initial treatment of choice, which leads to either complete or partial hair regrowth and has a success rate of between 60-83%. Trilostane is another substance deemed to be effective for this condition, but this must be administered daily and have a greater cost, and more potential side effects, compared to deslorelin, which will be discussed in this section [2].

There are few studies for the use of deslorelin implants as treatment for this condition. One is a case study and only includes two dogs, while the second includes a larger sample size and a greater variation of gender and gonadal function. The dogs in the first case report consists of two unrelated, sexually intact male Keeshonden aged 4 and 5 years old, living in the same household. They both had a history of progressive non-inflammatory alopecia along with skin hyperpigmentation and hair loss on certain areas of the body, especially the dorsal lumbar and caudal thigh region, which again progressed towards the trunk [40]. Neither of them experienced pruritus. Both dogs have undergone several tests, including blood samples, urine samples and various fungal cultures, as well as being on regular tick and flea preventatives, before starting with deslorelin implants. Previous treatment included antibiotics, fatty acid supplementation and melatonin [40]. Biopsy showed a predominance of kenogen follicles, which means that the follicles were in a physiological resting state.

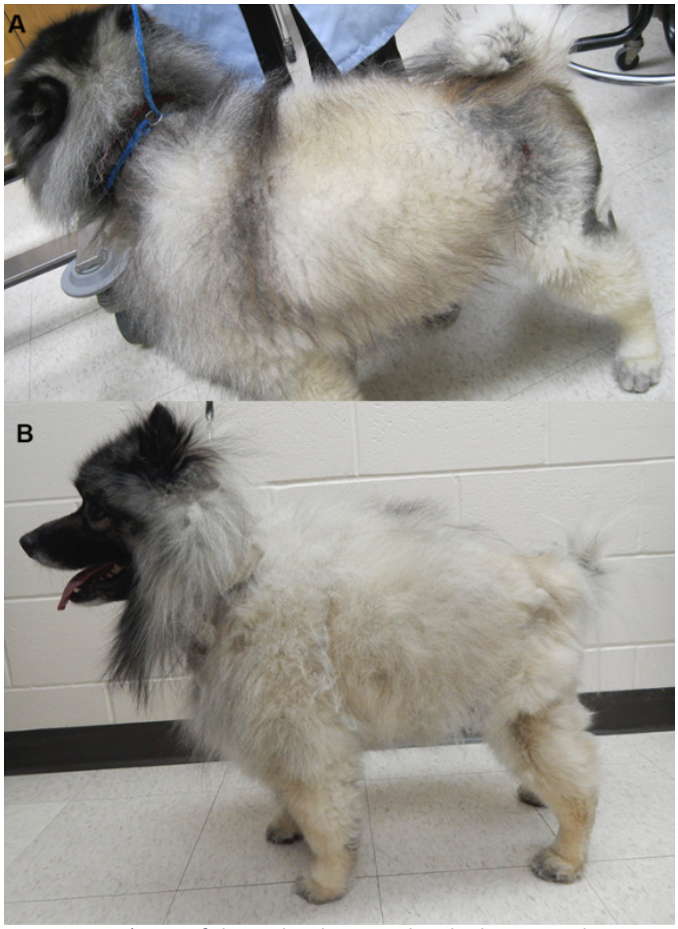

Figure 7: A) One of the males diagnosed with alopecia X showing characteristic loss of primary hairs. B) The same dog with hair regrowth 3.5 months after receiving deslorelin implant. [40]

These dogs were implanted with 4.7 mg deslorelin implant s.c in the intrascapular region. When re-examination 3.5 months later, both dogs experienced profuse regrowth of hair in the previously affected regions (figure 7). The color and texture of the regrown hair had an appearance of being lighter and softer than what was seen before [40]. When performing a new biopsy, the findings included predominantly anagen follicles, which correspond to the observed hair growth in the animals. The owners reported a full, but lighter hair coat at least 14 months after implantation. Neither of the dogs showed any side effects after implantation [40].

The second study which included a larger variety of dogs, sex, and gonadal function of the animals. The males (16) in this study were intact, while the females (4) were previously spayed. Inclusion criteria included breed predisposition, suitable clinical history, no appearance of systemic signs, normal thyroid, and adrenal function, as well as typical clinical distribution of the lesions. They were also subjected to routine CBC, serum biochemistry and urine analysis. The dogs showed no sign of physical or microscopic sign of infectious

microorganisms. This study used the 4.7 mg deslorelin implant, which were placed in the intrascapular region [2].

Signalment				Hair cycle arrest data					Clinical follow-up		
					Alopecic areas						
Case no.	Sex	Breed	Age (months)	Time from first clinical sign (months)	Neck	Trunk	Thighs	Tail	3 months	6 months	12 months
1	M	Pomeranian	32	12	+	+	+	+	HR	HR	HR
2	M	Pomeranian	91	12	+	+	+	+	HR	HR	HR
3	M	Pomeranian	96	84	+	+	+	+	NHR	NHR	NHR
4	M	Pomeranian	23	6	+	+	+	+	HR	HR	HR
5	M	Pomeranian	120	48	+	+	+	+	HR	HR	HR
6	M	Pomeranian	96	10	+	+	+	+	HR	HR	HR
7	M	Pomeranian	96	36	+	+	+	+	NHR	NHR	NHR
8	M	Pomeranian	20	6	+	+	+	+	HR	HR	HR
9	M	Italian spitz	132	9	+	+	–	+	HR	HR	HR
10	M	Italian spitz	108	6	+	–	–	+	NHR	NHR	NHR
11	M	Italian spitz	120	24	+	+	+	+	HR	HR	HR
12	M	Miniature poodle	72	12	+	+	+	+	HR	HR	HR
13	M	Miniature poodle	168	48	+	+	+	+	HR	HR	HR
14	M	Siberian husky	36	24	+	+	+	+	HR	HR	HR
15	M	Siberian husky	24	8	+	+	+	+	NHR	NHR	NHR
16	M	Chow chow	22	10	+	+	+	+	HR	HR	HR
17	FN	Pomeranian	31	8	+	+	+	–	NHR	NHR	NHR
18	FN	Pomeranian	23	12	+	+	+	–	NHR	NHR	NHR
19	FN	Italian spitz	42	6	+	+	–	+	NHR	NHR	NHR
20	FN	Miniature poodle	120	7	+	+	+	+	NHR	NHR	NHR

Figure 8: Case signalment, breed and clinical course. FN: female neutered HR: hair regrowth M: male NHR: no hair regrowth +: presence -: absence [2]

The dogs had follow-up examinations at 3, 6 and 12 months after implantation. Dogs which did not show hair regrowth at 6 months were not subjected to further treatment, while dogs that showed hair regrowth received a second implant at this time. The scoring system used for evaluating hair regrowth was classified as: absent (no change), partial (some alopecic areas still present) or complete (lack of alopecic areas). After 3 months, 12 of 16 intact males had visible hair regrowth, while all the spayed female dogs experienced no hair regrowth (figure 8). At 6 months from implantation, all animals that showed hair growth at 3 months had undergone a full recovery for hair growth, while there was still no response in those dogs which had not undergone any hair regrowth at 3 months [2].

To summarize, the overall response rate for treatment of hair cycle arrest in this study were 60%. The dogs in this study were subjected for follow up examinations until 1 year after treatment, so possible relapse after this time shall be considered. Since the pathogenesis for hair cycle arrest is not fully understood, the use of deslorelin implants seems to be a reasonable treatment method for this condition in dogs. The administration of the drug is deemed safe and easy, while being a good choice for owners which reject the option of surgical castration.

5.2. Off-label use of deslorelin implants in the female dog

Reproductive control of the female dog is a common request among dog owners, both due to physical and psychological changes during the pro-oestrus and oestrus [13]. Regarding overpopulation of both feral and stray dogs, surgical and medical contraception can help reduce this incidence and by doing so also reduce the risk of zoonotic diseases [52]. Traditionally synthetic progesterone, such as medroxyprogesterone acetate (MPA), megestrol acetate (MA) and proligestone has been used for prevention of oestrus since the 1960´s [60]. These substances causes suppression of ovarian activity due to negative feedback mechanisms of the hypothalamic-pituitary-gonadal axis. [13]. Deslorelin implants are not approved for the female dog for suppression of oestrus but have been used in clinical trials for reproductive control. Deslorelin is a reversible method for ensuring reproductive control and have less described side effects compared to other methods [4]. Since deslorelin is not authorized for use in female dogs, it is important to inform the owners of potential risks and side effects before implantation.

5.2.1. Oestrus induction in the bitch

Deslorelin implant have been researched for their possibility to induce oestrus in adult female dogs [16]. Oestrus can be induced due to the initial "flare-up" effect of the implant, which increases the level of FSH and LH [45]. The induction of oestrus can be indicated for primary anestrus, secondary anestrus and for bitches with prolonged interoestrus interval [45]. The protocols available for this type of treatment is the use of dopamine antagonists (cabergoline and bromocriptidine) and GnRH analogues such as deslorelin implant. For the induction to be successful, the bitch should be sexually mature, ideally be in the late anestrus phase and have progesterone levels of <1 ng/ml [16, 45]. This section will focus on the use of deslorelin implants.

The majority of the research found for this paper suggests that implantation of deslorelin should be placed subcutaneously on the ventral abdomen, by the post-umbilical region [16, 28]. This is to ensure easy removal of the implant. However, some research has also been done by using the medial side of the hindlimb as implantation site [72]. Various research concludes that prooestrus will be induced in the female dog within 1 week after implantation with deslorelin. Due to possible discrete signs of the impending heat, this process should be controlled one week post-implantation [16]. The majority of the papers described removal of the implant after detection of ovulation or 2-3 weeks after implantation if no ovulation is

detected [16, 45, 72]. Removal of the implant is done due to the risk of luteal insufficiency in the pregnant bitches and prolonged oestrus suppression in the non-pregnant bitch [16, 45]. If the bitch is confirmed to be pregnant there should be regular monitoring of the progesterone concentration throughout the pregnancy, to assess the luteal function [45].

The current research for induction of oestrus using deslorelin implants states that most dogs will exhibit signs of heat, but not all of them will ovulate. One study showed that ovulation was observed in 25 out of 32 bitches between 8-16 days after implantation [16]. The same study found that pregnancy was diagnosed in 18 out of 31 dogs. The number was reduced to 31 dogs since one dog did not allow mating and no artificial insemination was performed [16]. This study also found correlation between the time of ovulation and the pregnancy rates (figure 9). If the bitch ovulated within 14 days post-implantation they had a higher chance of becoming pregnant [16].

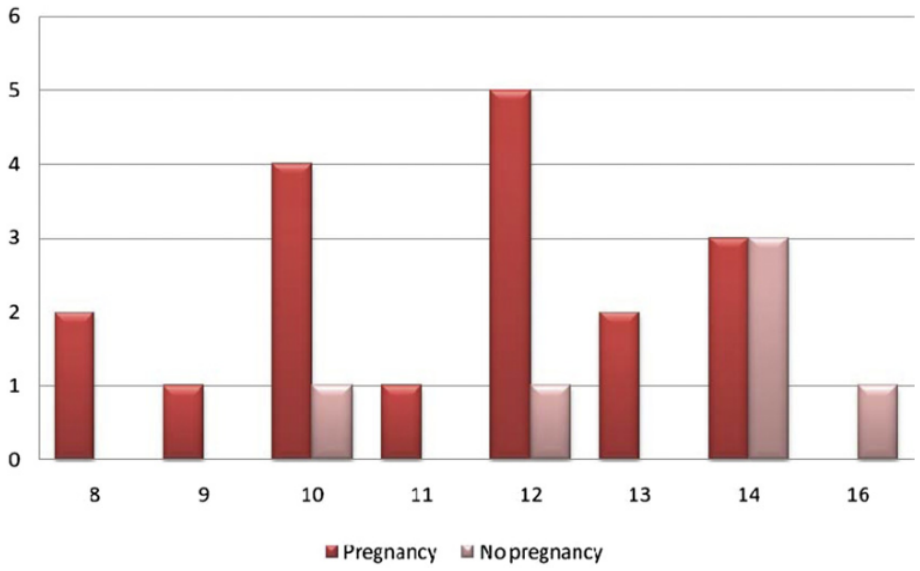

Figure 9: "Pregnancy status according to the interval between implant administration and ovulation". The Y-axis show the number of dogs while the X-axis show the days elapsed since implantation. [16]

5.2.2. Oestrus suppression

For suppression of the oestrus cycle in the bitch there are various drugs used throughout time. Progestins is one of the oldest and most widely, such as MPA, MA and proligestone. Androgens such as testosterone and mibolerone can also potentially suppress oestrus in the bitch, but is not so readily available in most countries [45]. Neither of these products should be used in prepubertal females and if used in a pregnant animal it can lead to masculinization of female fetuses [45]. Use of progestins, due to the progesterone effect, can increase the risk of dystocia [45].

Prevention and suppression of oestrus is deemed possible with deslorelin implants in clinical trials, as off-label use [43, 44, 60]. The deslorelin implant have been tested on fertile and prepubertal females in various trials [43, 62]. In fertile female dogs it will, in almost all cases, lead to an initial "flare-up" when first implanted during the stimulatory phase. Later the FSH and LH concentrations will reach base-level concentrations [45]. Prevention of this initial "flare-up" phase has been reported as a liability for the use of deslorelin implant as a contraceptive in female dogs. Various protocols have tried to prevent this reaction, such as implanting the bitch when in dioestrus. The female dog should undergo a thorough clinical and reproductive examination before implantation to be able to exclude existing ovarian or uterine pathology [4].

The duration of the oestrus suppression varies greatly among each individual and has a range from 2 months up until 27 months depending on the implant dose [44, 70]. Side effects after implantation is rarely described if this method is used in well selected patients. The side effects reported are persistent oestrus, lactation and behavioral changes and ovarian cysts. These side effects usually resolved within 15 days according to the majority of the published articles for this subject [43, 45], even though some individuals needed to undergo ovariectomy or ovariohysterectomy to resolve the side effects [3, 60]. Before implantation the owner should have a thorough discussion with the veterinarian about the possible side effects.

Puberty is defined as the process of physical changes when the animal matures into an adult and is capable of sexual reproduction [32]. In female this refers to the onset of the first oestrus. One article states that this definition is not complete, since it is found that puberty in the female probably starts earlier due to marked follicular growth, changes in vaginal cytology and increase in steroid hormone production or its precursors dehydroepiandrosterone (DHEA) [21].

There have been studies performed for the use of deslorelin implants in prepubertal females as well. In these studies, there are great variability of the study designs in regard to what is deemed prepubertal. There are also various definitions of the "flare-up" effect in these studies, ranging from increased cornification of superficial cells and serum-estradiol concentrations to vulvar swelling and vaginal discharges [62]. Most of these studies indicated that the "flare-up" effect could be avoided if the female dog is implanted at the age of 4 months [43].

Body development has been a topic of discussion for the use of deslorelin implants in prepubertal females, since prepubertal gonadectomy have been indicated to cause delayed

growth plate closure and extended growth periods in young, neutered animals [61]. Findings in regards to epiphyseal closure and body development when using deslorelin have concluded that either neither of these were impacted by the implant, or that the epiphyseal plate closure could be delayed but without any clinical impact [38].

In the studies, the time to puberty varied greatly and ranged from 9 to >25 months, and some individuals experienced an even longer suppression. For the females it is also difficult to determine if there is any form of dose-efficacy relationship, since the duration of efficacy is similar for the two implant doses (4.7 mg and 9.4 mg) [62].

The return of oestrus activity and cyclicity after treatment with deslorelin implants have been researched in various papers as well. These studies investigated the macroscopic and microscopic in the uterine tissue, and there was no influence on the cyclicity of the females investigated [37, 39]. Enzymes and hormones involved in the formation of CL and its function were also investigated and no long-term effect on the luteal function were observed during the first estrus. The enzymes investigated were steroidogenic acute regulatory proteins (STAR= and 3β-hydroxysteroid dehydrogenase (3βHSD), where the latter one was found to be increased in the prepubertal females treated with deslorelin [37]. P4 measurements were found to be normal during metoestrus following the first oestrus. The same study concluded that GnRH-R did not undergo significant changes in the first cycle after suppression [37].

5.2.3. Treatment of dermatological conditions

Various factors can influence the hair growth and quality in dogs, such as genetics, environmental factors, and the diet. Hormones, which includes androgens, oestrogens and prolactin, also influences this process [50, 67]. Certain breeds have a predisposition for spaying-induced coat changes. These changes involve increase of wool hair and decreased color intensity. The growth cycle of the coat consists of 3 phases: the growing (anagen), regressing (catagen) and the resting phase (telogen). This study aimed to see if the anagen: telogen ratio was impacted by spaying and GnRH treatment. One theory for the altered coat after spaying, suggests that the increased plasma level of FSH and LH during anoestrus, can contribute to this phenomenon. This study is performed on female dogs before and 1 year after spaying, and spayed dogs before and after GnRH treatment [58]. The owners of 14 dogs in this study had reported of altered coat characteristics after spaying. These dogs received treatment with deslorelin-acetate and were examined 8-16 weeks after treatment. In this instance, three of the dogs showed no improvement after treatment, while the remaining 11

dogs showed improvement. All dogs involved in this study has variable duration of effect for the coat improvement, ranging from 4-6 months [58]. In the group controlled 1 year after spaying, the anagen: telogen ratio was greatly increased, compared to before the procedure. This study showed that GnRH treatment did not impact the ratio of anagen and telogen follicles, when comparing the dogs that presented with improved coat quality after GnRH treatment and those who did not respond to treatment. They did however, show a higher percentage of catagen follicles after treatment [58]. The same study found a weak positive correlation between the LH concentration and the percentage of anagen follicles. Even though the study concluded that coat changes can be successfully treated with GnRH analogues, it is unclear how the underlying pathomechanisms are correlated for this change to be successful [58].

5.2.4. Treatment of urinary incontinence

Urinary incontinence can be a possible side effect of OE and OHE in the bitch. This side effect causes involuntary loss of urine. [1]. The percentage of dogs experiencing this side effect can be as high as 20% and will usually present itself within 3 years of the surgery and usually occurs when the dog is relaxed or sleeping [57]. This long period from the procedure to the onset of the urinary incontinence made it difficult to see the connection between the two [55]. The precise pathomechanism of urinary incontinence after spaying is not fully understood, but it is known that the urethral closure pressure is reduced significantly [55]. Another theory for urinary incontinence occurring after spaying is the lack of endogenous oestrogen after spaying, so oestrogen therapy was first suggested as therapy for this condition. Only 65% of the bitches showed improvement to this type of therapy [30]. Another possible cause of this can be the elevated concentration of FSH and LH, which can directly or indirectly, influence the sphincter muscle of the urethra [56]. Treatment consisting of deslorelin implant can cause a long-term reduction of the circulating FSH and LH. The dose of this implant was 5 mg and 10 mg. Some dogs were treated with both deslorelin and phenylpropanolamine [56]. Treatment with GnRH analogues showed great effectiveness even though the effect of the treatment varied greatly. The effectiveness of deslorelin ranged from 61-738 days in the dogs treated [56].

One paper from 2014 states that alpha-adrenergic agonists shall be used as the first line therapy for the medical control of this condition and that the success rate varies from 86%-97% for PPA, and the use of oestrogens in combination potentiated the effect in females not responsive to PPA alone [55]. The use of this drug is contraindicated if the patient has

increased blood pressure, kidney diseases, heart problems or suffers from glaucoma [5]. This paper suggested that deslorelin implants (4.7 mg) should be used in females showing serious side effects due to alpha-adrenergic agonists or if these were contraindicated in any way, which was deemed successful in 50% of the cases. It is also advised to use deslorelin in combination with the alpha-adrenergic agonist if deslorelin is not sufficient on its own [55]. One case study investigated the use of deslorelin implant (9.4 mg) in a 1-year-old female Golden Retriever bitch. This dog had struggled with urinary incontinence since a very young age and was diagnosed with dilated ureters, where the left ureter was more dilated compared to the right one [26]. The left ureter was corrected surgically, and OHE was performed at the same time at the request of the owner. 20 days postoperatively, the owner reported a 50% improvement in the urinary incontinence of the dog. A 9.4 mg deslorelin implant was administered s.c. in the interscapular region and the ureters were monitored by radiography and ultrasound each month after implantation. After 8 months it was reported that the urinary incontinence has disappeared completely [26].

5.3. Off-label use of deslorelin implants in the tom cat

5.3.1. Suppression of reproductive function

Traditionally the most common method of preventing reproductive function in tom cats is surgical gonadectomy. In some cases, this may not be possible, for example if the cat has increased anesthetic risk or in areas where surgical facilities are not readily available [15]. It may also be an option of the cat is supposed to be used for breeding purposes at a later time [23]. Progestins have been used as an alternative option for surgical castration previously, and in tom cats they can suppress sexual behavior. For long term use, this type of treatment can cause various side effects such as feline fibroadenomatosis and diabetes mellitus. The effect on semen quality is also not well documented [23]. Deslorelin implants in cats shows a biphasic response, as in dogs. There is an initial stimulation period before reaching the long-term suppression phase. Efficacy of the implant is measured using indirect markers such as testosterone, testicular size, body weight and behavior [23]. One study was performed using Suprelorin ® 4.7 mg implant in 10 European Shorthair tom cats. The cats age range was from 1 to 6 years old, and the implant was placed s. c in the neck [23].

The cats underwent blood collection two times weekly for a total of 4 weeks until implantation. Blood samples were taken every 24 hours from two days before implantation until five days after implantation. This was to monitor the initial effects of GnRH release on the testosterone secretion, before the interval was gradually decreased until the end of the monitoring period (figure 10) [23]. This paper set a testosterone concentration of <0.1 ng/mL as indication for a complete downregulation of testicular function.

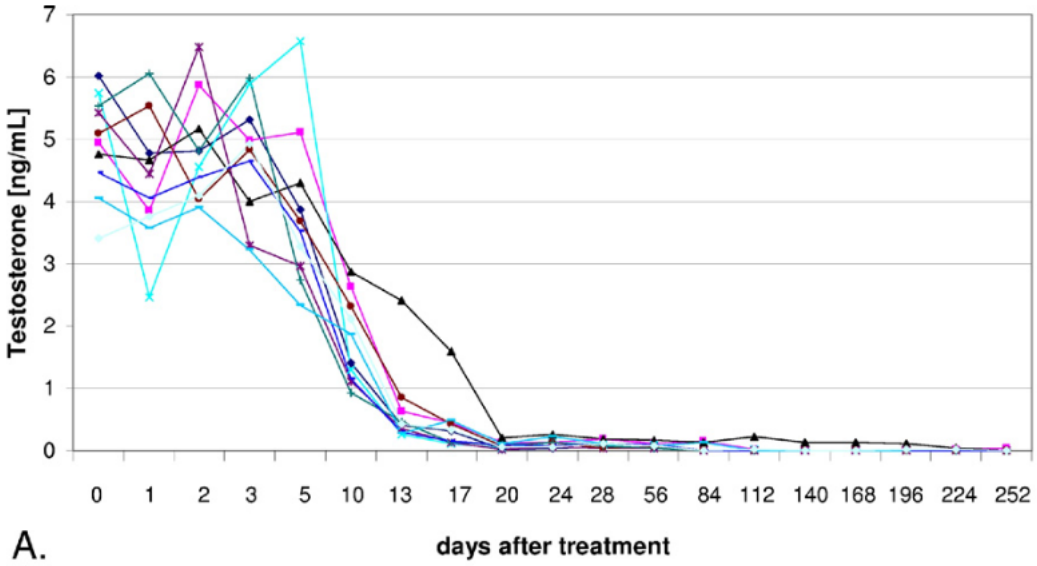

Figure 10: Individual course of testosterone concentration during treatment period. [23]

Blood samples obtained before implantation showed that the testosterone concentration ranged from 0.11-13.34 ng/mL, while the mean concentration was 4.11 ng/mL. Some cats showed a slight increase in testosterone concentration for a few days after implantation, which is consistent with the knowledge currently obtained for dogs [66], but not as significant. Inhibition of testosterone concentration were observed in all but one cat from day 20 after treatment. This complete downregulation lasted for more than 6 months in 9 tom cats [23]. One of the cats involved in this study mated an oestrus queen at day 20 post implantation. This resulted in a successful pregnancy which were detectable via ultrasound, even though this individual had a testosterone concentration at the lower limit of detection. Abortion was induced after detection on the queen. Since the mean duration of spermatogenesis in the tom cat is 46.8 days [18], they believed that the release of previously produced spermatozoa, when the testosterone concentration was higher, to be the cause of this successful mating [23]. This study concluded that Suprelorin ® can be used as alternative to surgical castration, all though the onset of infertility and duration of effect varies greatly for each individual.

5.4. Off-label use of deslorelin implants in the queen

5.4.1. Suppression of reproductive function

Suppression of the reproductive function in female cats is a huge topic in veterinary medicine, due to the increasing number of stray cats worldwide. This again can cause increased incidences of transmission of various diseases to humans, other pets and wildlife [68]. Traditionally the surgical OE/OHE have been used for suppression of the reproductive function in cats, but as mentioned in previous sections, this option may not be as readily available in all parts of the world [15]. Another possible setting where deslorelin implants may be used is in breeding populations, so a need for reversibility is a key issue. Regarding medical contraception in female cats, several questions have been raised. These includes the potential of oestrus induction, reversibility and if fertility is completely regained after the end of the efficacy period [24].

One study included 20 female cats (European Shorthair) known to be healthy due to previous examination and blood sample collections. Their age ranged from 2 to 5 years, and all animals were known to cycle regularly prior to the study [24]. This study aimed to investigate the effects of the 4.7 mg Suprelorin ® implant produced by Virbac. This study used hormonal changes of progesterone and estradiol as efficacy parameters (figure 11). The lower limit of detection were 0.1 ng/mL and 20 pg/mL, respectively [24]. They were grouped into group A and group B according to clinical signs. Group A were treated when in oestrus and group B underwent treatment 7 days after the end of oestrus.

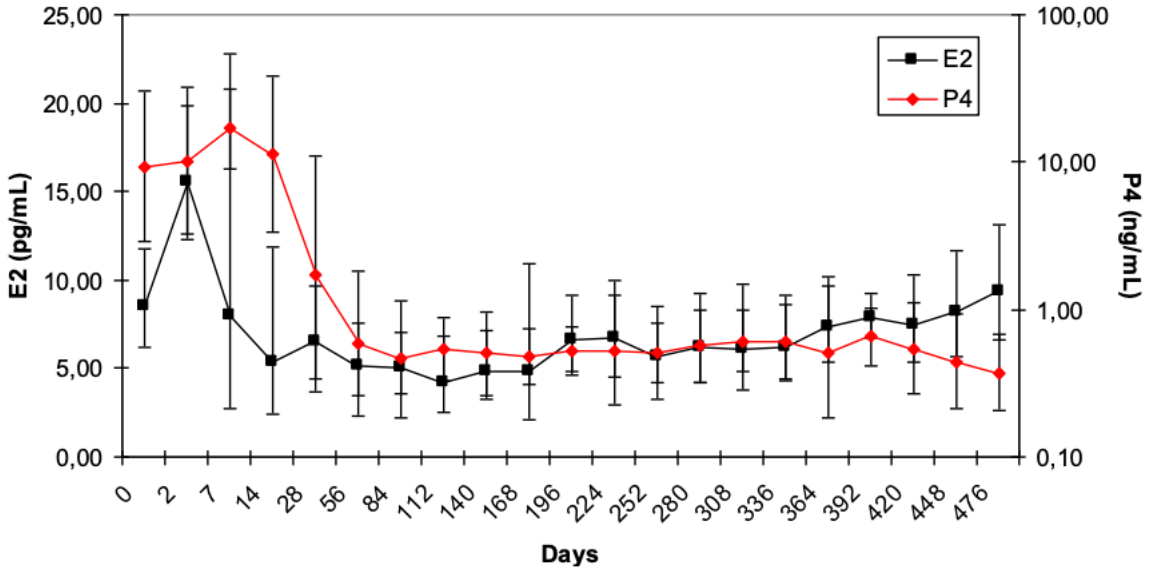

Figure 11: Hormonal changes of E2 and P4 for group B. [24]

Most cats treated in group A showed a significant increase in progesterone concentration which lasted until 28 days post-implantation, before reaching basal level on day 56. Estradiol reached basal concentration after 14 days. The estradiol concentration remained at this level until the end of the observation period. One cat in group A had basal levels of estradiol on day 7 after implantation. For group B, most of the cats had basal progesterone concentration at the time of implantation, all though it increased the week following implantation, while reaching steady basal level at day 56 post-implantation. Estradiol concentrations were slightly increased immediately following implantation, but decreased at day 7 and were at basal level for the rest of the observation period [24]. The duration of efficacy of the cats involved in this study ranged from 483 to 1025 days, and the mean duration were reported to be 680 days. To assess the fertility of the cats after treatment 8 queens were mated after the end of the efficacy period. All of them mated, while 7 of the 9 cats became pregnant and the litter size varied from 1 to 5 kittens. The length of efficacy was noted to be 7.5 to 14 months, since the first estradiol peak (>20 pg/mL) occurred during this time. This study also concluded that the time of implantation regarding the stage of cycle were not related to each other [24].

5.4.2. Postponement of puberty

Due to surgical gonadectomy not being an option for some cat owners and especially cat breeders, there has been increased attention for non-invasive and reversible methods for reproduction control over the last years [6].

One study focusing on this topic has a sample size of 9 European Shorthair prepubertal queens aged from 3-9 months old. All deemed healthy through clinical, hematological, hormonal tests and vaginal cytology. After implantation they underwent clinical examinations and blood collection every month [6]. This study used the 4.7 mg Suprelorin ® implant from Virbac. During this study the queens were living at home with their owners which lasted for a total of 18 months and queens not showing oestrus behavior after this time has a monthly phone consultation after this. Hematological parameters in this study involved P4 and E2 concentrations, where the minimum detectable concentration was set to 0.2 ng/mL and 20 pg/mL, respectively. Puberty was defined at the period where persistent, long-lasting oestrus behavior was initially displayed, along with fully keratinized vaginal smear and interest for breeding tom cats [6].

During the monitoring period 5 out of 9 queens either died, got lost or underwent OE at owners request. Out of the four remaining queens owners reported to observe oestrus behavior between 21 and 36 months of age (figure 12).

ID	Age at study onset (months)	Date at treatment onset	Duration of study: months of sampling (+ owner observation)	Still prepubertal at age (months)
1	8	Jan 2008	18 (+10) = 28	36
2	8	Jan 2008	7	15*
3	8	Jan 2008	7	15*
4	9	Jan 2008	18	27†
5	3	Jul 2008	11 (+ 5) = 16	19‡
6	3	Jul 2008	11 (+10) = 21	24
7	7	Oct 2008	8 (+10) = 18	25
8	7	Oct 2008	8 (+ 9) = 17	24§
9	5	Jan 2009	6 (+10) = 16	21

*lost to follow-up
†died from a feline leukaemia virus infection
‡died following a car trauma
§ovariectomised at owner's request

Figure 12: Table showing identification, age at study onset and total duration of observation. [6]

Hormonal levels during the study fluctuated between 0.2-1.2 ng/mL for P4 and <20-120 pg/mL for E2, but generally remained at or very close to basal concentration [6]. All remaining queens had successfully delay of the onset of puberty and the study concluded that if puberty delay is the main goal the queen should be implanted before reaching 8 months of age, ideally at 3-5 months of age. Return to fertility was not investigated in this study [6].

5.4.3. Post-spaying urinary incontinence

One case study involving a Norwegian Forest cat, which were diagnosed with acquired urinary sphincter mechanism incompetence after spaying was published in the Journal of Feline Medicine and Surgery [53]. Treatment of this condition is described in the literature for dogs, but not for cats. Since deslorelin implants have been proven to be effective for this condition in dogs, it seems logical to try the same type of treatment in queens as well.

Prior to implantation the queen was thoroughly examined for other conditions which could explain the urinary incontinence and to rule out UTI. The examination methods included basic clinical examination, ultrasound of the urinary tract along with cystocentesis. Blood samples were also collected for a complete hematological evaluation, along with measurements of E2, P4 and FSH. E2 and P4 plasma levels indicated that the cat was in anoestrus, while FSH was corresponding to data previously reported for spayed queens. Urinary culture showed a low number of colony forming units of E. coli. This queens was treated with marbofloxacin (2 mg/kg/q12h for 8 days), which was extended for 5 more days after follow up examination [53]. After completion of the antibiotic treatment the owners

reported no improvement of the urinary incontinence. Neurological examinations were also performed without detecting any abnormalities [53]. Owners were recommended deslorelin implants due to the proven effectiveness in dogs and owner gave written consent. The deslorelin implant (4.7mg) were then inserted in the right pre-scapular region according to label instructions [53]. Clinical follow-up examinations were performed at day 8, 15 and 30 post-implantation. At day 8 and 15, the queen was still incontinent, but US, urinalysis and urine culture did not show any abnormalities. At the follow-up on day 30, the owners reported that from day 20 the pillow the cat used to sleep on were no longer wet, even though the cat bas still showing mild urinary dribbling and from day 25 the urinary continence was restored [53]. The patient was followed up by monthly via telephone the following year and the queen was still continent and continued to be so up until the time when the case study was published (15 months after implantation) [53].

6. Discussion and conclusion

The use of GnRH analogues, such as deslorelin implants, are widely used today in veterinary medicine. In the European Union the deslorelin implants are licensed for suppression of reproductive ability in male adult dogs and ferrets, and recently Suprelorin ® received an extension of its marketing for use in tom cats and prepubertal bitches [14]. Deslorelin implants are proven to suppress the pituitary-gonadal axis for a longer period, depending on the dosage of the implant. The effect is also proven to be reversible, although some individual differences are to be found regarding the time from when the implants lose its effect or is removed, until normal fertility is achieved [42].

Postponement of puberty in male dogs is deemed successful, but to reduce the incidence of the "flare-up" effect, the implantation should occur at the age of 3-4 months old [62]. In both studies found for this topic, the implant did not affect the body development of the puppies, but further studies regarding the impact on bone and/or epiphyseal closure should be investigated [62, 64]. The studies performed on this topic is consisting of a small number of dogs, a larger pool of animals should be considered to give more weight to the usage of deslorelin to postpone puberty.

For treatment of behavioral problem in male dogs, deslorelin implants should be considered if the behavior can be linked to testosterone production, such as hypersexuality, territory urinary marking and intermale aggression [22]. For usage of deslorelin implants in this type of behavior it is important to distinguish the behavior exhibited due to testosterone production and fear mediated aggression [17]. If used for unwanted behavior linked to a type of behavioral disorder, the usage can be contraindicated. Providing thorough information to the owner is important so that an informed consent may be given. Deslorelin implants may be a good indicator to observe the behavior in the dog before a permanent, surgical castration is performed, especially due to its reversible nature [9].

Benign prostatic hyperplasia is a common diagnosis, especially in older male dogs [13]. The treatment of choice is usually surgical castration, but deslorelin may be an option if the dog, for various reasons, is not a candidate for surgical castration. Deslorelin will cause a reduction in prostatic size, but the reduction will take longer time compared to osaterone-acetate (Ypozane ®) [49]. All though the reduction of the size is slower, the duration of effect is proven to be more long lasting with deslorelin. A combination of both drugs may therefore be suitable for treatment of BPH if the animal is not a candidate for surgical castration [49].

Benign adenomas of the perianal region are strongly linked to sex steroid hormones [46]. Since the most common treatment for benign adenomas is surgical castration [73], usage of deslorelin implants should most likely lead to the same results, since both options will reduce the amount of testosterone circulating. Deslorelin may also be used to reduce the size of the tumor before surgical removal if surgical castration is not an option [46]. Few studies have been done on this topic, so further studies may provide further information about the success and potential errors of this option.

For dermatological conditions such as hair cycle arrest (Alopecia X) the deslorelin implants have been suggested as a treatment option. Since the pathogenesis of this condition is not fully understood, the treatment is not complete either [2]. Reports have suggested that male dogs previously have responded nicely to surgical castration. Use of deslorelin as treatment for this condition may be reasonable, due it being non-invasive and low risk of side effects, if the owner rejects surgical castration as a treatment option [2, 40].

Induction of oestrus in the bitch have been researched. This is possible due to the initial "flare-up" effect of deslorelin [16]. Most research states that oestrus should be induced within 1 week of implantation. Placement of the implant should be taken into consideration since it must be removed due to the risk of luteal insufficiency. It is recommended to place the implant ventrally on the abdomen [16, 28]. The bitch should also have regular progesterone measurements throughout the pregnancy [45].

Suppression of oestrus in prepubertal bitches are now possible with Suprelorin ® due to the extended marketing provided in the European Union in July 2022. For adult bitches suppression of oestrus is also possible. All ages should undergo a thorough physical examination before implantation [45]. The duration of effect has a large range, depending on the dose. Side-effects are rarely described in well selected patients [43, 45].

Surgical gonadectomy may lead to coat changes in bitches. A leading theory for this phenomenon is the increased level of circulating FSH and LH [58]. The study found for this topic did not consist of a large pool of candidates, but they did have thorough controls, since dogs were evaluated before spaying and one year after, as well as after treatment with deslorelin after spaying. Many dogs in this study showed improvement regarding the hair coat, but for various durations. Hair follicles were investigated and showed higher percentage of catagen follicles [58]. Due to the pathomechanism being unknown for the success, deslorelin may still be a readily available, low-invasive treatment method for this condition in bitches.

For treatment of post-spaying urinary incontinence, which has been linked to increased circulating levels of FSH and LH in a study, deslorelin may be a treatment option [56, 57]. Especially due to the product being non-invasive and readily available. Thorough communication with the owner should be provided regarding to the possible success and the duration, since the latter varied greatly in the studies compiled in this paper. Deslorelin can also be used in combination with alpha-adrenergic agonists, such as PAA, if this is not contraindicated in the patient [55].

Use in tom cats are now possible with Suprelorin ® in the European Union, as of July 2022. The use of deslorelin in tom cats can be a great option for breeders which would like to use the male for breeding in the future, but at the same time try to avoid unwanted mating until the time is ready [23]. Information should be provided to the owners of this type of treatment, due to the cat not being infertile straight away, so that precautions are taken in the meantime [23].

Since the cat population increases globally, deslorelin implants have been suggested as a contraceptive for queens where OE/OHE is not possible due to various reasons. It may also be an option for breeders, as mentioned previously, to avoid unwanted pregnancies. The studies found for this paper included a limited number of animals, so a larger pool for further studies may be suggested. Thorough sampling was done throughout the duration of the study, and the queens acted as their own control. For usage in catteries, the owner should be informed about the variations in duration of efficacy, so that an informed decision can be made [24]. Further research would also be beneficial to evaluate fertility parameters after removal of the implant or when the implant ceases its function [24].

For postponement of puberty in cats the sample size in the studies was not the largest as well, but the cats involved were thoroughly monitored. Due to the reversibility, it can be a suitable option for breeders [6]. Because of this the placement of the implant should be ventrally on the abdomen, close to the umbilicus, to facilitate easy removal [6].

Post-spaying urinary incontinence is not a commonly reported condition in cats. Only one case report was found for this topic, but due to it being a successful treatment in dogs, the same principle can be applied in cats [53]. Again, the treatment is readily available and non-invasive, so this should be considered as a way of treatment if the condition occurs in a cat [53].

Deslorelin implants, due to their availability and non-invasive nature can be considered as a treatment option for conditions where surgical gonadectomy has been proven successful previously. It has a limited amount of reported side effects, and the results is similar to

surgical gonadectomy [42]. A larger number of studies should be performed for the various topics, and for dermatological and urinary incontinence the impact may be greater and more easily understood if the pathomechanisms of these disorders will be discovered.

7. Summary

The main focus area for this paper was to investigate the off-label applications of deslorelin implants in dogs and cats of both sexes. As well as highlighting the large diversity of conditions that can benefit from the usage of deslorelin as a treatment option in clinical practices, due to the product being readily available and low-invasive.

Deslorelin, a GnRH-superagonist which has a receptor affinity that is 100x greater than endogenous GnRH. Its function is to provide constant exposure of GnRH to the pituitary gland, which will lead to a desensitization, leading to a drastic decrease of circulating LH and FSH. The product was commercially available in 2007, for male dogs and ferrets for reproductive control and is available as 4.7 and 9.4 mg doses. Recently it was approved for use in tom cats and prepubertal bitches. It has a low number of reported side effects, and its application is non-invasive. In later years, off-label applications of deslorelin implants have been researched both in dogs and cats, male and female. Several conditions have been considered, and especially those were surgical gonadectomy have been a treatment option previously. Proper patient examination and selection is important when using deslorelin as an off-label product, as well as providing detailed information to the owners, so that they can make a well-informed decision.

To summarize, deslorelin is a great option where surgical gonadectomy is not performed or rejected by the owner for personal reasons. Deslorelin will also give a good indication for what results should be expected before a surgical gonadectomy is performed.

8. References

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Name of student: Anja Allum Steinsholt

Neptun code of the student: B63IZ4

Name and title of the supervisor: Dr. Linda Müller, PhD, Assistant Professor

Department: Department of Obstetrics and Food Animal Medicine

Thesis title: Clinical application of deslorelin implants in dogs and cats

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2021	04	28	Choosing the right topic	
2.	2021	09	19	Topic, Thesis announcement form	
3.	2022	06	04	Methods of literature research	
4.	2022	07	04	Formal requirements	
5.	2022	08	31	Materials and methods	

Grade achieved at the end of the first semester: .....5.....

Consultation – 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2022	09	04	First draft	
2.	2022	10	11	Implemented second version	
3.	2022	11	08	Last version	
4.	2022	11	12	Last corrections	
5.	2022	11	14	The requirements of the presentation	

Grade achieved at the end of the second semester: .....5.....

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

.....
signature of the supervisor

Signature of the student: .....

Signature of the secretary of the department: .....

Date of handing the thesis in.....18 November 2022