Estrus Suppression in Dogs

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KEYWORDS

• Agonist • Androgen • Antagonist • GnRH • Hormonal downregulation
• Progestogen

KEY POINTS

- Although progestogen administration is the most commonly used method of estrus suppression in dogs, there has not been and it is unlikely there will be a universally safe or effective progestogen in dogs.
- Continuous treatment with androgens for up to 5 years has been demonstrated, but it is generally not recommended to treat continuously for more than 24 months.
- Following an initial flare-up in gonadotropin concentrations, sustained exposure to gonadotropin-releasing hormone (GnRH) agonists reduces gonadotropin secretion through GnRH receptor downregulation, internalization, signal uncoupling, and a decrease in GnRH receptor expression.
- GnRH antagonists directly block pituitary GnRH receptors resulting in immediate suppression of gonadotropin release without a flare-up, but currently available products are too short-lived to be clinically beneficial.

INTRODUCTION

Within the United States, suppression of the canine estrous cycle is predominately attained by surgically removing the ovaries (ovariectomy) with or without the uterus (ovariohysterectomy). However, not all owners have their pets surgically sterilized. For purpose-bred bitches, the safest and most effective and least expensive method to prevent unwanted pregnancy is indoor confinement and segregation from intact males. For those bitches not intended for breeding, pet owners may still be reluctant to consider traditional surgical sterilization given recent (albeit confounding) evidence of long-term health problems associated with gonad removal, including obesity,

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urinary incontinence, endocrine disorders (eg, hypothyroidism, diabetes), musculoskeletal disorders (eg, cranial cruciate ligament rupture, hip dysplasia), behavioral disorders (eg, aggression, fear) and cognitive dysfunction, and neoplasia (eg, osteosarcoma, hemangiosarcoma, mastocytoma, lymphoma).

There are numerous nonsurgical methods for estrus suppression that have been used previously and that are currently being used. Pharmacologic methods of estrus suppression must be safe, reliable, and reversible. Hormonal treatments using reproductive steroid hormones (progestogens or androgens) or gonadotropin-releasing hormone (GnRH) analogues result in negative feedback, effectively shutting down the hypothalamic-pituitary-gonadal axis.

PATIENT EVALUATION OVERVIEW

Indications for suppressing estrus for bitches intended for future breeding include inconvenient timing of estrus for owner (American Kennel Club [AKC] performance classes prohibit exhibition of bitches in season) and long-term medical management of pyometra. For bitches not intended for breeding and when surgical sterilization is not an option, estrus suppression is important for prevention of pregnancy. Commercially available options in the United States for estrus suppression in dogs have declined over the last 3 decades, although most are still available through veterinary compounding pharmacies. Estrus-suppression protocols mediate their action by inhibiting pituitary gonadotropin secretion and release, mainly that of luteinizing hormone (LH). These protocols include the use of progestogens, androgens, GnRH agonists, or GnRH antagonists. Because LH is luteotropic in the dog, administration of estrus-suppression drugs to pregnant dogs may result in abortion and/or fetal urogenital malformations (eg, hypospadias in males, masculinization in females). Practitioners should first confirm that patients are not pregnant or that their owners know about and are ready to accept the consequences.

PHARMACOLOGIC TREATMENT OPTIONS FOR ESTRUS SUPPRESSION

Progestogens

Canine estrus suppression using progestogens has been practiced for many decades with the first report by Murray and Eden[1] in 1952. The mechanism of the estrus suppressive activity of progestogens in dogs is still unclear. In many species, there is evidence that progestogens reduce serum concentrations of gonadotropins. However, high doses of medroxyprogesterone acetate (MPA) or megestrol acetate (MA) administered to ovariectomized beagle bitches for several months did not reduce the increased circulating concentrations of LH nor did it lower LH concentrations in intact bitches.[2,3] On the contrary, basal plasma follicle-stimulating hormone (FSH) and LH concentrations increase during the first months of MPA treatment,[4] which may be due to a direct inhibitory effect of MPA at the ovarian level, resulting in suppression of the ovarian secretion of estradiol or inhibin.[5,6]

MPA (Depo-Provera) is a long-acting injectable progestin that was labeled for estrus suppression in the bitch (Promone).[7] MPA may be administered as a single subcutaneous injection (2 mg/kg; maximum 60 mg per animal)[8] or orally (5 mg once daily [10 mg for large dogs during the first 5 days]) for a maximum of 21 days.[9] Delmadinone acetate is similar to MPA and is used to postpone estrus.[10] MA has been used extensively for temporary estrus suppression in the bitch and is rapidly metabolized when given orally.[11] When given at a daily dose of 2.2 mg/kg body weight orally for 8 days beginning in early proestrus, estrus was suppressed in 92% of cases.[12] Two- to 4-week administration of MA during anestrus alternating with an untreated