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Mucometra, cystic endometrial hyperplasia, and pyometra in the bitch: Advances in treatment and assessment of future reproductive success

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Abstract

Pyometra is a common reproductive disorder which affects nearly one fourth of all female dogs before they reach 10 y of age. An association between pyometra and the most common uterine disease of the bitch, cystic endometrial hyperplasia, has been established, as the latter allows commensal bacteria originating from the vagina to proliferate in the uterus at the end of estrus. The progressive degenerative process in the development of cystic endometrial hyperplasia is usually proposed as the initiating lesion for pyometra in bitches; this is mediated by progesterone and potentially aggravated by estrogens. However, a separate process caused by local uterine irritation to trophoblastic reaction and bacterial proliferation has been recently proposed as an alternate mechanism leading to the development of pyometra. Pyometra is clinically distinct in pathogenesis, signs, treatment and prognosis from postpartum metritis or mucometra. Treatment of pyometra has historically involved ovariohysterectomy, however, during the last 10 y, numerous effective treatments have been proposed to treat both open and closed cervix pyometra with good success and future fertility. Among the treatments available, the use of repeated low doses of prostaglandins alone or in association with either dopamine agonists or progesterone-receptor antagonists has been demonstrated to be a viable alternative for valuable breeding dogs.

Keywords: Mucometra; Cystic endometrial hyperplasia; Pyometra; Treatment; Dog

1. Introduction

Pyometra is a common reproductive disorder which affects nearly one fourth of all female dogs before they reach 10 y of age [1]. In a beagle colony followed over several years, the incidence of pyometra was 15.2% in female dogs >4 y old [2]. Pyometra is a clinical entity, distinct in pathogenesis, signs, treatment and prognosis from postpartum metritis or mucometra. An association between pyometra and the most common uterine disease of the bitch, cystic endometrial hyperplasia (CEH), has been established; the latter allows commensal bacteria originating from the vagina to proliferate in the uterus at the end of estrus. The progressive degenerative process of development of cystic endometrial hyperplasia is usually proposed as the initiating lesion for pyometra in bitches; this is mediated by progesterone and potentially aggravated by estrogens [3].

2. Etiopathogenesis

Pyometra is considered a disease diestrus, although some anestrous bitches can be diagnosed with pyometra

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[4]. In the anestrous cases (approximately one-third of the total pyometra cases), it is uncertain whether the animals described were observed after the end of a normal luteal phase or whether there had been, at least in some of the animals, a premature shortening of the luteal phase. This premature shortening of the luteal phase may be induced by production of endogenous prostaglandin in response to the uterine inflammation, as observed in other species. The relevance of the association between pyometra and diestrus was demonstrated by Lesboyries and Berthelon in 1936 [5]; they reported that ovariectomy without hysterectomy in bitches with pyometra was followed by clinical cure in 5–7 d. Similarly, in a retrospective study of >10 y, Janssens and Janssens [6] confirmed the evidence of the role of ovarian steroids in the pathogenesis of the disease, as bilaterally ovariectomized dogs never developed pyometra. The importance of progesterone in the pathogenesis of the spontaneous disease is attributed to its suppression of immune responses, stimulation of endometrial gland secretions which provide a suitable environment for bacterial growth, functional closure of the cervix which inhibits drainage of uterine exudates, and mediation of cystic endometrial hyperplasia [7,8]. Considering the role of progesterone, it is interesting to observe that some dogs with pyometra present with basal plasma progesterone concentrations and one would typically expect the pyometra to resolve in such conditions. Failure to resolve may be due to either the inability of the degenerated uterus to contract or failure of the cervix to relax. Another possibility is that although plasma progesterone concentrations are below the sensitivity of standard progesterone assays, there is enough progesterone produced to inhibit uterine contraction and cervical relaxation.

Although the association between pyometra and diestrus has been well-established, the precise mechanism is still not clear [9]. Early reports suggested that excessive or prolonged exposure to progesterone was responsible for the susceptibility to pyometra and, indeed, the disease can be induced experimentally by the administration of exogenous progesterone to ovariectomized bitches [10]. However, more recent studies have not been able to substantiate that either higher concentrations or more prolonged periods of progesterone secretion in bitches resulted in development of pyometra. In a Finnish study [11], no significant risk-enhancing effect of progestin treatment was detected and it was concluded that, if present, such risk is probably low. Likewise, the importance of potential predisposing factors such as nulliparity, irregular estrous cycles, or pseudopregnancy has not been determined [12]. In the same Finnish case-control study, pyometra was reported in animals ranging from 9 m to 18 y of age, with diagnosis at a median age of 9 y. Nulliparous bitches had a moderately higher risk of developing pyometra and prior administration of estrogen increased the risk for pyometra. Seventeen breeds had an increased risk, whereas the Wire-Haired Dachshund and mongrels had a decreased risk of developing the condition. Other studies suggested that an exaggerated response to progesterone, rather than progesterone concentrations, may be present in bitches which develop pyometra. However, studies targeting the evaluation of steroid receptors in normal and pathological tissues have not been able to clearly demonstrate any significant differences in receptor expression [13].

In the common dogma, CEH-associated degenerative changes within the uterine tissues (cystic distention of glands, fibrosis, etc.) are suggested to provide opportune conditions for establishment of uterine infections. The already compromised uterus is invaded by opportunistic pathogens (primarily *Escherichia coli*) from the vagina which, particularly when it possesses optimal adhesion factors, will proliferate and establish infection within the uterus. It is inferred that infection is established because of excessive amounts of secretory fluids accumulated within the lumen, the presence of numerous crypts and cysts where bacteria can proliferate, and reduced local immunity, either associated with or resulting from local tissue degeneration. This association is reflected in the naming of the condition ‘‘Cystic Endometrium-Pyometra Complex’’ [14,15].

However, while common dogma dictates that CEH usually precedes pyometra development, it is also obvious that CEH does not inevitably progress to pyometra in all bitches. This is evident, as all dogs develop CEH with age, whereas only some of them will develop a pyometra. Similarly, pyometra can develop in young animals which do not have prior clinical or pathological evidence of CEH.

Recent work by Nomura and co-workers [16–22] and the clinical observations of Koguchi et al. [23] have suggested that the classical sequence of progesterone leading to CEH and subsequently, CEH to pyometra may not be correct, and that the sequence may in fact be reversed with bacteria being the initiating factor. A subtle (sub-clinical) uterine infection or endometrial irritation by foreign bodies may first occur at the end of estrus or during the first half of diestrus, providing the stimulus for an excessive endometrial hypertrophy and hyperplasia, similar to what is observed at the time of

implantation (''trophoblastic or decidual reaction''). The resulting increase in endometrial glandular proliferation and luminal epithelial cellular secretions can initiate the development of a pyometra or a mucometra, depending on whether the promoter is of bacterial origin or not, respectively. This hypothesis is supported by results of experiments done in dogs which have shown that, at specific periods during the luteal phase of the cycle, a variety of physical, biological, and chemical substances will cause the endometrium to proliferate. This hypothesis, however questioned by De Bosschere et al. [15], can also be supported by clinical observations of pyometra in young animals where CEH is obviously not present.

The bacteria most frequently isolated from the uterus in case of pyometra include *E. coli*, *Staphylococcus aureus*, *Streptococcus* spp., *Pseudomonas* spp., and *Proteus* spp. These organisms are also those most commonly isolated from the vagina of normal bitches [24–27]. *E. coli*, the most predominant organism, adheres specifically to binding sites in the progesterone-stimulated endometrium through its uropathogenic virulence factor (UVF) genes such as pap, sfa, hlyA, cnF1 and fim. These genes have been shown in humans to enhance the pathogenicity of *E. coli* by facilitating attachment to the epithelium. Recently, Chen et al. [28] and Arora [29] demonstrated that small numbers of UVF genes bearing *E. coli* were associated with enhanced severity of pyometra as a result of increased binding to the uterine epithelium.

In conclusion, pyometra is currently believed to result from an interaction between potentially pathogenic bacteria and the progesterone primed (altered or not) endometrium, in a sequence which still needs to be validated.

3. Diagnosis

A variety of signs may be detected by the owners. The most obvious one is vaginal discharge, which may vary from serosanguinous to mucopurulent. In some bitches, the amount of discharge is minimal and fastidious grooming by the bitch makes that discharge difficult to detect. In other cases, signs of vaginal discharge may not be externally apparent, but vaginal smears and vaginoscopic examination reveal the presence of uterine exudate in the cranial vagina. The amount of vaginal discharge is also partially dependent on the degree of cervical patency. Many bitches with a ''closed'' pyometra and apparently less obvious discharge are presented in a more advanced stage of the disease and in a more serious clinical condition. Fortunately, some degree of discharge is evident most cases.

Usually the onset of clinical signs is gradual and insidious. Common signs include lethargy, depression, and inappetance. Vomiting may be present and is more common in the more severely affected patients. Polyuria and polydipsia are often cited as signs of pyometra, and renal impairment is a feature of the disease, but these clinical signs are not consistent, being recorded in $\leq$50% of bitches with confirmed pyometra. In one reported case, uveitis was the presenting clinical sign. Fever is not a common feature of pyometra. Dehydration may be present in more advanced cases.

Because the signs are not definitive, pyometra should be suspected in any post-estrus bitch with any of the following: vaginal discharge, depression and lethargy, polyuria or polydipsia, vomiting, and/or fever. Classically, pyometra cases are regarded as being accompanied by marked leukocytosis characterized by neutrophilia with a left shift and toxic degeneration of neutrophils, as well as a monocytosis. However, this is not always present, since as many as 25% of pyometra cases may have leukograms within the normal range. Many affected bitches have a mild to moderate normocytic, normochromic anemia (PCV 30–35%). This is believed to reflect the chronic nature of the disease and the toxic suppression of the bone marrow. Evaluation of the anemia is often complicated by concomitant dehydration. Hysterectomy leads to rapid improvement of hematologic and immunologic parameters in bitches with pyometra [30]. However, similar results are observed after medical treatments [31].

Despite modern treatment routines, the mortality rate due to pyometra is still approximately 4% [1]. Myocardial injury secondary to endotoxemia, inflammation, disseminated bacterial infection, or infarction is suspected to be a contributing factor in unexpected deaths [32].

The most consistent clinical blood chemistry finding is elevated serum alkaline phosphatase, present in approximately 50–75% of cases; occasionally serum alanine aminotransferase concentrations may also be mildly elevated. These changes reflect hepato-cellular damage in response to toxemia, or diminished hepatic circulation due to dehydration. Hyperproteinemia may develop in response to dehydration, and hyperglobulinemia reflects the chronic antigenic stimulation present with this disease.

Renal dysfunction has been mentioned as a feature of canine pyometra. Serum blood urea nitrogen and creatinine concentrations are not usually elevated, unless pre-renal azotemia develops as a consequence

of dehydration. In surgically treated animals, azotemia resolves promptly after fluid therapy, anesthesia, and surgery, confirming the pre-renal nature of the azotemia. Azotemia is generally associated with more severe clinical signs. Even in non-azotemic rehydrated patients, glomerular filtration is usually decreased, indicating that some factors associated with the disease affect renal perfusion either in the presence or absence of azotemia.

In a few cases, a urinary tract infection with the same organism infecting the uterus (usually *E. coli*) is found. However, cystocentesis is not recommended in bitches suspected of having a pyometra, as there is a high risk of perforating the distended uterus. Urine specific gravity is variable and is frequently within normal limits in the early stages of the disease. Bacterial endotoxins impair the ability of the loop of Henle to reabsorb sodium and chloride. *E. coli* endotoxins seem to have a specific ability to cause tubular insensitivity to anti-diuretic hormone (causing development of a secondary nephrogenic diabetes insipidus), resulting in further loss of urinary concentrating ability; this leads to polyuria and a compensatory polydipsia. Functional glomerular impairment is an early development, preceding tubular damage, and indicated by elevated urinary gamma-glutamyl transferase. Renal protein loss is uncommon, however, protein may be elevated on dipstick evaluation of free-catch samples of urine, due to contamination with utero-vaginal discharge.

On histological evaluation with light microscopy, tubulo-interstitial inflammation is observed in dogs with pyometra, but glomerular damage beyond age-related changes, could not be demonstrated as being more significant in dogs with pyometra compared with a normal population of dogs. Lympho-plasmacytic interstitial infiltrates, often seen in a peri-glomerular location, were accompanied by a higher prevalence of interstitial fibrosis and tubular atrophy in dogs with pyometra, confirming previous reports of renal lesions in those dogs [33]. Severe proteinuria after surgery may predispose to development of renal failure. Blood pressure control and ACE inhibition has become routine in canine nephrology and should certainly be followed carefully in dogs with pyometra. One recent study in humans demonstrated that proteinuria is a strong independent predictor of end-stage renal disease in a mass-screening context [34]. Some dogs with pyometra and severe proteinuria progress to renal failure. This finding illustrates the importance of proteinuria as a valuable prognostic indicator and post-surgical follow-up of urinary protein excretion patterns in dogs with pyometra. Heiene et al. [35] reported progression to renal failure in one proteinuric dog, out of six dogs with pyometra, despite close follow-up and treatment [36].

These data are not consistent with the commonly accepted notion that pyometra leads to an immune-mediated glomerulonephritis. Current literature is equivocal on that point. The two studies investigating immune-mediated glomerulonephritis did not include an age-matched control group [33] or just a control group [37]. Immune deposits in glomeruli of healthy individuals are documented in pigs [38] and in humans [39]. Glomerular immune deposits are documented in dogs without any known kidney disease and more predominantly in old dogs [40]. In one controlled study [41], pyometra-related changes in the kidneys were similar in severity to age-related changes in healthy dogs, as evaluated by light microscopy, electron microscopy, and immunohistochemistry.

Uterine enlargement may sometimes be palpable but may be demonstrated more safely and reliably with ultrasonography, which has made definitive diagnosis of pyometra much easier. The thickness of the uterine walls and the characteristics of the fluid may be determined, allowing differentiation between pregnancy, CEH, pyometra and mucometra. In pyometra, the uterine wall is usually thickened and the uterus is distended to a variable extent with serous to viscid heterogenic fluid often presenting flocculation, whereas mucometra will be characterized by thin uterine walls and hypoechoic fluid.

4. Treatment

Historically, pyometra has been most commonly treated by ovariohysterectomy (OHE), once the bitch has been adequately stabilized. This remains the recommended treatment in all cases for bitches without significant reproductive value, or when the owner has no strong desire to breed the bitch. Due to the insidious nature of the disease and its sometimes equivocal clinical signs, patients are often presented in poor condition for anesthesia and surgery. Although treatment should not be unduly delayed, patients should be stabilized prior to surgery, by administration of intravenous fluids and broad-spectrum antibiotics. Kidney function and liver enzymes should be evaluated and treated accordingly. Supportive measures should be continued during and after surgery; antibacterial therapy should be continued for at least 1 wk following surgical treatment. Despite these precautions, some complications may still be observed. The main advantage of OHE is the exclusion of any risk of recurrence. However, surgical treatment has its limits

when the risks of anesthesia and surgery are life threatening. During the last 10–15 y, other conservative strategies have been developed.

The earliest proposed medical therapy employed simply the use of systemic and local single antibiotics [42,43]. However, this generally leads to either a worsening or a delay in the worsening of the disease, with need for additional treatment at a later date.

More recent and successful medical treatments have involved the repeated administration of prostaglandin $F_{2\alpha}$ (PGF), which causes luteolysis and thus reduces plasma progesterone concentrations [44,45]. Reduction in progesterone concentrations induces cervical relaxation, a decrease in uterine secretions and, since prostaglandins also have a uterine spasmogenic action, the expulsion of uterine fluid. However, when high doses are used, prostaglandins have also been associated with substantial risk of uterine rupture, especially in cases of closed-cervix pyometra [46]. Furthermore, higher doses of prostaglandins are associated with substantial adverse effects, including salivation, vomiting, straining, diarrhea, pyrexia, some occasional respiratory distress [47], as well as cases of shock and death [48].

Historically, estrogen administration was proposed to relax and open the cervix, as well as to increase uterine contractility. However, the initial induced vasodilatation and the increased blood flow at the level of the uterus was associated with an abrupt increase in toxin resorption and this increased toxemia dramatically worsened the clinical picture. The therapeutic success was thus mediocre and the use of estrogens was abandoned [49–53].

During the last 10 y, new approaches have been proposed and numerous successful results of medical treatment for canine pyometra have been reported. Although these approaches have involved different protocols, they all essentially have the same goals (only the uterine aspects of the treatment are covered here):

(1) Preventing progesterone effects by either inducing luteolysis or preventing progesterone binding to its receptors. New protocols for the use of PGF have been proposed, either alone or in association with either dopamine-agonists or progesterone-receptor antagonists.
(2) Promotion of cervical relaxation in closed pyometra to allow for the expulsion of the uterine contents. This is generally achieved by the administration of either prostaglandins or progesterone-receptor antagonists.
(3) Induction of uterine contractions and emptying, either directly through the use of PGF, or indirectly via progesterone-receptor antagonists.
(4) Inhibition of bacterial growth and development through the use of broad-spectrum or specific-spectrum antibiotics.
(5) Facilitating uterine regeneration in animals with clear signs of uterine degeneration. This is accomplished by prolonging anestrus. Prolongation of anestrus allows for further apoptosis and regeneration of the endometrium, preparing the animal for a new pregnancy. The androgen-receptor agonist, mibolerone, is used for this goal.

4.1. Luteolysis, cervical opening and uterine contractions

When treating pyometra, the first objective after initially stabilizing the patient, is to remove the effects of progesterone either directly (luteolysis) or indirectly (progesterone receptor blockade). Inhibiting progesterone secretion or its effects should obviously be the first goal of any treatment; in that regard, progesterone inhibits uterine contractions, is responsible for the cervical closure, has negative effects on uterine immunity and protection against infections, and facilitates uterine secretion, and cystic endometrial development. Preventing these effects can be achieved by attacking the CL directly with prostaglandins, or indirectly by using a dopamine-agonist which, through prolactin inhibition, will induce functional arrest and finally luteolysis of the CL. This can also be achieved by preventing progesterone binding to its receptors by using a progesterone-receptor antagonist such as aglepristone.

4.1.1. Prostaglandins

The use of PGF to treat pyometra in dogs has been reported by several authors and the results have generally been positive, except when high doses were used [54–57]. Treatment with PGF, apart from its luteolytic effects, mediates functional opening of the cervix, which permits drainage of exudate, and promotes myometrial contractions, facilitating uterine drainage. Prostaglandin therapy is not approved for use in the dog in many countries, and, even if considered safe at new recommended dosages, the client's consent must be secured for this extra-label drug use.

Treatment with PGF at doses of 10–50 μg/kg, administered three to five times daily for 3–7 d, have been used successfully for treatment of canine pyometra, either solely or in combination with other

drugs. These dosages apply only to the natural forms of prostaglandin (i.e. dinoprost tromethamine). Natural prostaglandin is preferable to prostaglandin analogues, as it not only induces substantial luteolysis, but also results in more substantial uterine contractions. Extreme care should be exercised in calculating the dose, as the therapeutic index is relatively small (LD50 in dogs is approximately 5 mg/kg) and side effects are quite severe when high doses are used (>100 μg/kg). The drug should be given SQ or IM. Since side effects are dose-dependent and are known to diminish with repetition of treatment, it is recommended that one start with the lowest dosage to avoid the classic side effect of vomiting, and then to slowly increase the dosage to reach higher doses (50 μg/kg) after 2–3 d. We generally administer 10 μg/kg five times a day the first day, increase to 25 μg/kg five times a day the second day, and reach 50 μg/kg on Day 3. Doses of 50 μg/kg are then administered three to five times daily for the rest of the treatment. Side effects are uncommon with this regimen (<15% show signs). They are rarely observed after the first two or three injections, and may consist of vomiting, diarrhea, panting of moderate to mild intensity beginning 20–30 min after administration and never lasting for >30 min. Synthetic prostaglandins such as cloprostenol can be used instead of natural prostaglandins. Although their use is associated with reduced side effects (essentially emesis) and prolonged activity, they have a reduced ability to induce uterine contractions, resulting in slower evacuation of the uterus.

Intravaginal infusion of natural prostaglandins once or twice daily has also been tried with apparently good results and with the advantage of no side effects [58]. This approach needs further validation before being recommended, but opens new therapeutic possibilities for pyometra treatment.

4.1.2. Dopamine agonists

The most important luteotropic hormone in the bitch is prolactin and repeated administration of prolactin inhibitors from 25 d after ovulation onward results in a rapid and permanent reduction of plasma progesterone concentration [59], an effect that has been used to terminate unwanted pregnancy. More recently, prolactin inhibitors have been combined with low-dose prostaglandin regimens to treat pyometra in an attempt to hasten luteolysis, as demonstrated in studies of induced abortion [60,61].

Dopamine agonists such as bromocriptine or cabergoline, with substantial anti-prolactin activities, have been used in combination with either natural or synthetic prostaglandins. Cabergoline is the authors' first choice, as it is has few to no side effects and may be administered only once a day versus twice or thrice daily for bromocriptine. The combination of dopamine-agonist and prostaglandin potentiates the luteolytic effects of each drug and results in more rapid luteolysis [60,61]. When the combination is used, serum progesterone concentrations decline in <24 to 48 h, whereas low doses of prostaglandins alone will exert their effects only after 3–4 d. Cervical opening is generally observed after 1 d (or at most 2 d), with the combination protocol, versus several days when PGF is used alone.

4.1.3. Combination of PGF and dopamine agonists

Recently, England et al. [31] presented results for the treatment of 22 bitches with closed or open pyometra using the combination of cabergoline 5 μg/kg/d and cloprostenol at the same dosage administered every third day. There was a rapid clinical improvement associated with a reduction in plasma progesterone concentration, an increase in vulvar discharge and a reduction in the diameter of the uterus, in an average of 10 d. The hematological profiles of 21 of the 22 bitches returned to normal within 6 d of treatment, and their biochemical profiles returned to normal within 9 d. Nineteen of the bitches were managed successfully with 10 d of treatment, whereas two of the bitches required a further 3 d treatment, and in one bitch with a partial uterine torsion, treatment was not successful. Adverse effects of the treatment were limited to the 60 min immediately after the administration of prostaglandins, and included retching, vomiting, mild abdominal straining, diarrhea, and panting. The incidence of adverse effects was reduced after each successive dose of prostaglandins. Side effects may have been reduced by decreasing the cloprostenol dose to 1 or 2.5 μg/kg with the same luteolytic activity, but this would probably require more frequent administration. This treatment appears easier than the classical one, characterized by numerous repeated administrations of low doses of natural prostaglandins; however, side effects are more significant, and the interval from the beginning of the treatment and the resolution of the disease is longer than classically observed with natural prostaglandins.

When dopamine-agonists are used in a combined protocol with natural prostaglandins, similar doses and regimes are used with either cabergoline at 5 μg/kg once a day orally for 7 d, or bromocriptine at 25 μg/kg thrice daily orally for 7 d.

4.1.4. Progesterone-receptor antagonists

Recently, in countries where the drug is available, the use of progesterone-receptor antagonists has been

proposed with sometimes controversial results. Progesterone-receptor antagonists, such as mifepristone [62] or aglepristone [63–66], bind to the progesterone-receptor which they completely block, preventing any biological activity. Progesterone-receptor antagonists competitively prevent progesterone from binding to its receptor to induce transcription and exert all its biological effects at the cellular level. Consequently, the absence of receptor stimulation and activation mimics the effects observed when luteolysis is induced and thereby causes relaxation of the cervix.

Controversy still exists regarding the ability of this treatment to induce uterine contractions if used alone. Unlike the action of PGF, progesterone antagonists are not expected to induce myometrial contractions. However, some studies hypothesize that uterine contractions are indirectly induced by the local uterine release of endogenous prostaglandins as a consequence of the endometrial inflammatory process associated with the pyometra. In the authors' experience, uterine contractions associated with the use of progesterone-receptor antagonists have never been obvious enough to allow for the safe use of this type of drug without combination with prostaglandins. The use of this combination of medications results in both uterine contractions and induction of luteolysis, which in turn prevents all the effects of progesterone on the uterus and on the immune system.

Aglepristone, not available in United States, suppressed the biological actions of progesterone during pregnancy, interrupting gestation [67–69], causing cervical relaxation, and inducing parturition [70]. This product has been effectively used in the treatment of uterine infections associated with elevated plasma progesterone concentrations [64,71,72]. Some recent work has described the use of aglepristone, in combination with cloprostenol, to treat bitches with pyometra [73]. Treatment with aglepristone alone was a safe and effective treatment for pyometra, and was an effective means of inducing cervical opening in some cases of closed pyometra. Furthermore, the combination of aglepristone with cloprostenol was more effective in the medical treatment of open and closed pyometra than aglepristone alone [73,74].

4.1.5. Prostaglandin E

In many species, normal relaxation of the cervix at the time of estrus and ovulation is probably the result of the peri-ovulatory changes in reproductive hormones that occur at this time. The increases in estradiol (and possibly oxytocin) receptor concentrations [75] during the peri-ovulatory period are thought to increase prostaglandin E2 synthesis and receptors [76], leading to remodeling of cervical extracellular matrix [77,78] which allows relaxation of the cervix. In ewes, misoprostol has been demonstrated to improve cervical patency and penetrability at the end of estrus [79]. This effect appears to be related to misoprostol-induced increased expression of the mRNA for FSH-R in all cervical layers [80]. Anecdotcal results concerning the successful use of misoprostol intravaginally to promote cervical relaxation have been presented in dogs, but without scientific evidence of its efficacy.

4.2. Antimicrobial treatment

Concomitant broad-spectrum antimicrobial therapy should be administered during any treatment protocol. Ideally, identification and sensitivity should be determined from vaginal discharges as soon as possible and before initiating any antimicrobial treatment. Some bitches with pyometra are bacteremic and it is reasonable to propose that the increased uterine contractility associated with medical treatment may predispose bitches to further increases in bacteremia, or to potentially induce septicemia. Many antimicrobials have been used successfully, but *in vitro* sensitivity studies and clinical evidence suggest that amoxicillin, amoxicillin plus clavulanic acid, cephalosporins, or potentiated sulfonamides are good initial choices. The final choice should always be based on the culture, identification and sensitivity of the bacteria involved.

If drugs are administered orally, provision must be made for the possibility of vomiting which may follow PGF injections. It is recommended that the antimicrobial therapy be continued for 10–14 d after complete resolution of the pyometra, as assessed by ultrasonography, physical examination and blood work. The bitch should be re-evaluated 2 wk after completion of the prostaglandins (with or without dopamine agonist or progesterone-receptor antagonist treatment) by ultrasonographic examination and if vaginal discharge, fever or neutrophilia are still present, a prolonged course of antibiotic therapy is recommended.

4.3. Uterine regeneration

To avoid recurrence of the pyometra, particularly in animals with clear signs of uterine degenerative processes age-related (CEH), it is essential to facilitate uterine regeneration during the post-treatment anestrus. Prolongation of anestrus (and postponement of the next estrus), allows for further apoptosis and regeneration of the endometrium; this can be achieved with administration of an androgen-receptor agonist such as

mibolerone [81–82]. Postponing the next cycle for a few months (~2 mo, to a maximum 3 mo) will prolong the healing period and facilitate regeneration of the uterus, with a reduction of the major CEH lesions. Mibolerone can be administered following the manufacturer's recommendations, starting approximately 1 mo after the end of medical pyometra treatment. Estrus will be observed from a few weeks to months after cessation of mibolerone treatment. Uterine lavage, culture and/or uterine biopsies may be indicated in refractory cases. If performed, biopsies should be obtained in anestrus to reduce the risk of trophoblastic reaction induction (see above).

4.4. Disease evolution

The condition of dogs under treatment should be monitored closely. In some animals, due to the increase contractility of the uterus, resorption of toxins may increase and the overall condition of the animal may eventually deteriorate. Supportive treatments are absolutely required and should minimally include perfusion with IV fluids at 1.5–2 times the maintenance rate, and eventually renal and hepatic as well as cardiovascular support. The rupture of the uterus, never observed by the authors when prostaglandins are used at low doses (see above), but described by others when prostaglandins were used at doses >100 μg/kg, spontaneously or during treatment, may be observed by temporary improvement of the clinical status of the dog before a severe bacterial peritonitis supervenes and an acute-abdomen syndrome develops.

When prostaglandins alone, or in association with a dopamine agonist or a progesterone-receptor antagonist, are used, the condition of the animals usually improves within the first 48 h after the onset of treatment. This is accompanied with a noticeable increase in the amount of discharge 24 h after initiation of treatment. This increase in the amount of the exudate is associated with the decrease in plasma progesterone concentrations or progesterone inhibition. The discharge changes from purulent or serosanguineous to serous, and its cessation occurs in most cases, in 4–7 d.

The most commonly affected parameters include changes in the blood profile (leukocytosis with neutrophilia or leukopenia and inhibition of lymphocyte activity). It has been recently shown that following hysterectomy for pyometra treatment, all affected parameters return to normal within 7 d [30]. In medically treated dogs, the leukogram returns to normal within 10–15 d, although leukocytosis may be initially aggravated in some cases [31].

Evaluation of the efficacy of the treatment is documented with ultrasonography and is demonstrated by a reduction of the uterine lumen by at least 5% within 3–5 d after the start of treatment. In cases where such a reduction in the size of the uterus is not noted, the client should be informed of the possibility of unsuccessful medical treatment. The dog should be reassessed after another 2–5 d of treatment and if the uterus is no longer responding, either a complementary approach to the medical treatment (see above) or an ovariohysterectomy should be considered.

Disseminated intravascular coagulation (DIC) has been observed in some dogs when medical treatment is initiated in very chronic cases and is not followed by a significant improvement after 3–4 d. It is the authors' routine to serially monitor fibrinogen, fibrinogen degradation products, d-dimers, and platelet counts. It was noteworthy that DIC was essentially detected when dogs were treated with progesterone-receptor antagonists without prostaglandins. Subcutaneous administration of 100–500 IU/kg of heparin at the start of the medical treatment may prevent intravascular coagulation from developing. However, the effectiveness of this treatment has never been scientifically validated.

5. Recurrence of pyometra

The incidence of pyometra recurrence after medical treatment is still controversial, with contradictory results published. However, the percentage of recurrence is obviously decreasing over time with improvements in therapeutic approaches and treatments.

Meyers-Wallen et al. [44] described therapeutic success in 10 of 10 treated animals with recurrence in 40% of the bitches within 1 y, and 77% within 27 mo. Johnston et al. [83] gave an overview of success and recurrence rates after conservative treatment of pyometra with prostaglandins and reported that recurrence rates averaged 10%.

In a study published in 2003 by Trasch et al. [84], 18.9% of the treated dogs relapsed after treatment with aglepristone alone. In most cases of recurrence, there were cystic changes in the ovaries and endometrium. The authors concluded that the recurrence rate can be minimized by the selection of bitches without ovarian cysts and cystic endometrial hyperplasia. Although it could be possible to reduce the incidence of CEH and its effects on pyometra as discussed above, the presence of ovarian cysts is more difficult to assess, even with ultrasonography. Furthermore, it is not possible to differentiate some estrogen-producing ovarian cysts

from non-pathologic para-ovarian cysts or corpora lutea with a fluid-filled cavity [85,86].

In a case-based study comparing incidence of pyometra in a population of previously treated pyometra dogs ($n = 57$) and a control age-matched group of dogs not having presented with pyometra earlier ($n = 256$), we were not able to find any statistical difference in the probability that a dog of any specific age group either with or without prior disease would develop a pyometra (unpublished). Therefore, when treatment and uterine regeneration is successful, the probability for the bitch to develop pyometra again is the same as the probability for a naïve bitch of the same age to develop a pyometra. These conclusions were the same in terms of fertility, which is not affected. It appears that a delayed response to treatment is associated with the increased likelihood of recurrence of symptoms, i.e. dogs that respond rapidly are more likely to breed successfully in the future. Therefore, we consider evaluation of success of treatment after 5 d and usually recommend OHE to the client if the response is not good.

As pyometra is often observed in older dogs, breeding should be attempted at the first estrus following treatment and at every subsequent estrus, body and health condition permitting, until the desired number of offspring have been obtained or until the disease recurs. The main reason to breed at the ensuing cycle is essentially not to lose one more cycle in an animal that may already have age-related reductions in fertility.

Following treatment, fertility is generally considered to be good. Nelson and Kelly [87] reported that 8 of 15 bitches treated with prostaglandins for (post-estrous) pyometra whelped at least one healthy litter after treatment. The same group reported clinical resolution of uterine infections in 42 out of 44 dogs (93%); 38 of those bitches subsequently whelped healthy pups. Successful breeding was recorded in 9 of 20 treated bitches followed for 1 y or longer after treatment. Expected conception rates varied from 50 to 75%, depending on the age of the animal considered, with fertility generally being highest in younger animals.

6. Conclusions and perspectives

Substantial improvements in the treatment of pyometra have been made over the last decade. Results are good and continuously improving with the availability of better medications to achieve our goals: luteolysis and prevention of progesterone effects, uterine contraction and evacuation, uterine regeneration, and inhibition of bacterial development. In combination with good supportive and intensive care during the period of treatment, which obviously requires hospitalization of the animal, the old adage that is unfortunately still taught, ‘‘never let the sun set on a pyometra’’, is to be considered totally outdated. Any patient with pyometra, valuable breeding stock or not, may benefit from a medical approach to pyometra, either to preserve reproductive capacity of the patient or eventually to stabilize the patient and postpone the surgery for a few days. Future developments can be expected; for example, the authors have developed a new transcervical endoscopic catheterization technique (TECT) to treat pyometra (unpublished), allowing resolution of the disease in 3–5 d versus 7–10 d. This new approach should further improve our ability to successfully manage pyometra (closed or open cervix).

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