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# Reproduction

## How I Treat... Pyometra

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Surgical gonadectomy refers to the surgical

Canine pyometra is a diestral disease typical of adult intact bitches whose development is strongly influenced by sequential progestational stimulations (normal diestrus or treatment with progestins) of the uterus. Bitches whelping regularly throughout their reproductive life almost never develop pyometra, while those who whelp rarely or never in their lives have a greater chance of developing this condition.

During a progestational stimulation the canine endometrium proliferates and starts secreting endometrial fluids (the so called "uterine milk") while the cervix remains closed and myometrial contractility is inhibited (Table n° 1) . Fluid accumulates into the endometrial glands which then dilate becoming fairly large (up to 0.3-2.0 cm diameter). The endometrial pattern that develops is referred to as cystic endometrial hyperplasia (CEH) which is a prerequisite for the development of pyometra due to the fact that uterine milk in itself constitutes an inflammatory stimulus as well as an excellent culture media for bacteria. CEH is a physiological phenomenon whose regression starts during the second half of diestrus. However, with time and number of "open" (non-pregnant) cycles, CEH may not entirely disappear from some sections of the endometrium, thus increasing chances of causing endometrial inflammation. For unknown reasons gestation has a protective action on the canine endometrium, causing areas of the endometrium where placental attachment occurs not to develop any cystic endometrial hyperplastic lesion (although pyometra can occur in one horn with pregnancy in the opposite horn).

<b>Structure</b>	<b>Estrogens</b>	<b>Progesterone</b>
Endometrium	Growth, vascularity, edema of the whole endometrium	Proliferation and secretory activity of endometrial glands
Cervix	Relaxation and dilatation	Closure
Miometrium	Stimulation of contractility	Inhibition of contractility
Uterine Lumen	Stimulation of migration of PMNs into the lumen	Inhibition of migration of PMNs into the lumen

Table n° 1 – Effects of estrogens and progesterone upon different uterine structures in the bitch. These effects are observed during endogenous secretion as well as after exogenous administration. PMNs = polymorphonuclear cells

Being influenced by a progestational stimulus and characterized by accumulation of pus within the

uterus, canine pyometra has historically been approached from a clinical standpoint with drugs such as prostaglandin F<sub>2a</sub> which provides the double action of luteolysis and uterine contractility. Other drugs which have proven useful for this condition include antiprolactinics and, more recently, the progesterone antagonist aglepristone and prostaglandin E. This paper will focus on the most recent advances in the treatment of canine pyometra.

Treatment of pyometra – When treating canine pyometra one needs to be concerned about emptying the pus-filled uterus as well as causing luteolysis. When the cervix is open the uterus can be easily emptied stimulating myometrial contractility. Of all the drugs causing contraction of the uterine musculature (prostaglandins, oxytocin, ergot derivatives) prostaglandins (PG) are the most indicated for the clinical treatment of pyometra because of their more physiological action on the diestrous uterus. Prostaglandin-based drugs which have been tested in the canine and for which safe dosages have been developed include natural PGF<sub>2a</sub>, the PGF<sub>2a</sub> synthetic analogs cloprostenol and alfaprostol, and most recently the PGE misoprostol (see table n° 2).

Prostaglandin	Daily dose in the bitch	Administrations/day
Natural PGF <sub>2α</sub> , Dinoprost	Bitch – 50-100 mcg/kg (0.05-0.1 mg/kg)	2, SC 2, SC
Cloprostenol	Bitch - 1 mcg/kg (0.001 mg/kg)	1, SC
Alfaprostol	Bitch - 20 mcg/kg (0.02 mg/kg)	2, SC
Misoprostol	Bitch - 10 mcg/kg (0.01 mg/kg)	2, per os

Table n° 2 – Dosages of the most commonly used prostaglandin compounds in bitches to induce luteolysis and cause uterine contractility. Prostaglandins should never be used to treat a closed-cervix pyometra because of the risk of uterine rupture or of pushing uterine pus retrogradely into the uterine tubes. When treating a bitch with any prostaglandin, start with half the normal dosage and gradually achieve the full dose within the first 2-3 days of therapy.

PGF<sub>2a</sub> offers the advantage of a double (miocontractile and luteolytic) action, but may cause some side effects depending on dosage. For instance, higher dosages of natural PGF<sub>2a</sub> (150-250 mcg/kg) are characterized by a well known cascade of side effects, which are rarely observed when using lower doses. Side effects of prostaglandins should not be overemphasized as, when using i.e. doses of 50-100 mcg/kg of natural PGF<sub>2a</sub>, they are not observed in all bitches, tend to subside during the course of the treatment and are significantly less common when using dosages of natural PGF<sub>2a</sub> <50 mcg/kg. However, side effects tend to be more evident in bitches with pyometra, perhaps because of the deteriorated physical conditions which characterize the uterine disease.

PGE has been recently tested in dogs with pyometra and appears to be effective for causing evacuation of uterine content, although no information is yet available on its luteolytic properties. Oxytocin and ergot derivatives induce very strong, short-lasting contraction of the uterine wall which are not thought to be adequate for emptying a pus-filled uterus. However, no specific studies have ever been done on efficacy of oxytocin or ergot derivatives in bitches with pyometra. Based on studies done in diestrous bitches by Wheaton and Barbee (1993), PGF<sub>2a</sub> doses of 50 and 250 mcg/kg cause a maximum uterine pressure of 47±6 and 51±9 mm Hg, respectively (no significant difference), and a duration of the uterine contraction significantly lower at 23±3 minutes for the lower dosage vs 30±3 minutes for the higher dosage, respectively. The minor advantage of the 250 mcg/kg vs the 50 mcg/kg dose (the contraction is about 7 minutes longer with the higher dose) makes the lower dose (50 mcg/kg) actually preferable because of less side effects. Efficacy of low doses of natural PGF<sub>2a</sub> has been reported for bitches with pyometra (Lange et al., 1997). Such a treatment protocol is effective provided that prostaglandins are administered 2-3 times daily for as long as a vulvar discharge is present.

*Length of treatment* – In order for a pus-filled uterus to be emptied prostaglandin administration should be continued as long as a vulvar discharge is present. Although large amounts of pus in the uterus may require treatments of several weeks duration, even when the uterus is not greatly enlarged caution should be taken not to stop the treatment too soon. The decision on when to stop the treatment should be based on a) evaluation of uterine dimensions before, during and after therapy (in order to confirm that uterine diameter has gone back to normal) as well as b) disappearance of fluid within the uterine lumen detectable on ultrasound; in normal conditions the uterine lumen is not detectable, but it becomes distinguishable when liquid accumulates within the uterus.

*Risk of uterine rupture* - The administration of miocontractants may be dangerous if the uterus is fully dilated with pus and/or the uterine wall is thin and atrophied or the cervix is only partially dilated, as this may cause either a) the pus to be forced backward into the uterine tubes and then into the abdomen, or b) the uterine wall to rupture. Uterine rupture is a very rare event, and can be caused by any drug stimulating uterine contractility. The risk of uterine rupture can be subjectively assessed looking at the thickness of the uterine wall with ultrasound using 7.5-10.0 MHz probes.

*Using antibiotics* - Antibiotic treatment should be specific as soon as culture results are available (a broad spectrum antibiotic such as ampicillin at 22 mg/kg 3 times/daily can be started in the meantime) and it should also continue for as long as a purulent vulvar discharge is present (which may persist for a few days after uterine diameter has become normal again). At the following proestrus a cranial vaginal culture should be taken and the bitch treated with a specific antibiotic until ovulation, and then bred to a proven fertile male at the proper time in order to ensure conception. When reproduction is not deemed necessary any longer the bitch should be spayed, as the recurrence rate of pyometra in older dogs may be higher than 50%.

*Causing luteolysis* - When dealing with an open cervix pyometra in the bitch, prostaglandins are useful also for their luteolytic properties. Serum progesterone assay at the start of treatment will allow to monitor effectiveness of luteolysis which is important to avoid recurrence of pyometra during that same cycle. When presenting with a pyometra in early diestrus, a bitch might recover quickly following a specific antibiotic treatment, but if luteolysis is not achieved the clinical manifestations of the disease will recur as soon as the antibiotic concentration decreases in the general circulation. The use of antiprogestins such as aglepristone has an effect similar to the luteolysis produced by prostaglandin, in that progesterone receptors in all districts of the organism are blocked. For the treatment of open-cervix pyometra antiprogestins offer the advantage of causing virtually no side effects when compared to prostaglandin F2a.

*Treatment of closed-cervix pyometra* – The availability of antiprogestin-based drugs has completely changed the clinical approach to a problem whose only solution for the last decades has been ovariohysterectomy. The administration of aglepristone during diestrus in the bitch will cause opening of the cervical os with consequent emptying of the uterine content. Following treatment with a dose of 10 mg/kg aglepristone administered on days 1, 2 and 8 in 15 bitches with closed pyometra, opening of the cervix was reported to occur after  $26 \pm 13$  hours in all treated animals. Although the success rate in closed cervix pyometra following 3 administrations of aglepristone alone is reported to be around 20%, a follow-up treatment of the same dosage of the antiprogestin at day 14 and 28 associated to a prostaglandin treatment once the purulent vulvar discharge becomes evident has risen the success rate to 90%. Antiprogestins can be used to avoid recurrence of pyometra at subsequent cycles should the owner decide not to breed the bitch immediately. Bitches with a closed cervix pyometra and with liver or kidney insufficiency are not considered good candidates for a medical treatment with aglepristone.

*Concurrent clinical problems* - Faecal/perineal bacteria (*E. coli*, *Streptococcus* spp., *Staphylococcus* spp., *Klebsiella*, *Proteus* and *Pseudomonas* are the most common ones) often concur to the development of uterine lesions and clinical signs (especially if they cannot be cleared from the uterus prior to onset of the luteal phase), but are not necessary for the clinical manifestation of the disease. *E. coli* can produce an endotoxin which, upon bacterial death (i.e. following an antibiotic treatment), is released into the uterine lumen and absorbed. The resulting endotoxemia may cause a severe shock reaction

and death of the bitch depending on the amount of endotoxin released and on the physical condition of the dog (antibiotics have no effect on concentrations of endotoxins). Clinical signs of endotoxemia include disorientation, hypothermia and shock. Renal lesions are frequent in bitches with pyometra (especially in older bitches), being due to either the disease itself (because of pre-renal azotemia due to dehydration or glomerular/tubular disease due to the bacterial infection or endotoxemia) or because they were already present when pyometra developed. Bone marrow, liver and spleen disease can also be either already present or caused by the disease itself in bitches with pyometra.

Diagnostic challenges – Diagnosing pyometra in the bitch may be very easy, especially if uterine enlargement and leukocytosis (the only 2 clinical signs which are relevant to the diagnosis) can be appreciated along with the other classical signs of polyuria/polydipsia, anorexia, depression, vulvar discharge (in case of open cervix pyometra). Bitches with a closed cervix pyometra with only a slight to moderate increase in uterine size are the most challenging cases, especially if leukocytosis is absent or if there is neutropenia (which may be due to endotoxemia). The range of WBC count reported for bitches with pyometra is 2500-196,800 cells/mm<sup>3</sup>, with a left shift in 70-90% of cases. Average number of bands (toxic PMNs) is about 500 cells/mm<sup>3</sup>, with degree of toxic change correlated with the severity of disease. Other abnormalities (anemia, azotemia, hypergammaglobulinemia, hypoalbuminemia, metabolic acidosis, decreased urine specific gravity, proteinuria, bilirubinuria) may or may not be present and when present may or may not be related to the uterine disease. Although not always relevant to the diagnostic process, liver, kidney and bone marrow function tests should be carried out to allow for a proper clinical management of the disease, thus avoiding canine pyometra patients to die i.e. for a renal complication once the uterine problem has been cured. Pregnancy should always be ruled out, as it may coexist with pyometra. Less common differential diagnosis include diabetes mellitus, hyperadrenocorticism, renal disease, diabetes insipidus.

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