A review of pyometra in small animal medicine: incidence, pathophysiology, clinical diagnosis, and medical management

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Abstract

Pyometra is a common reproductive disorder involving an acute or chronic bacterial infection of the uterus, with accumulation of purulent exudate in the lumen. This disorder is hormonally driven, primarily by uterine exposure to progesterone and estrogen priming during repeated estrous cycles. Traditionally, pyometra is thought to occur in conjunction with cystic endometrial hyperplasia as "cystic endometrial hyperplasia-pyometra complex". Cystic endometrial hyperplasia commonly, but not necessarily, precedes development of pyometra. Pyometra is more widely recognized as a reproductive condition of bitches, but can also occur in queens. Pyometra is classified as being either open- or closed-cervix, based on the presence or absence of vaginal discharge. Diagnosis of pyometra is based on reproductive history, clinical signs, blood work, and imaging. Depending on extent of endotoxemia and cervical patency, patient presentation is variable, ranging from mild clinical signs to decompensated shock. Regardless, pyometra should be considered a potentially life-threatening medical emergency, independent of apparent stability, since sepsis, peritonitis, and uterine rupture are possible sequelae. In all cases, initial stabilization and institution of appropriate antibiotic therapy are warranted. Ovariohysterectomy is the traditional treatment of choice for pyometra. Recently, medical management has become a viable alternative to ovariohysterectomy, enabling preservation of future fertility of bitches and queens. The most effective medical protocols involve low-dose prostaglandin treatment in conjunction with antiprogestins or dopamine agonists. Although medical therapy can be effective in stable cases, recurrence during future estrous cycles is common.

Keywords: Pyometra, bitch, queen, medical management, cystic endometrial hyperplasia

Incidence and signalment

Affecting nearly 25% of intact bitches by 10 years of age, pyometra is a reproductive disorder primarily occurring in mature intact bitches and queens during diestrus.[1] Pyometra is essentially a disease caused by bacterial infection of a uterus primed with progesterone (P_4) and its risk of development increases with age and repetitive estrous cycles. In bitches, the mean age of pyometra diagnosis is reported to be 7.25 years (range, 4 months to 16 years).[2] The incidence of pyometra increases with maturity and may be >65% in intact bitches >9 years old.[2] Incidence increases in bitches >4 years and nulliparous bitches.[3] Prior hormonal treatment with progestins or estrogens can greatly increase the risk of pyometra development.[4-6] Even low doses of estradiol benzoate can increase (by a multiple of 6.5) the incidence of pyometra within 4 months after treatment.[5] Prior exposure to reproductive hormonal therapy and congenital abnormalities of the genital tract, e.g. vaginal strictures, can predispose to development of pyometra. Most bitches and queens present with pyometra during diestrus while their uterus is under progesterone dominance. The majority of bitches develop pyometra within 3 months (mean, 5 to 6 weeks) after the onset of their last proestrus.[7] However, bitches may present with pyometra at any stage of their estrous cycle. Pregnancy may confer a protective benefit, and there are reports of cases with a normal pregnancy in one horn and concurrent pyometra in the contralateral horn.[2,8] Pseudocyesis (aka pseudopregnancy) is not associated with pyometra.[8] In up to 30% of cases of canine pyometra that present during anestrus P_4 <1.0 ng/ml), it is believed the actual onset was during P_4 dominance. These may be

chronic insidious cases in which signs were not recognized until the end of a normal luteal phase.[9]

Lifetime risk of pyometra development is variable (15 to 24%), depending on characteristics of the female population (age, breed, and geographic location).[1,10] In recent studies, incidence varies dramatically among breeds, suggesting breed predisposition.[1,11-14] Furthermore, the strength of factors that confer protection against development of pyometra is variable depending on breed.[11] In a 2001 study of Swedish insured bitches, overall risk of developing pyometra was ~24% by 10 years; however, there was considerable variability among breeds (10 to 54%).[1] In a similar 2012 study, proportion of bitches affected by pyometra was highest in the following breeds: Bernese Mountain Dog (66%), Great Dane (62%), Leonberger (61%), Rottweiler (58%), Irish Wolfhound (58%), Staffordshire Bullterrier (54%), Bullterrier (52%), Newfoundland (50%), Collie (44%), and Old English Sheepdog (42%).[12] Other at-risk breeds identified include: Saint Bernard, Chow Chow, Miniature Schnauzer, Irish Terrier, Airedale Terrier, Rough Collies, Cavalier King Charles Spaniels, Golden Retrievers, Bullmastiffs, Dogue de Bordeaux, and English Cocker Spaniels.[1,13,14] There was a significant effect of breed on mean age of presentation, with some breeds being significantly younger, e.g. Dogue de Bordeaux (3.3 years) and Bullmastiff (5.4 years), whereas others presented significantly older, e.g. Yorkshire terriers (9.4 years) and Border Collies (10.3 years).[13] Breeds identified at decreased risk for development of pyometra include: Drevers, German Shepherd Dogs, Miniature Dachshunds, Dachshunds, and Swedish Hounds.[1] Breed popularity was accounted for in these studies.

Pyometra is less common in queens, likely because cats, as induced ovulators, have less cumulative uterine exposure to P_4. Regardless, pyometra is still one of the most common reproductive disorders in intact queens. The overall prevalence of pyometra in the queen has not been as well documented, but the incidence in Swedish insured cats was one cat per 588 cat years at risk, with overall prevalence of 2.2% by 13 years of age.[15] Dow reported clinically diagnosing pyometra in about one cat per three dogs diagnosed.[16] As in bitches, incidence in queens increases with maturity, with an average age reported 4 and 7.2 years.[15,17] Affected queens' age at presentation can range from 1 to 20 years.[2] The majority of queens present for pyometra during diestrus, within 2 to 5 weeks after induced ovulation.[17] Therefore, use of progestins that simulate diestrus (for long-term suppression of estrus) in queens increases the risk of developing cystic endometrial hyperplasia (CEH) and pyometra.[18,19] Recently, significant breed predispositions for pyometra development have been reported in exotic and oriental cat breeds, including the Siberian cat, Ocicat, Korat, Siamese, Ragdoll, Maine Coon, Bengal and Sphynx, with the latter breed being at greatest risk.[15] As in dogs, differences in incidence among cat breeds suggest a genetic component to development of pyometra.

Pathophysiology

Pyometra is a reproductive endocrine disorder typically associated with diestrus or the luteal phase, when the uterus is under the influence of P_4. As a bacterial infection of the uterus, pyometra causes intraluminal accumulation of purulent exudate and inflammatory infiltrates and often initiates systemic inflammation and sepsis, which can be life threatening. The complete etiology of pyometra has not yet been fully elucidated. However, pyometra is generally considered an abnormal uterine response to estrogen and P_4 affecting the endometrium that enhances bacterial colonization of the uterus.[20] Estrogen priming of the uterus enhances growth and vascularization of the endometrium and potentiates the stimulatory effect of P_4 on the uterus through sensitization of uterine P_4 receptors, enhancing their binding.[21] Physiologic formation of a corpus luteum after every ovulatory cycle leads to relatively prolonged uterine exposure to elevated serum P_4 concentrations. This prolonged P_4 dominance occurs with every estrous cycle in the bitch and each ovulatory cycle in the queen. P_4 increases endometrial proliferation and glandular secretions, decreases myometrial contractions and causes cervical closure.[21] Additionally, P_4 has an inhibitory effect on uterine cellular immunity by decreasing neutrophil chemotaxis

and phagocytic ability and facilitating bacterial adherence to the endometrium.[22,23] Effects of P_4 on the uterus promote accumulation of glandular secretions within the closed lumen; coupled with an inhibitory effect P_4 on leukocytes, this creates an ideal environment for pregnancy or bacterial growth by ascending infection in cases of pyometra. Uropathogenic strains of *Escherichia coli* are the most common bacteria isolated in bitches and queens with pyometra.[24, 25]

Pyometra is strongly associated with CEH, the most common uterine disorder in older intact bitches and queens. CEH is characterized by abnormal endometrial gland proliferation and hypersecretion leading to cyst formation, endometrial thickening, and accumulation of viscous intraluminal glandular fluid.[7] The cumulative effect of repeated P_4 exposure during diestrus leads to development of CEH.[26] Although CEH is a subclinical non-inflammatory disorder of the aging uterus, not associated with any signs other than infertility,[27] it can be associated with accumulation of sterile intraluminal uterine fluid, resulting in development of mucometra (viscous fluid), hydrometra (watery fluid), or hematometra (bloody fluid).

Due to their distinct clinical and histopathologic presentations, pyometra and CEH are generally considered separate disease entities. Historically, CEH was considered a prerequisite for pyometra.[26,28] Although CEH precedes pyometra-endometritis in the majority of cases, there is evidence that these conditions can develop independently.[29] Whereas all intact bitches will eventually develop CEH with age, not all will develop pyometra.[9]

In rare cases, pyometra can develop in the absence of CEH.[21] It was recently postulated that pyometra could develop as the result of local uterine irritation.[30] Subclinical bacterial infections have been postulated as causing excessive endometrial proliferation (aka a trophoblastic reaction, similar to implantation), leading to increased glandular secretions and bacterial proliferation and ultimately pyometra.[30-36] This was validated by evidence that CEH can develop from a trophoblastic reaction to any endometrial irritation in a P_4-primed uterus; consequently, uterine biopsies should not be collected during diestrus. [37, 38] Uterine reaction to bacterial invasion could explain concurrent presence of CEH in pyometra cases. In both theories, P_4 clearly has a critical role in development of pyometra, either by initiating CEH through chronic exposure, or as an essential component for induction of a trophoblastic reaction. This may explain development of pyometra in young bitches without pre-existing CEH.[9]

Although the full etiology of pyometra has not been completely elucidated, it is generally regarded as multifactorial. Innate immune response and bacterial virulence undoubtedly are important in development of pyometra. High serum P_4 concentrations during the luteal phase suppress local cellular immunity in the uterus.[9] It was recently reported that bitches could have subclinical endometritis without developing overt pyometra;[39] perhaps mild, chronic bacterial contamination of the uterus occurs in younger bitches prior to escalating into clinical pyometra.[39]

Ascension of vaginal bacterial flora through the relaxed cervix to infect a P_4-primed uterus presumably results in pyometra. The pathogen predominantly associated with pyometra is *Escherichia coli* (70% of cases), but other vaginal commensal bacteria, e.g. *Staphylococcus aureus*, *Enterobacter*, *Pseudomonas*, *Klebsiella*, *Proteus,* and *Streptococcus* spp., have less commonly been recovered.[24, 40] In most cases of pyometra, uropathogenic strains of *E. coli* are isolated with specific virulence factors enhancing adherence. These uropathogenic virulence factors, in conjunction with the diestral uterine environment, facilitate infection of the urogenital tract and development of pyometra.[41,42] Concurrent urinary tract infections are common (20 to 70%) in bitches with pyometra.[43]

Uterine infections with *E.coli* frequently release lipopolysaccharide (LPS), a bacterial endotoxin, which can lead to development of serious systemic disease and inflammation. For example, LPS produced by some pathogenic strains of *E. coli* can cause antidiuretic hormone insensitivity in the distal convoluted

tubules and collecting ducts, reducing renal concentrating ability. This endotoxin-induced transient glomerular and tubular kidney dysfunction leads to clinical signs of polyuria/polydipsia frequently associated with pyometra in bitches.[44]

Elevated serum endotoxin concentrations in dogs with pyometra have been associated with a higher risk of death.[45] A clinically applicable method to measure endotoxin or an indicator of its release, such as prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) metabolite, would be very valuable in rapid evaluation of pyometra.[46] Furthermore, in uterine tissues, pyometra significantly uterine up-regulates genes associated with chemokines, cytokines, proteases, inflammatory cell extravasation, antibacterial action, the complement system, and innate immunity.[47]

Endotoxemia associated with pyometra may progress to sepsis, systemic inflammatory response (SIR), or disseminated intravascular coagulation. Systemic inflammatory response has been reported in up to 50% of bitches with pyometra and has been associated with a poor prognosis and longer hospitalization.[46,48] In cases of pyometra-induced sepsis/SIR, serum concentrations of inflammatory markers such as C-reactive protein (CRP), serum amyloid A (SAA) and $PGF_{2\alpha}$ metabolite significantly increased.[46,49,50] Appropriate surgical treatment of pyometra should abrogate the marked inflammatory response. Therefore, monitoring serum concentrations of acute phase proteins, e.g. SAA, CRP, and haptoglobin, may be useful to determine necessity for surgical intervention, post-operative detection of complications (ongoing infection), and resolution.[51] Additional complications of pyometra-induced sepsis include bacteremia or thomboemboli to other organs (e.g. brain, heart, or eye), leading to multi-organ dysfunction.[47]

Clinical presentation

The majority of patients with pyometra present with a history of recent estrus. In bitches, the classic time frame is 1 to 4 months after estrus,[14] whereas queens typically present within 4 weeks.[17] In any ill intact female patient, pyometra should be considered as a differential and a thorough reproductive history taken (i.e. parity, last estrus and prior hormonal therapy). Affected bitches typically present with lethargy, anorexia, vomiting, polyuria/polydipsia, and/or vaginal discharge (depending on cervical patency). Presentation can vary widely from gait abnormalities and hind limb lameness (more common with closed cervix pyometra), abdominal distention alone, nonspecific symptoms, or decompensated septic shock.[52] No relation has been demonstrated between nature of clinical signs and severity of uterine lesions.[9] Classic presenting signs of pyometra in queens (Figure 1) include purulent vaginal discharge, anorexia, lethargy, emesis, unkempt appearance, and a palpable uterine enlargement/abdominal distention.[17,53] In contrast to the bitch, clinical signs in queens are typically fewer, milder, or more nebulous, with polyuria/polydipsia rarely present.[54]

Cervical patency determines the presence or absence of vaginal discharge and is an important consideration in case management. Open-cervix pyometra typically results in milder systemic signs; commonly a hemorrhagic purulent discharge may be the only clinical abnormality. In contrast, closed-cervix pyometra cases typically present without overt vaginal discharge, but marked systemic signs of illness are often apparent due to resorption of endotoxins into circulation leading to endotoxemia and/or bacteremia. Severe cases may present in septic shock.

Classic clinical findings of pyometra include vaginal discharge (80%), pyrexia (47%), polyuria/polydipsia (<50%), and emesis.[9] Unspecific findings include lethargy and anorexia and in more advanced cases, signs of shock may include tachycardia, tachypnea, hypotension and pale or injected mucous membranes. Abdominal palpation may reveal large tubular organ/uterine enlargement[55,56] (more common in queens) and may elicit pain. When pyometra is suspected, abdominal palpation should be performed very carefully, as excessive pressure can rupture a friable uterus. Volume of vaginal discharges

are related to cervical patency and character is purulent to hemorrhagic to mucoid. Fastidious grooming may mask a vaginal discharge.

Abdominal imaging

Ultrasonography of the urogenital tract is the most important diagnostic tool in a pyometra workup. Typical findings include uteromegaly, thickened uterine walls, proliferative endometrial changes, fluid-distended convoluted tubular horns and anechoic to hyperechoic luminal fluid.[57,58] Uterine fluid in pyometra is usually homogenous, but can be flocculent and there may be slow swirling.[59] Ultrasonography is an important tool to differentiate pyometra from other soft tissue causes of uterine distention such as early pregnancy (>24 days gestation), uterine torsion, mucometra, hydrometra and hematometra. Furthermore, if uterine torsion or rupture is suspected, ultrasonography can be used to detect abdominal free fluid, which is suggestive of peritonitis and has a poor prognosis. Mucometra and hematometra commonly appear ultrasonographically as thin-walled uterine distention with homogenous echodense to hypoechoic luminal fluid, whereas luminal contents are typically anechoic in hydrometra.[54] Ultrasonography is also critical for detection of CEH, endometrial integrity, and uterine wall thickening (Figures 2 and 3). CEH is reliably diagnosed ultrasonographically once it has progressed to a moderate to advanced state, characterized by 1 to 4 mm anechoic cysts within a thickened endometrium.[60] Furthermore, ultrasonographically apparent (i.e. severe) CEH was associated with a poorer response to medical therapy (antibiotics and $PGF_{2\alpha}$).[60] The ultrasonographic appearance of uterine luminal fluid and endometrium in conjunction with cytology and bloodwork can help differentiate sterile uterine disorders from pyometra, although definitive diagnosis is ultimately based on uterine culture and uterine histopathology after ovariohysterectomy (OVH).

Abdominal imaging by radiography is not as sensitive or specific as ultrasonography. In dogs with pyometra, the uterus appears as a sausage-like fluid filled tubular organ between the descending colon and the urinary bladder (Figure 4). However, conditions causing soft tissue/fluid uterine distention, including early pregnancy (<45 days gestation, prior to fetal calcification), sterile uterine luminal fluid disorders, uterine cancer and uterine torsion can yield similar images. Additionally, abdominal radiographs may be non-diagnostic in open-cervix pyometra with minimal uterine distension.

Vaginal diagnostics

If pyometra is suspected, vaginal discharge cytology, culture, and vaginal mucosal cytology should be performed. If the cervix is at least slightly patent, the discharge present in the pericervical cranial vagina may be representative of uterine contents; a sample should be collected with a guarded swab and speculum, subjected to cytology and also subjected to aerobic culture and sensitivity, especially if medical management is planned. In most pyometra cases, a large number of degenerate neutrophils and intracellular or extracellular bacteria are apparent. Cytology of the cranial vaginal discharge can be useful to differentiate pyometra from the following sterile uterine disorders producing luminal fluid and potentially associated with CEH: mucometra (low neutrophil count, endometrial red blood cells (RBCs) and proteinaceous debris), hydrometra (few RBCs and white blood cells (WBCs) with abundant mucus), and hematometra (abundant RBCs with minimal WBCs and mucus).[56] Vaginal mucosal cytology should also be performed to rule out other causes of discharge, e.g. estrus or vaginitis.

If purulent vaginal discharge is present but uteromegaly is not apparent on ultrasonography, endoscopic vaginoscopy can be pursued. Due to the friable nature of the vaginal tract during diestrus, vaginoscopy should be performed with caution and may require sedation. The purpose of endoscopic vaginoscopy would be to evaluate cervical patency and to evaluate the vaginal tract for alternate sources of vaginal discharge such as a vaginal mass or polyp, foreign body, lower urinary tract infection (UTI), or idiopathic vaginitis.

Laboratory findings

Complete blood count
    Pyometra classically presents with a marked leukocytosis characterized by neutrophilia with a left shift, toxic neutrophilic changes, and monocytosis. The leukocytosis is typically more severe in closed-cervix pyometra cases. Percentage of band neutrophils is the most sensitive laboratory parameter for differentiating pyometra from sterile uterine luminal fluid disorders: >19.9% band neutrophils is 94.2% sensitive and 70% specific for pyometra.[40] Mild to moderate normocytic, normochromic, non-regenerative anemia of chronic disease may be present, though evaluation of anemia can be complicated by concurrent dehydration/hemoconcentration. Up to 25% of dogs with pyometra have a normal complete blood count (CBC), especially if pyometra is incidentally detected early in its course by ultrasonography.[9]

Blood serum chemistry
    Patients with pyometra have variable changes in serum chemistry values. The most common abnormalities include: azotemia [increased blood urea nitrogen (BUN) and creatinine], increased liver enzymes (alkaline phosphatase and alanine transaminase), hyperbilirubinemia, hypercholesterolemia, hyperglobulinemia, hypoalbuminemia, and hyperproteinemia.[40] Azotemia may be variably present (12 to 37%) in affected bitches, and may be due to pre-renal dehydration and/or transient, endotoxin-induced renal tubular damage.[43] These renal changes are typically transient and reversible once appropriate treatment is instituted. However, BUN >60 mg/dl has been associated with acute renal failure and a poor prognosis. Some strains of *E. coli* produce cytotoxic necrotizing factors, which in conjunction with dehydration, can cause reversible hepatocellular damage or hypoxia.[23] Serum concentrations of inflammatory markers, C-reactive protein (CRP) and $PGF_{2\alpha}$ metabolite, are typically elevated in serum of animals with pyometra and can help differentiate pyometra from sterile cystic endometrial hyperplasia disorders.[61,62] Lactate concentrations are variable and not considered diagnostic.[63,64]

Urinalysis
    In patients with pyometra, urinalysis may reveal dilute urine (isothenuria to hyposthenuria), bacteriuria (concurrent UTI), glucosuria, and/or proteinuria. Free-catch urine collection is acceptable since the main purpose of the urinalysis in cases of pyometra is to evaluate specific gravity, renal function, and presence of co-morbidities. Ultrasound-guided cystocentesis is not recommended due to the potential puncture of a friable, distended uterus.

Hormone assays
    Serum P_4 concentrations should be evaluated to determine stage of the estrus cycle. In the majority of cases of pyometra, P_4 will be significantly elevated, indicative of diestrus. However, in a minority of cases, P_4 may be baseline (<1 ng/ml) indicating anestrus. In medical management of pyometra, baseline P_4 is necessary to determine the degree of luteolytic drugs needed; serial P_4 measurements are done until luteolysis is achieved (P_4 <1.0 ng/ml).

Therapy

Stabilization
    Due to the insidious onset and nonspecific signs of pyometra, many patients present in advanced stages and may require stabilization prior to initiating diagnostics, surgical or medical therapy. Initial examination should include immediate evaluation of metabolic, hemodynamic, hydration, and

hematologic status. These parameters should be monitored closely throughout diagnostics, treatment, and post-therapy. Once pyometra is diagnosed, all patients should be started on broad-spectrum bactericidal antibiotics. Prior to initiating therapy, especially surgery, correction of electrolyte, hydration, and acid-base imbalances should be instituted. For patients presenting hypovolemic and dehydrated, appropriate intravenous (IV) fluid therapy with crystalloids should be immediately initiated. Azotemic patients with persistent hypotension may require constant rate intravenous infusion of low-dose dopamine or dobutamine, in addition to aggressive fluid resuscitation. Therapy for other concurrent life-threatening abnormalities (e.g. renal failure, pulmonary dysfunction, cardiac arrhythmias, and hypoglycemia) should be instituted before surgery.

In patients presenting in decompensatory septic/endotoxic shock, more aggressive treatment with oxygen therapy and IV hypertonic saline and colloids should be instituted.[65] Deteriorating cases with endotoxemia may benefit from corticosteroids (prednisolone sodium succinate 30-60 mg/kg IV). [66] Endotoxemia due to systemic LPS released from bacteria may reach severe to lethal levels in pyometra cases.[67] Initiation of antibiotic therapy can worsen endotoxemia by increasing systemic LPS concentrations (up to 2000-fold). Therefore, it was proposed that endotoxemic bitches be given anti-LPS (e.g., polyvalent equine anti-endotoxin hyperimmmune plasma) at a dose of 0.5 mg/kg subcutaneously (SC) in cases of delayed surgery or administered IV after dilution in 100-300 ml lactated ringer's solution (LRS) if surgery is to be performed immediately. No side effects were reported, but overall efficacy is unknown.[67]

Treatment to promote stabilization should be immediately instituted in all patients presenting with pyometra. In very critical cases, surgery may be required after only a few hours of emergency medical stabilization. However, if the patient is more stable, surgical and anesthetic risks may be reduced and stability improved by initiating medical therapy to lyse the corpora lutea, dilate the cervix, and promote evacuation of purulent uterine fluid.[66]

Antibiotic therapy

Broad-spectrum antibiotic therapy should be started at presentation in all pyometra cases. Since *E. coli* is by far the most common pathogen isolated in pyometra, empiric antibiotic selection should target gram-negative bacteria. *E. coli* isolates in pyometra are typically identical to those in the patient's urine or blood[48] and in some cases (10%) may be multidrug resistant.[68] Acutely, a combination of a fluoroquinolone and an extended spectrum penicillin is preferred. Fluoroquinolones have superior penetration in the genitourinary tract.[69] Other appropriate antibiotic choices for certain cases of pyometra include third-generation cephalosporins and aminoglycosides; however due to risk of renal damage, the latter should not be used in patients with renal dysfunction. [70] Long-term antibiotic therapy should be based on results of a bacterial culture and sensitivity profile of purulent exudate and continued for at least 2 weeks post-surgery or 4 to 6 weeks with medical management.

Surgical versus medical management

After diagnosis, stabilization, and initiating antibiotic treatment, the underlying cause of pyometra should be addressed. The severity of clinical presentation and breeding potential of the animal informs the decision to pursue medical or surgical management. Historically, surgical OHE was the only treatment for pyometra. OHE is still the treatment of choice in the majority of pyometra cases, especially in non-breeding animals, because it directly removes the source of the purulent exudate and endotoxin release. However, surgery and anesthesia, especially in critical patients, can be risky, and OHE sterilizes the animal. Over the last 20 years, new, successful medical approaches have been proposed, and medical management of pyometra is now considered a viable alternative to surgery in stable cases where there is a desire to preserve fertility. Medical management of pyometra may be pursued in the following cases:

valuable breeding bitches/queens (< 6 years), animals with increased anesthetic risks (normothermic critical cases or geriatric cases with significant co-morbidities), cases with monetary restrictions, or to improve patient status prior to surgery.[55] Medical therapy is contraindicated if peritonitis is suspected. If the patient's condition deteriorates or if clinical improvement is not apparent within 2 days of initiating medical therapy, reconsideration of surgical management is warranted.

Surgical management

Ovariohysterectomy is generally the preferred treatment for pyometra. Once the patient has been stabilized, antibiotic therapy instituted, and surgical risk minimized, surgery can be performed, under general anesthesia and careful monitoring. The uterus can be grossly enlarged and quite friable, especially with closed-cervix pyometra. Therefore, careful handling of the uterus with minimal pressure is essential to minimize risk of uterine rupture and/or purulent material leaking from the uterine tubes into the peritoneal cavity.[66] A ventral abdominal approach, with an incision from xyphoid to pubis, is recommended to minimize risk of uterine rupture. The abdominal cavity should be closely examined for the presence of purulent material or evidence of peritonitis, which has a poor prognosis. A traditional three-clamp technique is sufficient for ligation of ovarian pedicles, although large vessels in the broad ligament should be individually ligated. It is essential to avoid lacerating the distended uterine body. The uterus should be carefully isolated from the abdominal cavity with saline-soaked laparotomy sponges before transection just anterior to the cervix. Clamping the uterine body is not recommended, as it may rupture. The uterine body should be transfixed prior to ligation. After removal of the uterine stump, the residual uterine lumen should be lavaged with warm isotonic saline and omentalized. After complete removal of the uterus, cervix, and both ovaries, the peritoneal cavity should be copiously lavaged. A sample of uterine fluid should be obtained directly from the lumen of the uterus after removal and submitted for aerobic and anaerobic culture and sensitivity. In ~10% of cases, peritonitis may be present.[50] In these cases, a culture of the peritoneal cavity should be obtained prior to lavage and a closed active suction drainage system placed before abdominal closure.[71] Otherwise, the laparotomy incision should be closed with the same routine triple layer closure used in routine OHE. In the case of uterine stump pyometra, surgical management should be performed as outlined above, to remove the uterine stump, with exploration to identify and remove residual hormone-producing ovarian tissue.

All surgically managed pyometra cases should be intensively monitored for 24-48 hours post-operatively. Signs of sepsis, hypovolemia, hypotension, azotemia, anemia, hypoglycemia, hyperproteinemia, liver or renal dysfunction, and acid-base derangement should be immediately addressed. Supportive treatments and intravenous fluids should be continued for at least 24 hours, or until the patient is eating and drinking on their own. Serum biochemistry and complete blood cell counts which may dramatically increase after OHE should be monitored post-operatively until abnormalities resolve (typically within 5 days). Peritonitis is the most common complication, followed by septicemia/endotoxemia, anorexia, pyrexia, vomiting, renal insufficiency, and hepatic disease. Most complications resolve within 2 weeks.[66] The survival rate after surgery is 92%, thus the prognosis is generally very good.[43] Renal status pre- and post-operatively is the best prognostic indicator. For patients that have renal dysfunction at initial presentation, follow-up measurement of persistent proteinuria (urine protein creatinine ratio) is recommended. Other factors that affect prognosis for pyometra include cervical patency, dehydration status, uterine rupture (septic abdomen/peritonitis) and important co-morbidities.

Medical management

Medical management of pyometra is a viable treatment option in cases of pyometra with stable presentation and there is a desire to preserve breeding potential (Table). It also can be used to further stabilize cases prior to surgery by converting a closed-cervix pyometra into an open-cervix pyometra.

Medical treatment can be successful, but owners should be warned of possible future recurrence and potential reduction in fertility. Case selection for medical therapy is important to optimize outcome. Ultimately, multiple factors contribute to efficacy of medical treatment, including cervical patency, degree of systemic involvement, age, follicular cysts, or presence or absence of CEH.[55]

Medical treatment involves $PGF_{2\alpha}$ (natural or synthetic agonist), dopamine agonists, and P_4 receptor antagonists (antiprogestins), either alone or in combination. There are many protocols for medical management of pyometra, but the aims are similar. The first goal is to remove effects of P_4, either by luteolysis or blocking P_4-receptor binding. Removing the P_4 influence facilitates cervical relaxation, permits myometrial contractions, and improves local uterine immunity, enabling natural expulsion of purulent uterine discharge through an open cervix (enhanced with ecbolics). This goal can be accomplished using prostaglandins (alone or in combination with dopamine agonists) and/or P_4-receptor antagonists. Uterine contractions that facilitate uterine drainage are induced directly by $PGF_{2\alpha}$ or indirectly by P_4 receptor antagonists by removing the effect of P_4 on the uterus. The second goal of medical management is prevention of bacterial proliferation through appropriate antibiotic therapy.

Prostaglandin $F_{2\alpha}$ and agonists

Success in treatment of pyometra has been reported with the use of $PGF_{2\alpha}$ therapy alone or in combination. Repeated microdosing of $PGF_{2\alpha}$ acts directly on corpora lutea to induce luteolysis or block P_4 synthesis, decreasing P_4 concentrations, resulting in cervical opening and decreased glandular secretions.[72] Furthermore, prostaglandins directly promote uterine contractions, which with a patent cervix, permit expulsion of uterine discharge. $PGF_{2\alpha}$ treatment is therefore contraindicated in closed-cervix pyometra, especially if uterine walls are thin, due to the increased risk of uterine rupture and ensuing peritonitis.

Therapeutic $PGF_{2\alpha}$ is available in a natural form (e.g., dinoprost tromethamine, Lutalyse®, Zoetis, Parsippany-Troy Hills, NJ) and in a synthetic form (e.g., cloprostenol sodium, Estrumate®, Merck Animal Health, Madison, NJ). Synthetic prostaglandins ($PGF_{2\alpha}$ analogs) can be used in lieu of natural $PGF_{2\alpha}$, and have been associated with prolonged activity, enhanced specificity for uterine smooth muscle, and less side effects (especially emesis). However, $PGF_{2\alpha}$ analogs have reduced ability to stimulate uterine contractions.[9] Although $PGF_{2\alpha}$ is standard of practice for medical management of open pyometra in the USA, these compounds are off-label in dogs and cats, so it is imperative to obtain written consent before starting treatment.

Treatment with $PGF_{2\alpha}$ can have important, dose-dependent side effects, especially at higher doses. These side-effects include panting, emesis, hypersalivation, hypothermia, diarrhea, urination, anxiety/shivering, ataxia, and abdominal contractions. Additional side effects present only in queens include vocalization, grooming, kneading, mydriasis, and lordosis.[53] Prostaglandin $F_{2\alpha}$ has a narrow therapeutic index, and in rare cases (especially with higher doses and a closed cervix) may cause shock and death. Therefore, frequent administration of low doses through subcutaneous (SC) or intramuscular (IM) injections is recommended. Adverse effects typically develop within 5-30 minutes and should abate within another 30 minutes. Tolerance develops quickly, and reduction of side effects generally occurs with each subsequent dose. Hospitalization (at least at the onset of $PGF_{2\alpha}$ therapy) is recommended, due to frequency of side effects and dosing, as well as potential toxicity. Reduction of side effects is accomplished with low-dose protocols (administered frequently), fasting 1 to 2 hours before treatment, walking the patient 15-30 minutes after administration, using $PGF_{2\alpha}$ analogs, and pre-treating with atropine 0.025 mg/kg SC 15 minute prior to injection, to minimize parasympathetic effects.[55,73] Additionally, combination protocols of prostaglandins with antiprogestins or dopamine agonists are reported to minimize side effects and may improve overall therapeutic success.[74,75]

Multiple protocols for $PGF_{2\alpha}$ therapy have been proposed. Cloprostenol, a synthetic $PGF_{2\alpha}$ agonist, can be dosed at 1-5 µg/kg SC every 24 hours until resolution.[2,76] For dinoprost tromethamine, low-dose, high-frequency dosing protocols have been most successful, including substantial reductions in side effects. Protocols progressively increasing doses have also been successful and minimize adverse reactions. Most authors now recommend natural $PGF_{2\alpha}$ dosing at 100-250 µg/kg/day divided into small frequent doses (three to six times daily), and in some cases, the overall dosage is gradually increased over a few days. In dogs, a successful well-tolerated low-dose protocol for dinoprost tromethamine is as follows: 10 µg/kg SC, given in three to five doses on Day 1; 25 µg/kg SC in three to five doses on Day 2; and 50 µg/kg SC in three to five doses on Days 3 to 10, or until resolution of vaginal discharge.[9] In cats, the preferred protocol for dinoprost is similar: 10-15 µg/kg SC every 8 hours on Day 1; 25 µg/kg SC every 8 hours on Day 2; and 50 µg/kg SC every 8 hours for Days 3 to 10, or until complete uterine evacuation.[66] Anecdotally, intravaginal administration of dinoprost tromethamine has been described in the dog (150 µg/kg inserted vaginally at 0.3 ml/kg every 12 hours until resolution) with reported success.[77] $PGF_{2\alpha}$ treatment may need to be continued for 7 to 10 days, or until complete uterine emptying occurs.[48]

Clinical improvement is expected within 48 hours of initiating prostaglandin treatment. Copious vaginal discharge is typically observed for ≥48 hours, then gradually diminishes. A rapid reduction in uterine diameter (determined with ultrasonography) should be evident within 24-48 hours.[55] Ultrasonographic monitoring of uterine evacuation is important to determine efficacy and duration of therapy. The uterus should be re-assessed frequently enough to assess uterine emptying to determine duration of therapy, and a follow-up uterine ultrasonographic examination is recommended after conclusion of therapy. Resolution of pyometra involves complete uterine emptying confirmed ultrasonographically as lack of intraluminal fluid, cessation of vaginal discharge, baseline P_4 (<1 ng/ml), and return to normal appetite and activity. Pyometra resolution is reported with $PGF_{2\alpha}$ therapy in 75 to 100% of cases, depending on the study and protocol.[23] Medical prostaglandin treatment in queens is recommended only for open-cervix pyometra, as success with closed-cervix pyometra is poor.[78] Future fertility after prostaglandin therapy is 75 to 87% in bitches.[21] Recurrence of pyometra after $PGF_{2\alpha}$ treatment is variable, with 5% recurrence for bitches that became pregnant on their next estrus to as high as 70% recurrence in all treated bitches followed for 27 months.[21,79]

Dopamine agonists

Dopamine agonists, such as cabergoline or bromocriptine, can be used (off-label) in combination with $PGF_{2\alpha}$ to treat pyometra. Prolactin is a major luteotroph that supports long-term maintenance of a functional corpus luteum in the bitch. Dopamine agonists have antiprolactin activity and therefore decrease P_4 synthesis by the corpus luteum by decreasing lueeotrophic prolactin concentrations as early as 25 days after the luteinizing hormone peak. When used synergistically in conjunction with $PGF_{2\alpha}$, dopamine agonists can potentiate the rapid P_4 decrease which leads to cervical patency typically within 24-48 hours.[75] Bromocriptine is less popular, as it must be given more frequently (TID) with food and is more likely to cause emesis. The dosing protocol is similar in both bitches and queens. The typical dosage regimen of bromocriptine is 10 to 20 µg/kg PO every 8 hours. Cabergoline is traditionally dosed at 5 µg/kg PO every 24 hours, but the dose can be divided and given every 12 hours to reduce gastrointestinal side effects. Both are given until P_4 concentrations return to baseline (<1 ng/ml) when used in combination with $PGF_{2\alpha}$.

Progesterone receptor antagonists (antiprogestins)

Antiprogestins such as aglepristone can be successfully used alone or in combination with $PGF_{2\alpha}$ for medical management of pyometra. Unfortunately, aglepristone is not currently available in North

America, but is marketed in Europe and Australia for veterinary use (RU 534, Alizin® Virbac Animal Health, France). As a P_4 receptor antagonist, aglepristone is a competitive inhibitor for intrauterine P_4 receptors (binds receptors at three times the fixation rate of P_4); consequently, it dramatically inhibits the action of P_4 on the uterus and decreases intraluminal P_4 concentration.[80] Very few adverse effects have been reported with the use of aglepristone. However, it should not be used in patients with compromised hepatic or renal function. Aglepristone can be used relatively safely in both closed- and open-cervix pyometras, since it has negligible uterotonic effects. When used to convert a closed-cervix pyometra into an open-cervix case, aglepristone (administration on Days 1 and 2) safely perpetuates cervical opening with minimal uterine contractions by 25 hours (range 4 to 48 hours) after the first injection.[74] Cervical opening is associated clinically with voiding of copious amounts of purulent discharge and significant improvement and increased appetite. In bitches with baseline P_4 (<1.0 ng/ml) there is a positive effect of aglepristone alone.[80,81] Recurrence of pyometra on subsequent estrous cycles after treatment with aglepristone is generally thought to be lower, from no occurrence within 1 year to ~18%.[55,80,82]

Multiple protocols have been developed for the use of aglepristone. To optimize the efficacy of aglepristone the following protocol was developed: 10 mg/kg SC once on Days 1, 2, 8, +/- days 15, and 30 (after Day 8, treatment efficacy is determined weekly prior to additional injections).[55] Pyometra is considered completely resolved once all vaginal discharge ceases and the uterine lumen has returned to its baseline diameter. Resolution rates of 45 to 60% have been reported with this method.[74] The use of aglepristone in combination with prostaglandin therapy results in better recovery rates for pyometra, due to their synergistic actions. In the treatment of closed-cervix pyometra, $PGF_{2\alpha}$ therapy should start 24-48 hours after initial aglepristone injection, once the cervix opens; this allows cervical opening by aglepristone prior to $PGF_{2\alpha}$ inducing uterine contractions, thereby optimizing uterine evacuation. Combining aglepristone treatment with $PGF_{2\alpha}$ for 5 to 10 days increases reported success rates to 72 to 100% in bitches and 90% in queens.[10,80,83]

Follow up care and monitoring with medical management

Medical therapy for pyometra should be accompanied by careful monitoring. A dramatic increase in vaginal discharge should be apparent within 24-36 hours and persist for 7-10 days. Weekly CBC's are recommended; the left shift should resolve within the first week, with neutrophilia resolved within 10 to 15 days after starting medical management.[66] Any biochemistry abnormalities on presentation should also be followed until resolution. Serial uterine ultrasonographic examinations are recommended to assess response to treatment, with a visible reduction in luminal diameter in 5 to 7 days. The patient should be re-evaluated 10 to 20 days after recovery to assess the need for additional treatment, including antibiotics.[81] With medical management, the rate of pyometra recurrence within 2 years is 20 to 70% in bitches and 14% in queens.[53,75,84] After medical management for pyometra, 40 to 70% of bitches whelp normally,[2] with fertility generally better in younger animals. Since pregnancy is considered protective, it is recommended the bitch or queen be bred on her next cycle.

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Table. Medical management protocols for the treatment of pyometra.

| References	Side Effects and Indications	Drug(s) and Dosing	Protocols
Romagnoli 2002[76]	May require hospitalization due to high dosing frequency.	***Lutalyse®*** (low dose) 20-50 mcg/kg SC every 2-4 hours until complete uterine evacuation	Low dose $PGF_{2\alpha}$
Verstegen et al. 2008[9]	This dosing regimen minimizes side effects of $PGF_{2\alpha}$	***Lutalyse®*** (titrating dose) 10 mcg/kg SC for 3-5 doses on Day 1; 25 mcg/kg SC for 3-5 doses on Day 2; 50 mcg/kg SC for 3-5 doses on Days 3-10 (or until resolution of vaginal discharge)	Titrating dose $PGF_{2\alpha}$
Meyers-Wallen et al. 1986[84]	Worse $PGF_{2\alpha}$ side effects Increased risk of	***Lutalyse®*** (high dose) 250 - 500 mcg/kg SC every 24 hours for 3 days	High dose $PGF_{2\alpha}$ (>0.2 mg/kg every 24)

	uterine rupture Contraindicated in closed-cervix pyometra (risk of peritonitis/rupture)	No longer recommended	
Gabor et al. 1999[77]	Treatment of open-cervix pyometra. Intravaginal administration helps minimize systemic side effects of $PGF_{2\alpha}$	*Lutalyse®* (intravaginally) 150 mcg/kg topically (as a vaginal infusion at 0.3 ml/kg) every 12 hours for 3-12 days (until resolution)	Intravaginal infusion of $PGF_{2\alpha}$
Davidson 1992[53] Krekler and Hollinshead 2013[66]	Significant side effects of $PGF_{2\alpha}$ dosing (especially with first doses) Decreased side effects of $PGF_{2\alpha}$ with this dosing regimen	*Lutalyse®* (medium dose) 100 mcg/kg SC every 12-24 hours for 3-5 days OR *Lutalyse®* (titrating dose) 10-15 mcg/kg SC every 8 hours on Day 1; 25 mcg/kg SC every 8 hours on Day 2; 50 mg/kg SC every 8 hours for Day 3-10 (or until complete uterine emptying)	$PGF_{2\alpha}$ in queens*
Johnston, Kustritz and Olson 2001[2] Romagnoli 2002[76]	Treatment may need to be continued for 7-10 days or until complete uterine emptying is observed[32,79,34]	**Cloprostenol** (synthetic $PGF_{2\alpha}$ agonist) 1-5 µg/kg SC every 24 hours until resolution	$PGF_{2\alpha}$ analog**
Corrada et al. 2006[75] Krekler and Hollinshead 2013[66]	Dosing protocol is similar in both bitches and queens Dopamine agonist should be given for at least 7 days or until resolution when used in combination with $PGF_{2\alpha}$ Bromocriptine is less popular since it must be given every 8 hours with food and is associated with more emesis	**Cloprostenol** ($PGF_{2\alpha}$ analog) 1-2 µg/kg SC every 24 hours X 7 days WITH **Cabergoline** (dopamine agonist) 5 mcg/kg PO every 24 hours for up to 14 days OR **Bromocriptine** (dopamine agonist) 10-20 µg/kg PO every 8 hours for up to 14 days	$PGF_{2\alpha}$ analog + dopamine agonist
Fieni 2006[74]	Not currently	**Aglepristone**	Antiprogestin

|			
Fieni, Topie and Gogny 2014[55]	available in US Very few adverse effects, but aglepristone is contraindicated with compromised hepatic or renal function Negligible uterotonic effects, so can be used with open or closed-cervix pyometras. (Reported resolution rates of 45% by 28 days to 60% by 90 days)	10 mg/kg SC once for only on Days 1, 2, 8, 15*, and 30* *(after dosing on Day 8, evaluate treatment efficacy weekly prior to additional doses)*	
Gobello et al. 2003[80]	100% resolution rates reported when protocol used in open-cervix pyometra With closed-cervix pyometra, PGF$_{2\alpha}$ therapy is commenced 24-48 hours AFTER initial aglepristone dose (allows cervical opening by aglepristone)[74]	**Aglepristone** (antiprogestin) 10 mg/kg SC Once on Days 1, 3, 8, and 15* **Cloprostenol** (PGF$_{2\alpha}$ analog) 1 mcg/kg SC Once on Days 3 and 8 (OR Once on Days 3, 5, 8, 10, 12, and 15) after dosing on Day 15, then weekly doses until complete resolution on U/S	Antiprogestin + PGF$_{2\alpha}$ analog

*In queens, the early CL is refractory to PGF$_{2\alpha}$-induced luteolysis, therefore a higher daily dosing of PGF$_{2\alpha}$ may be required for a longer period in early diestrus.[66] Use of ecbolics is contraindicated in both dogs or cats unless patency of the cervix can be induced or develops naturally. Medical prostaglandin treatment in queens is recommended only in the treatment of open-cervix pyometra, as it has had poor success in inducing cervical patency in close-cervix pyometra cases in cats.[78]

**Synthetic PGF$_{2\alpha}$ analogs have been associated with prolonged activity, enhanced specificity for uterine smooth muscle, and reduced observable side effects (especially emesis). However, they have comparatively reduced ecbolic activity therefore are not as effective as natural PGF$_{2\alpha}$ for uterine emptying.[9]
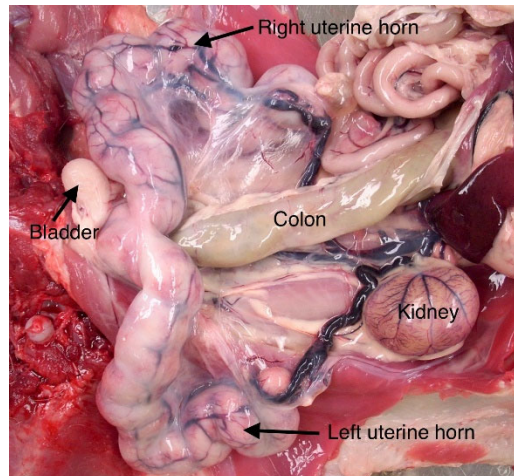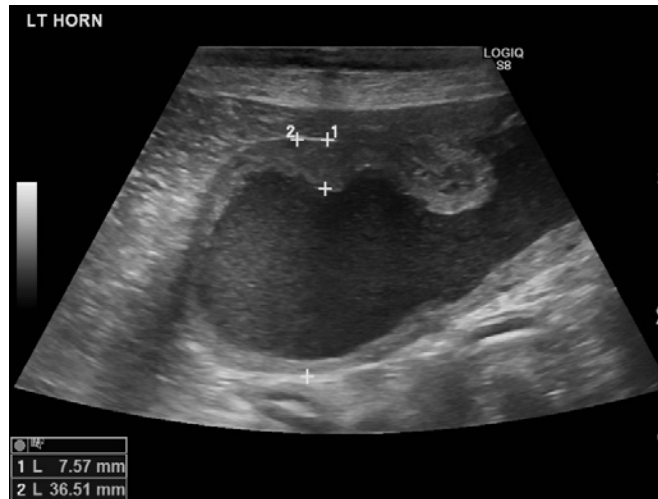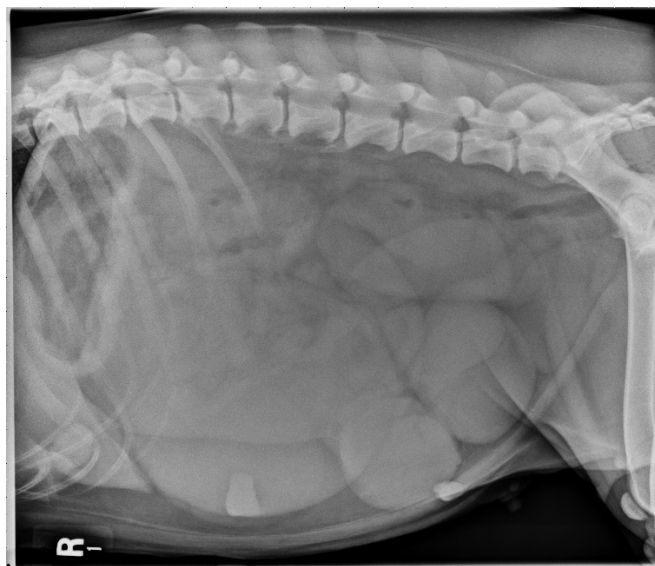
Figure 1. Pyometra in a two-year-old intact female cat. The uterine horns are moderately enlarged and mildly segmented. After the uterus was opened, purulent material containing neutrophils and bacteria was discovered.
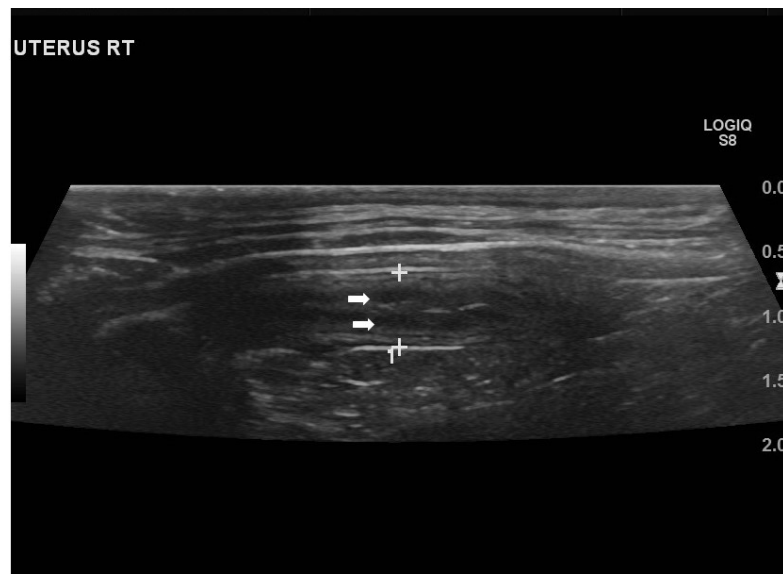
Figure 2. Ultrasonographic appearance (longitudinal view, right horn) of early cystic endometrial hyperplasia in a five-year-old intact female cocker spaniel. The uterus is empty with normal wall stratification. Cursors indicate uterine thickness. There are few small cysts (arrows) throughout the endometrium up to three mm in diameter.

Figure 3. Ultrasonographic appearance (transverse view, left horn) of a pyometra in a two-year-old intact female pit bull terrier. The uterine horn is markedly distended with echogenic fluid (36.5 mm in diameter). The uterine wall is thickened (7.57 mm) with irregular and heterogeneous endometrium with numerous cystic lesions representing cystic endometrial hyperplasia.

Figure 4. Radiological appearance (LL view) of a pyometra in an eight-year-old intact female pit bull terrier. The abdomen is distended and there is a tortuous, large tubular, well-defined soft tissue opacity present in the caudal abdomen. The structure displaces the descending colon dorsally, the urinary bladder ventrally, and the small intestine cranially. Differential diagnoses for this radiographic appearance include hydro-, muco-, hemo-, pyometra, and pregnancy before fetal ossification.

(Editor's note: Online edition of the manuscript has color photographs)