

# Medical control of reproduction in the male dog with deslorelin subcutaneous implants



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## Abstract

Slow-release subcutaneous implants containing GnRH agonist deslorelin were released into the European market in 2007. Since then, they are widely used per label by European veterinarians for the prevention of fertility in adult male dogs. Additionally, they are also used 'off-label' to postpone puberty, reduce unwanted behavior potentially linked to testosterone, eliminate clinical signs induced by benign prostatic hyperplasia, reduce the size of perianal adenomas, or reverse hair loss due to alopecia X in intact male dogs. After an initial 'flare-up' effect (short-duration increases in blood testosterone concentrations immediately after implantation) there is a perceptible decline in testosterone concentrations within a few weeks, due to pituitary downregulation. The dog becomes 'medically castrated' and infertile, with a reduction in testes size and spermatogenic arrest. Normal plasma testosterone concentrations are recovered in 18 months in 98% of dogs and reimplantations are possible for life. Preferably, reimplantation should occur prior to disappearance of previous implant action to avoid another 'flare-up' effect of reimplantation. After loss of implant function, it usually takes 1 - 2 months for complete sperm quality restoration before dog is potentially fertile again.

**Keywords:** Male dog, fertility control, prostate, unwanted behavior, hair loss, deslorelin

## Introduction

Since 2007, the release of subcutaneous implants containing a GnRH superagonist (deslorelin) into European market has led to several changes in veterinary practice regarding approaches to fertility control in the male dog. For example, France is a country with a 'Latin spirit', where many owners do not like the idea of having their male dog castrated. More and more owners are also reluctant to seek a surgical procedure for their pet that is perceived as mutilation, a source of suffering, and considered as potentially risky because it requires general anesthesia. In some Northern European countries or in Germany, there are now many male dogs that are first 'implanted' to test the effect of a potential surgical orchidectomy that could be subsequently performed. In this article, we review the potential uses of deslorelin subcutaneous implants in male dogs and share our experience at Alfort National Veterinary College, Paris.

### Mode of action of slow-release deslorelin implants

GnRH, a decapeptide with a highly conserved structure in vertebrates, is the key hormone in mammalian reproductive function. Secreted in a pulsatile manner in the hypothalamo-pituitary portal system and transported to the pituitary gland where it releases gonadotropins (FSH and LH) into systemic circulation. Gonadotropins stimulate production of steroids

by the gonads, mainly testosterone in males, and estrogen in females and in males. The pulsatile secretion of GnRH is the real conductor of reproductive function. More than 2000 GnRH agonist and antagonist molecules have been synthesized in the last 30 years. These compounds are used in human medicine and in veterinary medicine, but mostly in large animals (rarely in carnivores). Whereas the use of GnRH antagonists in veterinary medicine is complicated and costly,<sup>1</sup> the agonist forms have been widely used. Their mode of action depends on treatment conditions: a single injection stimulates pituitary gonadotropins and, consequently, sex steroid hormones, whereas treatment over several days leads to secondary desensitization of gonadotropic cells that prevents secretion of FSH and LH and 'silences' the pituitary-gonadal axis. This desensitization is due to a postreceptor mechanism that induces an arrest of the synthesis of the subunits LH $\beta$  and FSH $\beta$ .<sup>2</sup>

Regarding deslorelin, modifications in the initial sequence of the amino acids of GnRH make this molecule a super-agonist; its stability is increased and its binding affinity for specific GnRH receptors is increased 7-fold.<sup>3</sup> The implant, the vector of the molecule, is composed of a lipid matrix (triglyceride) that does not pose any biocompatibility problem. Subcutaneous implantation using an implanter the size of a microchip allows continuous release of deslorelin.

Two implants are sold to veterinarians in Europe for veterinarians, with label indications for the suppression of fertility in male dogs: Suprelorin 4.7 mg® and Suprelorin 9.4 mg® (the latter is also authorized for male ferrets).<sup>4</sup> These implants have a minimum duration of efficacy of 6 months for the former and 1 year for the latter. However, the initial release kinetics of the product from the implant matrix are different in these 2 products, and the ‘castrating’ effect is more rapidly obtained with the 4.7 mg implant than with the 9.4 mg implant. Therefore, we recommend an initial implantation with a 4.7 mg implant, followed by an optional reimplantation 6 months later with either a 4.7 or a 9.4 mg implant. The dog can thus be reimplanted, for example every year, and thus ‘chemically castrated’ throughout its life.<sup>4</sup>

### Action of deslorelin implants on testosterone in male dogs

Often, the implants are easily placed under the skin in the inter-scapular area, without clipping. After implantation, deslorelin stimulates the pituitary secretions of LH and FSH; this initial ‘flare-up’ effect causes a transient increase in testosterone concentrations that may be accompanied by a slight increase in the dog’s activity and/or urinary marking.<sup>3</sup> This initial ‘flare-up’ effect is often mentioned and feared by veterinarians and owners, but it seems to be extremely short with deslorelin implants. In a study with frequent sampling, testosterone concentrations increased 20 minutes after implant (6 mg deslorelin), reached peak concentrations at 40 minutes, and at 5 hours the concentrations were not significantly different from before treatment or from control dogs treated with a placebo.<sup>5</sup> The castration effect occurs in a second phase; testosterone concentrations become basal in ~ 80% of dogs < 20 days after implant.<sup>6</sup> After

an initial ‘flare-up’ for 2 - 3 days, testosterone concentrations decreased substantially and remained closer to 0 for 200 - 400 days, whereas the dog with a placebo implant had normal testosterone concentrations (Figure). Diminishing effectiveness of the implant is evident by the progressive resumption of testosterone secretion. Normal plasma concentrations recovered in 18 months after implantation of a 4.7 mg implant in 98% of dogs. However, the inhibitory effect lasts an average of 10 months in medium and large dogs and 13 months in small breeds.<sup>6</sup> Miniature breeds (chihuahua, miniature pinscher, pomeranian, toy poodle, etc.) may have more prolonged inhibition, occasionally almost definitive. Therefore, owners should be advised of this in case they wish to breed these dogs in the future (Virbac, unpublished data).

### Clinical modifications after implantation

After implantation, most studies observed a decrease in the volume and consistency of testes. In general, testicular volume decreased ~ 3 times 5 weeks after implantation.<sup>5</sup> Regarding eventual behavioral changes, it has similar effects as surgical castration. In particular, some dogs may experience an increase in appetite that presents a risk of weight gain. Nutritional advice is therefore essential. Also, as with surgical castration, the effect on certain behaviors is uncertain, such as roaming, attraction to estrous bitches, mounting people’s legs or other dogs and urinary marking.<sup>7</sup> In 50 - 60% of cases, these annoying behaviors are improved but rarely completely eliminated. Aggression towards other males is most often substantially reduced. Treatment with deslorelin implants improved 4 behavior problems in male dogs (roaming, dominance, urine marking, and mounting) in 50% of male dogs.<sup>8</sup> These authors suggested that sterilization

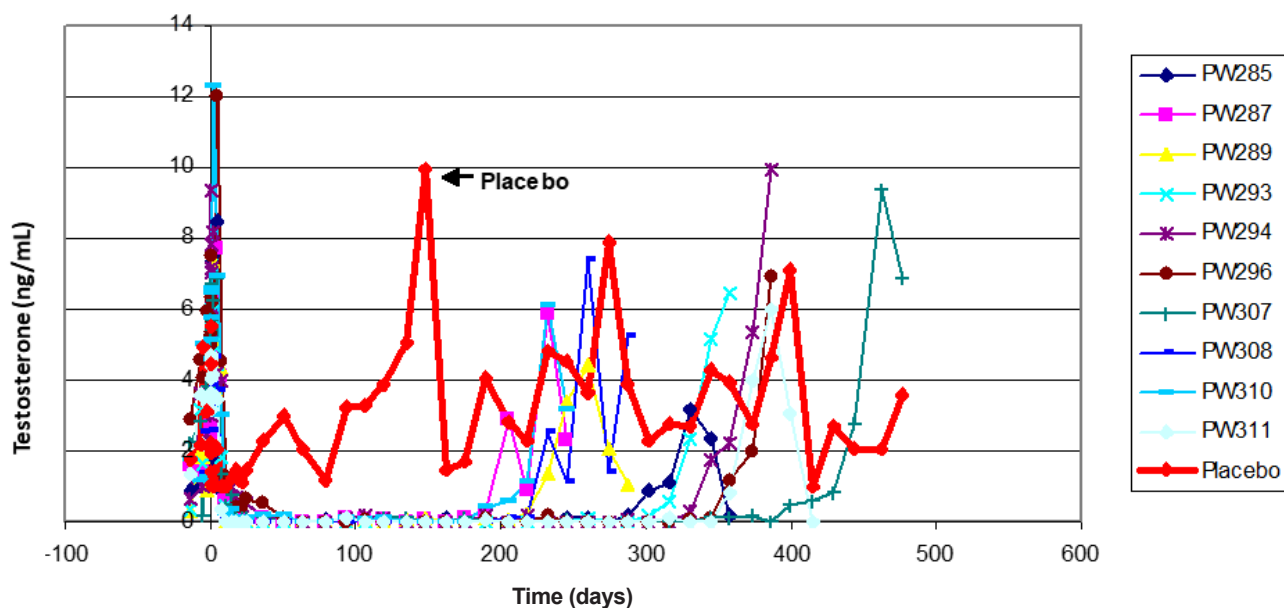


Figure. Testosterone concentrations in 10 dogs (PW 285 to PW 311) that had a 4.7 mg deslorelin implant (time 0); data from Virbac Corporation, used with authorization.

obtained with these implants might accurately predict changes that can be expected after surgical castration in individual dogs that was confirmed in an another study by the same group.<sup>9</sup> Behavioral disorders in male dogs improved after treatment with implants containing azagly-nafarelin (another GnRH agonist that has not been commercialized).<sup>10</sup> However, some dogs had temporary increases in 1 of 4 behavior problems during the first few days after implantation,<sup>8</sup> probably due to the initial rise in testosterone concentrations. As no clear protocol is currently described to avoid potential side effects linked to the initial rise in testosterone concentrations, this indication should be applied with great care.

A recent study<sup>11</sup> was conducted in Swiss military dogs to assess their working abilities compared to intact males via a standard behavioral test series for Swiss military dogs (obedience, protection of the handler against an attacker, searching for a hidden person in a building, and reaction to social environment during a city walk). Treatment with deslorelin in these military dogs had no measurable effect on any of the test situations compared to intact males.

In order to obtain continuous medical castration, a new implant must be placed, ideally while the current implant is active. It is not advisable to wait to reimplant until testes increased in size.<sup>4</sup> Waiting too long to reimplant will generate a new transient stimulating effect of 'flare-up' and the increase in testosterone concentrations may lead to undesirable male behavior for 1 - 2 weeks. If testes have already increased in size, use a 4.7 mg implant. To avoid owners forgetting reimplantation, many veterinarians use software to automatically send reminder letters or e-mails regarding reimplantation. Note that the matrix of the implant is biocompatible and it dissolves very slowly. Therefore, it is not necessary to remove the implant and furthermore reimplantation is required only after several months.

### Effects on fertility

There is a decrease in the number of sperm in the ejaculate. After an average of 4 - 6 weeks of treatment, the dogs become azoospermic. The transition to azoospermic state is however progressive with increased teratozoospermia. After a deslorelin implant, percentage of sperm with abnormal morphology, mainly tail abnormalities, may increase from an average of 7 - 70% in 35 days.<sup>6</sup> However, teratospermia was not observed<sup>12</sup> and veterinarians should be aware of the risk of fertile matings within 1 month after implantation. After 5 weeks, dogs usually have atrophic and aspermatogenic seminiferous tubules, with spermatogenesis blocked at the spermatogonial stage.<sup>13</sup> At the end of action of the implant, testicular histological architecture is restored and it takes 7 - 9 weeks, the duration of spermatogenesis, for sperm to appear. After initial implantation, it usually takes another 1 - 3 months for sperm quality to be completely restored before the dog is potentially fertile again.<sup>6</sup> However, to the best of our knowledge, there are no published studies on potential for complete recovery after successive implantations.

### 'Off-label' potential indications of deslorelin implants

#### Postponement of puberty

Early-age neutering is an effective technique for canine population control; however, surgical neutering may not be possible in various situations. Eleven dogs, 4-month-old, were implanted with 4.7 or 9.4 mg deslorelin, or placebo<sup>14</sup> and their sexual behavior and testicular size monitored every 2 months. Ejaculates were collected and evaluated at 8, 12, 15, 18, 24, 30, 32, 34, and 36 months of age. Most dogs (3/4) implanted with 4.7 mg deslorelin had normal male sexual behavior at 34 months. From this group, 2 dogs had normal semen quality whereas semen could not be collected from the other dog, and after castration, sperm were not obtained after epididymal flushing. One dog implanted with 4.7 mg deslorelin and 4 dogs implanted with 9.4 mg deslorelin remained in a prepubertal reproductive status at 30 - 34 months. The delay in puberty was longer in dogs implanted with a higher dose of deslorelin. However, to date, implantation of young male dogs before puberty does not seem to be frequent in Europe.

#### Behavioral disorders potentially linked with testosterone

'Off-label' treatment of deslorelin implants may be of interest for management of some real behavioral disorders.<sup>15</sup> To address this question, a test course<sup>16</sup> was set up in 9 pedigree dogs. Animals were included according to 5 criteria, including intra-species aggression or inter-species aggression. Each dog received a 4.7 mg deslorelin implant and was monitored for 6 months. Success was defined as at least a 50% decrease in the occurrence of the primary problem and a case progress rating of 6 - 10 was given by the dog owner at the end of the study. Nine cases were classified as successful. In 8 cases, the number of occurrences of the primary pattern was zero. The remaining cases had a reduction of up to 90%. The best scores were for intra-species aggression. However, castration in male dogs may increase some aggressive behaviors towards humans, especially strangers.<sup>17</sup> To date, it is still impossible to know if treatments with deslorelin implants may be beneficial in case of real behavioral problems, such as separation anxiety or aggression.

#### Prostatic problems

In dog, prostate diseases are very frequent. Nearly 80% of elderly dogs have benign prostate hyperplasia (BPH). One of the main principles guiding the treatment of these conditions is to reduce prostate size. This is generally achieved subsequent to decline in serum testosterone concentrations after surgical castration. However, some owners are reluctant to castrate their dogs, or some older animals may be at-risk if general anaesthesia is performed. Long-term treatment based on GnRH agonists results in 40 - 60% reduction in prostate volume. This reduction is achieved in 4 - 6 weeks,<sup>18,19</sup> regardless of the agonist used. A deslorelin implant (4.7 mg) were used in 14 dogs that had BPH.<sup>20</sup> Authors observed a decrease in the prostatic volume from day 14 after implantation, with ~ 60% decrease in prostatic volume at 1 month, with reduction of prostatic cysts (determined by ultrasonography). Moreover,

there was a quick suppression of clinical signs in all dogs and no apparent increase in the clinical signs during the 'flare-up' period after implantation. Other authors, using Doppler ultrasound to estimate the degree of blood supply of the prostate, observed a rapid decrease beginning as early as 5 days postimplantation, a quicker response to treatment.<sup>21,22</sup> A recent study<sup>23</sup> observed a minimum efficacy of 36 weeks after deslorelin implantation in suppressing clinical signs of BPH. It remains controversial, however, due to the initial 'flare-up' effect, if it is recommended to use deslorelin implants as a first-line treatment in dogs presenting clinical signs related to BPH, or to first use an antiandrogenic drug to suppress these signs and implant the dog 3 or 4 months later after clinical resolution in order to avoid recurrence. Of course, the dog will have to be reimplanted regularly thereafter.

#### Perianal adenomas

Due to the role of testosterone in development of perianal adenomas, some authors have tried deslorelin implant to decrease the size of these tumors to facilitate further surgical treatment. Nine dogs with perianal adenomas diagnosed cytologically or histologically were followed several months by measuring with a caliper the largest diameter of the tumor, and testosterone concentrations were measured on days 1, 45, 90, and 180. Eight of 9 dogs had a 30% reduction in tumor size on day 30, and in 6/9 dogs there was complete resolution on day 180.<sup>24</sup>

#### Dermatological problems

Deslorelin implants have also proved to be beneficial in dermatology. Ten pomeranian dogs (including 8 intact males), 4 Italian spitz (3 intact males, 1 neutered female), 3 miniature poodles (2 intact males, 1 neutered female), 2 Siberian huskies (intact males) and 1 intact male chow chow dog with confirmed hair cycle arrest (alopecia X) were included in a study.<sup>25</sup> Each dog was treated with a subcutaneous implant containing 4.7 mg deslorelin. Responder dogs were reimplanted 6 months after the first implant to obtain a 1-year pharmacological exposure and to have 1-year follow-up. Hair regrowth was visible within 3 months in 12 of 16 intact male dogs (75%); no hair regrowth was observed in any neutered female dogs. The overall response to therapy was 60%. No adverse effects were noted. Based on these findings, deslorelin may be a treatment option for intact male dogs with idiopathic hair cycle arrest.

#### Final considerations

When using implants 'off-label', due to potential side effects, we recommend to implant the dog under the abdominal skin, posterior to the umbilical area.<sup>26</sup> In case of any further problem, it will be easy, with a small skin incision, to remove the implant under slight sedation. However, others prefer implanting under the skin on the medial part of the rear leg.<sup>27</sup>

#### Conflict of interest

None to report.

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