Estrous Cycle Manipulation in Dogs

Michelle Anne Kutzler, DVM, PhD

KEYWORDS

- Dopamine agonist • Estrus induction
- Gonadotropin releasing hormone (GnRH) agonist

KEY POINTS

- Although many methods of estrus induction exist for both canids and felids, success rates vary between and within various protocols.
- Long-acting preparations are convenient for the owner and less stressful for the patient, but are associated with premature luteal failure and subsequent reduced birthing rates.
- Knowledge of the strengths and weakness of each regimen will assist the veterinarian in making a selection that will be best suited for the patient and client.

INTRODUCTION

Canine reproductive physiology has unique characteristics that make extrapolation from farm animals (horses, cows, sheep, goats, pigs) unsuccessful in this species. Domestic bitches are nonseasonally monoestrous. Bitches ovulate only once or twice per year with few exceptions.[1] The period from the onset of proestrus to the onset of the next proestrus is referred to as the interestrous interval (IEI). Unique to dogs, the IEI includes proestrus, estrus, diestrus, and anestrus. During anestrus, neither the ovary nor the pituitary are quiescent. The IEI averages 31 weeks[2,3] with a typical range of 16 to 56 weeks.[2] However, the IEI may be more or less frequent depending on the duration of anestrus, which varies between and within individual bitches.[4] Estrous cycle manipulation in dogs is used for both shortening and lengthening the IEI, depending on the desired outcome. This review focuses on shortening the IEI for purposes of estrus induction.

In the bitch, progression from early to late anestrus is characterized by a higher amplitude and a greater number of hypothalamic gonadotropin-releasing hormone (GnRH) pulses.[5] The GnRH pulse frequency is significantly increased during late anestrus.[5] The sensitivity of the pituitary to GnRH and the indirect response of the ovary to

Disclosure Statement: The author has nothing to disclose.
Department of Animal and Rangeland Sciences, Oregon State University, 112 Withycombe Hall, Corvallis, OR 97331, USA
E-mail address: michelle.kutzler@oregonstate.edu

Vet Clin Small Anim ■ (2018) ■–■
https://doi.org/10.1016/j.cvsm.2018.02.006 **vetsmall.theclinics.com**

GnRH also changes from early to late anestrus, with both a significant increase in pituitary sensitivity to GnRH (as expressed by circulating luteinizing hormone [LH] concentrations)[6] and an increase in ovarian responsiveness to LH and follicle-stimulating hormone (FSH).[6,7] Serum FSH concentrations are increased throughout much of canine anestrus, but are significantly higher during late anestrus compared with during mid and early anestrus.[8] Conversely, LH concentrations are low except near the end of anestrus.[9] An increase in plasma FSH concentration is critical for the initiation of folliculogenesis and, consequently, for the termination of anestrus in dogs.[8,10] In most domestic mammals, FSH is regarded as the most important factor in the early stages of follicular development, whereas LH is regarded as the primary regulatory factor in the more mature follicles.[11,12] It has been suggested that, for canine anestrus to end, an increasing plasma FSH concentration must exceed some threshold level of enough sensitive antral follicles to result in the progression of these follicles to the preovulatory stage.[13] FSH induces expression of LH receptors in the ovarian granulosa cells.[4] After initial follicle recruitment, LH is progressively able to replace FSH in the support of follicular maturation.[12] In fact, supraphysiologic doses of LH alone administered to bitches in anestrus will induce follicle growth and proestrus.[9,14]

PATIENT EVALUATION OVERVIEW

Methods for inducing estrus in bitches need to be safe and reliable. Methods for estrus induction in bitches include the use of dopamine agonists (bromocriptine, cabergoline, metergoline), GnRH agonists (lutrelin, buserelin, fertirelin, deslorelin, and leuprolide), and exogenous gonadotropins (LH, FSH, human chorionic gonadotropin [hCG], equine chorionic gonadotropin [eCG], and human menopausal gonadotropin). These methods vary greatly in their efficacy of inducing estrus as well as in the pregnancy rates after the induced estrus. In addition, the applicability of some of these methods for clinical practice is questionable. Indications for inducing estrus include management of prolonged anestrus (prologed IEI) in conjunction with routine breeding management when breeding opportunities are missed or after conception failure, or if a particular mating must be timed around the availability of the stud dog or whelping around a certain time of the year (eg, before hunting season). Estrus induction is most successful in fertile females that are at least 120 days from the onset of their last proestrus.[15] Although several studies have demonstrated that ovulation can be induced after diestrus termination, bitches rarely become pregnant from this approach.[16–18] In the dog, histologic changes similar to endometrial involution are not complete until 135 days after the last proestrus, regardless of whether the bitch was pregnant or not.[19]

PHARMACOLOGIC OPTIONS FOR ESTRUS INDUCTION

Dopamine Agonists

Dopamine agonists are ergot derivatives that inhibit prolactin secretion by directly stimulating dopamine receptors.[20] In species other than the dog, dopamine agonists inhibit gonadotrophin secretion during anestrus and dopamine antagonists induce reproductive activity. In the bitch, however, dopamine agonists induce the onset of estrus. It was previously believed that prolactin inhibition was necessary for canine estrus induction to occur. However, Beijerink and colleagues[21] (2003) demonstrated that bromocriptine shortens the IEI in the bitch, even when the dose is so low that it does not lower the plasma prolactin concentration. In addition, bitches treated with low doses of a serotonin receptor antagonist (metergoline) had reduced prolactin concentrations, but did not go into estrus.[22–24] These observations suggested that dopamine agonists induce estrus with another mechanism other than via lowering plasma