Review Report

Estrous cycle manipulation in dogs

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Abstract

Domestic dogs provide a unique challenge to the veterinary practitioner to manipulate estrous cycle. Due to an obligatory 120-day anestrus, dogs cycle much less frequently than other domestic species. This can pose a problem for owners and breeders wishing to produce pups at a certain part of the year or temporarily prevent pregnancy due to competition, health, or convenience. We describe the most common pharmacological methods available to practitioners for induction and suppression of the canine estrous cycle with a brief discussion on the efficacy of anecdotal nonpharmacologic methods.

Keywords: Dogs, estrus suppression, estrus induction

Introduction

The domestic dog estrous cycle has 4 stages: anestrus, proestrus, estrus, and diestrus. Unlike other species, dogs cycle infrequently, typically only once or twice a year, which can be problematic for breeders and owners wishing to produce pups during the most fertile years. The reason for this prolonged period between estrous cycles is a prolonged anestrus that is necessary to complete uterine involution. In dogs, this process takes ~ 120 days to ensure a fertile cycle.[1] Anestrus is defined as the period between estrous cycles and can range from 5-14 months (average 7 months).[1]

If the dog is not cycling regularly, owners may wish to induce an estrous cycle sooner than what is physiologically normal for that individual. Additionally, in certain instances, owners may wish to alter when a dog comes into estrus due to availability of a stud dog or convenience around a show or availability to assist with whelping and raising a litter. In some cases, anestrus may be abnormally prolonged. Abnormal anestrus can be primary or secondary; primary anestrus is defined as having no estrus by 24 months of age whereas secondary anestrus is exhibiting no signs of estrus 10-18 months after an estrus.[2,3] Alternatively, owners may wish to suppress estrous behavior temporarily such as during performance competition or when pregnancy is undesirable. Therefore, practitioners need to have knowledge of available protocols.

There are many well-written reviews published in the literature that thoroughly outline all mechanisms studied to alter the period of estrus.[1,3] To list all protocols is beyond the scope of this article, and instead we aim to illustrate the most clinically useful and relevant techniques currently available to veterinary practitioners.

Estrus induction

To chemically induce an estrous cycle, the closer the manipulation mimics the natural hormonal events prior to proestrus, the better the outcome. Largely, this has been attributed to increased frequency and concentrations of gonadotropin releasing hormone (GnRH) pulses, and subsequently luteinizing hormone (LH) and follicle stimulating hormone (FSH).[2–5] The most common means to induce a fertile estrus include dopamine agonists, GnRH agonists, gonadotropins, and estrogens.[1,3,6]

Dopamine agonists

Dopamine agonists inhibit prolactin and directly act on the hypothalamus to provide a GnRH stimulatory effect.[3] Few dopamine agonists have been studied, with the most clinically applicable being bromocriptine and cabergoline. Estrus induction with bromocriptine is successful and relatively inexpensive but has been associated with vomiting when used as a sole medication.[1,6,7] The recommended dose for oral bromocriptine is 0.3 mg for 3 days then an increased dose of 0.6-2.5 mg/kg (depending on dog's size) continuing for 3-6 days after the onset of estrus. The primary benefit of this altered protocol is to reduce the side effect of vomiting.[7] Cabergoline works similar to bromocriptine and is less likely to induce

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vomiting; however, 23% of dogs that received cabergoline for at least 14 days also had reversible coat color changes.[8] Although not life-threatening, these coat changes can be problematic for owners who are continuing to show their dogs during treatment and should be communicated to clients as a possible unwanted side effect of the drug.

Another dopamine agonist, cabergoline, is most commonly used in practice. The protocol for oral cabergoline is 0.005 mg/kg (once daily until 1-8 days after proestrus has started)[1,2,9]; it is very important not to discontinue this medication too soon since ovulation failure can occur. Return to estrus will vary depending on the stage of the cycle in which cabergoline treatment is started. On average, if used in early anestrus the treatment duration is 20 ± 2 days, if in mid anestrus 14 ± 3 days, and if in late anestrus 6 ± 1 days.[9,10] In many cases, cabergoline can be expensive, especially when compounded, and therefore the potential for prolonged duration of treatment should be disclosed to clients. Another benefit of using cabergoline is that when used in primary and secondary anestrus resulted in better pregnancy and whelping rates on the induced cycle.[2]

GnRH agonists

GnRH agonists, used short term, can increase the amount of FSH and LH and has been used to induce estrus. There are a few published protocols to induce estrus that recommend intravenous or subcutaneous GnRH agonist (0.2-0.4 µg/kg every 90 minutes) to mimic the pulsatile fashion in dogs.[1] However, because of the cost and labor involved in intravenous or subcutaneous treatment, using long-acting implants, mini-pups, or long-acting injections have also been studied. Although effective, these methods are not currently available.

Deslorelin implants (Ovuplant®, Dechra, UK and 4.7 mg or 9.5 mg deslorelin acetate (Suprelorin-F®, Virbac Animal Health, Westlake, USA) have been used. Ovuplant implant is no longer available in the USA but is labeled for use in horses in other countries. Suprelorin-F® is available in the USA but is only on label for use in ferrets. Its use in other species is strictly prohibited in the USA; however, it is labeled for use in dogs in other countries and can be legally imported in special circumstances. These implants should be placed in the dog somewhere easily accessible (e.g. caudal to umbilical area or medial aspect of the thigh) as they need to be removed after ovulation.

The primary benefit of the implant is that estrus induction and fertility were high as long as the implant was removed appropriately.[4,5] Implants removal at LH surge resulted in anovulatory cycles in some dogs[11] Due to this, it is now recommended to remove the implant after ovulation. Most dogs come into estrus between 2-7 days after treatment regardless of the time during anestrus the implant was placed.[4,5,11] Seven out of 32 dogs failed to ovulate and their implants were removed after 15 days to prevent unintended effect of suppressing estrus.[11]

Gonadotropins

Porcine FSH has been used to induce estrus; however, these protocols have not been successful, and anaphylaxis has been reported.[1,12] Other protocols used equine chorionic gonadotropin (eCG) and human chorionic gonadotropin (hCG) with varying degrees of success. Used alone, eCG did not always induce spontaneous ovulation; therefore, eCG is often combined with hCG in these protocols.[1] It has also been noted that hCG decreased progesterone expression leading to reduced pregnancy and ovulation rates.[1,13] An injectable product containing 80 IU eCG and 40 IU hCG per ml is available in the USA and is labeled for swine (P.G. 600®, Merck Animal Health, Summit, NJ). Although highly effective in inducing estrus, this product resulted in a high degree of anovulation and therefore is not recommended due to the availability of more effective protocols.[1] Unfortunately, a commercial product containing only eCG is not currently available. Additionally, a few protocols sequentially (50 IU/kg intramuscular eCG and 500 IU of hCG after 7 days) were used, resulting in 80% pregnancy rate.[14] Treatment with eCG (20 IU/kg eCG) and hCG (25 IU/kg) after 5 days resulted in pregnancy in 10% of dogs and neither whelped due to embryonic resorption.[2]

Estrogens

Prior to LH pulses increase there is an increase in estradiol concentrations that occur naturally in dogs. This potentially primes the system for the increased pulses of LH. Oral diethylstilbestrol (0.1-5 mg/kg once daily for 6-14 days) was used[6] to induce estrus; ovulation and pregnancy rates were 46-100% and 31-100%, respectively. Domestic dogs are very sensitive to estrogens; usage has been associated with increasing risk for pyometra, myelotoxicity, fever, petechiation, melena, hematuria, and dyspnea.[15] Due to these risks, and the availability of other protocols, estrogens are not currently recommended for estrus manipulation.

Nonpharmacological therapies

Anecdotally, breeders have tried many other nonpharmaceutical methods to induce estrus. It is widely known that cycling dogs when housed with others will often synchronize estrus in what is known as the 'dormitory effect.' It is believed that pheromones have a role in this synchronization that can shorten anestrus by as much as 30 days.[6] This option however is not feasible for breeders with 1 dog or those that are actively competing and travelling. The additional stress of these events may also have an inhibitory effect on estrus due to increases in circulating cortisol concentrations.

Another anecdotal method that has been suggested is the addition of B-complex vitamins to the diet. B-complex vitamins such as biotin, riboflavin, and folic acid are essential for reproduction. In human studies, the addition of vitamin B12, folic acid, and folate have improved fertility, especially in women with polycystic ovary syndrome.[16,17] High supplementation (50 mg/kg/day) of vitamin B6 was able to suppress prolactin in pseudopregnant dogs as effectively as cabergoline.[18] Therefore, it may be possible for vitamin B6 to have a similar effect in estrus induction. Unfortunately, as no controlled studies have been performed in dogs, it is unknown if additional supplementation beyond a balanced diet is beneficial to induce cyclicity.

Increasing daylength and exposure to artificial lighting has also been suggested as a method to improve cyclicity in anestrous dogs. Domestic dogs are nonseasonal breeders, as evident by the ability for them to become pregnant at any time of the year; however, it is still perpetuated that daylength has a role in their cycle. In free-roaming dogs, especially in tropical areas (e.g. India), temperature and season appear to have a

role in number of offspring produced.[19] However, this does not seem to be true when evaluating controlled populations of domestic dogs in kennel environments. There was no evidence in seasonal variation of estrus or litter size in a guide dog population in the UK.[19] Addition of melatonin implants did not have any effect on the interestrus interval of dogs, suggesting lack of involvement in regulation of the reproductive cycles.[20]

Estrus suppression

Some pet owners may be reluctant to surgically sterilize their pets but still want to suppress the breeding behavior and the estrous cycle. Alternatively, owners or trainers do not want competition dogs to have estrus during the competition season. An ideal estrus suppression method should be effective, safe, and reversible.

Progestogens

Synthetic progestogens have been widely used for years to prevent estrus.[21] The exact mechanism is unknown, but it may be simulation of a diestrus phase. There are many formulations available, with variable affinity for the progesterone receptor. Progestogens include megestrol acetate (MA), medroxyprogesterone acetate (MPA), and proligestone. Oral MA can be given daily and is metabolized well. Oral MA (2.2 mg/kg, once a day for 8 days) was given to dogs (n = 389) in early proestrus; estrus was suppressed in 92%.[22] A dose of 0.55 mg/kg given to anestrous dogs for 32 days resulted in estrus suppression in 98%.[22] There was a 0.8% incidence of pyometra but no other side effects were noted.[22] Oral MA given for 2-4 weeks during anestrus followed by 3-4 months without treatment and another 2-4 weeks of treatment has also been reported to be effective.[1] Treatment should begin ~ 1 month before the expected estrus. Medroxyprogesterone acetate (MPA or depo-provera) is available as a long-acting injection or oral tablet. The injection should be given at a dose of 2-3 mg/kg with a maximum of 60 mg per animal.[23] Injections may be repeated every 3-5 months. Proligestone is labeled for estrus suppression and is given subcutaneously at a dose of 10-30 mg/kg. Chlormadinone acetate that is similar to MA is given orally at a dose of 2 mg/kg once weekly.[24,25] Progestogens listed have a variable return to estrus. For MPA, the average return to estrus is 2-9 months.[26] Average return to estrus for proligestone is 9-12 months but could be up to 2 years.

Although progestogen supplementation for the suppression of estrus is common, it has side effects that must be noted. Side effects are dependent on the formulation used, dose given, the duration of treatment, and cycle stage of the female at treatment. The most common side effects are weight gain, lethargy, and increased appetite.[22,27] Hair loss, thinning of skin, or hair color change is possible due to the progesterone effects on the glucocorticoid receptor. Mammary development and neoplasia are also reported to have a higher incidence after progestogens treatment.[22] A more serious complication is the increased incidence of cystic endometrial hyperplasia resulting from prolonged exposure to progestogens; 45% of dogs treated with MPA for estrus suppression had uterine lesions at spay.[28]

Progestogen treatment is not recommended in dogs that have underlaying uterine pathology, diabetes mellitus, mammary neoplasia, or liver disease.[3] The best use of progestogens is during anestrus in young, healthy dogs for as short a duration as possible and at the lowest possible dose. It is recommended that a maximum of 2 estrous cycles be suppressed followed by a natural estrus.[3] Progestogens should not be used in prepubertal animals. If used during pregnancy, they can cause dystocia and fetal death at whelping by failing to allow cervical relaxation.

Androgens

Androgens (e.g. testosterone and mibolerone) are widely used for estrus suppression. Androgens negatively feedback on the hypothalamus that downregulate GnRH and therefore FSH and LH; androgens do not have direct effects on the uterus like progestogens. These androgens can cause masculinization (e.g. mounting behavior) of the female, enlargement of the clitoris (Figure 1), and increased aggression. Vaginal discharge and vaginitis have also been described.[29] Anabolic steroid use is contraindicated in females with liver disease or breeds (e.g. Bedlington Terrier) that are prone to liver dysfunction. They should not be used in prepubertal or pregnant dogs. The dose of mibolerone is 16 µg/kg orally once a day. Mibolerone should be started at least 30 days before the start of proestrus and should be continued no more than 24 months.[30] It is important to note that mibolerone is only available via compounding pharmacies in the USA and is frequently unavailable. Return to estrus occurs on average within 70 days but could be as long as 7 months. Testosterone can be oral (25-50 mg/kg twice weekly) or injectable (testosterone propionate 110 mg once weekly).[1]

GnRH agonists

Suppression of GnRH leads to suppression of both LH and FSH that suppress cyclicity in the dog. GnRH agonists can be used off-label to prevent estrus. Deslorelin is the most common GnRH agonist and is available in an implant form.

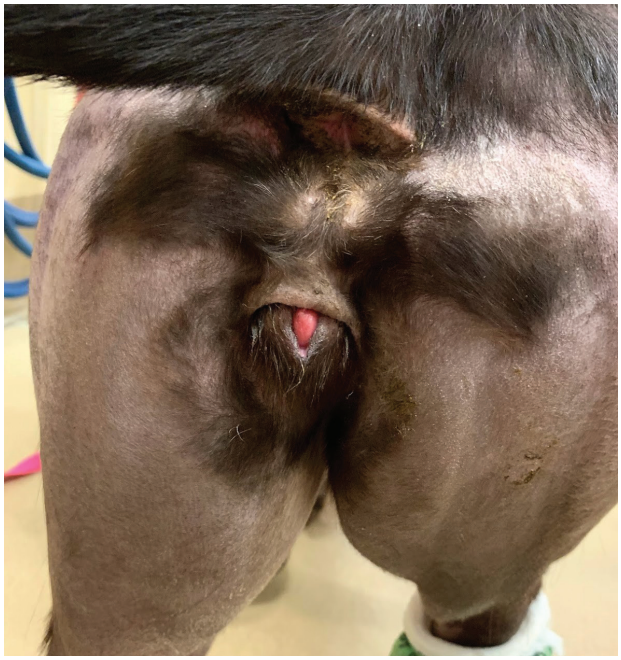

Figure 1. Clitoral hypertrophy in a racing greyhound treated with testosterone for estrus suppression

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The constant release of deslorelin cause an initial stimulation followed by inhibitory desensitization of GnRH receptors in the pituitary. The initial stimulation usually leads to estrus in most dogs. However, once over, hormones reach baseline concentrations. The implant should be placed during anestrus to avoid estrogen stimulation in the face of high progesterone of diestrus leading to hormone imbalance and risk of pyometra.[31] Once the implant is placed, it will induce an initial estrus 5-8 days after placement, followed by prevention of estrus for 2-27 months.[31] Use in prepubertal dogs resulted in estrus suppression for up to 23 months.[32] However, the length of estrus suppression is extremely variable among dogs. A clinically available implant is Suprelorin® (4.7 mg deslorelin) authorized for treatment of adrenal disease in ferrets. As previously mentioned, this implant can be difficult to attain and is not available in some countries (e.g. USA). The most important issue with the use of the deslorelin implant is the initial flare-up. Treatment with progestogens (megestrol acetate at 2 mg/kg) starting 1 week before the implant suppressed the initial estrus.[33] Side effects of deslorelin implants include ovarian cysts, prolonged estrus (15%), induced lactation (11%), and 2-6% other effects (e.g. vomiting, cystitis, behavioral changes, and allergic reactions). Removal of the implant is implicated in these cases; therefore, most practitioners place it subcutaneously just cranial to the umbilicus or medial to the thigh.

GnRH antagonists

GnRH antagonists directly suppress GnRH and therefore LH and FSH. Because it is a direct suppression, there is no initial flare-up. GnRH antagonists have been widely used in human medicine, but not much has been recently published in dogs. Subcutaneous acycline to females in early proestrus caused estrus suppression for 3 weeks; there were no side effects noted.[34]

Conclusion

Although many methods have been tried, only limited pharmacologic methods are commercially available, safe, and reliable to manipulate dog's estrous cycle. For estrus induction, dopamine agonists and deslorelin implants are the best methods; however, availability and adverse effects still need to be considered. For estrus suppression, more options have been researched, however availability is often unreliable and dependent on compounding. Regardless of the protocol, a thorough discussion with the client is warranted regarding efficacy, side effects, and expectations before choosing any pharmacological method. Nonpharmacological methods have fewer adverse effects but without formal research, no concrete recommendations can be made. Therefore, these therapies may be unreliable on a large scale. In conclusion, further research is needed to develop the ideal treatment for estrous cycle manipulation in dogs.

Conflict of interest

None to declare.

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