Proceedings of the
World Small Animal Veterinary Association
Mexico City, Mexico – 2005

Hosted by:

Reprinted in the IVIS website with the permission of the WSAVA
Some unique aspects of canine and feline female reproduction important in veterinary practice.

P. W. Concannon and J Verstegen
Cornell University, Ithaca NY 14853 and University of Florida, Gainesville, FL USA

Veterinary practitioners providing reproductive services for small animals should be aware of the aspects of reproduction that are unique or nearly unique to these species. These reproductive features in some instances represent challenges not encountered with other species, and in other cases represent phenomena that can be clinically useful in the reproductive management of individual animals.

**Canine Reproduction - Introduction**

Features of canine reproduction that are unique among domestic animals include ovarian cycles that involve a delay in oocyte maturation until after ovulation; a preovulatory rise in serum progesterone associated with the preovulatory luteinization of follicles; an elevation in serum progesterone for periods as long as or longer than the 2 months of normal gestation; and, an obligate anestrus of apparent ovarian inactivity that persists for variable times ranging from 2 months to 10 months. There is not only a delay in oocyte maturation until 2-3 days after ovulation, but uniquely the canine oocyte may remain viable for an additional 3 to 5 days, with fertilization occurring as late as 6 to 8 days after ovulation and up to 10-11 days after the preovulatory LH surge. Other unique features include the occurrence of a clinical pseudopregnancy in a significant proportion of ovarian cycles in which bitches are not bred; a high incidence of pyometra associated with the luteal phase of the cycle and an increase incidence associate with administration of contraceptive progestins; the occurrence of acromegaly and insulin resistance in association with otherwise normal luteal phases in some older intact bitches and the appearance of these problems with an increased incidence and in younger bitches administered contraceptives doses of progestins. The high incidence of mammary tumors seen in dogs also is unique among domestic animals. Dogs may also be unique in the ability of progesterone or progestin treatment without estrogen supplementation or pretreatment to elicit nearly maximal amounts of mammary and uterine hypertrophy and hyperplasia, and the ability of progestin treatment to results in an increase incidence of mammary tumors. Possibly unique among domestic animals is the extremely long periods that canine sperm can survive in the tract of the bitch – in some cases up to 8 days. This along with the potential long life span of canine oocytes likely explains fertility rates of normal bitches in experimental colonies as high as 90 - 96%. Variability between individuals and breeds in the lengths of the different stages of the reproductive cycles and in age at puberty is also greater than encountered in other species, and makes characterization of reproductive events difficult.

**Feline Reproduction - Introduction**

Cats are unique among domestic animals in their reproduction in that: ovulations are typically reflex ovulations in response to mating or genital stimulation; and, despite being classified as reflex ovulators, cats have been demonstrated to often ovulate spontaneously, or at least in the absence of vaginal penetration; spontaneous ovulation or non fertile mating lead to a physiological pseudopregnancy without obvious clinical signs ; , their seasonal anestrus when it occurs is typically limited to late autumn and very early winter. In some counties there are no approved contraceptive steroids for use in cats, and where there are, the doses suggested are often inappropriate and a matter of concern since cats are susceptible to many of the side effects of progestins seen in dogs. Cats are also unique in the occurrence and significant incidence of mammary fibroadenoma.

**Clinical Considerations In Canine Female Reproduction.**

Delayed oocyte maturation. Maturation is estimated to occur 60 hours after the preovulatory LH surge and thus any time between late proestrus to mid estrus depending on when the behavioral
shift occurs in the individual cycle. Furthermore, the time of estrus behavior onset in an individual cycle can differ depending on whether the parameter used is lordosis and estrus body posture, the acceptance of mounting and/or pelvic thrusting, or the first intromission achieved by a male which is typically one day later than first steady acceptance of mounting. Likewise it can vary due to exposure to experienced versus less experienced males, and by exposure to one experienced male versus another. Because of the variable onset of behavioral estrus, and potential difficulties in determining the onset of estrus behavior, especially in the absence of an experienced mate, the timing of ovulation is best by monitoring additional hormone-dependent parameters including vulval swelling, vaginal cytology and endoscopically viewed vaginal mucosal morphology. Additional accuracy is obtained by monitoring progesterone concentrations in serum or plasma samples obtained every 1-3 days, depending on availability and expense of assays. Although in some cases canine sperm can survive in the tract of the bitch and retain ability to fertilize ova for as long as 8 days after estrus and ova may remain within the uterus and undergo non-pregnant ovulation, this is often not the situation when dealing with problem bitches that have failed to become pregnant previously, or with many stud dogs selected for pedigree rather than fertility, or scenarios requiring the use of chilled or frozen semen.

**Preovulatory luteinization.** In bitches there are two types of preovulatory luteinization. Firstly, there is the minor but morphologically and endocrinologically detectable luteinization that occurs in small patches on the interior wall of individual follicles in mid to late proestrus during the 2 to 3 days prior to the preovulatory LH surge; it results in minimal increases in serum progesterone from non-detectable or nearly non-detectable level to levels of 0.4 to 0.8 ng/ml. Secondly, there is the dramatic preovulatory luteinization that occurs throughout and following the preovulatory LH surge; during the LH surge there which last 1-3 days there is a rapid and generalized proliferation of luteinizing cells more or less throughout the periphery of the preovulatory follicles and accompanied by a rise in serum progesterone form levels of 0.4 to 0.8 ng/ml to reach levels of 1.0 to 3.0 ng/ml. With a further rise to 2 to 30.0 ng/ml. This rapid rise in progesterone associated with the rapid phase of preovulatory luteinization can be used to time the occurrence of the LH surge and thus allow the estimation of the time of ovulation as being 2 days or later. It has been shown that the abrupt progesterone increase during the pre-ovulatory LH surge is important for the full generation of the LH t60 normal peak values; Clinical abnormalities in the LH surge and ovulation (including false estrus and anovulation, limited ovulation and/or prolonged pro-estrus) can occur as a result of insufficient surge release of LH.

**Serum progesterone.** The initial rise in serum progesterone has been used in a variety of ways to time a managed breeding or insemination. The practice involves the following concepts. For managed breedings, inseminations (i.e., matings) prior to oocyte maturation are unnecessary and potentially wasted if one or more inseminations can be performed one or more days apart beginning at or shortly after oocyte maturation. In cases of single matings or chilled semen, insemination is best accomplished near the time of oocyte maturation. In cases of frozen semen where sperm lifespan may be on the order of hours, it is critical that one or more inseminations occur after the time of oocyte maturation, at 5-6 days after the LH surge and 3-4 days after ovulation. This critical time has been estimated to be (1) at 5-6 days after the LH peak and the associated progesterone rise above 1 ng/ml, (2) at 1-2 days after serum progesterone reaches 5 ng/ml, or (3) at the time progesterone reaches 10 ng/ml – all based on high success rates using those values and the assays available to the researchers involved. The assays in each case are quantitative immunoassays (RIA, ELISA, or chemiluminescence) with high specificity and accuracy, as opposed to the semi-quantitative assay-kits marketed for in-clinic use.

**Luteal phase.** The prolonged (approx. 2 months) durations of the luteal phase and associated elevation in serum progesterone in non-pregnant bitches can be as long or longer than observed in pregnant bitches. Thus, progesterone assay can at no time be used as a means to test for pregnancy or for non-pregnancy as it can be used in ruminants. It also means that the uterine endometrium is under the influence of elevated estrogen and/or progesterone for nearly 3 months or longer, and undergoes proliferative and/or secretory activity which are not-infrequently sufficient to result in a mucometra, endometritis, or a pyometra involving any one of a variety of potential pathogens that are part of the normal vagina flora if not a more infectious agent.

**Pseudopregnancy.** Likewise there is a progesterone-induced hyperplasia and hypertrophy of the mammary glands that occurs to some but usually minor extent during and following the luteal phase in all canine ovarian cycles (physiological or covert pseudopregnancy). This change can become exacerbated and result in more extensive, clinically obvious, and unexpected mammary proliferation possibly accompanied milk secretion, and is apparently due to either an idopathic increase in sensitivity to progesterone or an increase in sensitivity to either the “clinical pseudopregnancy” or “ overt-pseudopregnancy” that is represented by the prolonged luteal phase itself. Clinical pseudopregnancy is typically accompanied by changes in behavior similar to those seen at normal parturition or immediately postpartum. Although usually self limiting and resolving within a period of several weeks, the conditional can culminate and/or persist for many weeks or months. The physical, clinical and behavioral components can be treated by daily oral administration of a dopamine agonist (bromocriptine at 50 to 100 ug/kg; cabergoline at 5 ug/kg) until resolved, androgen therapy has also been used.(anecdotally, testosterone cypionate or enanthate, 1 mg/kg, i.m., once; or, mibolerone, daily, p.o., to effect). There is growing evidence that the condition in many instances may be caused by a premature and/or abrupt decline in
progesterone late in the luteal phase resulting in a “parturition-like” progesterone withdrawal that causes increased prolactin secretion and or prolactin sensitivity. Repeated overt pseudopregnancy in bitches has been demonstrated to promote or influence mammary tumor development in the bitch. Mammary gland distension, milk accumulation and retention, milk in situ are effects suspected of inducing tissue anoxia and increasing exposure to free radicals and other carcinogens leading to neoplastic transformation. Thus, some clinics routinely offer dopamine agonist treatment for overt pseudopregnancy rather than wait for spontaneous resolution as a means to potentially reduce the future risk of mammary tumor development.

**Luteal Function.** In most domestic animals luteal function is positively regulated almost entirely by the presence of available amounts of LH and or estrogen, and negatively by periodic increases in prostaglandin F either in the peripheral circulation and/or within the corpus luteum. In carnivores, in addition to LH, prolactin is also a required luteotropic hormone for normal progesterone production, and the administration of prolactin lowering doses of dopamine agonist have been used separately or in conjunction with luteolytic doses of PGF or PGF analog to terminate the luteal phase and/or terminate unwanted pregnancies. In dogs there is no evidence of spontaneous periodic production of luteolytic amounts of PGF other than that by the pregnant uterus at the end of gestation as a means to trigger parturition. Nevertheless exogenous PGF is luteolytic in dogs, but only at doses (ug/kg) and frequencies far greater than required in large domestic animals. Natural PgF2a doses of 30-100 ug/kg administered at a minimum of 2 times per day for at least 3 or 4 days and usually longer are required to cause complete luteolysis and termination of unintended pregnancy. Larger doses are needed to effect complete luteolysis but at the risk of increased PGF side effects. Typically treatment is continued until confirmation of efficacy by ultrasound (preferably), progesterone evaluation or palpation. More potent prostaglandin-F agonists can be administered at lower doses (1 to 5 ug/kg), once a day for 5 to 7 days to achieve similar results. PGF can be further reduced when given in association with a dopamine agonist.

**Progesterone side effects. Mammary.** Mammary tumors are not common in most domestic animals, but they are common in dogs. The high incidence of mammary tumors, typically benign “mixed” mammary tumors, in older bitches is apparently the result of repeated exposures to prolonged elevations in luteal-phase progesterone as they are rare in bitches ovariectomized early in life and especially before puberty. Some of the benign tumors are often classified as pre-malignant in appearance and may be the precursors to malignant tumors that also occur with a greater frequency in dogs than other animals. The occurrence of mammary tumors both benign and malignant has also been associated with prior overt pseudopregnancies. Thus, clinics now routinely treat with prolactin suppression with dopamine agonists and surgically address all obvious mammary tumors, and perform mastectomies in bitches with multiple tumors in one or both mammary chains. **Uterus and pyometra.** The prolonged luteal phase in dogs not only provides an environment conducive to uterine infection, but may also result in cystic endometrial hyperplasia, which may represent an idiopathic abnormal hyperplastic response of the endometrium. However, some data suggest that the excessive hyperplasia may be in response to irritation caused by foreign material and/or bacteria resulting in an inflammatory-like proliferative response that is actually a response to infection. Interestingly, in both pyometra and in normal pregnancy at the time of implantation there is an often an obvious elevation in acute phase proteins concentrations similar to that normally associated with infection. Pyometra associated with the luteal phase of a recent luteal phase is amenable to medical treatment in many situations where the bitch is not febrile. Approaches differ among clinics and involve treatment with moderate to high luteolytic doses of PGF, lower and often more frequent doses of PGF alone or in conjunction with a dopamine agonist. Approaches differ among clinics and involve treatment with moderate to high luteolytic doses of PGF, lower and often more frequent doses of PGF alone or in conjunction with a dopamine agonist. Many of these protocols call for supportive systemic antibiotic therapy, uterine lavage when uterine drainage is particularly copious or thick, and/or intrauterine administration of broad-spectrum antibiotics or specific antibiotics selected based on culture of uterine discharge. Medical treatment of closed vs. open pyometra is controversial. However, some clinicians do not distinguish greatly between the two, and start with especially low doses of PGF (20-30 ug/kg) 2-3 times a day to achieve cervical patency and initiation of drainage before proceeding to higher doses of PGF (50-100 ug/kg). Along with antibiotic therapy. Ultrasonography can help determine cases at greater risk due to thinning of the uterine wall, and can be used to monitor uterine responses in animals that are managed medically. **Acromegaly and insulin resistance.** The normal luteal phase in older bitches can also result in the spontaneous development of signs of acromegaly due to elevated concentrations of growth hormone and somatomedin. The syndrome when it occurs spontaneously appears to have a lessened severity during the anestrus phase of the cycle The elevated GH concentrations involve mammary tsecretion of GH. The luteal phase can also increase insulin resistance and increase the insulin requirement in diabetic dogs. The extent to which this is a direct effect of progesterone and/or a progesterone-induced increase in growth hormone remains unclear but elevated growth hormone does cause insulin resistance. Destabilization of diabetes mellitus during the luteal phase in dogs and cats; ovarectomy is generally advised to prevent problems in diabetic animals. **Exogenous progestins.** Any of the synthetic progestins available for contraceptive use in dogs, including all oral and injectable formulations, can induce or increase the incidence and severity of all these progesterone-related side effects. They do so in a dose-dependent and duration-dependent manner. There are no universally “safe” progestins. Of concern is the fact that indications, suggested doses, and administration frequency can vary for
the same formulations marketed in different countries, and clinicians should seek information on minimal effective doses and appropriate regimens from independent sources as well (Romagnoli and Concannon, 2002). Excessive doses or prolonged treatment can easily result in pyometra, acromegaly, diabetes, multiple benign mammary tumors and/or mammary carcinoma. Therefore the use of minimal effective doses and administration at appropriate times and intervals are critical. Growth hormone hypersecretion and acromegalic syndrome. These responses to endogenous progesterone in some aged bitches and to progestins in younger bitches may be unique to dogs or carnivores, and have not been studied well in other species. The excessive GH secretion appears to involve not only pituitary hyper secretion evidenced by increased pituitary acidophil cell activity, but also mammary gland secretion GH. The mammary may not only be the major source of increased GH but the increased GH (and somatomedin) concentrations may in turn play a significant role in the extent of the mammary hyperplasia observed and in the occurrence of mammary tumors in progestin-treated bitches.

Obligate Anestrus. Canine ovarian cycles involve an obligate anestrus of variable length following the end of the luteal phase. The end of the luteal phase occurs at parturition in the pregnant bitch. In non-pregnant cycles, it has been generally defined as when peripheral progesterone concentrations fall below 1 ng/ml, which in most studies has been shown to vary from as short as 50-60 days after the onset of estrus or as long as 80-90 days, the average being 60-70 days in most studies. Full repair of the endometrium to its basal condition, and presumably full reversal of the effect of prior progesterone exposure appears to typically occur at around 120-140 days based on histological studies. Indeed normal cycles typically range from as short as 135 days (4.5 months) up to 13 months; however, apparently normal and repeatedly fertile cycles can occur in some bitches at intervals as short as 120 days (4 months), especially in some lines of Alsatian dogs. The 120 days minimal interestrus interval in fertile spontaneous cycles is thought to “make sense” in that it matches the best estimates for the time of uterine repair. Whether or not repeatedly short cycle intervals involve bitches with repeatedly shorter than average luteal phases is not known. The expected interestrus interval for a particular cycle is further affected by external influences may be influenced by the fact that. Anestrus bitches typically cycle 1-3 months earlier than they otherwise would if they are exposed to bitches in estrus, presumably due to a pheromone influence. A few breeds may be seasonal, although most all are not and cycle at any time of the year; in at least the basenji, cycles appear to be seasonal, cycles occurring at 12 month intervals in autumn after a puberty at 10 months of age. Interestingly, there is evidence of seasonal changes in peripheral concentrations of prolactin in dogs, and there may be an interaction with the time that progestrogen effects are lost and the timing of critical changes in serum prolactin or in the hypothalamic factors that control prolactin. It is logical to think that an anestrus period of considerable length is reproductive-wise important to allow a critical amount of uterine repair following a prolonged luteal phase. However, the occurrence of fertile ovarian cycles rapidly induced by GnRH agonist treatments as early as 30-60 days after a luteolytic regimen of PGF suggests that the minimal interval between the decline in progesterone and a fertile estrus may considerably less than what occurs naturally. Ongoing studies using pituitary anestrus suggest that a minimum “anestrus” of 30 days between completion of luteolysis and onset of estrus is likely a prerequisite for uterine repair sufficient to support pregnancy (Verstegen, 2005, unpublished).

Feline Cycles, Ovulation, Fertility. Many cats cycle at intervals of 10 to 20 days and are fertile throughout most of the 3-8 days of pronounced estrus. Cats are prolific and can produce and raise up to three litters a year. Reflex ovulation. Cats are considered unique in that the main physiological mechanism for the occurrence of ovulation is reflex ovulation involving a vaginal-spinal-hypothalamic reflex arc in which copulatory stimulation leads to vagal stimulation of the hypothalamus results in bursts of LH from the pituitary. Single copulations may or may not release sufficient LH to cause ovulation, even during mid-estrus. It also appears that LH release is greater in response to stimulation in mid estrus than during late-proestrus or very-early estrus, or late estrus. Confusion as to what breeding protocol to recommend to breeders and catteries comes from the diverse regimented breeding protocols that have been used to research the subject, in that ovulation can result from a single mating alone, and from single matings permitted on sequential or alternate days of estrus. However, some cats fail to ovulate with such limited exposures to males. Our research suggests that estrus cats respond with the most robust and prolonged elevation in LH when submitted to multiple, ad libitum matings on a single day with the ovulation rate for several copulation being better than for two, and hat for two better than for only one copulation. Some queens will permit up to 36 copulations within a 36 h period, and typically allow 5-6 in the first 2 hours; however, the releasable pool of LH is nearly depleted after 12-24 hrs and 14 or more copulations. Preovulatory LH surge release like that observed in other species is most easily obtained by ad libitum mating over an 8-12 hr period or longer. One can reasonably recommend 4 or more ad libitum copulations in a single 4-8 h period for cats that are clearly in full estrus and are not in the first 1-2 days of the “heat” that are associated with a proestrus period of inconsistent behavior and receptivity prior to the onset of full receptivity. As with dogs, managed breedings are best orchestrated by bring the female to the male’s cage, pen, or territory or bringing both animals to a quiet, neutral territory into which the male is introduced for an hour or more before the female. Spontaneous ovulation. Queens have also been demonstrated to experience with variable frequency apparently spontaneous ovulations when housed single and in the absence of males. However, the frequency of spontaneous ovulation has been demonstrated to increase in the presence of male but absent of sexual contact, suggesting a possible role of pheromones in this process. Whether these are truly spontaneous ovulations as occur in most
domestic animals or are a responses to non-copulatory genital stimulation has not been determined. Such ‘spontaneous’ ovulations can occur more than once a year in a significant proportion of cats, based on cat colony studies, and can clearly be the cause of prolonged interestrus intervals. **Luteal function.** The luteal phase following spontaneous ovulation is similar in duration to that following induced ovulation in queens that fail to become pregnant, i.e., 30–40 days and followed by an interestrus of 10 to 20 days leading to a global interestrus interval of 40–60 days. Luteal regulation is similar to that in dogs but cats are even more resistant to PGF as a luteolysin. Pregnancy is more easily terminated by administration of PGF in combination with a dopamine agonist. **Anestrus.** In cats that show pronounced seasonal anestrus during which they fail to show estrus for 2-3 months or more in the late autumn and early winter, the prior occurrence of cycles that involved spontaneous ovulation can result in an apparent interestrus interval as long as 4-5 months.

**Contraception And Progestins In Cats.** In some countries there are no contraceptive drugs approved for prevention of cycles in cats (e.g., USA) while in other countries one or more of the progestins marketed for dog contraception also are indicated for use in cats, but often at doses that are not consistent from one country to another and typically in the absence of any substantial database. . . Cats are susceptible to nearly all the same side effects and disease sequelae that can result from progestin use in dogs including uterine disease, mammary tumors, and diabetes. Therefore, as with dogs, progestin doses and administration duration and/or frequency must be carefully considered and multiple resources considered to determine the most appropriate regimen, preferably one involving dosing on a body weight basis. Cats are unique in the not-infrequent spontaneous occurrence of mammary lesions at a young age (versus old age in dogs), and usually in association with the first luteal phase and/or fist exposure to a progestin ; the tumors are mammary fibroadenomas and referred to variably as feline mammary hypertrophy, mammary fibroadenomatosis, mammary fibroadenoma, or fibroglandular mammary hypertrophy. Although many if not most resolve spontaneously, the extent of involvement can be extensive and debilitating. The condition has been reported to develop rapidly and extensively after either single injections of recommended doses of depot-medroxyprogesterone acetate or after oral administration of megestrol acetate. The lesions may sometimes become so extensive, lacerated and necrotic as to cause systemic illness and require partial or complete mastectomy. Ovariectomy is the recommended treatment in all spontaneously developing cases observed after the ovulation. In many contraception related cases, ovariectomy is not therapeutic because of the continued effect of the depot progestin. Administration of an antiprogestin such as aglepristone, alone or in combination with a prolactin-suppressing regimen of a dopamine agonist like cabergoline has been suggested as a way to treat such seriously affected queens, as well as treat affected queens with less extensive involvement and/or early in the development of the condition to prevent further exacerbation. The same medical treatments might be considered for queens in which the condition develops spontaneously but becomes too extensive and/or debilitating or fails to undergo sufficiently rapid resolution, either alone or in combination with therapeutic ovariectomy or ovariohysterectomy.

**References.**


Onclin K, Verstegen J.; Termination of pregnancy in cats using a combination of cabergoline, a new dopamine agonist, and a synthetic PGF2αc cloprostenol. JRF. 1997, 51, 259-263
