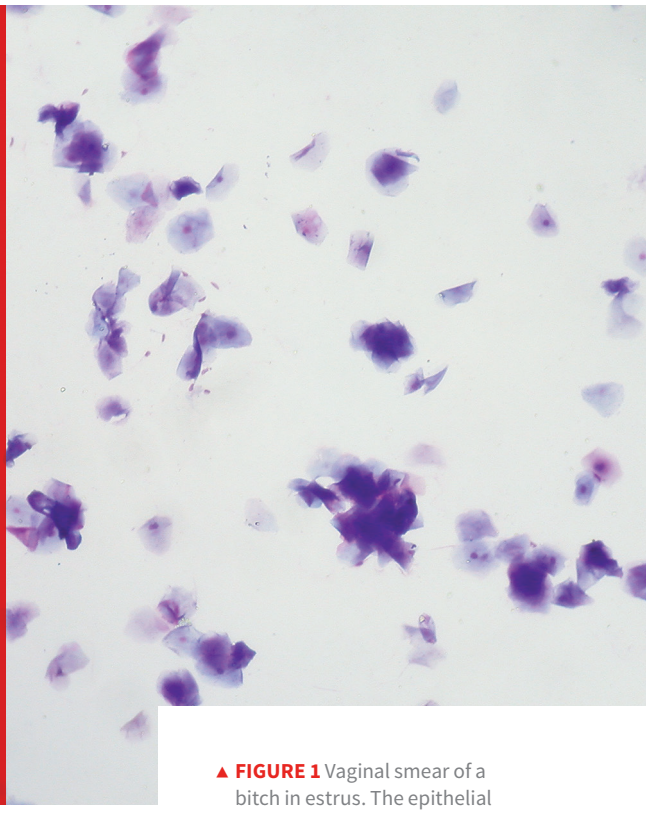
Top 5 Reproduction Concerns in Dogs

Stefano Romagnoli, DVM, MS, PhD, DECAR
University of Padua
Padua, Italy



▲ **FIGURE 1** Vaginal smear of a bitch in estrus. The epithelial cells can be defined as keratinized (or cornified) because of their angular borders and because most of their nuclei are pyknotic, faint, or absent. The percentage of keratinized epithelial cells is >80%, which is typical of full heat. *100× objective*

Canine breeding is increasing in popularity worldwide, and subsequently, reproduction problems are becoming increasingly common. Following are the most common veterinary reproduction concerns presented to the author.

1 Ovulation Timing

Identifying the day of ovulation in the bitch is becoming increasingly important in small animal practice, not only for maximizing fertility but also for proper management of canine parturition, high-risk pregnancy management, and cycle manipulation with hormone therapy (***Table 1***). The most practical way to identify canine ovulation is to perform vaginal cytology every 2 to 3 days starting from the onset of proestrus and then running progesterone assays once vaginal epithelial cells reach ≥50% superficial cells (***Figure 1***). Serum progesterone is typically <1.0 ng/mL in early proestrus, around 2.0 (±0.5) ng/mL on the day of luteinizing hormone (LH) surge, and 4-10 ng/mL at the time of ovulation. Canine ovulation may take up to 2 to 3 days; oocytes then require an additional maturation period of 48 to 72 hours before fertilization is possible.[1] Canine oocytes are viable for up to 170+ hours postovulation, but because of the time required for canine oocytes to mature, the optimal breeding time is 2 to 4 days postonset of ovulation. Conception can occur, albeit with likely a small litter size, if the bitch is bred as early as 7 days before or as late as 5 days after ovulation.

TOP 5 REPRODUCTION CONCERNS IN DOGS

1. Ovulation Timing
2. Pyometra
3. Urinary Incontinence
4. Benign Prostatic Hypertrophy
5. Ovarian Remnant Syndrome

2 Pyometra

Pyometra is a diestrual disease typical of adult intact bitches. Its occurrence is strongly influenced by sequential progestational stimulation (normal diestrus or treatment with progestins) of the uterus. Females giving birth regularly throughout their reproductive lives are less likely to develop pyometra than those that do so rarely or never (author experience). During the luteal phase of the estrous cycle, the canine endometrium proliferates and secretes endometrial fluid (ie, uterine milk) while the cervix remains closed and myometrial contractility is inhibited (***Table 2***). Fluid accumulates in the endometrial glands, which then dilate and can become fairly large (diameter, 0.3-2.0 cm; author experience). The endometrial pathology that develops is referred to as cystic endometrial hyperplasia (CEH), which is a precursor to some pyometras, as uterine milk itself constitutes an inflammatory stimulus and is an excellent culture medium for bacteria. CEH is a physiologic phenomenon; its regression starts during the second half of diestrus. CEH may not entirely disappear from some sections of the endometrium with time and repeated open (nonpregnant) cycles; this increases the chance of persistent endometrial inflammation. Gestation is widely thought to be protective and to prevent CEH lesions from developing in areas of the endometrium where placental attachment occurs. However, pyometra can occur in a single uterine horn or part of a horn, with pregnancy in the opposite horn or another portion of the same horn.

Pyometra should always be treated with specific antibiotics (based on culture and susceptibility testing) and fluid therapy. Bitches not intended for breeding should undergo ovariohysterectomy (***Figure 2***, next page). Medical management includes myocontractant drugs such as prostaglandin F2 α (PGF2 α) or prostaglandin E (***Table 3***, next page). Treatment is continued until

TABLE 1

REASONS TO TIME OVULATION IN THE BITCH

Goal	Method
Maximize conception rates and litter size	Breed on days 2 and 4 postovulation with fresh or fresh-chilled semen or on day 3 and/or 4 postovulation with frozen semen
Predict date of parturition	Due date is 63 days (+/- 1 day) from ovulation; ovulation must be properly timed using vaginal cytology and serum progesterone assay
Evaluate proper breeding management in the diagnostic investigation of fertility cases	Bitches bred outside their optimal fertile window will have questionable fertility
Choose the right time for hormonal administration	Progestogen treatment or estrus-inducing drug administration should be avoided during the 2-month diestrus window to avoid overdosing or lack of efficacy, respectively

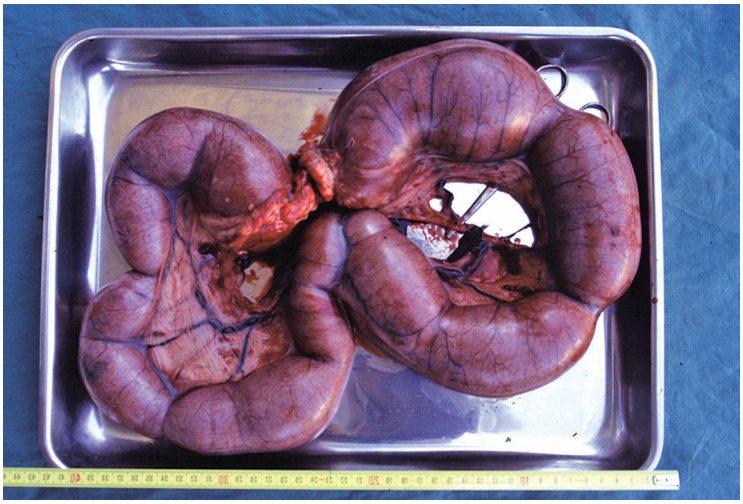
TABLE 2

EFFECTS OF ESTROGEN & PROGESTERONE ON REPRODUCTIVE TISSUES*

Structure	Estrogen	Progesterone
Endometrium	Growth, vascularity, edema of the endometrium	Proliferation and secretory activity of endometrial glands
Cervix	Relaxation and dilatation	Closure
Myometrium	Stimulation of contractility	Inhibition of contractility
Uterine lumen	Stimulation of migration of polymorphonuclear cells into the lumen	Inhibition of migration of polymorphonuclear cells into the lumen

*These effects are observed during endogenous secretion as well as after exogenous administration.

CEH = cystic endometrial hyperplasia
LH = luteinizing hormone
PGF2 α = prostaglandin F2 α



▲ **FIGURE 2** Dilated uterus of a bitch with pyometra

TABLE 3

COMMONLY USED PROSTAGLANDIN COMPOUNDS TO INDUCE LUTEOLYSIS & CAUSE UTERINE CONTRACTILITY IN BITCHES

PGF2 α or E*	Daily Dose	Administrations Per Day/Route
Natural PGF2 α (PGF2 α) Dinoprost (PGF2 α)	50 µcg/kg	2-4/SC (author experience)
Cloprostenol (PGF2 α analog)	1 µcg/kg	1/SC
Alfaprostol (PGF2 α analog)	20 µcg/kg	2/SC
Fenprostalene (PGF2 α analog)	2.5 µcg/kg	1/SC
Misoprostol (PGE)	10 µcg/kg	2/PO

*Prostaglandins should be used with caution to treat a closed-cervix pyometra because of the risk for uterine rupture or for pushing uterine pus retrograde into the oviducts. Most PGF2 α compounds cause some side effects (eg, panting, vomiting, diarrhea) for the first few days of treatment, but adverse events can be avoided by starting with half the normal dose and gradually achieving the full dose within the first 2 to 3 days of therapy. Misoprostol is a human compound that causes only uterine contractions (no luteolysis) in bitches and queens with only mild GI side effects in a few patients.

ultrasonographic images show an empty, normal uterus and there is clinicopathologic evidence of absence of leukocytosis. When available, aglepristone (a progesterone-receptor antagonist) can be effective in treating closed-cervix pyometra and can be used safely in breeding bitches. If no progesterone-receptor antagonist is available, surgery is the only option for a closed-cervix pyometra.[1]

3 Urinary Incontinence

Urinary incontinence (UI) is the involuntary loss of urine that occurs when the bladder is still in its filling phase and the animal is typically recumbent and/or standing.

The most common reason for UI in spayed bitches is urethral sphincter mechanism incompetence (USMI)—a reduced urethral closure due to weakening of the urethral sphincter that commonly develops after spaying. USMI is thought to result from lack of estrogenic stimulation.[2] Ovariectomy or ovariohysterectomy increases the risk for developing UI, as evidenced by its incidence in spayed bitches (up to 20%), and a relative risk for UI ≈8× higher in spayed than intact bitches.[3,4] Spayed bitches account for ≈75% of canine cases, although the problem is sometimes observed in prepubertal dogs due to congenital conditions.[4] In prepubertal animals, 1 or both ureters terminating at the apex of the bladder neck, the level of the urethra, or the cranial vagina can cause continuous dribbling of urine. Pathologic development of the urogenital system in intersex conditions can also cause UI.

The treatment of choice for UI caused by USMI involves oral administration of sympathomimetic drugs or estriol (other estrogens should not be used).[5]

Phenylpropanolamine, an α-agonist available for veterinary use in many countries, can be used at 1 mg/kg PO q8-12h. Pseudoephedrine

can also be used at 1.5 mg/kg PO q8-12h. Having the bitch maintain a small bladder during periods of recumbency is helpful. In many animals, the efficacy of both sympathomimetic and estriol medications tends to decrease over time despite increasing dosages, perhaps because of estrogen-receptor desensitization. Because of the multifactorial character of this condition, no single treatment is 100% effective, especially long-term. Recently, the gonadotropin-releasing hormone agonist deslorelin has shown some efficacy, providing full continence in ≈50% of treated bitches and an improved response to other drugs in ≈20% of bitches.[6]

4 Benign Prostatic Hyperplasia

The prostate of intact male dogs increases in weight until 4 years of age.[7] The growth process is characterized by cellular hyperplasia resulting in a smooth, symmetrical, nonpainful enlarged gland. Benign prostatic hyperplasia (BPH) may result in androgen-dependent hypertrophy and the development of cysts of increasing size within the prostatic parenchyma. Small retention cysts may be evident in as many as 16% of dogs by 2 years of age.[8] Prostatic infectious disease is associated with more cysts and larger gland size; bacteria ascend the urethra and settle in the cystic fluid. Hematogenous spread of bacteria, bacterial seeding from the kidneys and bladder via urine or from the testicles, and epididymis via semen can also occur. BPH incidence increases to >80% with advanced age,[7,9] but not all dogs show clinical signs. Prostatic growth and secretion are modulated by 5α-dihydrotestosterone (5α-DHT), the active androgen at the intracellular level. DHT is a metabolite of testosterone produced via the action of 5α reductase.

The most common clinical signs of BPH are bloody penile discharge and hematuria or hematospermia.[10] As the prostate enlarges, dyschezia, dysuria, poor semen quality, or infertility may be observed; this depends on the degree of prostatic fluid alterations. Increased prostatic size and presence of prostatic cysts on abdominal ultrasound are common findings (***Figure 3***). Urinalysis helps rule out urinary tract disease as a cause of penile discharge. Cystitis, if present, should be treated concurrently. BPH can be distinguished from prostatitis by lack of pain on transrectal prostatic palpation. Acute and chronic prostatitis will both present with leukocytes in the prostatic fluid sediment. Differentiating BPH from prostatic adenocarcinoma (PA) is more challenging, but PA is rare and is less common in intact males. A treatment course for BPH quickly eliminates clinical signs. Fine-needle aspiration or prostatic biopsies are diagnostic for PA.

Castration is curative. Recent studies suggest that incidence of prostatic carcinoma may be higher in castrated dogs than in intact dogs.[11] Treatments that do not decrease libido and fertility are finasteride (0.1-0.5 mg/kg [maximum, 5.0 mg] q24h for life) and osaterone acetate (0.25-0.5 mg/kg q24h for

BPH = benign prostatic hyperplasia

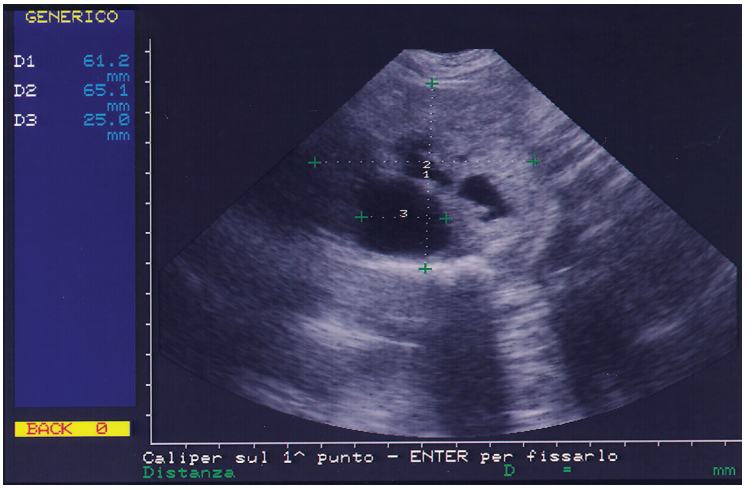
DHT = dihydrotestosterone

LH = luteinizing hormone

PA = prostatic adenocarcinoma

UI = urinary incontinence

USMI = urethral sphincter mechanism incompetence



▲ **FIGURE 3** Ultrasonographic image of a typical aspect of canine benign prostatic hyperplasia. The prostate is increased in size (measuring 61.2 [diameter 1] × 65.1 mm [diameter 2]) and features 3 cysts, the largest of which (diameter 3) has a diameter of 2.5 cm.

7 days). Finasteride works by blocking conversion of testosterone to DHT by interfering with the 5α-reductase enzyme.[12] Osaterone, a progestogen, competitively binds androgen receptors, which prevents testosterone from binding within the prostatic parenchyma. Other treatments include:

- Chlormadinone acetate (0.1-0.3 mg/kg PO q24h for 1 month)[13]
- Deslorelin (one 4.7-mg or 9.4-mg implant works for 6 or 12 months, respectively)
- Delmadinone acetate (1-2 mg/kg IM or SC; repeat in 4-7 days if needed)

5 Ovarian Remnant Syndrome

Ovarian remnant syndrome (ORS), the occurrence of heat after ovariectomy/ovariohysterectomy, is normally caused by ovarian tissue not completely removed during surgery. It should not be confused with ectopic adrenocortical tissue, which does not produce enough gonadal steroid to produce estrus signs. A less common cause of ORS can be a piece of ovarian tissue accidentally dropped into the abdominal cavity during surgery. Such pieces of tissue can establish vascular connections with the omentum or the serosa of abdominal viscera and become active again, allowing follicular development. Normal cyclicity has been reported in experimental cases of bitches in which a sliced fragment of ovary was purposefully left in the abdomen and later revascularized.[14]

MEDICATIONS CITED IN THIS ARTICLE NOT COMMERCIALLY AVAILABLE IN THE UNITED STATES FOR TREATING DOGS:

- Aglepristone
- Deslorelin
- Osaterone
- Delmadinone

AMH = anti-Müllerian hormone

DHT = dihydrotestosterone

LH = luteinizing hormone

ORS = ovarian remnant syndrome

Bitches with ORS may display signs of proestrus or estrus at regular or irregular intervals. Signs of heat may appear from several months and up to 10+ years.[13] Estrus signs are often characterized by the normal sequence of physical changes typical of proestrus and estrus (eg, attractiveness to males and acceptance, vulvar swelling and discharge, cornified vaginal cytology), and breeding may be observed. Bitches with ORS may exhibit signs of false pregnancy several weeks to a few months following estrus behavior, and false pregnancy may be the only sign if estrus was silent.

Diagnosing ORS begins with confirmation of estrogen stimulation via a cornified vaginal smear in a spayed dog showing signs of heat and exclusion of exposure to exogenous estrogen. LH or anti-Müllerian hormone (AMH) testing may aid with diagnosis. A negative LH test or a positive AMH test is consistent with retained ovarian tissue. If these are nondiagnostic, further testing involves stimulation testing measuring estradiol and/or progesterone following gonadotropin administration. Lack of response to stimulation testing does not always rule out ORS because some remnants do not seem to respond in a typical fashion; in these cases, exploratory laparotomy may be necessary.

Serum progesterone should be assayed on a serum sample collected 1 to 2 weeks after the end of estrus. A serum progesterone concentration of >2.0 ng/mL indicates presence of active luteal tissue. Laparotomy can be performed looking for a small piece of yellowish tissue at the level of the ovarian stump or the broad ligament. All tissues removed at surgery should be submitted for histopathology.

Conclusion

Practitioners should stay abreast of these challenges to be able to fulfill client expectations and patient needs.

See page 88 for references.

ROYAL CANIN®

A MAGNIFICENT COMBINATION

For over 45 years we've partnered with veterinarians who share our obsession for bringing out the best in cats and dogs. We discovered nearly 1 in every 2 pets suffers from multiple health conditions. That's why, through science and research, we developed a precise MULTIFUNCTION line. When you prescribe Royal Canin you have the power to transform the health of each cat and dog.

Find out more at royalcanin.com/multifunction

Available in 4 formulas:

- Urinary + Hydrolyzed Protein
- Urinary + Satiety
- Urinary + Calm
- Renal Support + Hydrolyzed Protein

STAY CONNECTED

References

1. Gobello C, Castex G, Klima L, Rodríguez R, Corrada Y. A study on two protocols combining aglepristone and cloprostenol to treat open cervix pyometra in the bitch. *Theriogenology.* 2003;60(5):901-908.
2. Holt PE. Investigation and therapy of incontinent animals. *Eur J Comp Anim Pract.* 2000;10:111-116.
3. Thrusfield MV, Holt PE, Muirhead RH. Association between urinary incontinence in bitches: its incidence and relationship to neutering practices. *J Small Anim Pract.* 1998; 39(12):559-566.
4. Holt PE. Urinary incontinence in the bitch due to sphincter mechanism incompetence: prevalence in referred dogs and retrospective analysis of 60 cases. *J Small Anim Pract.* 1985;26(4):181-190.
5. Mandigers RJ, Nell T. Treatment of bitches with acquired urinary incontinence with oestriol. *Vet Rec.* 2001;149(25):764-767.
6. Reichler IM, Hubler M, Jöchle W, Trigg TE, Piché CA, Arnold S. The effect of GnRH analogs on urinary incontinence after ablation of the ovaries in dogs. *Theriogenology.* 2003;60(7):1207-1216.
7. Brendler CB, Berry SJ, Ewing LL, et al. Spontaneous benign prostatic hyperplasia in the beagle. Age-associated changes in serum hormone levels, and the morphology and secretory function of the canine prostate. *J Clin Invest.* 1983;71(5):1114-1123.
8. Johnston SD, Kamolpatana K, Root-Kustritz MV, Johnston GR. Prostatic disorders in the dog. *Anim Reprod Sci.* 2000;60-61(5-6):405-415.
9. Johnston SD, Root-Kustritz MV, Olson PNS. Diseases of the canine prostate. In: Johnston SD, Root-Kustritz MV, Olson PNS, eds. *Canine and Feline Theriogenology.* Philadelphia, PA: Saunders; 2001;337-355.
10. Sontas BH, Milani C, Mollo A, Romagnoli S. Blood dripping from the penis of a German shepherd dog. *Aust Vet J.* 2010;88(6):242-244.
11. Teske E, Naan EC, van Dijk EM, Van Garderen E, Schalken JA. Canine prostatic carcinoma: epidemiological evidence of an increased risk in castrated dogs. *Mol Cell Endocrinol*. 2002; 197(1-2):251-255.
12. Sirinarumitr K, Johnston SD, Root-Kustritz MV, Johnston GR, Sarkar DK, Memon MA. Effects of finasteride on size of the prostate gland and semen quality in dogs with benign prostatic hypertrophy. *J Am Vet Med Assoc*. 2001;218(8):1275-1279.
13. Murakoshi M, Tagawa M, Ikeda R. Atrophic effects of antiandrogen chlormadinone acetate (CMA) on dog prostate with spontaneous benign prostatic hyperplasia. *J Toxicol Sci*. 2000;25(3):143-150.
14. Wallace MS. The ovarian remnant syndrome in the bitch and queen. *Vet Clin North Am Small Anim Pract*. 1991;21(3):501-507.

Dechra
Veterinary Products

Is it the same pattern of illness time after time?

Maybe it's time to think Addison's disease?

Although rare, Addison's could be the hidden disease that causes some canine patients to continually be ill. With many of the symptoms mimicking those of other conditions, it can easily mask the real reason why a dog is frequently unwell.

Correct diagnosis of Addison's disease is one of the greatest barriers to tackling the problem. The clinical signs associated with Addison's disease can be non-specific and often wax and wane. Becoming more Addison's aware can help speed up the recognition of this chronic condition that is making your patient sick.

ZYCORTAL® Suspension (desoxycorticosterone pivalate injectable suspension) can safely and effectively replace the mineralocorticoid deficiency in dogs with primary hypoadrenocorticis (Addison's disease) and help you manage your patient's health. It's time to look beyond the obvious and break the pattern of illness. If it's a question of Addison's, ZYCORTAL Suspension is part of the answer.

24 Hour Technical Support: 866-933-2472, www.dechra-us.com, support@dechra.com

ARE YOU ADDISON'S AWARE?

ZYCORTAL®
SUSPENSION (desoxycorticosterone pivalate injectable suspension)

As with all drugs, side effects may occur. In field studies the most common side effects reported were polyuria, polydipsia, depression/lethargy, inappropriate urination, alopecia, decreased appetite/anorexia, panting, vomiting, diarrhea, shaking/trembling, polyphagia, urinary tract infection, urinary tract incontinence and restlessness. ZYCORTAL Suspension should be used with caution in dogs with congestive heart disease, edema, severe renal disease or primary hepatic failure. Dogs presenting in Addisonian crisis must be rehydrated with appropriate intravenous therapy before starting treatment with ZYCORTAL suspension. Refer to the prescribing information for complete details or visit www.dechra-us.com.

NADA 141-444, Approved by FDA CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

See page 88 for product information summary.