

# Aggressive Behavior in a Bitch After Deslorelin Implant Insertion

## Key words

bitch;  
aggression;  
behavior;  
deslorelin implant;  
long-lasting GnRH

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**Abstract:** In male dogs, long-acting gonadotropin-releasing hormone (GnRH) analogs are widely accepted as an alternative to surgical castration but are also used to suppress and induce estrus in bitches (off label). Behavioral changes reported in bitches in association with the use of long-acting GnRH analogs have included male-like behavior associated with triggered estrus, increased food intake, enlargement of mammary glands and milk production, pseudopregnancy, and urinary incontinence. In male dogs, intra-species and rarely inter-species aggression may occur during the flare-up effect. However, at the time of downregulation, this behavior should no longer occur if it is testosterone dependent.

An intact, three-year-old female cocker spaniel with Addison's disease was admitted to our clinic for consultation on spaying options because of pseudopregnancies followed by mastitis, which had to be treated with antibiotics, after her heat cycles. The owners were hesitant about surgical sterilization and therefore, deslorelin implant was inserted. Approximately one month after implantation, owners observed the onset of aggressive behavior, including incessant barking, extreme irritability, and aggression toward other dogs and towards family members. The behavior problems started to escalate and the owners were not able to handle her anymore. After removal of the implant, the observed aggression ceased, and the bitch returned to normal behavior.

Although aggressive behavior toward other dogs and sometimes even toward owners has been observed after neutering or insertion of a deslorelin implant, this is the first report of extremely aggressive behavior toward owners and other dogs in a female dog after insertion of a 4.7 mg deslorelin implant.

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## Introduction

Aggression is the most common and serious behavioral problem in dogs. It is also the most common reason pet owners seek professional help from veterinarians and behaviorists (1). Aggression in dogs can be directed toward familiar people, toward strangers, or toward other dogs. Aggressive behavior in dogs is a common problem in society and a frequent cause of dog-human bites (2), surrender of adult dogs to shelters, and euthanasia of adult dogs (3).

Gonadectomy is commonly used to treat and prevent behavior problems, including aggressive behavior in dogs and it is advocated by veterinarians as a way to make dogs better-behaved companions (4). However, researchers provide conflicting information. In a study by Hopkins et al. (5), it was found that in gonadectomized dogs, aggressiveness toward other dogs decreased by 62%, but territorial and fear-induced aggressive behavior remained

unchanged. The same observations were made in another study in which neutering had an effect on all behavioral problems related to aggression except aggressive behavior toward strangers (6). In contrast, other studies suggest no discernible pattern of changes in aggression (7, 8). Some studies note that gonadectomized dogs of both sexes are significantly more likely than intact dogs to bark, growl, lunge, snap, open their eyes wide, and raise or curl their lips when approached by an unknown human or dog (9, 10). A recent study of 15,370 dogs concluded that no single factor is responsible for aggressive behavior in dogs, but that there are multiple environmental and genetic factors that contribute to aggressive behavior. Neutering does not result in a predictable decrease in aggressive behavior in all male and female dogs, although it may be effective in some (4). This supports the previous 2013 recommendation from the Society for Theriogenology and the American College of Theriogenology Board of Directors that gonadectomy should be decided on a case-by-case basis (11).

Gonadotropin-releasing hormone (GnRH) is a key regulator of reproductive function. It is released in a pulsatile fashion from hypothalamic neurons. The peptide binds to specific GnRH receptors on pituitary gonadotrophs. Its activation leads to synthesis and secretion of LH and FSH. In females, gonadotropin secretion from the pituitary gland is modulated by estradiol and progesterone. These feedback effects of ovarian steroids initiate the LH surge and lead to suppression of GnRH release in the luteal phase. The pulsatile release of GnRH from the hypothalamus is essential for the maintenance of ovarian function (12). Slow-release GnRH agonist implants are widely accepted as an alternative to surgical castration in male dogs and cats. Although deslorelin implants are approved in the EU for male dogs and, as of June 2022, for male cats and prepubertal bitches (13), numerous studies have been conducted in the adult bitch to investigate its use as a contraceptive and/or method of estrus induction (14, 15, 16). The first step in the mechanism of action is a flare-up effect with an increase in gonadotropin synthesis. Such increased gonadotropin synthesis leads to estrus induction in females, when treated in anestrus (14, 15). This was indeed observed when females in anestrus were treated with GnRH analog (14). However, when females in diestrus with  $P4 > 5$  ng/ml were treated, the first report concluded that there is no flare-up effect (17). Later studies showed that the initial flare up effect is associated with estrus induction when deslorelin is administered to bitches both in anestrus as well as (although more rarely) in diestrus (18). Most authors have confirmed that all adult bitches respond in the same manner regardless of size and age; however, depending on the stage of the cycle, the bitch's response may vary (19, 20, 21). After the flare-up effect desensitization of the GnRH receptors occurs, resulting in a transient, long-term, and fully reversible down-regulation of reproductive endocrine functions in dogs (21, 22, 23). These promising results led to the use of the implants for estrus induction and suppression in bitches predisposed to the side effects of sterilization (off-label

use). Although many adult bitches do well when treated with deslorelin, some signs such as persistent oestrus, pyometra, urinary incontinence, ovarian tumors, and minor behavioral and physical changes may occur (24).

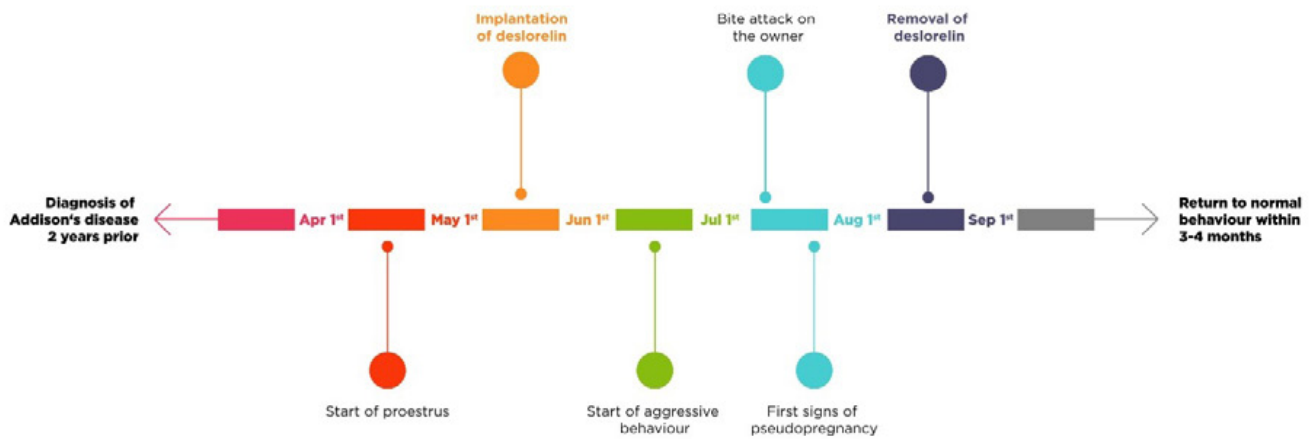
## Case

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An intact, three-year-old female cocker spaniel was admitted to our hospital for consultation on spaying options. The dog was diagnosed with Addison's disease at one year of age and was well controlled with a combination of oral hydrocortisone (Hydrocortisone Roussel, Sanofi Winthrop Industrie, France) at a dosage of 0.4 mg/kg/12h and subcutaneous desoxycorticosterone pivalate (Zycortal, Dechra, UK) at a dosage of 1.3 mg/kg/30 days. Based on clinical response to therapy and biannual laboratory checks, her disease was stable. Her first heat occurred at 9 months of age, and since then she has had regular cycles every 6 months. After the fourth cycle, she developed pseudopregnancy followed by mastitis, which had to be treated with antibiotics. The owners wanted to stop the cycles and prevent the pseudopregnancy but were hesitant about surgical sterilization because of the risk of anesthesia, due to her condition. Moreover, they feared irreversible consequences of gonadectomy, especially weight gain. They decided to use a deslorelin implant because its effect is reversible and can be implanted without surgical intervention.

Deslorelin (Suprelorin 4.7 mg implant for dogs, Virbac, France) was implanted subcutaneously in the umbilical region on day 23 after the onset of visible signs of proestrus. Diestrus was confirmed by vaginal cytology, but progesterone was not measured. Approximately one month after implantation, owners observed the onset of aggressive behavior, including incessant barking, extreme irritability, and aggression toward other dogs. Such behavior was not normal for this previously very well-mannered dog. The aggression escalated rapidly with her becoming aggressive also toward people, firstly toward strangers but later toward family members as well, culminating in a bite attack requiring medical intervention on one of the owners. The change in behavior was so extreme that the owners were unable to physically interact with her any more as she attacked anyone who approached her. About 70 days after implantation signs of pseudopregnancy became visible with enlarged mammary glands but no milk production and lethargy. Another side effect of the implant was polyphagia and about 10% weight gain.

Approximately two and a half months after administration, the implant was removed. All signs of aggressive behavior ceased within the next few months, and according to the owners, she returned to the gentle dog she was prior to implantation. Within two weeks, she also lost 600 g in weight despite being fed the same diet. In the two years after the implant removal, once resolved, the aggressive behavior never reoccurred although her heat cycles returned to



**Figure 1:** The exact course of events that took place from the insertion of the implant to its removal

normal as before deslorelin implantation. The exact course of events are shown in Figure 1.

## Discussion

The present case is the first report of the occurrence of severe aggression in a bitch after the insertion of a deslorelin implant. Surgical sterilization is often suggested to the owners to alleviate unwanted and aggressive behavior in some dogs (25). Because of their ability to suppress sex steroid hormones, GnRH agonist-releasing implants may also be useful in modifying or minimizing testosterone-related behaviors. In castrated male dogs and dogs with deslorelin implants, improvements have been noted in sexually dimorphic male behaviors described as libido, hypersexuality, intermale conflict, and excessive urine marking (26). Therefore, it has been suggested that implants releasing GnRH agonists are an alternative for clients seeking to alter testosterone-mediated behavior in their male dogs without having to perform castration or as a trial to what could be achieved by permanent sterilization (27). On the other hand, recent studies have shown that the likelihood of undesirable behavior increases significantly in neutered animals. Neutered dogs were more aggressive, more fearful, more restless, more difficult to train, and less responsive to signals (2, 4, 23). In addition, and of bigger importance, there is a risk of an increase in dominance aggression toward family members (28), with owners (2) and children (29) being bitten more likely by neutered animals. Another study found that these effects were more pronounced when animals were neutered before puberty (27).

The behavioral aspect of GnRH agonist implants in bitches has not yet been described, but it is generally expected that the effects should be similar to those of sterilization. However, there is a major difference between surgical and medical castration, namely that gonadotropin levels are

very high after surgical castration (30) whereas they are likely to be low to basal during deslorelin treatment because of the inhibitory effect of deslorelin on gonadotropin release. In general, it is not known whether such a change may have an impact on disease and possibly on behavior. In the present case, severe aggressive behavior toward other dogs and strangers was initially observed. Subsequently, the aggression toward family members escalated and the dog became so aggressive that the owners could no longer safely handle her. Most studies have found that the risk of unwanted aggressive behavior after sterilization is higher in dogs that already showed behavioral problems before gonad removal (31). However, in our case, no aggression was observed in this bitch before implant placement, and the aggression resolved after implant removal.

We must mention that the dog suffered from Addison's disease and was treated with a physiological dose of corticosteroids and mineralocorticoids. Exogenous corticosteroids are synthetic analogues of natural steroid hormones and are used in both human and veterinary medicine mainly for their anti-inflammatory and immunosuppressive effects. The synthetic analogues of cortisol have increased glucocorticoid activity (32). Exogenous corticosteroid treatments have been reported to cause negative emotional states in human patients and laboratory animals, with similar changes noted in domestic dogs (33). Behavioral changes associated with exogenous corticosteroid treatments in dogs have been reported in only a few studies (33, 34), showing increased anxious behavior and avoidance of contact with humans. This may include a greater tendency to retreat when approached or attempts to snap or bite under these circumstances. It has been reported by owners that dogs treated with corticosteroids tended to react aggressively when petted or even approached, and that their dogs also appeared to be significantly more prone to avoid people or situations (34, 35, 36). It was also found that dogs receiving corticosteroids after being referred for behavioral

problems were significantly more likely to exhibit negative behavior compared to dogs not treated with these medications (33). Thus, aggressive behavior in this bitch could potentially be caused by treatment with corticosteroids. However, it should be mentioned that the bitch had been taking these medication for more than two years before implantation of deslorelin and returned to her normal behavior after the implant was removed despite continued treatment with the same dose and type of corticosteroids.

In humans, it has recently been found that Addison's disease can cause psychiatric symptoms that often accompany the cardinal symptoms of adrenal insufficiency and are related to the severity of the disease (37). Therefore, untreated and uncontrolled Addison's disease in dogs could cause similar problems and lead to aggressive behavior. However, as mentioned earlier, the bitch had been treated with medication for more than two years and was very well controlled. Because both corticosteroids and gonadectomy produce behavioral changes in some animals, it is possible that the corticosteroid treatment with the implant increased the behavioral changes. Despite physiologic doses of corticosteroids used in this case such scenario can not be fully excluded.

A possible mechanism to investigate may be that deslorelin treatment somehow stimulated minor adrenal function by stimulating ACTH-secreting neurons of the pituitary gland, thereby increasing adrenal cortisol production and causing a hyperadrenocortical state (due to concomitant exogenous corticosteroid administration). A recent article (13) reported the development of pituitary carcinoma causing a Cushing-like syndrome in a bitch chronically treated with deslorelin for urinary incontinence. A relationship between the pituitary tumor and the clinical signs could not be confirmed, but the possibility that deslorelin causes a minor stimulation of the pituitary corticotrophs should not be discounted. From this point of view, it would have been interesting to know the status of Na-K balance in this bitch during the period of increased aggressiveness, but we do not have these data.

This case also raises the question of the risk of taking multiple endocrine drugs at the same time and their possible interactions on general health and behavior. Since inappropriate behavior is the most common cause of animals ending up in shelters or abandoned by their owners, it is very important to inform owners before sterilization about possible behavioral side effects which, although rare, are irreversible following surgical gonadectomy. The use of GnRH agonist implants to determine the effects of gonad removal is therefore beneficial and strongly recommended for male dogs and cats, perhaps even prepubertal females, but we cannot say with certainty at this time that such treatment is also recommended for adult females, given all the reported side effects. The veterinary profession should increase awareness about treatments that alter animal behavior and the importance of monitoring and reporting behavioral side

effects as adverse events. Drug-drug interactions should be discussed more frequently, as they can affect the effectiveness of the medication and treatment, cause unexpected side effects, or enhance the effects of a particular medication.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## **Agresivno vedenje psice po vstavitvi implantata deslorelina**

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**Izveleček:** V veterinarski praksi so dolgo delujoči analogi gonadotropin-sproščujočega hormona (GnRH) široko sprejeta alternativa kirurški kastraciji psov. Uporabljajo se tudi pri psicah bodisi za supresijo ali indukcijo estrusa, pri čemer gre za neoznačeno uporabo zdravila. Pri uporabi dolgo delujočih analogov GnRH so pri psicah opazili vedenjske spremembe, kot so moško obnašanje, povečan apetit, rast mlečnih žlez, laktacija, navidezna brejost in urinska inkontinenca. Pri pasjih samcih pa se lahko v začetnem obdobju, ko implantat spodbudi izločanje testosterona, pojavlja agresivnost do drugih psov ali redko drugih živali.

Na naši kliniki smo obravnavali nesterilizirano, tri leta staro psico pasme koker španjel z diagnosticirano Addisonovo boleznijo. Lastniki so želeli nasvet glede možnosti kontracepcije, saj je pri psici v preteklih ciklikih prihajalo do navidezne brejosti in posledičnega mastitisa, ki je zahteval antibiotično zdravljenje. Lastniki so bili zadržani do kirurške sterilizacije, zato so se odločili za vstavev deslorelinskega implantata. Približno mesec dni kasneje so pri psici opazili začetek agresivnega vedenja, ki je vključevalo stalno lajanje, izjemno razdražljivost in agresijo do drugih psov ter do družinskih članov. Neželeno vedenje se je stopnjevalo do te mere, da lastniki niso mogli več obvladovati svoje psice. Po odstranitvi implantata je opažena agresija umirila, in psica se je vrnila v normalno stanje.

Čeprav je agresivno vedenje do drugih psov in včasih tudi do lastnikov opisano po kirurški kastraciji ali vstavitvi deslorelinskega implantata pri psih, je ta prispevek prvi, ki opisuje izjemno agresivno vedenje do psov in lastnikov pri psici po vstavitvi 4,7 mg deslorelinskega implantata.

**Ključne besede:** psica; agresija; vedenje; deslorelinski implantat; dolgo delujoči GnRH