Pharmacologic Advances in Canine and Feline Reproduction

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Substantial improvements in therapeutic options for companion animal reproduction and gynecologic emergencies have been made over the last decade. New, alternative drug treatments, with fewer side effects and improved efficacy, are available. This has widened the spectrum of therapeutic possibilities for diseases that were previously treated only by surgical intervention. New drugs are available for estrus induction and pregnancy termination, as well as for the treatment of pyometra. This review summarizes the pharmacology and toxicology of reproductive agents currently in use for contraception, pyometra, dystocia, eclampsia, premature labor, agalactia, mastitis, metritis, and prostatic disorders, and compares their efficacy and safety with newer agents. Drug use and exposure during pregnancy and lactation, and subsequent risks to the fetuses, are also explored, with emphasis on antimicrobials, antifungals, anthelminthics, anesthetics, and vaccinations.

Keywords: veterinary theriogenology, canine reproduction, feline reproduction, estrus induction, mastitis, pyometra, dystocia, eclampsia, premature labor

The scope of all drugs used in canine and feline reproduction is too broad a topic to be reviewed in one article. There are many good articles already written on a variety of topics such as estrus induction/synchronization and pregnancy termination in canine and feline patients, and these should be referred to for more in-depth discussions.[1-17] In general, drug options in the field of veterinary theriogenology have recently expanded, with new agents available for estrus induction (gonadotropin-releasing hormone [GnRH], dopamine agonists) and pregnancy termination (dopaminergic agonists, antiprogestational agents). However, current lack of availability in the United States and expense have limited the use of these agents. Because of manufacturer discontinuation of some older products and limited availability of newer agents, there has been an overall decline in drug options in some areas such as contraception. However, new therapeutic options for pyometra, dystocia, eclampsia, and premature labor are available and will be discussed. The use of therapeutic drugs during pregnancy and lactation in canine and feline patients has not been currently reviewed, and there is little to no collated information in general for many of these agents. New and potentially less harmful anesthetics, antibiotics, antifungals, anthelminthics, and vaccines that can be used during pregnancy and lactation will be discussed as well as current treatment concepts for agalactia, mastitis, metritis, and prostatic disorders.

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The Canine and Feline Estrous Cycle

To evaluate current pharmacologic interventions in canine and feline reproductive disorders, it is essential to have an understanding of normal reproductive physiology in both species. There are many good textbooks and published articles available on this topic, so only a very brief overview will be discussed below.

The Canine Estrous Cycle

An understanding of the canine time course of ovulation and fertilization and specific changes in the maternal physiology is essential when providing clinical services such as breeding management and determination of gestational time for surgical intervention. Although canine gestational time is consistent with the timing of hormone surges, it is not predictable based on the time from mating. In general, gestation length in dogs is relatively constant when measured from the beginning of ovulation or the ovulatory surge in luteinizing hormone (LH). Because the LH surge can be measured or estimated (via serial serum progestrone levels) with some accuracy, timing events with the LH surge as a reference point (day 0) can be helpful. The LH surge typically triggers ovulation within 2 days of the surge, and, if fertilization occurs, gestation is 64 to 66 days from the LH surge to parturition.

Using the LH surge as a reference point (day 0), proestrus (heat) may occur anywhere from day −25 to day −3 (average, day −9), and estrus occurs anywhere from day −3 to day +6 (average day, 0-1). Mating with the chance of significant fertility starts at day −3, followed by the LH surge and

onset of peak fertility at day 0. Ovulation may then occur between 38 and 58 hours after the LH surge.

Canine Stages of Pregnancy

To assess the effects of drugs during pregnancy, it is important to have an appreciation for the various stages of embryonic development and the hormonal milieu that occurs during each phase. There are 3 well-defined stages in canine pregnancy as discussed below.

Stage 1: Canine Fertilization to Implantation

- Positive pregnancy difficult to confirm at this stage.
- Implantation at approximately 18 days from the LH surge (day 0 = day of the LH surge).
- Progesterone required for initiation and maintenance of pregnancy.
- Need progesterone level of >2 ng/mL to maintain pregnancy.
- Progesterone maintains endometrial integrity and placental attachment, and inhibits myometrial contractility.
- Corpus luteum relatively refractory to exogenous chemicals/drugs during first 30 days.
- Changes in estrogen:progesterone ratio or decline in corpus luteum progesterone secretion can lead to impaired implantation or abortion.
- Drugs used to terminate pregnancy at this stage include: 1) estrogens: inhibit oocyte transport/embryotoxic effects; 2) prostaglandins: high doses induce luteal arrest; and 3) inhibitors of progesterone secretion (epostane) or progesterone antagonists (mifepristone, aglepristone).

Stage 2: Implantation to Fetal Ossification

- Positive pregnancy more easily confirmed (approximately 25-30 days with ultrasound).
- Fetal ossification occurs at 40 to 42 days from the LH peak.
- Embryogenesis and fetal growth and development occur rapidly at this stage.
- Exposure to exogenous drugs or chemicals here may result in limb, skeletal, organ, or neurological deformities during this time.
- Prolactin is the main pituitary hormone that sustains corpus luteum steroidogenesis.
- Dopamine antagonists or prolactin-secretion inhibitors can lead to luteolysis, blockade of progesterone secretion, and abortion.
- Abortion induction usually associated with embryonic/fetal resorption.
- Drugs used to terminate pregnancy at this stage include: prostaglandins, dopamine agonists/antiprolactinic agents (bromocriptine, cabergoline), antiserotoninergic (methergoline), steroids (dexamethasone), progesterone-secretion inhibitors (epostane) or progesterone antagonists (mifeprestone, aglepristone), and GnRH antagonists (not available; efficacy remains to be determined).

Stage 3: Fetal Ossification to Parturition

- Fetus is well developed.
- Prostaglandins are the natural inhibiting factors causing luteal functional arrest before parturition.
- Prostaglandins reduce corpus luteum blood supply and luteal steroidogenesis.
- Abortion induction at this stage is likely to result in fetal expulsion.
- After days 50 to 55 from the LH surge, induced abortion may result in premature parturition and delivery of live pups.

The Feline Estrous Cycle

In feline patients, proestrus (0.5-2 days; female is attractive to the male, but will not allow mating) is followed by waves of folliculogenesis or estrous activity (average, 7 days; female has slightly swollen vulva, scant bloody discharge, vocalization, rolling behaviors, reduced appetite, and is receptive to males). The first estrous cycle in cats is at 6 to 12 months on average, but can be as early as 4 months. Cats are seasonally polyestrous and induced ovulators; ovulation will only occur with adequate coital stimulation. Multiple matings in cats can result in multiple ovulations and more than 1 sire in a litter of kittens. If the queen does not ovulate, an interestrus follows for 2 to 3 weeks, and the cycle repeats until fall. If she ovulates without proceeding to fertilization, metestrus or diestrus results for 30 to 40 days; if pregnant, this will last for 60 to 65 days.

Feline Stages of Pregnancy

Generally, cats do not show obvious signs of pregnancy until 5 to 6 weeks of gestation, so most owners may not even recognize that their animal is pregnant. Studies indicate that ultrasound detection of cardiac activity can be used as early as gestational day 16, with fetal morphology seen by day 26 of gestation. Fetal membranes become apparent by 21 days of gestation, and movement is first noted at day 28.[18] Because of the short gestational period in cats, owners or veterinarians may inadvertently administer drugs or vaccines during this time.

Estrus Induction in Canine and Feline Patients

Estrus induction in canine and feline patients has been accomplished with a variety of pharmaceutical agents.[1-6] Estrous induction is most successful in normal females; its efficacy in bitches and queens with reproductive disorders is unknown. Agents reported to be effective include synthetic estrogens (diethylstilbestrol [DES]), dopamine agonists (bromocriptine, cabergoline), GnRH agonists (lutrelin, buserelin, fertirelin, deslorelin, and leuprolide), exogenous gonadotro-